THEORETICAL AND EXPERIMENTAL BEHAVIOR OF SUSPENSION PRESSURIZED METERED DOSE INHALERS

by

Poonam Sheth

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DEDICATION

This dissertation is dedicated to my parents, Nilam and Pradip Sheth, for their vision and belief that I could do anything that they put their minds to.
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ABSTRACT

Pressurized metered dose inhalers (pMDIs) are widely utilized to manage diseases of the lungs, such as asthma and chronic obstructive pulmonary disease. They can be formulated such that the drug and/or nonvolatile excipients are dissolved or dispersed in the formulation, rendering a solution or suspension formulation, respectively. While the formulation process for solution pMDIs is well defined, the formulation process of pMDIs with any type of suspended entity can be lengthy and empirical. The use of suspended drug or the addition of a second drug or excipient in a suspension pMDI formulation may non-linearly impact the product performance of the drug of interest in the formulation; this requires iterative testing of a series of pMDIs in order to identify a formulation with the most potential for success. One of the primary attributes used to characterize the product performance and quality control of inhaled medications is the residual aerodynamic particle size distribution (APSD) of the aerosolized drug. Along with clinical factors, formulation and device parameters have a significant impact on APSD. In this study, a computational model was developed using the principles of statistics and physical chemistry to predict the residual APSD generated by suspension pMDIs based on formulation, device, and raw drug or excipient substance considerations. The formulations modeled and experimentally evaluated consist of a suspended drug or excipient with/without a dissolved drug or excipient in a cosolvent-propellant system. The in silico model enables modeling a process that is difficult to delineate experimentally and contributes to understanding the link between pMDI formulation and
device to product performance. The ability to identify and understand the variables that affect atomization and/or aerosol disposition, such as initial droplet size, suspended micronized drug or excipient size, and drug or excipient concentration, facilitates defining the design space for suspension pMDIs during development and improves recognizing the sensitive of the APSD is on each hardware and formulation variable. This model can later be applied to limit batch-to-batch variation in the manufacturing process and selecting plausible suspension pMDI formulations with quality design as the end goal.
SECTION 1

OVERVIEW OF PRESSURIZED METERED DOSE INHALERS

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CHAPTER 1
INTRODUCTION TO PRESSURIZED METERED DOSE INHALERS

Summary

While the currently recognized device technologies for pulmonary drug delivery are fairly new, treating localized conditions of the lung via inhalation has been practiced for the past few millennia. One of the recent technologies is the pressurized metered dose inhaler (pMDI), which was developed and marketed in the 1950s. The efficiency of the pMDI relies heavily on the residual aerodynamic particle size distribution (APSD), traditionally determined through tedious and resource-intensive cascade impactor (CI) experimentation. Modeling APSD is proposed as a supplement to CI testing and as a means to design pMDIs with quality as the end goal.
1. Inhalation Drug Delivery

While the term “aerosol” was not coined until 1920, the use of inhalation therapy for medicinal purposes dates back at least 4,000 years (1). Around 2000 B.C., traditional Ayurvedic medicine in India included an herbal paste of powdered *Datura* roots with ginger and pepper which was smeared on a reed that could be dried and smoked through a pipe. The *Datura* roots contain an alkaloid (i.e., atropine) with potent bronchodilating properties. The first documented use of inhaled therapeutics originates from Egypt, around 1550 B.C., where black henbane was heated on hot bricks and the resulting vapor was inhaled for its anticholinergic, bronchodilating properties (2). Many years later, the first “inhaler” was depicted by Christopher Bennet in 1654 and defined in 1778 by an English physician, John Mudge, as an invention crafted from a pewter tankard to administer opium vapors for relief of a catarrhous cough (2).

Since then, the methods and utility of delivering medications to the lungs has progressively become more complex and sophisticated. The inhalation route is a noninvasive method of delivering drugs to the lung. It traditionally affords the benefits of delivering drugs to the site of action for diseases localized to the lungs, such as asthma and chronic obstructive pulmonary disease. It also permits treating systemic conditions while bypassing the gastrointestinal system. It has been successfully used to deliver insulin and anesthetics. The three current methods used for pulmonary drug delivery include pressurized metered dose inhalers (pMDIs), dry power inhalers (DPIs), and nebulizers. Pressurized MDIs are devices that deliver a specific volume of liquid
formulation to the lungs in the form of a short burst of aerosolized medication (i.e., aerosol plume), which is generated primarily by the vapor pressure of the propellant. DPIs deliver medications in the form of dry powders, where the powder is commonly held in a capsule or blister within the device; the capsule or blister is punctured upon actuation of the device. DPIs rely on inspiratory force to entrain the powder from the device and deagglomerate it into particles that are fine enough to inhale. Nebulizers deliver medication to the lung in the form of a mist. The formulation in nebulizers is atomized by the use of oxygen, compressed air, or ultrasonic power.
2. What are pMDIs?

Pressurized MDIs were originally developed in 1955 by Riker Laboratories, now a subsidiary of 3M Healthcare (3). They were developed in response to the market need for a more portable, efficient, and less fragile alternative to squeeze bulb nebulizers. The initial pMDIs manufactured represented a convergence of three state of the art technologies for the time: a chlorofluorocarbon (CFC) propellant as an energy source to atomize the formulation, a plasticized glass bottle that is more resilient to breakage compared to glass for housing the formulation, and a Meshburg metering valve (originally designed for perfume bottles) to dispense the formulation (3). By 1956, Riker Laboratories had received the approvals for the first pMDIs: the Medihaler-Epi™ (epinephrine) and Medihaler-Iso™ (isoprenaline) as rescue inhalers for asthma exacerbations (3).

Much like the pMDI system developed by Riker Laboratories, current pMDI systems are still two component systems with the device (i.e., hardware) and formulation of the pMDI. While typically discussed independently of each other, the hardware and formulation function intimately to affect product performance of pMDIs. The hardware includes a canister to house the formulation, a metering chamber to dispense the formulation, and an actuator, which is a plastic mouthpiece, to direct the spray from the metering valve, as depicted in Figure 1.1. The recent technological improvements in pMDI hardware design are detailed in Chapter 2, which was originally published as a review article in 2014.
Pressurized MDI formulations are composed mostly of propellant. The propellant, either 1,1,1,2-tetrafluoroethane (HFA 134a) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227), is highly volatile at ambient temperature and it atomizes the formulation into $10^5$ to $10^8$ droplets of approximately 8 to 13µm in diameter weighted by mass (4,5). In addition to the propellant, the pMDI formulation may also contain a semi-volatile cosolvent, such as ethanol, to solubilize the drug, improve metering valve performance, or modify the formulation or aerosol plume characteristics. Occasionally, surfactants are included in the formulation to either improve the physical stability of a suspension or solubilize the drug. The drug(s) in pMDI formulation can be in solution or suspension with the propellant-cosolvent-surfactant system. Through the atomization process, the propellant and semi-volatile excipients evaporate, leaving only particles containing drug and any nonvolatile excipient, which ideally deposit in the human lung. More information regarding recent advances in pMDI formulation are discussed in Chapter 3, which was published as a review article in 2014. A list of FDA-approved marketed pMDIs is provided in Table 1.1.
Figure 1.1: Anatomy of the pMDI.
<table>
<thead>
<tr>
<th>Product*</th>
<th>Manufacturer</th>
<th>Drugs</th>
<th>Marketed Strength^ (µg, ex-actuator)</th>
<th>Dose (µg, ex-valve)</th>
<th>Fine Particle Dose (µg)</th>
<th>MMAD (µm, GSD [if reported])</th>
<th>Weight per Actuation (mg)</th>
<th>Propell -ant</th>
<th>Other Excipients (likely concentration presented as % w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advair HFA</td>
<td>GlaxoSmith -Kline</td>
<td>fluticasone propionate (FP) / salmeterol xinafoate (SX)</td>
<td>45/21, 115/21, 230/21 as salmeterol base</td>
<td>50/25, 125/25, 250/25 as salmeterol base</td>
<td>45/21µg: FP – 17.4 SX – 8.9 230/21µg: FP – 3.3 (1.7) SX – 3.1 (1.3)</td>
<td>75</td>
<td>HFA 134a</td>
<td>9.98% ethanol</td>
<td></td>
</tr>
<tr>
<td>Aerospan*</td>
<td>Forest Pharmaceuticals, Inc. Sunovion Pharmaceuticals, Inc.</td>
<td>flunisolide hemihydrate</td>
<td>80</td>
<td>139</td>
<td>54</td>
<td>1.2</td>
<td>58</td>
<td>HFA 134a</td>
<td>8% ethanol</td>
</tr>
<tr>
<td>Alvesco*</td>
<td>Merck &amp; Co., Inc.</td>
<td>ciclesonide</td>
<td>80, 160</td>
<td>100, 200</td>
<td>80µg: 42.4 80µg: 1.1</td>
<td>59.3</td>
<td>HFA 227</td>
<td>2 – 5% ethanol, 0.001 – 0.012% oleic acid</td>
<td></td>
</tr>
<tr>
<td>Asmanex HFA</td>
<td>Merck &amp; Co., Inc.</td>
<td>mometasone furoate</td>
<td>100, 200</td>
<td>115, 225</td>
<td>200µg: 48.1</td>
<td>200µg: 4.17 (1.6)</td>
<td>69.6</td>
<td>HFA 227</td>
<td>0.5% water, 5% dehydrated alcohol, 0.004% anhydrous citric acid</td>
</tr>
<tr>
<td>Atrovent HFA*</td>
<td>Boehringer-Ingelheim Pharmaceuticals, Inc.</td>
<td>ipratropium bromide</td>
<td>17</td>
<td>21</td>
<td>6.7</td>
<td>0.9 (1.8)</td>
<td>56</td>
<td>HFA 134a</td>
<td></td>
</tr>
</tbody>
</table>
Table 1.1: FDA-Approved and Marketed pMDIs as of May 2014 (continued)

<table>
<thead>
<tr>
<th>Product*</th>
<th>Manufacturer</th>
<th>Drugs</th>
<th>Marketed Strength^ (µg, ex-actuator)</th>
<th>Dose (µg, ex-valve)</th>
<th>Fine Particle Dose (µg)</th>
<th>MMAD (µm, GSD [if reported])</th>
<th>Weight per Actuation (mg)</th>
<th>Propellant</th>
<th>Other Excipients (likely concentration presented as % w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulera</td>
<td>Merck &amp; Co., Inc.</td>
<td>mometason furoate (MF) / formoterol fumarate dihydrate (FM)</td>
<td>100/5, 200/5, 115/5.5, 225/5.5</td>
<td>100/5 µg: MF – 44 to 48, FM – 2.2 to 2.3</td>
<td>100/5 µg: MF – 2.95 to 3.00 (1.75), FM – 2.91 to 2.97 (1.56)</td>
<td>69.6</td>
<td>HFA 227</td>
<td>2.5 – 3.5% anhydrous alcohol, 0.01 – 0.267% oleic acid</td>
<td></td>
</tr>
<tr>
<td>Flovent HFA</td>
<td>GlaxoSmithKline</td>
<td>fluticasone propionate</td>
<td>44, 110, 220, 50, 125, 250, 110 µg: 48.9</td>
<td>110 µg: 2.4, 250 µg: 2.6</td>
<td>44 µg: 60</td>
<td>HFA 134a</td>
<td>11.4% ethanol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProAir HFA</td>
<td>Teva Respiratory, LLC</td>
<td>albuterol sulfate</td>
<td>108, 120</td>
<td>57.8 as albuterol base</td>
<td>2.35</td>
<td>HFA 134a</td>
<td>5 – 15% (probably ≈14%) ethanol, 0.004 – 0.2% (probably ≈0.02%) oleic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proventil HFA</td>
<td>Merck &amp; Co., Inc.</td>
<td>albuterol sulfate</td>
<td>108, 120</td>
<td>45.1 as albuterol base</td>
<td>2.6 (2.1)</td>
<td>HFA 134a</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1.1: FDA-Approved and Marketed pMDIs as of May 2014 (continued)

<table>
<thead>
<tr>
<th>Product*</th>
<th>Manufacturer</th>
<th>Drugs</th>
<th>Marketed Strength(^\wedge) (µg, ex-actuator)</th>
<th>Dose (µg, ex-valve)</th>
<th>Fine Particle Dose (µg)</th>
<th>MMAD (µm, GSD [if reported])</th>
<th>Weight per Actuation (mg)</th>
<th>Propellant</th>
<th>Other Excipients (likely concentration presented as % w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QVAR*</td>
<td>IVAX LLC part of Teva Respiratory, LLC</td>
<td>beclomethasone dipropionate</td>
<td>40, 80</td>
<td>50, 100</td>
<td>80µg: 51</td>
<td>80µg: 1.1</td>
<td>59</td>
<td>HFA 134a</td>
<td>8% ethanol</td>
</tr>
<tr>
<td>Symbicort</td>
<td>AstraZeneca</td>
<td>budesonide (B) / formoterol fumarate dihydrate (FF)</td>
<td>80/4.5, 160/4.5</td>
<td>91/5.1, 181/5.1</td>
<td>80/4.5µg: B – 43.2, FF – 2.7</td>
<td>80/4.5µg: B – 3.5, FF – 3.3</td>
<td>72</td>
<td>HFA 227</td>
<td>0.0001% povidone K25, 0.3% polyethylene glycol 1000 NF</td>
</tr>
<tr>
<td>Ventolin HFA</td>
<td>GlaxoSmithKline</td>
<td>albuterol sulfate</td>
<td>108</td>
<td>120</td>
<td>34.8 as albuterol base</td>
<td>2.4 (1.5)</td>
<td>75</td>
<td>HFA 134a</td>
<td></td>
</tr>
<tr>
<td>Xopenex HFA</td>
<td>Sunovion Pharmaceuticals, Inc.</td>
<td>levalbuterol tartrate</td>
<td>59</td>
<td>76</td>
<td>39.5</td>
<td>2.6</td>
<td>73</td>
<td>HFA 134a</td>
<td>4.76% ethanol, 0.005% oleic acid</td>
</tr>
</tbody>
</table>

Data in this table for each product are from prescribing information leaflets, patents, published studies, and deduction (6-32).

Note: 21µg of salmeterol base is equivalent to 30.45µg of salmeterol xinafoate; 90µg of albuterol base is equivalent to 108µg of albuterol sulfate; 59µg of levalbuterol tartrate is equivalent to 45µg of levalbuterol free base.
* The product is a solution product; if not noted, the drug(s) in the product are in suspension as formulated.
\(^\wedge\) This represents the strength of the drug (as the salt form, if applicable) delivered from the actuator, unless otherwise noted.
3. In Vitro Product Performance Metrics for pMDIs

The residual aerodynamic particle size distribution (APSD) is among the metrics used to evaluate pMDIs for drug delivery efficacy and batch-to-batch variations based on the “FDA Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products – Chemistry, Manufacturing and Controls Documentation,” (33). APSD is characterized by mass median aerodynamic diameter (MMAD) and geometric standard distribution (GSD). An aerodynamic diameter of a particle is defined as the diameter of a spherical particle with unit density that has the same settling velocity as the particle of interest. The mass median diameter (MMD) is the physical diameter at which half of the aerosolized mass lies above the indicated diameter; MMD can be converted to MMAD by multiplying with the density of the droplet. The GSD represents the spread of the lognormal distribution of the particles, where a GSD of 1 indicates a sample of monodispersed particles and a GSD greater than 1 indicates polydispersed particles.

Particles with aerodynamic diameters of less than approximately 5μm are more likely to penetrate into the lung (34). Along with clinical factors, formulation parameters (e.g., amount of cosolvent, nonvolatiles, and propellant), device parameters (e.g., metering valve size and actuator orifice diameter), and variability in micronized drug lot (e.g., MMD and GSD of input suspended drug) have a significant impact on APSD and thereby the success of an aerosolized product. The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) has focused on APSD as it pertains to
quality control of pMDIs and other inhaled medications (35-37). These papers highlight the correlation of APSD to drug deposition in the lung and further present the necessity to determine and understand APSD with faster, higher throughput methods than by cascade impactors (CI).
4. Quality of pMDIs by Design

The current approach to formulating pMDIs is largely empirical, which involves repetitively making and testing a series of vials, including performing numerous CI experiments, for a given formulation and hardware configuration until a pMDI system with optimized characteristics is found. This process is then repeated should any formulation or hardware variable change due to manufacturability requirements or limitations. A useful model that predicts APSD from pMDIs and does not require an arsenal of technical calculations and experimentation would benefit the formulation and quality control process for pMDI manufacturing. It would facilitate the formulation process by allowing for improved high throughput screening of plausible pMDI products and decreased time and resource investment in current trial-and-error approach to evaluating test pMDIs. Furthermore, it may provide guidance in defining the design space for potentially successful pMDI products with one to two nonvolatile components, where the components can be in solution or suspension.

The study described herein, seeks to develop and validate a tool for predicting APSDs from suspension pMDIs. Specifically, the model’s application includes predicting APSD for any type of nonvolatile component in solution and suspension in the HFA 134a-ethanol system. For instance, the model can be extended to evaluate formulations such as (1) suspended excipient with dissolved drug, such as that presented in Stein’s patent (38); or (2) suspended drug with dissolved excipient, such as that seen in Proventil® HFA formulation. From a quality control standpoint, such a model would
provide better understanding of the sensitivity of various device and formulation components on product performance, which permits an *a priori* evaluation of batch-to-batch variation. While such a model is extremely useful in decreasing the time required to find or perfect a potential pMDI product, it will not eliminate the need for rigorous *in vitro* testing of pMDI products, since the model presents a best-case scenario.
CHAPTER 2

ADVANCES IN METERED DOSE INHALER TECHNOLOGY: HARDWARE DEVELOPMENT

Published by: Stephen W. Stein, Poonam Sheth, P. David Hodson, and Paul B. Myrdal


Summary

Pressurized metered dose inhalers (pMDIs) were first introduced in the 1950s and they are currently widely prescribed as portable systems to treat pulmonary conditions. Pressurized MDIs consist of a formulation containing dissolved or suspended drug and hardware needed to contain the formulation and enable efficient and consistent dose delivery to the patient. The device hardware includes a canister that is appropriately sized to contain sufficient formulation for the required number of doses, a metering valve capable of delivering a consistent amount of drug with each dose delivered, an actuator mouthpiece that atomizes the formulation and serves as a conduit to deliver the aerosol to the patient, and often an indicating mechanism that provides information to the patient on the number of doses remaining. This review focuses on the current state-of-the-art of pMDI hardware and includes discussion of enhancements made to the device’s core subsystems. In addition, technologies that aid the correct use of pMDIs will be discussed. These include spacers, valved holding chambers, and breath-actuated devices. Many of the improvements discussed in this article increase the ability of pMDI systems to meet
regulatory specifications. Innovations that enhance the functionality of pMDIs continue to be balanced by the fact that a key advantage of pMDI systems is their low cost per dose. The expansion of the health care market in developing countries and the increased focus on health care costs in many developed countries will ensure that pMDIs remain a cost-effective crucial delivery system for treating pulmonary conditions for many years to come.
1. Introduction to pMDI Hardware Technology

Since the commercialization of the first pressurized metered dose inhaler (pMDI) more than a half century ago, pMDIs have become the most widely used delivery system for the treatment of lung diseases such as asthma and chronic obstructive pulmonary disease (COPD). The pMDI is readily recognized by the majority of patients who have ever received treatment for asthma in developed countries and, increasingly so, in developing countries. Between 2002 and 2008, 47.5% of inhaled medications sold in Europe were pMDIs (39). The relatively low cost (particularly on a cost per dose basis) of pMDIs and wide variety of medications delivered by pMDIs has contributed to the popularity of this delivery system. Indeed, the relatively low cost of pMDIs has contributed to a significant growth in pMDI use in developing countries and will ensure continued use in developed countries that are facing increased pressure to reduce health care costs (40).

The world’s first pMDI (Medihaler-Epi™; Riker Laboratories that was later acquired by 3M Pharmaceuticals) was initially marketed in 1956 (3). Many of its features are still evident in the hardware of the pMDI systems being prescribed today. These include the general form and the key mechanical subsystems (metering valve, canister, and actuator mouthpiece) that make up the device. However, while modern pMDIs have much in common with the original pMDI, there have been many enhancements of pMDI technology. Many of these changes may not be perceived by the average user, but have
resulted in significant improvements in product performance characteristics such as dosing reproducibility, delivery efficiency, and product stability.

The principal hardware developments that have recently been introduced, or which are currently being brought towards the market, will be reviewed. As has been the case for pMDI formulation development, pMDI hardware technology has been significantly advanced as a result of chlorofluorocarbon (CFC) to hydrofluoroalkane (HFA) transition and also in response to growing competition from dry powder inhalers (DPIs). Much of the innovation and improvement of pMDI hardware has its roots in the significant corporate investment that began in the early 1990’s as the industry transitioned to HFA propellants. Innovations in pMDI technology continue today and represent an invigoration of a well-proven base technology. In addition, much of the technical innovations of pMDI hardware have centred on incorporating novel features that address patients’ concerns associated with conventional hardware (41). Primary concerns for using pMDIs efficiently include poor coordination of inhalation and actuation, inhaling too quickly or too slowly, high oropharyngeal deposition, and patients not knowing when to replace their pMDI.
2. Pressurized MDI Valve Designs and Innovation

It is appropriate to start any review of pMDI hardware with the metering valve, as it is the heart of the system and is of greater complexity than any other hardware subsystem. The basic function of any metering valve is to ensure that a consistent amount of formulation (and ideally drug) is released from the canister each time the patient actuates the device. In order to do this in a way that enables meeting regulatory requirements on dosing uniformity, the valve must meet two critical criteria. First, the valve must release a consistent total mass of the bulk formulation in each actuation. Secondly, the valve must uniformly sample from the bulk formulation such that the concentration of drug in the sampled volume is representative of the concentration of drug in the bulk formulation.

In a sense, a pMDI valve acts as two separate valves, one at either end of the metering chamber. The outer valve (which seals the system from the outside world) is kept closed while formulation is allowed into the metering chamber. The inner valve then closes, isolating a single dose of the correct volume from the bulk of formulation in the pMDI canister. Once the correct volume has been sampled, the outer valve is then allowed to open, dispensing the dose under the vapor pressure of its own propellant. The outer valve then recloses and the inner valve then reopens, in preparation for the next dose.

In addition to these fundamental steps, the metering valve must also meet a long list of other criteria. These include accurate metering of the formulation, acceptable
sampling of suspension formulations, low leakage during storage, low moisture transmission, low actuation forces, low extractables, low leachables, low drug-uptake, low drug degradation, and low particulate generation. Metering valves must also be simple, reliable, and cheap.

2.1. Conventional pMDI Valve Designs

Traditionally, pMDI metering valves have been of a press-to-fire design with a protruding male valve stem being depressed inwards towards the canister to dispense a dose. In reality, it is the canister that is pushed down relative to the valve stem. At rest, the inner valve is open and the outer one is held closed by an internal compression spring that returns the valve stem to this position after the patient has taken a dose. An example of such a valve is the Spraymiser™ valve design shown in Figure 2.1. When the ferrule is crimped onto the canister, the ferrule gasket provides a seal between the canister and the valve. The performance of the ferrule gasket and the diaphragm determine the rate of leakage of propellant out of the canister. The seal properties also influence the rate of moisture ingress into the formulation.
Figure 2.1: Schematic of the Spraymiser™ valve.
During final assembly, the valve stem is inserted into the actuator nozzle block and couples the canister to the actuator. The valve stem acts as a conduit through which the formulation passes as it exits the metering chamber and flows into the expansion chamber and then out of the actuator nozzle. As the valve stem is depressed slightly, the groove (or the orifice in the case of some other valves) in the valve stem passes through the tank seal, thus sealing the metering chamber and defining the formulation to be delivered during dosing. The volume of formulation delivered with each dose typically has a target value between 25 and 100µL. As the valve stem is further depressed, the valve stem side piercing passes through the diaphragm and enters into the metering chamber and the formulation is discharged from the metering chamber due to its high pressure. The fit between the valve stem and the openings in the diaphragm and tank seal are optimized in order to minimize leakage while maintaining the force required to actuate the dose at an acceptable level.

Many pMDI valves include an enclosure, referred to as a retaining cup, around the components associated with forming the metering chamber and releasing the dose (see Figure 2.1). The purpose of the retaining cup is to prevent formulation from draining out of the metering chamber when the valve is stored in an upright position (3). The retaining cup has a gap at the top that allows formulation to pass through the retaining cup and into the metering valve when the pMDI is in the inverted position (the position when the patient administers a dose and thus when the metering valve refills for the next dose). Retaining cups are required for many valve designs in order to avoid unacceptable “loss of prime” (LOP) behavior upon storage with the valve in the upright position. In
addition, retaining cups provide greatly enhanced consistency of delivery as the canister is approaching the end of the labelled number of doses (see Figure 2.2) (42).

When CFC to HFA transition started to occur, the main pMDI metering valve manufacturers (3M, Bespak, and Valois) adapted their existing valve designs to suit the new propellants and cosolvents. Primarily, this involved developing new rubbers (typically ethanol-extracted ethylene propylene diene monomer - EPDM, nitrile, or chloroprene rubbers) for the seals. As a result, HFA pMDIs have been developed using the same press-to-fire valve designs.
Figure 2.2: (A) Formulation delivery for a CFC albuterol pMDI. (B) Formulation delivery for an HFA albuterol pMDI. Adapted from Ross and Gabrio, 1999 (5).
2.2. Alternative Valve Designs

While conventional pMDI valve designs are often adequate, shortcomings of conventional pMDI valves have been identified as the requirements of product developers and regulatory authorities have become more strenuous. LOP, imperfect sampling of suspension formulations that flocculate rapidly, drug accumulation in restricted corners as a result of vibration during transportation, drug uptake on valve components, drug degradation, and generation of unwanted particles are issues that must be avoided. These challenges have led to numerous improvements in valve designs.

LOP can be caused in several ways. One principle cause is loss of liquid from the metering chamber due to “shake-out” by the patient. Alternatively, vapor bubbles may form in the metering chamber during prolonged storage or temperature cycling, or air can replace some of the residual vapor in the metering chamber while the valve is in its firing position. This vapor or air may then not be completely displaced by liquid formulation when the next dose is metered. Two very different valve design strategies have been utilized to avoid LOP as well as problems sampling suspension formulation. One strategy is to make the inlet passageway(s) to the valve narrow and tortuous, and/or to close them off at rest with an additional seal. An example of a commercially successful valve that takes this “dose retention” approach is the Valois DF30 valve. A second, essentially opposite strategy is to design valves with much more open inlet passageways. Examples include Bespak’s Easifill™ valve (Figure 2.3), the 3M Face Seal Valve™ (Figure 2.4) (43) and Valois’ ACT valve. Such “free flow” or “fast-fill, fast-empty” (FFFE) valves work on the principle that access to the metering chamber is sufficiently open and
unrestricted such that the liquid formulation readily displaces any accumulated air or vapor bubbles. Proper shaking is still required to ensure that suspended particles are uniformly distributed throughout the system. One concern with FFFE valves is the potential of increasing dose through the life of the pMDI, which may occur when a dose is not completely delivered (44). Since the metering chamber is open to the bulk of the formulation, the partial dose that is not delivered can wash back into the bulk, causing a rise in the drug concentration. Alternatively, poor suspension quality (e.g., creamed formulations) can also contribute to this problem. This effect is more pronounced for slow creaming suspension and concentrated solution formulations compared to fast settling suspension and dilute solution formulations. Carefully designed sediment collectors (45,46) have been devised to provide additional protection, if required, against sedimentation into the region around the valve inlet. Such FFFE design concepts remove the need to prime before use and are less sensitive to patient use technique. Other FFFE design concepts have been proposed (47).
Figure 2.3: The Easifill™ valve, which fills via open channels in its stem. Drawing courtesy of Bespak plc.
Figure 2.4: A schematic of the 3M Face Seal Valve™ utilizing a virtual metering chamber. The drawing on the left shows the valve in the “at rest” position; the drawing on the right shows the valve in the “during actuation” position. Drawing courtesy of 3M Healthcare Ltd.
Concepts for improving FFFE valve designs include using a “virtual” metering chamber that forms only as the valve is actuated (48). This works on the principle that the metering chamber volume is almost zero at rest, eliminating the concerns about loss of formulation or migration of drug in and out of the metering chamber during shaking or storage. Further related valve designs have been patented (49,50). Other hardware features devised to improve the consistency of sampling of suspensions include parts that move to improve homogenization of the formulation as the pMDI is shaken (51).

Some other unique valve designs are also being investigated. Namely, Chiesi Farmaceutici S.p.A. is developing a valve that can deliver two different drugs, sequentially, from one pMDI canister (52). The canister is designed to have two formulation reservoirs, one within the other, that contain two different formulations. Upon actuation, the metering valve is designed to deliver the first metered dose from the first formulation (outer reservoir) and the second metered dose from the second formulation, which is housed in the inner reservoir. Typical pMDI valves are designed to deliver between 25 and 100µL of formulation per actuation. In order to delivery high doses of drug, it would be desirable to utilize larger valve sizes. However, a challenge with this approach is that the efficiency of the drug delivery decreases as the size of the valve increases (53). During dose delivery, the propellant expands to continuously fill the volume the expansion chamber causing the propellant to cool. This leads to a decrease in the vapor pressure, and thus limits the delivery efficiency that can be obtained with large valves. In order to overcome this limitation, a novel valve has been envisioned that uses a
built in “pressurizer” to apply pressure to the formulation within the metering chamber while the formulation is being released from the metering chamber (54).

2.3. Valve Materials and Coatings

A typical pMDI valve consists of three elastomeric components, a metal spring, a metal ferrule, and the remaining components that can be either metal or a molded plastic. An advantage of molded parts is that they allow for increased flexibility in part design compared to the drawing process used to form metal components. Advantages of metal components include lower cost, reduced temperature cycling effects (55), and reduced moisture ingress into the formulation for metal valve stems. Increased regulatory requirements on dosing uniformity and on extractables and leachables have resulted in changes in the materials used in valve components. Cleaner elastomers continue to be developed for use in pMDIs. Unextracted nitrile rubber components have been replaced by pre-extracted components. EPDM rubbers have been introduced in order to reduce extractables and leachables levels. Clean thermoplastic elastomers (TPEs) (56) are being employed as canister sealing gaskets. While the use of TPEs as dynamic valve seals has not yet proved possible, due to the creep properties of such materials, it is likely that materials will be developed for valve seals that have improved cleanliness, reduced drug uptake, and reduced swell in formulation. In addition to providing acceptable extractables and leachables profiles, the elastomer must be optimized to account for any swelling of the elastomer that occurs after exposure to the formulation. Elastomer swelling is highly formulation dependent and is usually lower using EPDM elastomers compared to nitrile
elastomers. Elastomer swelling can cause changes in the force profile and metering volume of the valve.

Surface coatings are being developed for valve components in order to reduce drug deposition on the valve surfaces and to reduce the friction between the moving parts of the valve. The highly electronegative mantle of HFAs leads to strong interactions between the drug and other drug particles or surfaces (57). This can lead to significant particle deposition on the canister or valve surfaces. Coating the surfaces of valve components is more challenging than coating canisters due to the intricate geometries of these components and the tight dimensional tolerances needed in order to achieve acceptable valve performance. As a result, the use of fluoropolymer-based lacquers is not suitable for valve coatings. Additionally, the high temperature of the curing process limits the utility with molded plastic valve components (58). Plasma-based coating technologies are more suitable for providing dimensionally insignificant coatings on valve components. A dual-layer coating less than a micrometer thick, consisting of a vapor deposited inorganic layer and a fluorine layer, has been shown to greatly reduce friction and drug deposition in HFA formulations using both metal and plastic valves (58,59). Other approaches for providing valve components with low surface energy have been described including an approach for providing a monolayer surface treatment by exposing metal components to an organic surface treatment that covalently bonds to the metal surface (60).

Silicone oil is a common valve lubricant utilized in pMDIs and has been found at levels between 50 and 350μg per valve (61). Depending on the method of application of
the silicone oil to the pMDI valve and method of storage of the canister, the oil may leach into the liquid formulation and cause particle growth over time, thus influencing the overall performance of the pMDI. Storing the canister upright orientation has been shown to cause less particle coarsening than if the canister is stored inverted (62). In a study by Fallon et al. (61), commercial HFA 134a (1,1,1,2-tetrafluoroethane) suspension pMDI formulations were spiked with 200 to 550μg silicone oil. With the addition of silicone oil, the mass median aerodynamic particle size (defined as aerodynamic diameter at which 50% of the aerosolized mass lies below the stated diameter, MMAD) increased from 2.60μm to 2.62 and 2.68μm for the formulations with 200 and 550μg silicone oil, respectively. For HFA 227 (1,1,1,2,3,3,3-heptafluoropropane) steroidal suspension formulations, increasing the amount of valve lubricant, was shown to increase the amount of silicone oil found in the formulation and cause particle coarsening, which affected the fine particle fraction (the mass of aerosol particles delivered from the device with aerodynamic diameters that are approximately less than 5μm divided by the total mass of drug delivered from the device, FPF) (62,63). The change in particle size distribution over time was attributed to the drug product having an increased propensity to aggregate in the presence of silicone oil.
3. Pressurized MDI Canister Designs and Innovation

Improved canisters are also being utilized in new and future pMDI products. Canisters are typically made from metals such as aluminum or stainless steel, but glass canisters have been used as well. The size of the canister depends on the size of the valve to be utilized as well as the total number of doses to be administered. The typical canister volume is about 10 to 20mL. The most widespread recent innovation on pMDI canisters is the introduction of new internal coating materials, usually incorporated to minimize formulation-canister interactions. Some solution formulations are susceptible to catalytic degradation in the presence of aluminum (64,65). Many HFA suspension formulations are susceptible to drug deposition on the canister surfaces (57-59). Surface coatings are utilized to overcome these formulation challenges. In particular, low energy surface coatings are widely used in order to reduce unwanted drug deposition on the surface of the canister. Examples being developed include fluorinated ethylene propylene (FEP), perfluoroalkoxyalkane (PFA) and related materials and blends (53,64,66,67). In addition, non-fluorinated materials, such as submicron layer of fused silica glass (68), anodized aluminum and epoxy-phenolic resin (69), are also being investigated as potential coatings for aluminum canisters. Internally coated canisters are now commercially available from Presspart, 3M, and Intrapac, amongst others. Other coating approaches are being developed as well that provide thinner coatings (58,60,70,71); however obtaining thin coatings is not as critical for the canister as it is for valve components. Other canister technology now available includes improved plastic coated glass bottles (e.g., Schott
AG’s Purgard™ system) and reduced headspace canisters with external metal sleeves to fit standard actuators (72). The latter are a response to market trends towards smaller numbers of doses per inhaler. Whereas 200 or more doses used to be standard, 60 to 120 is becoming the norm for new asthma and COPD drugs, sometimes with 30 dose sample packs for the USA market. In the future, still smaller canisters (73,74) may be required for treating other therapeutic indications.
4. Pressurized MDI Actuator Designs and Innovations

The pMDI actuator is a key subsystem that significantly influences the delivery characteristics of a pMDI. Figure 2.5 shows a schematic of a typical press-and-breathe pMDI actuator. The atomization of the formulation is significantly influenced by the atomization orifice (sometimes referred to as “spray nozzle”). The actuator sump, the valve metering chamber, and volume of the valve stem that the formulation flows through after exiting the valve side pierce form an “expansion chamber,” which also impacts the atomization. The actuator nozzle block contains a ledge that fixes the position of the tip of the valve stem. It is critical that the nozzle block fit tightly around the valve stem in order to prevent leakage of the formulation during the atomization event. On the other hand, the fit must not be so tight that the valve stem cannot be inserted into the nozzle block without discharging a dose. The atomized aerosol is delivered to the patient through the actuator mouthpiece, which can influence the efficiency with which the atomized droplets penetrate the patient’s oropharynx.

While in many respects pMDI actuators are quite similar to the original designs, numerous improvements have been evaluated and implemented. Many of these improvements focus on the desire to improve the drug delivery by: (1) modifying the nature of the atomized spray; (2) manipulating the disposition of the atomized particles; and (3) improving patient coordination. Most press-and-breathe pMDI actuators are molded out of plastics such as polypropylene or high density polyethylene. Materials providing novel properties may be utilized in the future, but the material selection is
significantly influenced by regulatory considerations, particularly extractable and leachable propensities. Key aspects of pMDI actuators will be described in further detail.

4.1. Influence of Spray Nozzle Design

The aerosol formation that occurs when the patient discharges the device is a highly dynamic and complex process. Once the valve stem is depressed, the propellant-based formulation exits the valve metering chamber through the side piercing in the valve stem and flows through the expansion chamber and out of the spray nozzle. This process has been described in great detail elsewhere (75-77). In addition to formulation parameters, the actuator nozzle orifice diameter (OD) significantly influences the dynamics of the atomized spray (75-79). The valve metering volume and the diameter of the valve stem side piercing also influence the dynamics of delivery (75,79). Figure 2.6 shows the influence of the OD and valve delivery on the FPF delivered from Andersen Cascade Impactor (ACI) testing of HFA 134a formulations containing 0.167% (w/w) beclomethasone dipropionate (BDP) and 8% (w/w) ethanol. The most efficient delivery is obtained using small ODs and low valve sizes. Interestingly, HFA 227 suspension pMDIs showed a similar increase in FPF with decreasing OD, but the size of the metering valve did not have significant influence on the product performance.
Figure 2.5: Schematic of a pMDI press-and-breathe actuator. Drawing courtesy of 3M Healthcare Ltd.
Figure 2.6: The influence of valve size and nozzle orifice diameter on the fine particle fraction delivered using HFA 134a solution formulation of 0.167% (w/w) beclomethasone dipropionate and 8% (w/w) ethanol.
The FPF delivered from various pMDI formulations has been shown to increase with decreasing OD (79,80). This increase in FPF is driven primarily by a decrease in the momentum of the plume for smaller ODs, which, in turn, leads to a decrease in deposition in the United States Pharmacopeia (USP) inlet or oropharynx (78). The OD also influences the initial diameter of the atomized droplets slightly (81). A previous study examined four different HFA 134a solution formulations tested with three different valve sizes and actuators with ODs ranging from 0.29 to 0.49mm (82). In this study, the average initial droplet diameters increased by only about 10% as the OD increased from 0.29 to 0.49mm.

While decreasing OD is desirable from a drug delivery standpoint, there are practical limits on how small the OD can be. Lewis et al. (83) demonstrated that the FPF of an HFA 134a solution formulation containing 0.45% (w/w) BDP, 15% (w/w) ethanol and 1.3% (w/w) propylene glycol could be increased from 19% with an OD of 0.42mm to in excess of 70% at ODs less than 0.14mm but at the expense of increased plume duration (greater than 1 second for 0.14mm OD compared to about 200 milliseconds for 0.42mm OD). Improvements in delivery associated with decreased ODs are thus limited due to the need to accommodate the limited duration of typical patient inhalation profiles. Nozzle blockage also becomes problematic when small actuator ODs are used. Thus, while decreasing OD is desirable from a drug delivery standpoint, commercialized pMDI products to date have all had OD of about 0.3mm or greater.

The influence of spray nozzle shape and design has also been investigated in significant detail. Nozzle configurations including multiple nozzles, slot nozzles, cross-
shaped nozzles, and other nozzle shapes have been evaluated in vitro and found to result in no improvement in the FPF relative to conventional round nozzle geometry of similar cross-sectional area (84). This may be due to the fact that visualization of the atomization in HFA systems has indicated that the atomization appears to occur at the exit of the spray nozzle (83). Actuators with spray nozzles that swirl the emerging spray are well known (85), but more recent examples of patented systems include a vortex nozzle system from Kos Pharmaceuticals (86-88). The benefit of such novel spray nozzles has been readily established for the atomization of other lower volatility fluids (89), but has not yet been clearly established for HFA based pMDIs. Kakade et al. (88) did show a slight increase in the delivery efficiency from an actuator using a vortex nozzle compared to two commercial actuators using conventional nozzles.

Various nozzle exit geometries have been incorporated into pMDI actuators and can significantly influence performance. Often the exit of the nozzle is in the shape of a cone; however numerous other exits, such as flat and spout geometries, have been evaluated (90,91). A “double-cone” nozzle configuration (in which a smaller inner cone and a larger outer cone with a short cylindrical distance between them) was shown to significantly reduce the width of the spray and increase the droplet diameter measured via laser diffraction (91). A recent study indicated that nozzle exit geometry could impact the electrostatic charge of the atomized particles. Not only does the geometric difference between flat and cone nozzle impact the electrostatic charge carried by the aerosol particles, but also the present of a very small radius on the exit of the orifice significantly influences both electrostatic charge and drug delivery. Chen et al. (92) evaluated
triboelectrification and mass deposition of BDP HFA 134a formulations (containing 15% w/w ethanol) from sharp edge and curved edge nozzle designs for flat and cone polytetrafluoroethylene (PTFE) actuator nozzles using a modified electrical low-pressure impactor and the USP inlet. PTFE tends to charge negatively with friction between an aerosol plume and the nozzle due to the electronegativity of the fluorine atoms. It was noted that all four nozzle geometries produced the similar particle MMAD results, but the mass deposited on the USP inlet was consistently higher for actuators with the curved edge at the orifice exit compared to those with a sharp edge at the orifice exit.

4.2. The Influence of Sump Volume

The expansion chamber volume, which is comprised of the volume of the actuator sump and the internal valve stem bore, can influence the ratio of propellant in the liquid and vapor phases during the atomization process (75-77,93-96) and thus has the potential to influence drug delivery. However, in practice the influence of sump volume on delivery is minimal since the sump contributes only a small fraction of the overall expansion chamber volume (83). Lewis et al. (83) examined the influence of sump volume on the drug delivery from solution formulation of BDP containing 8% ethanol in HFA 134a and found no difference in delivery when sump volume was varied by a factor of two. Similarly, Dunbar and Hickey observed negligible differences in drug delivery for a six-fold increase in sump volume (79).
4.3. The Influence of Mouthpiece Configuration and Airflow Manipulation

The plume leaving the exit nozzle is highly dynamic and rapidly changes in droplet size, composition, and velocity (75-77,93). The disposition of these droplets depends on a number of factors including the nature of the initial atomized spray (e.g., the initial droplet size, velocity, spray angle, and the overall plume momentum). However, the actuator mouthpiece configuration and the flow that it induces can also significantly impact the particle disposition. By increasing the mouthpiece length, drug deposition that would otherwise occur in the USP inlet can be transferred to the mouthpiece (83) much in the same way a spacer works. In this way, the mouthpiece collects droplets that would otherwise collect in the oropharynx due to the high turbulent intensity in this region (97). The shape of the actuator mouthpiece may also influence the shape of the patient’s oral cavity during inhalation, which can also impact deposition profiles. Lin et al. (98) showed that deposition in human airway replicas was decreased as mouthpiece diameter increased from 1.5 to 2.7cm indicating that improved delivery can be obtained using larger mouthpiece diameters. The decrease in oropharyngeal deposition was generally most significant for larger particles and at higher inhalation flow rates.

Novel actuator designs have been developed to manipulate the airflow in the actuator mouthpiece with the objective of decreasing oropharyngeal deposition by reducing the velocity of the droplets exiting the mouthpiece. The Tempo™ inhaler system (MAP Pharmaceuticals Inc.) reduces the airflow momentum using an opposing airflow jet system (99). Additionally, a porous mouthpiece is used to allow air to flow perpendicular to the mouthpiece in order to reduce deposition in the mouthpiece. A
system from 3M has been shown to greatly reduce the momentum of the plume by restricting airflow in the vicinity of the spray nozzle during the aerosolization process (100). Other similar systems include the Gentlehaler™ (101) from Schering-Plough, and an actuator from Bespak (102) in which the incoming air is made to swirl in an opposing vortex that slows the aerosol spray. These systems offer the benefits of slower, gentler sprays, and therefore a reduction of the unwanted deposition of drug in the patient’s oropharyngeal region. However, these approaches for slowing down the plume result in significant airflow turbulence in the mouthpiece, which leads to increased mouthpiece deposition as well as increased complexity and cost of the device. Shrewsbury et al. (103) describe delivery from a scintigraphic evaluation of a CFC fluticasone propionate formulation (Flovent®) in which the Tempo™ inhaler increased lung deposition from 14% to 42% compared to a standard press-and-breathe actuator, but actuator deposition was increased from 9 to 39%. An in vitro evaluation of the same formulation showed an increase in delivery efficiency from 34% to 54% by using the Tempo™ inhaler with an increase in actuator deposition from 15 to 44% (104).

4.4. Breath Actuation

One of the biggest challenges associated with effective lung delivery using pMDIs is the difficulty some patients have actuating the device at the appropriate point in the inspiratory cycle (105,106). Lung deposition is reduced (sometimes, greatly) when the patient actuates the device before or after inhaling (107). Young children and elderly individuals have a particular difficulty coordinating inhalation and actuation of the
device. One approach to overcome this problem is to utilize breath-actuated pMDI actuators. Leach et al. (108) and Newman et al. (107) observed that lung deposition from the patients using the 3M Autohaler™ device was essentially identical to lung deposition for patients with good coordination using a press-and-breathe pMDI of the same formulation, but was significantly higher than that for patients with poor coordination using a press-and-breathe pMDI. Numerous studies have shown improved deposition and increased patient confidence that a dose was successfully delivered associated with the use of breath-actuated delivery (107,109,110). Overall, incorporating breath-actuated inhalers into patients’ regimen may improve overall disease control and reduce health-care costs associated with asthma or COPD compared to conventional pMDIs (111) in spite of increased device cost and complexity.

The Autohaler™ (Figure 2.7) was the first breath-actuated pMDI system and was commercialized by 3M Riker in 1970 (3). The IVAX Easi-Breathe™ device (developed by Norton Healthcare) is similar in function to the Autohaler™, but automatically prepares the device for use when the patient opens the mouthpiece cover (112). Patients who used Maxair Autohaler™ achieved greater pulmonary drug deposition than did patients who had poor coordination while using conventional pMDIs (111). Other breath-actuated devices available include Meridia’s system based on a cascade of collapsing knee-joints (113), Cambridge Consultants’ mechanical system (114), and an automatically resetting pneumatic system under development by Kos (115). In addition, less sophisticated breath coordination systems have been devised (116), in which either the patient is prevented from mechanically depressing the canister until he/she inhales or
patient inhalation is blocked until he/she depresses the aerosol canister. Although slightly more complex for the patient, such systems have the advantage (for the developers and manufacturers) in that they do not tend to impose any additional requirements on the metering valves. The MD Turbo™ by Respirics was developed as an independent device designed to fit a variety of commercially available pMDIs. A system (117) that offers an interesting alternative approach is the K-Valve™ (Figure 2.8) which is a breath-actuated secondary valve formed as a kink in a plastic tube. The patient presses the canister downwards to release a metered dose from the primary valve in the usual manner, but the aerosol of the medication is then held in the plastic tube until the patient’s inhalation moves a vane that un-kinks the tube.

At the other end of the scale of complexity are several electronic based breath-actuation systems. Devices developed to an advanced state include Aradigm’s SmartMist™ device (118), which is no longer promoted, that used a miniature pneumotachograph to trigger drug delivery at the appropriate point during the inspiratory maneuver (119) and GW Pharmaceuticals’ Advanced Dispensing System for cannabinoids (120), which has a large number of usage pattern monitoring and control capabilities, amongst other features.
Figure 2.7: Schematic of the 3M Autohaler™ breath-actuated inhaler. During priming, a spring is compressed and pushes on the canister, but the canister is prevented from moving by the rocker (in pink) which is held in place by the catch (in blue). During inhalation, the patient airflow moves a vane (in yellow) which releases the catch and allows for the rocker to rotate. At this point, the energy stored in the spring during priming depresses the canister relative to the valve and the dose is discharged to the patient. Drawing courtesy of 3M Healthcare Ltd.
Figure 2.8: Schematic of the K-Valve™ breath-actuation system. The image to the left shows the plastic tube at rest (the valve tip would be inserted at the top of the open tube). The middle image shows the plastic tube in the “kinked” position which occurs after the patient depresses the canister to retain the metered dose. A breath actuated triggering system is then used to un-kink the tube to release the dose as shown in the image on the right. Drawing courtesy of Clinical Designs Ltd.
5. Use of Add-on Devices with pMDIs

Spacer and add-on devices are sometimes used with pMDIs as a means of improving delivery. Add-on devices can improve delivery by intercepting and therefore removing coarser particles that would otherwise collect in the oropharynx, increasing the FPF by providing increased time for the droplets to evaporate and slow down, or reducing the sensitivity of delivery on patient coordination of inhalation and actuation. Various types of add-on devices have been developed. Using the nomenclature proposed by Dolovich (121) and adopted by Newman (122), these include “spacers” which are simply extensions of the pMDI actuator mouthpiece, “holding chambers” which are extensions (often larger in volume) that contain a one-way inhalation valve, and “reverse flow devices” in which the spray is actuated in the direction away from the patient’s body and into a chamber that is subsequently emptied through a mouthpiece port by the patient inhalation. Add-on devices are typically developed independently of the pMDI and are prescribed by physicians in conjunction with pMDIs. The significant bulk associated with add-on devices has greatly limited their use since patients prefer readily portable inhaler systems. In order to overcome this, collapsible spacers have been integrated into the pMDI actuator (such as an integrated spacer developed by Forest Laboratories).

Numerous studies have shown that the reduced oropharyngeal deposition of inhaled corticosteroids when add-on devices are used can result in decreased systemic side effects (123,124). Large volume spacers and holding chambers allow for pMDIs to be actuated prior to patient inhalation, avoiding the need to coordinate actuation and
inhalation. Increasing delay time between firing and inhalation and firing multiple actuations into the device results in increased deposition of drug in the add-on device and thus decreases the delivery efficiency (125). The geometry of the spacer also impacts the amount of drug deposition (126). Electrostatic charge on the surface of the add-on device can decrease the efficiency of drug delivery (125,127). A detailed discussion of add-on devices can be found elsewhere (122).
6. Dose Counters and Content Indicators

The patient’s desire for some form of content indicator or dose counter has long been recognized (128) due to the difficulty that patients have in determining when the pMDI should be replaced. In a study assessing patients’ satisfaction with current pMDIs, 52% of patients reported that they are extremely unsure and 10% are somewhat unsure of how much medication remains in their current rescue inhaler. With the addition of an integrated dose counter, 97.4% of patients reported that they could tell when to replace their inhalers (129). A complicating factor is the fact that pMDIs require that a significant amount of excess formulation (often 20-30 doses worth) be filled into the canister during manufacturing. Once the labeled number of doses for a pMDI has been delivered and the pMDI begins delivering the excess formulation, the delivered dose can become erratic. While end-of-life profiles for HFA valves are significantly improved compared to older CFC valves (42), it is still difficult for the patient to know when the dose delivery from the pMDI has become compromised. This is particularly important for pMDIs delivering drugs, such as albuterol, that are used to treat acute asthma attacks. As a result, various approaches have been proposed and developed for helping the patient know when to replace his/her pMDI.

Patients utilize a variety of approaches for deciding when to discard an inhaler including determining if the canister floats, shaking the canister, counting doses on a piece of paper, test-firing the inhalers, evaluating the taste or feel of the spray, among others. Holt et al. (130) described a survey of seventeen patients using Ventolin® pMDIs
and reported that fifteen of the seventeen subjects determined when they needed to replace their inhaler at least in part by shaking the pMDI, two of the subjects test-fired the inhaler, one of the subjects determined if the canister floated and one subject looked for changes in taste. In a separate study, 100 patients returned Ventolin® pMDIs that they deemed to be ready to discard (130). Gravimetric evaluation of the returned units indicated that 84% of the pMDIs had been actuated more than the labeled number of actuations (130). On the other hand, approximately 11% of the units returned in this study had at least 40 doses remaining. This study demonstrates the difficulty patients have discerning whether or not doses remain in pMDIs that do not have some type of dose indication system.

Systems have been proposed ranging from clear canisters that allow the patient to see if there is formulation remaining in the canister to electronic dose counters with built-in compliance monitors that keep track of when doses have been taken or even indicate to the patient that a dose must be taken. Contents indicators refer to features that provide feedback to the patient on the amount of formulation remaining in the device, but do not provide an assessment of the number of doses remaining in the unit and thus provide limited information to the patient. Examples of content indicators include plastic covered glass canisters, built-in balance systems (131), or floating internal rattles (132). While these dose indicators provide some information to the patient, the patient can easily misinterpret the indicator. As a result, they have not been readily adopted and are not deemed acceptable by many regulators (133). Dose counters, on the other hand, provide an actual representation of the number of doses remaining in the device and are thus
preferred. GlaxoSmithKline launched the first dose counter fitted pMDI product (the Seretide™ Evohaler™) in 2004.

While the need for dose counters has been long acknowledged, the amount of innovation in dose counters has greatly increased since the United States Food and Drug Administration (FDA) issued a guidance document (134) in 2003 requiring the industry to implement plans for the introduction of dose counters onto pMDIs. The key requirements from this document are summarized below:

1. Dose counters should provide a clear indication of when the pMDI is approaching the end of the labeled number of actuations as well as when it has reached or surpassed this number.

2. The indication to the patient that he/she is approaching the end of the labeled number of actuations must occur early enough to provide the patient time to obtain a new pMDI.

3. If a numeric count is used, the device must count down from the labeled number of doses to zero (with zero indicating that no doses remain).

4. The reliability of the dose counting mechanism should be as close to 100% as possible.

5. If some low frequency of error is unavoidable, the device should specifically avoid undercounting, since it could lead to the dangerous situation of the patient thinking that doses are available when the pMDI is actually empty.

6. The reliability of a dose counter must be demonstrated in vitro (simulating both use and potential abuse) as well as in clinical use.
7. Pressurized MDIs may include a “lock-out” feature that prevents delivery of doses after the labeled number of doses has been delivered, but this must not be used for rescue bronchodilators.

The pMDI dose counters under development themselves offer a wide range of different approaches. An ideal dose counter directly measures whether a dose has been delivered, for example by measuring a decrease in mass of the inhaler or the flow of fluid out of the nozzle. However, this approach is currently prohibitively expensive and as a result, most dose counters under development measure something linked with the event (135). Current pMDI dose counters generally fall into two categories: (1) force-driven counters; and (2) displacement-driven counters. The key challenge in designing force-driven counters is matching the force associated with advancing the dose counter to the force required to actuate the valve. In order to avoid undercounting (a critical requirement of the FDA Guidance), it is necessary to set the force to count slightly below the lower limit of the force to fire the valve. Similarly, for displacement-driven counters, the distance required to advance the counter must be designed to be slightly less than the minimum displacement required to fire the device. Thus for both approaches, it is necessary to design the dose counter in such a way that the dose counter may over-count if the canister is depressed with enough force or displacement to advance the counter but insufficient force or displacement to fire a dose. Thus, control from lot-to-lot of the force and displacement required to fire the valve is critical for good dose counter function. Bradshaw (135) concluded that variability in the force required to advance the dose counter is actually a more significant factor limiting the accuracy of force-driven counters.
than is variability in valve forces and that force-driven counters are more likely to undercount than are displacement-driven counters. However, the practical significance of this with patients has yet to be established. In a study of the Ventolin® HFA integrated displacement-driven dose counter, a discrepancy rate between the dose counter and patient diary-recorded actuations of 0.76% was observed in 43,865 actuations (136). The incidence rate of undercounts in this study was 0.09%. A study of the integrated dose counter performance for Advair® HFA showed a similar miscount rate of 0.94% and an undercount rate of 0.13% (137). A study of the integrated dose counter used in Dulera® pMDIs yielded a lower total miscount rate of 0.13% and an undercount rate of 0.05% (138,139).

An example of a commercially available force-driven dose counter is the top mount actuation indicator, AeroCount® from Trudell Medical International (133) (see Figure 2.9). Examples of displacement-driven dose counters currently available are the Valois Pharma Landmark™, GlaxoSmithKline Evohaler™ dose counter and the 3M™ Integrated Dose by Dose Counter (140). Others have also been proposed (141). An excellent summary of pMDI dose counters can be found elsewhere (135).

When it comes to the nature of mechanical counters’ displays, again several approaches are being taken, such as movement of a single numbered and colored band every tenth dose in the Trudell Medical International top-mount actuation indicator, incremental movement of a single band every dose (142), or multi-ring dose-by-dose numerical counting (143). Both direct numeric and color coded displays can be acceptable based on the FDA dose counter guidance (134). In addition to mechanical
dose counters, several electronic counters have been developed or proposed. Examples include one developed by Kos (144-146), the Aradigm SmartMist™ device, the Meditrack Doser™, the Smartinhaler Tracker™, and the Respirics MD Turbo™ counters which are available as add-on devices. These are able to offer greater sophistication than mechanical systems, and some might also be used as dosing regimen calendars or compliance monitoring aids. Electronic systems may, however, require additional validation to satisfy the regulatory authorities, and issues of cost and battery reliability certainly need consideration.
Figure 2.9: An exploded view of the four components of a Trudell Medical International top mount actuation indicator. Drawing courtesy of Trudell Medical International.
7. Nasal pMDIs

Pressurized MDIs were once used widely in the treatment of allergic rhinitis, but have been replaced with aqueous pump sprays since the Montreal Protocol (147) did not provide a “medical use” exception for the use of pMDIs to treat allergic rhinitis. However, there are several benefits of using pMDIs that are leading to the development of new HFA pMDIs for treatment of allergic rhinitis. One benefit of pMDI systems is the ability to avoid the use of preservatives in the formulation. The design of pMDI systems and pMDI formulations inherently inhibit microbial growth. This is not true with aqueous pump spray systems. Because of this, most commercially available aqueous pump sprays contain the preservative, benzalkonium chloride. Benzalkonium chloride has been shown to adversely affect nasal mucosa (148-150) and prolonged exposure has been shown to induce nasal mucosal swelling (148).

An additional factor that is likely to lead to the re-emergence of nasal pMDIs is the fact that the same corticosteroid formulations used in asthma therapies are often therapeutically effective for treating allergic rhinitis. As a result, the development activities to optimize the formulation and container closure system (i.e., the valve and canister) and demonstrate stability for an pMDI to treat asthma can be directly leveraged for an pMDI to treat allergic rhinitis (or vice versa). For example, QNASL™ (nasal pMDI formulation of BDP) leveraged the formulation and container closure development associated with QVAR® and Zetonna™ (nasal pMDI formulation of ciclesonide) leveraged Alvesco® development. An additional benefit is the fact that some patients
prefer nasal pMDI systems over aqueous pump sprays due to the dripping sensation in the nasal cavity and throat after administration of some aqueous pump spray products. Due to these and other considerations, several HFA pMDIs have recently been commercialized or are currently in development for treatment of allergic rhinitis.
8. Conclusions

More than 50 years after its invention, the pMDI remains a mainstay of asthma and COPD therapy worldwide. Pressurized MDIs are a compact and convenient delivery system that has the advantage of being well understood by patients, physicians, and regulators. The inherent multi-dose nature of pMDIs makes them more affordable than most competing inhalation delivery systems. Despite many similarities, pMDIs have changed in many ways since the humble starting point in which they were made with glass vials and valves designed for perfume bottles (3). Pressurized MDI valves have been redesigned to be compatible with HFA propellants, to have reduced extractables and leachables, to enhance dosing uniformity, and to overcome loss of prime during storage. Pressurized MDI canisters have been developed with surface modifications that greatly reduce drug deposition and drug or canister degradation. Pressurized MDI actuators have been developed to enhance drug delivery efficiency and provide a more aesthetically pleasing user interface for the patient. Breath actuated technologies and add-on devices have been developed to further enhance drug delivery efficiency and minimize patient coordination challenges. Dose indicators and dose counters are now utilized to provide patients with information so that they know when to replace their pMDI. Further pMDI device technologies are in development and will continue to enhance pMDI delivery in the future. Many of the future improvements in pMDI technology will increase the ability of pMDI systems to meet regulatory specifications, but will be transparent to the patients using the devices. Innovations that enhance the functionality of pMDIs will be balanced
by the fact that a key advantage of pMDI systems is their low cost per dose. The expansion of the health care market in developing countries and the increased focus on health care costs in many developed countries will ensure that pMDIs remain a crucial delivery system for treating lung diseases for many years to come.
CHAPTER 3
ADVANCES IN METERED DOSE INHALER TECHNOLOGY: FORMULATION DEVELOPMENT

*Published by: Paul B. Myrdal, Poonam Sheth, and Stephen W. Stein*


**Summary**

Pressurized metered dose inhalers (pMDIs) are a long-standing method to treat diseases of the lung, such as asthma and chronic obstructive pulmonary disease. Pressurized MDIs rely on the driving force of the propellant, which comprises of the bulk of the pMDI formulation, to atomize droplets containing drug and excipients, which ideally should deposit in the lungs. During the phase out of chlorofluorocarbon (CFC) propellants and the introduction of more environmentally friendly hydrofluoroalkane (HFA) propellants, many improvements were made to the methods of formulating for pMDI drug delivery along with a greater understanding of formulation variables on product performance. This review presents a survey of challenges associated with formulating pMDIs as solution or suspension products with one or more drugs, while considering the physicochemical properties of various excipients and how the addition of these excipients may impact overall product performance of the pMDI. Propellants, volatile and nonvolatile cosolvents, surfactants, polymers, suspension stabilizers, and bulking agents are among the variety of excipients discussed in this review article.
Furthermore, other formulation approaches, such as engineered excipient and drug-excipient particles, to deliver multiple drugs from a single pMDI are also evaluated.
1. Introduction to pMDI Formulation Technology

In 1956, Riker Laboratories (later acquired by 3M Pharmaceuticals) introduced the first pressurized metered dose inhaler (pMDI), Medihaler-Epi™, for the management of asthma and chronic obstructive pulmonary disease (COPD) (3). Upon introduction of the pMDI, medical treatment of lung diseases changed significantly. Since that time, pMDIs have become the most widely used treatment modality for controlling symptoms of asthma and COPD. More recently, formulation and device modifications were merited when chlorofluorocarbon (CFC) propellants were linked to the depletion of the ozone layer (151). With the successful transition to new propellant systems, pMDIs are still well accepted and highly utilized by patients across the globe, with the annual production of over a half billion units and nearly one trillion pMDI doses inhaled by patients to date (20,152). Looking forward, the effectiveness, ease of use, and relatively low cost of these aerosol preparations in combination with modifications in delivery technology and formulation sciences, will likely result in pMDI use expanding to include the treatment of diseases previously untreated via the respiratory tract.

In developing pMDI systems, there are two major areas that need to be considered: the device hardware and the formulation. The hardware consists of the vial (i.e., aluminum can or plasticized glass vial), metering valve, actuator, and for newer pMDIs usually a dose counter. The formulation comprises primarily of the propellant, drug, and often other excipients. In many respects, modern hydrofluoroalkane (HFA) pMDIs appear very similar to patients as their CFC predecessors. However, beneath the
apparently unchanged surface of the pMDI device, significant technological changes have occurred and new hardware components and formulation approaches are in development for the next generation of pMDIs.

Although only the current state and future prospects of pMDI formulations are in this review, it is important to note that, in reality, they function together with the device hardware to determine the eventual performance characteristics of the pMDI system (153). Key performance attributes of a pMDI include the delivered dose content uniformity, aerodynamic particle size distribution (APSD) of the delivered aerosol, chemical and physical stability of the drug over the product shelf life, and extent of leachables from device components, among other attributes.

The fine particle mass of drug (mass of aerosol particles with aerodynamic diameters that are approximately less than 5µm) and the residual APSD are critical performance metrics that are intuitively linked to the efficacy of the product. The fine particle mass, is frequently represented by the fine particle fraction (FPF; the fraction of total mass of aerosol particles delivered from the device with aerodynamic diameters that are approximately less than 5µm), and is a characteristic in vitro metric that represents the amount of drug that is considered respirable. The residual APSD is characterized by in vitro performance attributes, such as mass median aerodynamic diameter (MMAD; aerodynamic diameter at which 50% of the aerosolized mass lies below the stated value) and geometric standard deviation (GSD). Typically, aerosolized particles with aerodynamic diameters between 0.5 and 5µm are delivered to the lungs, and smaller particles are more likely to deposit in the deep lung compared to larger particles (154).
This review seeks to present current state-of-the-art and future prospects for various formulation components for pMDI drug delivery systems. The article is organized to review formulation strategies based on if the drug is in solution or suspension in the propellant system, with additional excipients. Thus, topics such as cosolvents and suspension stabilizers are described as they pertain to solution or suspension formulations.
2. Propellants

Propellants comprise the bulk of any pMDI formulation and are thus required to be toxicologically safe, nonflammable, and chemically inert with appropriate boiling points and densities. They are liquefied compressed gas, which function as a driving force and energy source for atomization of the formulation upon actuation. Propellant within the canister exists in two phases (liquid and saturated vapor) and ideally provides the same vapor pressure regardless of whether the pMDI canister is full or nearly empty. For example, carbon dioxide is not suitable for pMDI formulations even though it is a compressed gas, because the vapor pressure steadily declines as the canister empties, which leads to changing performance characteristics over the lifetime of the inhaler (152).

Pressurized MDIs were initially formulated with CFCs as the propellant. However, the signing of the Montreal Protocol on Substances that Deplete the Ozone Layer (more commonly referred to as “the Montreal Protocol”) in 1989 led to the reformulation of pMDIs with environmentally acceptable alternative propellants. HFAs were found to not deplete stratospheric ozone and were demonstrated to be safe as pharmaceutical excipients. Thus, they were developed to replace CFC propellants. However, HFAs could not directly substitute for CFC propellants, as previously used excipients and hardware components were not compatible with HFA formulations. As a result, significant effort was required to develop new device hardware and formulation approaches.
2.1. The Transition from CFCs to HFAs

Historically, pMDIs utilized CFC propellants because of their limited toxicity, inertness, and suitable vapor pressures (155). The CFC propellants in marketed pMDIs contained trichlorofluoromethane (CFC 11), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), or blends of these propellants (see Table 3.1). CFC 12 has a lower boiling point and is more volatile than CFCs 11 and 114, thus it was widely used to provide a formulation vapor pressure sufficient to achieve suitable atomization of the CFC pMDI formulations. CFC 11 and CFC 114 mainly functioned to modify the vapor pressure of CFC 12 and to facilitate manufacturing when used in formulations with propellant blends (156). CFCs were not only readily used in pMDIs but were also highly utilized in household aerosol sprays, air conditioners (as refrigerants), fire extinguishers, industrial manufacturing of foams and insulations, as well as many other industrial applications.

A factor that led to their widespread use was the extremely low reactivity of CFC propellants. However, CFCs were implicated in the depletion of stratospheric ozone (151). The extensive destruction of the ozone by CFCs is due to two factors: (1) the chemical stability under ambient environmental conditions and low aqueous solubility of CFCs result in long lifespans of these chemicals that permit ample time for CFC molecules to diffuse into the upper atmosphere (157); and (2) once in the stratosphere, CFCs break down under exposure to ultraviolet light and form chlorine radicals (151). The chlorine radicals formed from a single CFC propellant molecule can destroy 100,000 molecules of the ozone (158).
Considering the environmental ramifications of CFC use, the Montreal Protocol was devised, and then ratified in 1989, initiating the phase out of CFC propellants, including those used in pMDIs. As of February 2013, the Montreal Protocol has been ratified by 197 countries (159). However, as pharmaceutical inhalers are considered life saving for many asthmatic and COPD patients, they were exempted from the protocol pending availability of suitable alternatives (160).

The Montreal Protocol provided motivation to the pharmaceutical industry to develop non-CFC-containing inhaler products. As a result, there were significant studies and investments in dry powder inhaler and liquid nebulizer technologies, in addition to the identification of suitable propellants to replace CFCs for use in pMDIs. Two candidates for CFC replacement were identified, 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227). These HFAs, first mentioned in patents as suitable propellants for pMDIs in 1987 (161,162), lack the ozone-depleting characteristics of their predecessors; however, they still contribute to the greenhouse effect, albeit to a lesser degree than their CFC counterparts, as displayed in Table 3.1 (163). Additionally, the half-life of these HFA propellants in the atmosphere is a fraction of that of the CFCs they replaced (20). Other propellants have been explored as replacements for CFCs, namely, 1,1-difluoroethane (HFA 152a), propane, n-butane, isobutane, n-pentane, isopentane, neopentane, dimethylether, and hydrofluoro-olefins (HFO) (164-170). Many of these propellants have not been extensively studied and toxicological risks have not been assessed because they are flammable and thus pose an inherent safety risk.
Both HFAs 134a and 227 have broadly similar thermodynamic properties (i.e., boiling point and vapor pressure) as CFC 12 but are chemically different. Presumably, this is due to the lack of polarizability of the fluorinated hydrocarbons as compared with the partially chloro-substituted CFCs (155). This decrease in polarizability relative to CFC propellants could explain some solubility differences of solutes in HFA-based systems, despite their increased polarity over CFCs. Another difference between the propellants is the hydrogen(s) on the HFAs, resulting in an increased dipole moment relative to CFC propellants which are completely chloro- and fluoro-substituted. As a result of this dipole, the highly electropositive hydrogen(s) appear to make the environment much less amiable to nonpolar solutes while potentially enabling a degree of hydrogen bonding. The propellant polarity affects the solubility of drugs and excipients in the liquefied propellant. The reformulation from CFC to HFA propellants is further complicated by the fact that no comparable HFA equivalent for CFCs 11 and 114 is available. These considerations prevent simple substitution of HFA propellants for CFCs and contribute to the challenge of transitioning to HFA pMDI products.
Table 3.1: Physicochemical and Environmental Properties of CFC and HFA Propellants

<table>
<thead>
<tr>
<th>Chemical Properties</th>
<th>Propellant</th>
<th>CFC 11</th>
<th>CFC 12</th>
<th>CFC 114</th>
<th>HFA 134a</th>
<th>HFA 227</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical Name and Structure&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CCl&lt;sub&gt;3&lt;/sub&gt;F</td>
<td>CCl&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;F&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>C&lt;sub&gt;3&lt;/sub&gt;F&lt;sub&gt;7&lt;/sub&gt;H</td>
<td></td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>137.4</td>
<td>120.9</td>
<td>170.9</td>
<td>102.0</td>
<td>170.0</td>
<td></td>
</tr>
<tr>
<td>Liquid Density at 20°C (g/mL)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.49</td>
<td>1.33</td>
<td>1.47</td>
<td>1.21</td>
<td>1.41</td>
<td></td>
</tr>
<tr>
<td>Dipole Moment (Debye)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.46</td>
<td>0.51</td>
<td>0.50</td>
<td>2.06</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Boiling Point (°C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>22.8</td>
<td>-29.8</td>
<td>3.6</td>
<td>-25.8</td>
<td>-17.3</td>
<td></td>
</tr>
<tr>
<td>Vapor Pressure at 20°C (psi)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.9</td>
<td>82.1</td>
<td>26.4</td>
<td>83.0</td>
<td>56.6</td>
<td></td>
</tr>
<tr>
<td>Water Solubility (ppm)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>130 at 30°C</td>
<td>120 at 30°C</td>
<td>110 at 30°C</td>
<td>2220 at 25°C</td>
<td>610 at 25°C</td>
<td></td>
</tr>
<tr>
<td>Log P (octanol/water)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.0</td>
<td>2.2</td>
<td>2.8</td>
<td>1.1</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Environmental Effects</td>
<td>Ozone Depletion Potential&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atmospheric Life (years)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>50</td>
<td>102</td>
<td>300</td>
<td>14.6</td>
<td>36.5</td>
<td></td>
</tr>
<tr>
<td>Global Warming Potential&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4000</td>
<td>8500</td>
<td>9300</td>
<td>1300</td>
<td>2900</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative to CFC 11
<sup>b</sup> Represents 100-year global warming potential relative to CO<sub>2</sub>
<sup>c</sup> Source: Vervaet and Byron, 1999 (57)
<sup>b</sup> Source: Smyth, 2003 (155)
<sup>c</sup> Source: McCulloch, 1999 (171)
2.2. Characteristics of HFAs 134a and 227

Although the above characteristics may begin to explain the difference in observed propellant-excipient or propellant-drug interactions, it is arguably academic, as CFC propellants are not options for future therapeutics. Thus, when formulating pMDIs, there are only two propellants currently available, HFAs 134a and 227.

HFAs 134a and 227 share many similar characteristics. Both propellants show a very low degree of impurity, with both being more than 99.9% pure (172). Compared with CFC propellants, both HFAs have relatively low boiling points (as seen in Table 3.1) which afford sufficient vapor pressure, even at reduced temperatures, to enable efficient drug delivery (42,173-175). Additionally, they are completely miscible in one another and vapor pressure upon mixing behaves ideally, thus they may be blended in different proportions to obtain a specific vapor pressure or density (176). Both propellants have excellent safety profiles (177) and are chemically stable under normal storage conditions (172).

Although, seemingly subtle, some differences in the physical and chemical properties of HFAs may be significant for formulating a given drug in the HFA formulation. HFA 227 has a logP of 2.05 versus 1.06 for HFA 134a (155), and as such, water has nearly 4-fold increased solubility in HFA 134a versus 227 (2200 and 610ppm, respectively) (155). Of note, both HFAs 134a and 227 have significantly greater water uptake as compared to the aforementioned CFC propellants (all approximately 120ppm), likely due to the relatively increased polarity (172). Thus, when formulating a suspension pMDI of a compound, physical stability as a function of water is a consideration.
Likewise, for compounds that are susceptible to degradation pathways in which water is involved, the amount of water in the formulation could be important. While the absolute solubility of water in HFA 134a and 227 may be different, it is important to note that water levels start relatively low and increase slowly over time. The migration rate of water will depend not only on the propellant and additional excipients (e.g., ethanol), but also on the valve components and storage conditions (178). Williams and Hu (179) showed that the emitted particle size and FPF can change depending on the drug and extent of moisture ingress. Interestingly, water scavengers (such as hydroxypropyl methylcellulose coated silica gel, aluminum desiccant, and molecular sieve beads) have shown some promise as desiccants in prototypical HFA formulations (179). An additional factor to consider for suspension formulations is the difference in density of the two propellants (see Table 3.1), which can affect particle settling or creaming behavior. It may be advantageous in some cases to match the density of the formulation to the density of the suspended drug particles.

2.3. Novel Propellants

The political dynamics of the global warming debate has the potential to influence the future of pMDIs as HFA propellants are greenhouse gases that may contribute to global warming, albeit to a lesser degree than CFCs. As a result, there is the potential for future restriction of their use in pMDI formulations. In reality, the contribution to global warming of medicinal HFA pMDIs is minimal. HFA propellants contributed approximately 3% of total emissions of CO₂ equivalents in 2007 (180); of those
emissions, less than 2% is due to pMDIs, resulting in a minimal contribution of HFA pMDIs to global warming (181). Nevertheless, due to the global warming potential of HFA propellants, new propellants have been evaluated.

Recently, isobutane has been investigated as an alternative to HFA. Laboratorio Pablo Cassara, in Argentina, began exploring the use of isobutane, a commonly used flammable refrigerant, as a propellant for pMDIs. Cassara supplies 60-70% of the market’s albuterol CFC pMDIs and has made plans to phase out these inhalers and replace them with isobutane, as a propellant (170,182). Thus far, Ding and Zhang (183) have begun expanding upon the current knowledge of the toxicology (184) and application of tracheal instillation of albuterol sulfate pMDI driven by isobutane in guinea pigs; clinical studies have yet to establish safety in humans. In comparison to HFAs, isobutane has a significantly lower global warming potential (3.3 for 100-year global warming potential relative to CO$_2$). Isobutane has a boiling point of -11.7°C, liquid density of 0.563g/mL (at 21°C), vapor pressure of 31.1psi (at 21°C) with a water solubility of 80ppm (185).

Additionally, HFA 152a has also received attention as an alternative propellant in pMDIs (186,187). HFA 152a has a boiling point of -24.7°C, liquid density of 2.70g/mL, vapor pressure of 88psi (at 25°C), dipole moment of 2.30 Debye and a water solubility of 2.671g/L (at 25°C) (188). It has a 100-year global warming potential relative to CO$_2$ of 140. Abuse of HFA 152a, found in canned air, has been linked to transient central nervous system symptoms including euphoria, confusion, and tremor. Furthermore, it is also linked to pulmonary irritation, asphyxia, cardiac arrhythmias, and death (189).
However, short-term inhalation of 200 and 1000 ppm HFA 152a for 2 hours with light exercise did not prove to have significant central nervous system symptoms or pulmonary irritation in human subjects (190). Further investigation of HFA 152a will determine if formulating pMDIs, rescue inhalers or control medications, is feasible from the safety standpoint.

HFO propellants have been developed by Honeywell Special Chemicals and they include trans-1,3,3,3,-tetrafluoropro-1-ene (HFO 1234ze) and 2,3,3,3,-tetrafluoroprop-1-ene (HFO 1234yf) (166,167). These are not flammable. HFO 1234ze and HFO 1234yf have significantly lower global warming potential (6 and 4, respectively for 100-year global warming potential relative to CO₂) than HFAs. HFO 1234ze, known as Honeywell’s Solstice™, has a boiling point of -19°C, liquid density of 1.12 g/mL, vapor pressure of 46.4 psi (at 21°C), dipole moment of 1.443 Debye, and a water solubility of 225 ppm (166,167,191). HFO 1234yf, known as DuPont’s Opteon™, is an air conditioning refrigerant commonly used in motor vehicles; it has a boiling point of -29°C, liquid density of 1.09 g/mL, vapor pressure of 98.2 psi (at 25°C), dipole moment of 2.543 Debye, and a water solubility of 260 ppm (166,167,192). These characteristics closely mimic those of HFA propellants, suggesting that they may be suitable alternative for pMDI formulations. Furthermore, HFOs appear to be as compatible as HFAs 134a and 227 with standard pMDI valves designed by Aptar Pharma (166). Results from toxicology studies for HFOs still remain to be published.

While lower global warming potential propellants for pMDI are being explored, no serious discussion of banning HFA pMDIs has been made to date. Indeed, despite the
strong scientific justification for eliminating CFC propellants, CFC pMDIs were not phased-out until two decades after the signing of the Montreal Protocol. There is a far weaker scientific rationale to eliminate HFA use and it is unlikely that current pMDIs will be forced off the market in the near future (181).
3. Solution Formulations

Pressurized MDIs can be formulated with the drug completely dissolved in the formulation, rendering a solution formulation, or with the drug practically insoluble in the formulation, rendering a suspension formulation. Compared to suspension formulations, solution pMDIs offer the benefits of homogeneous formulation (i.e., patients do not need to shake the vial immediately prior to use and there is no concern related to sampling homogeneity), a finer residual aerosol (193) and potentially larger fine particle doses (i.e., fine particle mass per actuation) (152,194). When formulating solution pMDIs, the total amount of fine particle drug delivered cannot simply be increased by increasing the drug concentration in a formulation. Many drugs are not readily soluble in HFA propellants, which frequently limit the amount of drug that can be dosed using pMDIs. Previously, surfactants or complexation aids were used in pMDIs to increase drug solubility in CFC systems (57,155). However, many of the conventional excipients used in CFC formulations and approved for human use, are insoluble in HFA systems (195). Thus, to create a solution pMDI and use previously approved excipients (see Table 3.2), cosolvents are often added to the formulation to help increase the solubility of the drug or other excipients. These excipients may also alter the dissolution of residual particles from the aerosol spray in the lungs, which results in modulating the pharmacological effect (12,196).
**Table 3.2: Excipients Used in Inhalable Drug Products**

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Product Examples</th>
<th>Function</th>
<th>Maximum Approved Concentration (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone sodium bisulfate</td>
<td>Bronkosol*</td>
<td>Antioxidant</td>
<td>0.5003</td>
</tr>
<tr>
<td>Ammonia</td>
<td></td>
<td>Preservative</td>
<td></td>
</tr>
<tr>
<td>Ascorbic acid</td>
<td>Asthmahaler Mist*, Isuprel, Primatene Mist, Tornalate</td>
<td>Antioxidant</td>
<td>1.02</td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>Combivent Respimat, Proventil, Ventolin</td>
<td>Preservative Wetting Solubilization</td>
<td>20</td>
</tr>
<tr>
<td>Cetylpyridinium chloride</td>
<td>Asthmahaler Mist*, Bronkaid Mist, Duo-Medihaler</td>
<td>Preservative Emulsification</td>
<td></td>
</tr>
<tr>
<td>Chlorobutanol</td>
<td>Isuprel</td>
<td>Preservative</td>
<td>0.5</td>
</tr>
<tr>
<td>Citric acid (anhydrous)</td>
<td>Atrovent HFA, Brovana*, Perforomist*, Pulmicort Respules*</td>
<td>Flavoring</td>
<td>0.4404</td>
</tr>
<tr>
<td>Edetate sodium/Edetate disodium</td>
<td>Airet*, Alupent*, Combivent Respimat, DuoNeb*, Pulmicort Respules*</td>
<td>Chelating</td>
<td>0.02 / 0.05</td>
</tr>
<tr>
<td>Ethanol, Dehydrated alcohol, Alcohol</td>
<td></td>
<td>Dehydrated: 34.548 Alcohol: 95.89</td>
<td>Co-solvent</td>
</tr>
<tr>
<td>Glycerin</td>
<td>Bronkosol*, Isuprel*</td>
<td>Co-solvent Humectant Preservative Tonicity</td>
<td>7.3</td>
</tr>
<tr>
<td>Glycine</td>
<td></td>
<td>Buffering agent Drug stabilizer</td>
<td>0.013</td>
</tr>
<tr>
<td>Lecithin (Soya)</td>
<td>Atrovent, Combivent, Flovent, Serevent</td>
<td>Dispersion Solubilization</td>
<td>0.28</td>
</tr>
<tr>
<td>Lysine monohydrate</td>
<td>Cayston*</td>
<td>Buffering agent Drug stabilizer</td>
<td>5.25</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>Breo Ellipta*</td>
<td>Dispersion</td>
<td>0.0028</td>
</tr>
<tr>
<td>Menthol</td>
<td>Aerobid-M, Tilade CFC-free, Tornalate</td>
<td>Flavoring</td>
<td>0.0502</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>Bronkosol*</td>
<td>Preservative</td>
<td>0.07</td>
</tr>
</tbody>
</table>
Table 3.2: Excipients Used in Inhalable Drug Products (continued)

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Product Examples†</th>
<th>Function</th>
<th>Maximum Approved Concentration (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitric acid</td>
<td></td>
<td>pH adjustment</td>
<td>1.67</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>Airomir, Airomir Autohaler, Beclovent, Dulera, Proventil, Proventil HFA, Ventolin, Xopenex HFA</td>
<td>Dispersion Emulsification</td>
<td>0.267</td>
</tr>
<tr>
<td>Polyethylene glycol 1000</td>
<td>Intal CFC-free, Symbicort, Tilade CFC-free</td>
<td>Dispersion Valve lubricant</td>
<td>0.0224</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>Pulmicort Respulesa</td>
<td>Suspending aid</td>
<td>0.02</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone K25</td>
<td>Intal CFC-free, Symbicort, Tilade CFC-free</td>
<td>Suspending aid</td>
<td>0.0001</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Tornalatea</td>
<td>Cosolvent Preservative</td>
<td>25</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>Bronkosolb</td>
<td>Preservative</td>
<td>0.0375</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Tornalate</td>
<td>Flavoring</td>
<td>0.1127</td>
</tr>
<tr>
<td>Saccharin sodium dihydrate</td>
<td></td>
<td>Flavoring</td>
<td>0.045</td>
</tr>
<tr>
<td>Sodium bisulfate</td>
<td></td>
<td>pH adjustment</td>
<td>0.011</td>
</tr>
<tr>
<td>Sodium bisulfite</td>
<td></td>
<td>Preservative</td>
<td>0.2</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>AccuNebb, Aireta, Alupentb, Atroventb, Bronkosolb, Brovanaa, Caystonb, DuoNebb, Duovenb, Isuprelb, Perforomista, Proventilb, Pulmicort Respulesa, Pulmozymeb, Tobi, Tyvasob, Ventavis, Xopenexa</td>
<td>Tonicity</td>
<td>3.16</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td></td>
<td>Buffering Chelating Flavoring</td>
<td>0.6</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>Exubera, Tornalatea, Tyvasoa</td>
<td>pH adjustment</td>
<td>8</td>
</tr>
<tr>
<td>Sodium metabisulfite</td>
<td>Isuprela</td>
<td>Preservative</td>
<td>1</td>
</tr>
<tr>
<td>Sodium sulfate (anhydrous)</td>
<td></td>
<td>Tonicity</td>
<td>0.025</td>
</tr>
<tr>
<td>Sodium sulfate</td>
<td></td>
<td>Preservative</td>
<td>0.1</td>
</tr>
</tbody>
</table>
### Table 3.2: Excipients Used in Inhalable Drug Products (continued)

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Product Examples†</th>
<th>Function</th>
<th>Maximum Approved Concentration (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitan trioleate</td>
<td>Aerobid, Aerobid-M, Alupent, Duo-Medihaler, Intal, Maxair, Tilade</td>
<td>Dispersion, Emulsification, Solubilization</td>
<td>0.0694</td>
</tr>
<tr>
<td>Sulfuric acid</td>
<td>AccuNeb®, Proventil®, Tobi®, Ventolin®, Xopenex®</td>
<td>pH adjustment</td>
<td>12.5</td>
</tr>
<tr>
<td>Thymol</td>
<td></td>
<td>Preservative</td>
<td>0.01</td>
</tr>
<tr>
<td>Tromethamine</td>
<td>Ventavis®</td>
<td>pH buffering</td>
<td>0.0121</td>
</tr>
<tr>
<td>Water</td>
<td>Atrovent HFA, Combivent Respimat, Primatene Mist</td>
<td>Cosolvent</td>
<td></td>
</tr>
</tbody>
</table>

† Product examples are subscripted based on formulation type, such that (a) denotes nebulizer products and (b) denotes dry powder inhalers. All other products are MDIs.

* The data provided in this table is from the FDA Inactive Ingredient Search for Approved Drug Products (last updated March 29, 2013) and Drugs@FDA databases (197,198), along with the product information for each medication.
3.1. Effect of Ethanol on Solubility and Performance

The primary cosolvent utilized in pMDI formulations is ethanol. Typically, it is utilized in an HFA formulation to increase drug or excipient solubility or to enhance valve function. However, the effect of ethanol on solubility varies significantly based on solute structure. Hoye et al. has investigated the effect of ethanol on the solubility of 21 different compounds, having logPs of -0.17 to 9.85 (199). It was found that the addition of 20% ethanol in HFA 134a could increase the solubility of these compounds by as little as 1.3 times to as much as 99.4 times, relative to the solubility of these compounds in pure HFA 134a. Interestingly, solubility increased for all compounds; however, a direct correlation with logP was not observed. Representative ethanol cosolvent solubility profiles for a variety of compounds are given in Figure 3.1.

The addition of semi-volatile ethanol has multiple effects on the delivery process. Ethanol concentration can influence the delivery characteristics of pMDIs in three ways: (1) by changing the formulation density and thus changing the total mass of formulation atomized during actuation of the device; (2) by changing atomization of the formulation and the size of the atomized droplets; and (3) by changing the evaporation rate of these droplets towards their residual particle sizes (93). As the concentration of ethanol increases, the vapor pressure of the formulation decreases, this in turn affects the atomization process. The decreased atomization force leads to an increase in the initial droplet size distribution (see Figure 3.2). This results in larger residual particles being present after evaporation of the droplets in the aerosol spray. Additionally, the larger droplets cause increased deposition in the mouth and throat. Thus, increased ethanol
concentration leads to a decrease in FPF and fine particle mass, thereby decreasing the overall dosing efficiency (93).

Several investigators have illustrated the effect of ethanol concentration on product performance for solution pMDIs (200-202). As presented in Figure 3.3, Gupta et al. showed that when ethanol concentration increased from 0% to 20% (w/w), the solubility of beclomethasone dipropionate (BDP) increased linearly in HFA 134a (200). While the drug concentration in the formulation increased linearly with ethanol, the corresponding FPF decreases. As a result, the net gain in fine particle mass delivered (or “effective solubility”) diminishes as the ethanol concentration increases to 20% (w/w).

Myrdal et al. (201) found similar effects of ethanol on product performance for HFA 227 using the drug cyclosporine, as shown in Figure 3.4. For example, a cyclosporine solution pMDI in HFA 227 could achieve a fine particle mass of approximately 750µg/actuation with no ethanol, at a drug concentration of 1.5% (w/w). However, the fine particle mass decreases to approximately 350µg/actuation when 10% (w/w) ethanol is added for the same drug concentration. This corresponds to a reduction in FPF from approximately 66% to 38% when ethanol is increased from 0% to 10% (w/w) in HFA 227. These trends were found to be true for dissolved cyclosporine drug concentrations ranging from 0.1% to 1.5% (w/w). Similar results were also found with a model drug (fluorescein sodium) and HFA 227 (203). Thus, when the concentration of ethanol is increased, the overall delivery efficiency of the formulation decreases, thereby limiting effectiveness of using ethanol as a solubilizing aid.
Figure 3.1: Solubility of a variety of solutes in ethanol cosolvent systems in HFA 134a (S$^{SHFA-EtOH}$) relative to their solubility in a pure HFA 134a system (S$^{SHFA}$) as a function of ethanol concentration. LogP for each solute is represented in parentheses in the legend of the graph. Adapted from Hoye and Myrdal, 2008 (199).
**Figure 3.2:** The effect of ethanol concentration on the resulting initial droplet MMD for HFA 134a solution pMDI with 1% (w/w) drug. Andersen Cascade Impaction measurements were made using a large volume chamber as the inlet. From Stein and Myrdal, 2006 (93)
Figure 3.3: The effect of ethanol concentration on the solubility of beclomethasone dipropionate (BDP) and the resulting fine particle fraction in HFA 134a. The dashed line represents the effective solubility of BDP, which is the net gain in the delivered fine particle mass with change in ethanol concentration. Adapted from Gupta et al., 2003 (200).
Figure 3.4: (A) The effect of ethanol on the fine particle dose and (B) the effect of ethanol on fine particle fraction for 0.1%, 1% and 1.5% (w/w) cyclosporine (CSP) formulations in HFA 227. Adapted from Myrdal et al., 2004 (201).
There are two primary mechanisms that lead to reduced delivery efficiency for formulations with higher ethanol concentration. First, the size of the atomized droplets is larger with increased ethanol in a formulation. Second, the atomized droplets that contain a greater proportion of ethanol evaporate more slowly than droplets containing less ethanol or only the propellant (93). The net result of both of these mechanisms is that the droplets from a formulation with high ethanol concentration remain for a longer duration at sizes that are likely to deposit in the turbulent region of the airways (i.e., oropharynx and upper airways) (97). Figure 3.2 presents the effect of ethanol concentration on initial droplet mass median diameter (MMD) for HFA 134a formulations; the initial droplet MMDs were calculated based on experimental measurements of the residual MMAD using Equation 3.1 (82).

\[
\text{MMAD}_R = (\rho_I \times C_{NV})^{1/3} \times \rho_R^{1/6} \times \text{MMD}_I
\]  

(Equation 3.1)

where \(\text{MMAD}_R\) is the MMAD of the residual particles, \(\text{MMD}_I\) is the mass median diameter of the initial droplets, \(\rho_I\) is the density of the initial droplet (which is assumed to be the same as the formulation density), \(\rho_R\) is the density of the nonvolatile residual particles, and \(C_{NV}\) is the weight fraction of the nonvolatiles in the formulation. Modest increases in ethanol concentrations resulted in a notable increase in initial droplet MMD (5). Stein and Myrdal (93) theoretically and experimentally evaluated several semi-volatile cosolvents (such as butyl acetate, ethyl acetate, acetonitrile, methanol, and methyl acetate) and demonstrated that FPF increases as the rate of evaporation increases.
It was hypothesized that the droplet size of the atomized spray decreases more rapidly for formulations containing cosolvents that evaporate more rapidly. This results in decreased turbulent deposition in the mouth-throat region (93). Furthermore, it was theoretically determined that for the same concentration of drug, modulating the initial droplet MMD had a greater impact on solution formulations compared to suspension formulations (5).

Although the addition of ethanol to the formulation decreases the rate of evaporation of the atomized droplets, the droplets still evaporate rapidly (typically in less than approximately 10 milliseconds) (93). Thus, while depending on ethanol level, the atomized droplets could reach a “dry” residual particle size prior to depositing in the lung. Other cosolvents, such as water or propylene glycol, are significantly less volatile and may not evaporate prior to deposition in the lung. In some cases, the use of low volatility cosolvents can be used to increase the residual aerodynamic particle size to a target range.

### 3.2. Effect of Nonvolatile Concentration on Performance

The primary determinants of residual particle size from solution pMDIs are the size of the initial droplets and the composition of the formulation. For a solution formulation, this relationship is summarized by Equation 3.1 (204). In the simplest case, where the drug is not volatile and no other volatile excipients are in the formulation, the nonvolatile concentration, $C_{\text{NV}}$, is simply the concentration of the drug and the residual particle density, $\rho_R$, is the density of the drug. As presented in Figure 3.5, the residual MMAD increases as a cube-root function of the concentration of the drug (for
formulations without other nonvolatile excipients). It is important to recognize that if the drug density value utilized in Equation 3.1 is obtained from crystalline material, this may be an overestimation of the of the true density since the residual particle generally contains amorphous drug that typically has a lower density than the crystalline form.

In formulations where nonvolatile (or low volatility) excipients are present in addition to the drug, the $C_{NV}$ in Equation 3.1 is the sum of the weight fractions of the drug and the nonvolatile excipients and the $\rho_R$ is the density of the residual particle. The addition of nonvolatile excipients is expected to increase the residual MMAD of the formulation and potentially decrease the FPF. For instance, with the addition of 1.22% (w/w) Pluronic L81 to a formulation with 0.04% (w/w) dissolved drug in HFA 227 with ethanol, the residual MMAD increased from 1.56 to 3.70μm while the FPF did not change significantly (203). However, further increase in Pluronic L81 concentration (up to 5.45%), resulted in a significant increase in the MMAD and decrease in the FPF compared to formulations with 0% and 1.22% Pluronic L81.
Figure 3.5: The influence of nonvolatile drug concentration (oligolactic acid was used as a drug surrogate) on the residual particle MMAD for a series of HFA 134a solution pMDIs. Each data point represents an average of four tests and the error bar represents the standard deviation. Measurements were made using the USP inlet. From Stein and Myrdal, 2004 (204).
3.3. Novel Solubilization Aids

Using traditional cosolvents, the fine particle dose that can be achieved is limited based on the drug solubility in the cosolvent-propellant solution and the decrease in delivery efficiency at high cosolvent levels. Novel solubilization aids have been investigated which avoid, to an extent, the decrease in delivery efficiency associated with the use of ethanol. Below, several approaches to improve the solubility of drugs in HFA systems are provided. This list is not exhaustive; however, it does present the variety of compounds that are currently explored to solubilize drugs to render solution pMDI formulations.

Micellar solubilization was used to enhance the solubility of albuterol and triamcinolone actonide in CFC-solution formulations using an isotropic solution of soya phosphatidylcholine (205). The solubility of the drugs increased proportionally with the addition of the surfactant but decreased with the addition of increased water relative to the surfactant.

More recently, Stein et al., Scherrer et al. and Stefely et al. (53,206,207) studied the effect of solubilizing two new chemical entities (NCE) using carboxylic acid functionalized methyl polyethylene glycol (f-mPEG) and/or oligolactic acid (OLA) in combination with ethanol. These excipients were shown to be synergistic with ethanol in increasing drug solubility in the formulation (208,209) such that acceptable dissolved drug concentrations can be obtained at reduced ethanol concentrations. Stein et al. (53) found that with 20% ethanol in HFA 134a, 0.82% NCE #1 rendered a maximum fine particle dose of 69µg/actuation, which was significantly improved to 245µg/actuation
with 0.82% drug, 2.1% f-mPEG and 5.3% ethanol, by weight. Similar results were seen with NCE #2, whose conventional formulation (25% ethanol and 0.3% NCE #2 by weight) had poor delivery efficiency but changing the formulation by adding 1.6% OLA or 1.1% f-mPEG (with 1% or 2.1% ethanol, respectively) improved drug delivery.

In addition, Stefely et al. (208) explored the use of two classes of HFA-compatible excipients: hydrophobic and hydrophilic counterions. Hydrophobic counterions, such as lauric acid or mono-functionalized lauric acid with an amide or ester (e.g., lauroyl sarcosine and lauroyl lactylate), may be used along with ethanol to synergistically increase the solubility of drugs that contain an amine functional group. Hydrophilic counterions, such as functionalized polyethers (i.e., carboxylic acid functionalized PEG) (209) could also be used to increase drug solubility. Increasing the amount of the excipient in a formulation or decreasing the length of the PEG chain resulted in increased drug solubility of a drug with amine functionality. Furthermore, the excipient was found to be synergistic with ethanol in solubilizing the drug.

Rogueda found that partially and fully acetylated cyclodextrins (CD), while commonly studied as suspension stabilizers, may also solubilize drug (210). Peractylated β-CD has a solubility of 0.1% (w/w) in HFA 227 but is significantly more soluble in HFA 134a (> 1% w/w). It was found that for a fixed 1:1 molar ratio of budesonide/CD, co-spray drying the two agents yielded a solution, whereas a physical mixture of budesonide and CD or simply budesonide in HFA 227 formed a suspension in HFA.
3.4. Solution Formulation Strategies

As companies began developing HFA pMDI products to replace marketed CFC products, the fact that HFA propellants differ from CFC propellants in both chemical and physical properties caused numerous challenges. For example, Beclovent™ pMDIs were CFC suspension formulations of BDP. However, HFA suspension formulations of BDP proved to be problematic due to the increased solubility of BDP in the HFA propellant systems. As a result, HFA BDP pMDIs have been developed as solution formulations. Two distinct formulation strategies have been utilized to create HFA solution formulations of BDP: (1) take advantage of the extrafine aerosol production of HFA solutions and produce an pMDI with increased efficacy and decreased deposition in the central airways; or (2) try to match the dose and particle size to the respective CFC formulation so that patients can continue with the same dose that they were used to. An example of the first approach is the development of QVAR® (211); an example of the latter approach is BDP Modulite® pMDI (212).

The Modulite® approach provides a rational and empirical methodology that allows for the modulation of several dependent variables to anticipate the performance of an HFA-based pMDI solution formulation. These variables include the quantity of the cosolvent, actuator orifice geometry, nonvolatile concentration, metering valve size, and the vapor pressure of the propellant. The Modulite® approach has be utilized to formulate HFA-formoterol fumarate in 6 and 12µg/actuation strengths with 12% (w/w) ethanol, 0.024% or 0.038% 0.1M aqueous hydrochloric acid and 50 or 63µL valves, respectively for the 6 and 12µg doses (213). To match the residual particle size distribution from CFC
formoterol suspension formulation, the actuator nozzle orifice diameter (OD) was selected to be 0.3mm, which provided an HFA formulation that would replace the CFC formulation without a change in FPF and the efficacy of the medication. This approach has also been utilized to develop an HFA formulation of budesonide to match CFC formulations, Pulmicort® and Desonac® DA (214). In this case, the addition of a nonvolatile component and the actuator OD were varied such that the aerosol cloud would have similar characteristics as the CFC suspension formulations and the residual particle APSD would also be equivalent. Since the CFC formulations were suspensions, adding a nonvolatile component (water and glycerol), in addition to the drug, increased the residual particle APSD of the Modulite® solution pMDIs. Furthermore, actuator ODs were decreased from those used with the marketed CFC formulations, in order to reduce the velocity of the pMDI plume. Similar approaches have been taken in transitioning from the CFC formulation of BDP (suspension, Beclazone®) to the BDP-HFA formulation (solution, Clenil Modulite®) (215). Beclazone® and Clenil Modulite® have a similar residual particle size distribution (3.1μm with a GSD of 3.26 versus 2.8μm with a GSD of 2.71 for 50μg/actuation dose, respectively), similar FPF (34.2% versus 31.6%, respectively) and fine particle dose (14.4 versus 16.6μg/actuation, respectively). Chaplin and Head (216) propose that these factors permit switching patients from the CFC formulation directly to the Modulite® formulation, without changing the drug dosage.

By contrast, an alternate solution formulation strategy leverages the extrafine aerosol formulation for HFA solution pMDIs to improve the fine particle dose of the HFA pMDI compared to the CFC-formulation (211). This strategy enables similar
efficacy to be obtained using a decreased total dosage of the drug compared to the CFC or Modulite® formulation approaches (216,217). Alternatively, if the dose of the extrafine formulation is comparable to that of the CFC or Modulite® formulations, the extrafine formulation will have an increase fine particle dose and a "leftward shift" in the dose-response curve with potentially an increase in the maximum response (218). QVAR® 80µg/actuation, an HFA formulation of dissolved BDP, has a residual MMAD of 1.1µm (211). With a small residual particle size, it is expected that a greater extent of the drug deposits in the peripheral airways (airway diameters ≤ 2mm), compared with a CFC BDP formulation with a residual size of approximately 3µm (215), which primarily deposited in the central airways (219). The extrafine aerosol formulation approach permits QVAR® to have a lower formulation drug concentration, increased inhalation technique tolerance, and increased ratio of therapeutic efficacy to adverse effects because of the deposition of the drug in the peripheral airways compared to the CFC formulation (220,221). Treating the peripheral airways is important especially for a large proportion of asthmatic patients who experience persistent small airway dysfunction (218) and has been shown to improve the probability of patients achieving asthma control over a period of 1 year (222). Other marketed extrafine HFA pMDI formulations include ciclesonide (Alvesco® HFA), flunisolide hemihydrate (Aerospan® HFA), and formoterol fumarate (Atimos®). In addition, a solution combination product with BDP and formoterol (Fostair®) is available in Europe. A solution formulation of salmeterol xinafoate is being investigated, which utilizes up to 2% (w/w) water to solubilize the drug (223).
Chiesi Farmaceutici has claimed that certain solution formulations can be stabilized using small amounts of strong mineral acids, such as hydrochloric, nitric or phosphoric acids (224). For instance, the marketed CFC formoterol formulation, Foradil®, had a shelf life of 12 months in the refrigerator and only three months at room temperature. It is speculated that phenylakylamino β2-agonists may be inherently unstable due to their susceptibility to oxidation and the presence of a highly polar vehicle may accelerate their degradation (224). It has been disclosed that the chemical stability of dissolved formoterol in HFA can be substantially improved by the selection of appropriate vials (i.e., canisters) and tight control of the pH of the formulation (224). The formulation is much more stable at apparent pH values below 5.6; the inventors selected an apparent pH range of 3.0 to 3.5 for this formulation. At an apparent pH of 7.4, 67.2% of the initial formoterol content was still present after 20 days, while at an apparent pH of 3.3, 89.9% of the initial drug content was still present after 20 days. In addition, the use of inert canisters (stainless steel, anodized aluminum, or organic coated) that do not leach metal ions or alkali as a consequence to the addition of acid to the formulation appear to inhibit catalysis of radical oxidative reactions.
4. Particle Preparation for pMDI Formulations

The solid form of a drug can affect solubility, dissolution, and stability in a formulation. For instance, different salts of drugs can have different solubility, dissolution, and stability properties in propellant systems, which significantly impact the pMDIs product performance (e.g., albuterol base versus albuterol sulfate) (225). The primary objectives for inhalation drug particle engineering are to produce drug particles with an appropriate particle size distribution and desired dispersibility. For instance, surface modifications of drug particles with magnesium stearate or glycerol monostearate can be done to improve the aerosolization and deagglomeration of micronized drug particles (226). In addition, particle engineering can be utilized for optimizing bioavailability, targeting receptors, evading clearance mechanisms, and affording controlled drug release. While particle engineering for inhalation drug products is briefly discussed below, please refer to Shoyele and Cawthorne’s (227) and Chow et al.’s (228) articles for an extensive review of the topic.

Typically, prior to formulating a drug, the size of the crystalline material needs to be reduced to obtain suspension pMDI formulations with particles of a suitable size for inhalation. This can be achieved by milling, spray drying, or using supercritical fluids (229,230). Ball mills and fluid-energy mills (such as jet mills) are the primary modes of milling powders to achieve particles with diameters of 1 to 5μm (231). Ball mills utilize balls that grind the drug as the balls tumble inside the mill. This method is relatively slow and is difficult to scale up (232). Jet milling, which is the primary method of micronizing
drugs, reduces particle size of coarse powders by high velocity particle-particle collisions. The mechanical process of milling can affect the crystallinity of the material and amorphous regions can be produced at the newly formed surfaces of the micronized material (233). In addition, milling typically yields nonspherical particles, with flat surfaces that may increase adhesion between the micronized particles (231). Alternatively, spray drying may be used to manufacture drug particles for pMDI formulations. Spray drying converts a solution or liquid dispersion (also known as “feed”) to dried particulates by the process of atomizing a spray of the liquid containing the drug followed by quickly drying the droplets, which yields solid particles. Factors such as the feed composition, drug concentration, liquid feed rate, drying rate, temperature, and relative humidity can be varied, allowing one to optimize the size distribution, shape, morphology, and density of the particles. Compared to milling, spray drying often produces relatively spherical, amorphous particles. Finally, supercritical fluids may also be utilized to manufacture particles for inhalation. A supercritical fluid is any substance at a temperature and pressure above its critical point. Supercritical fluids can be used in multiple ways to micronize drug particles. They may be used to micronize drug material through rapid expansion of supercritical solutions, using supercritical fluid as an anti-solvent, and precipitation of particles from gas saturated solutions (231). All three of these methods rely on dissolving the drug in the supercritical fluid, at high pressure and temperature, followed by decrease in pressure and/or temperature which yields a reduction in the density of the solution, thereby decreasing the solvation power of the supercritical fluid, leading to precipitation of the drug.
The method for preparing drug particles for pMDI formulations needs to be selected based on the chemical stability of the drug. Proteins, for instance, require additional care when micronizing, due to being heat-labile and need to preserve any three-dimensional conformation. Frequently, spray drying with another agent (i.e., sodium carboxymethylcellulose (234,235), trehalose with polyvinyl alcohol (236), and/or polyvinylpyrrolidone (PVP) (237)) is utilized for protein drugs due to the need to preserve the three-dimensional conformation and biological activity of the protein. Proteins and nucleic acids have been lyophilized providing a morphology that reduces van der Waals interactions, which may serve to protect their integrity and also decrease suspension settling rate relative to milling (238). In addition, well-dispersed nanoparticles containing proteins have been produced by freeze-drying with the intention to be used with HFA systems by Tan et al. (239). The process involves dissolving the protein in a tert-butyl alcohol-water system with lecithin (as a surfactant) and lactose (as a cryoprotectant) followed by freeze-drying and purifying.

More complicated preparation of the drug matrix may be required if modifying drug release is an objective. For example, drug loaded into swellable hydrogel microparticles (240) has been shown to modify drug release. The swelling of these particles are governed by the hygroscopic growth of the particles (excipients and/or drug) in the respiratory tract. Hygroscopic growth depends on the hygroscopicity of the excipient and the drug, the properties of the engineered particle, and the respiratory parameters (241). Namely, the particles developed by Selvam et al. (240) are composed of drug-loaded polylactic-co-glycolic acid nanoparticles which are encapsulated in PEG-
chitosan copolymer microparticles. These microparticles swell upon deposition in the deep lung, thus evading alveolar macrophages and permitting modified drug release. Some other hygroscopic excipients, in decreasing order of hygroscopic potential, include: sodium chloride, citric acid, propylene glycol, and mannitol (241). Alternatively, chitosan microspheres have been investigated to protect and afford sustained release of proteins and plasmid nucleic acids via pMDI drug delivery (242). Also, the addition of glycerol to solution BDP pMDI formulations has shown to affect the extent of drug metabolism across a cell layer, suggesting increased residence time of the drug particles in the lungs (243).
5. Suspension Formulations

Many pMDI applications are formulated as suspensions in which the drug particles are suspended in the HFA system, creating a heterogeneous formulation. A primary concern for formulating suspension pMDIs is instability due to nonideal dispersion of the drug. This can occur because of phase separation, flocculation, agglomeration, drug particle interaction with other drug particles or device material, or moisture ingress (244). Depending on the relative density of the suspended drug to that of the continuous phase, the drug will either cream or settle in the formulation. The drug content of each subsequent dose can increase or decrease over time if the drug is not adequately dispersed by shaking the vial. Considering this nature, suspensions inherently present the concern of dose uniformity, from dose-to-dose as well as over the life of the pMDI (57). As drug particles associate to form large flocculates that cream or settle, a nonuniform suspension gradient is created, leading to variability in metered dose (22,245). Even more detrimental to suspension formulations is the irreversible agglomeration or caking of particles.

A principal consideration for a suspension formulation is that the drug must be practically insoluble in the formulation. The inherent drug properties or the addition of ethanol will afford different levels of drug solubility in the formulation. Thermodynamic solubility in combination with kinetics, over time, can lead to an increased particle size distribution, a phenomenon known as Ostwald ripening (155). Surface molecules on relatively smaller particles have higher free energy than molecules inside of the particle
or molecules on the surface of larger particles. Thus, thermodynamics favor the
dissolution of the smaller particles and a corresponding growth of the larger particles,
which results in the reduction of the overall free energy of the system (57).

Interestingly, the formulation and drug form may affect particle growth. For
instance, BDP grows rapidly when exposed to CFC propellants. For instance, 6 hours
post-exposure to CFC 11, the mean particle size of micronized BDP grew from 1.6 to
22.2μm. However, the ethyl acetate solvate of BDP experiences minimal growth when
exposed to CFC 11 (244). Aside from the growth of micronized material affecting the
residual APSD, it may also affect the propensity of the particles to settle or cream within
the pMDI vial.

Solid drug particles in a suspension formulation often cream or settle. The
sedimentation velocity (or creaming velocity) of suspended drug particles can be
determined by Stokes’ law (Equation 3.2),

\[ \nu = \frac{g \times d_p^2 \times (\rho_p - \rho_{form})}{18 \times \eta} \]  

(Equation 3.2)

where \( \nu \) is the sedimentation velocity (such that \( \nu > 0 \) is in the direction of gravity), \( g \) is
the gravitational acceleration constant, \( d_p \) is the diameter of the suspended particle, \( \rho_p \) is
the density of the suspended particle, \( \rho_{form} \) is the density of the formulation, and \( \eta \) is the
viscosity of the formulation (155). Thus, suspensions are inherently susceptible to
gravitational sedimentation or creaming. Larger suspended particles will cream or settle
faster than smaller particles. Furthermore, particles with diameters less than 0.5μm will be affected by Brownian motion, which may oppose settling or creaming, assuming that the particle density is not starkly different from the formulation density (244). Brownian motion and particle diffusivity increases with lower viscosity of the formulation and smaller particle size. Therefore, at ambient temperatures, increasing particle diffusivity can lead to increased particle-particle or particle-device interactions, leading to increased coagulation rates or larger flocculate sizes. In addition, most crystal drug densities vary between 1.15 and 1.40g/cm$^3$. Gravitational stability can be enhanced by matching the density of the system to the density of the drug by adding excipients or blending propellants to increase or decrease the overall density of the HFA formulation (246). For formulations with only blended HFAs 134 and 227, the density of the formulation can range between 1.21 and 1.41g/cm$^3$; however, the addition of ethanol ($\rho = 0.789$g/cm$^3$) can lower the overall formulation density. The benefit of this density-matching approach is limited by the fact that the density of propellant formulations varies significantly with temperature changes. Alternatively, the drug particles can be engineered to match the density of the formulation (247), which is the approach utilized by the PulmoSpheres® platform, described in Section 5.3 of this chapter. Secondly, excipients can be utilized to ensure decreased agglomeration of suspended drug particles, which will be discussed in much detail in the proceeding sections.
5.1. Effect of Nonvolatile Content

Unlike solution formulations, the nonvolatile concentration does not impact the residual particle size of suspension pMDIs in a direct, predictable manner. In fact, the drug concentration along with the properties of the micronized drug (i.e., raw drug MMAD, GSD, and density) impact the residual particle size distribution. For formulations with dilute suspended drug content, the MMAD of the residual particles is very close to that of the micronized drug (see Figure 3.6). This occurs as most of the drug laden atomized droplets contain only a single suspended drug particle. However, as the drug concentration increases, more of the atomized droplets contain multiple drug particles which lead to an increase in the residual particle MMAD. Consequently, the residual MMAD increases more rapidly with change in drug concentration for suspension formulations containing smaller micronized drug than that for larger micronized drug (248,249). Major predictors for the residual particle MMAD of suspension pMDIs are the size of the micronized drug, the number of drug particles per unit volume in a given formulation (which is a factor of the concentration, size distribution, and density of the micronized drug and the density of the formulation), and the initial droplet size distribution. As droplet size and particle concentration increase, droplets have increased propensity to contain multiple drug particles (5), resulting in larger residual particle size distributions, which may further decrease the FPF (250). Thus, suspension pMDI formulations with very fine micronized drug at a low concentration may result in a relatively high FPF (251).
Figure 3.6: The theoretical effect of concentration and MMAD of micronized drug on the residual aerodynamic particle size distribution (MMAD of residual particles) for suspension pMDIs derived from simulations with 50μL metering chambers, 0.3mm orifice diameters, 8.5% (w/w) ethanol in HFA 134a. From Stein et al., 2012 (249).
Sometimes nonvolatile impurities can leach into the formulation from device components or other sources and impact suspension formulations. For example, silicone is often added to valve components during valve manufacturing. Silicone can leach into the formulation over time, particularly when the pMDIs are stored at high temperatures and inverted. It appears that the silicone leached in to the formulation can lead to an appreciable particle size coarsening of the formulation potentially through the aggregation of particles into clusters (62,63). Furthermore, depending on the material utilized in the valve, there may be an increased attraction of suspended drug in the formulation to the component, resulting in poor dose uniformity (252).

5.2. Stabilizing and Suspending Agents

Surfactants, a primary class of suspension stabilizers, required extensive reevaluation with the transition from CFC to HFA propellants. Surfactants, such as soya lecithin, sorbitan trioleate, and oleic acid, which are readily soluble in CFC propellants (especially CFC 11) have very low solubility in HFA propellants (see Table 3.3). Surfactant polarity, indicated by their respective hydrophilic-lipophilic balance (HLB), correlates with the incompatibility of the aforementioned surfactants in the more polar HFA environment (57,253). A high HLB value indicates that the surfactant is highly hydrophilic and a low HLB value indicated that the surfactant is highly lipophilic.

Surfactants are frequently utilized in pMDI formulations for a myriad of reasons. In solution formulations, surfactants serve to increase drug solubility, moderate temperature-dependent drug solubility, and overcome valve sticking issues (57).
However for suspensions, surfactants are primarily used to prevent irreversible particle agglomeration, prevent drug particle adhesion to the container walls and valve components, decrease the rate of separation between the drug and the propellant system, and prevent valve sticking problems. Surfactants stabilize the dispersion by decreasing the electrostatic forces between the micronized drug particles thus decreasing crystal growth or particle agglomeration during storage conditions (155). Surfactants typically must be adequately soluble and stable in HFA systems to be used for suspension formulations. For instance, oleic acid has substantially lower solubility in HFA propellants than in CFCs. In order to utilize oleic acid to stabilize albuterol sulfate suspension in the Proventil® HFA formulation, sufficient ethanol is used to solubilize oleic acid. Similarly, although lecithin is effectively insoluble in HFA (< 0.01% (w/w) in HFAs 134a and 227 (57)), it is soluble in dimethyl ether and propane propellant systems, and can be utilized to form water-in-oil (inverse) microemulsions that further stabilize suspension formulations (168,254).
<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Chemical Structure</th>
<th>Hydrophilic-Lipophilic Balance (HLB)</th>
<th>Apparent Solubility (% w/w) in*:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HFA 134a</td>
</tr>
<tr>
<td>Sorbitan alkanoates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbitan monolaurate</td>
<td></td>
<td>8.6</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Span 20</td>
<td>Sorbitan monooleate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorbitan monooleate</td>
<td></td>
<td>4.3</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Span 80</td>
<td>Sorbitan trioleate</td>
<td>1.8</td>
<td>&lt; 0.02</td>
</tr>
</tbody>
</table>

R = \text{CH}_2(\text{C}_6\text{H}_5)\text{CH}_2
Table 3.3: Solubility of Select Surfactants in HFAs (continued)

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Chemical Structure</th>
<th>Hydrophilic-Lipophilic Balance (HLB)</th>
<th>Apparent Solubility (% w/w) in*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyethylene glycol (polyoxyethylene)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>4.0 ≈ 3.6</td>
<td>HFA 134a: 1.5 – 15.3, HFA 227: 32.0 – 60.3</td>
</tr>
<tr>
<td>Propoxylated polyethylene glycol</td>
<td>n = 5-8</td>
<td>20 ≈ 4</td>
<td>HFA 134a: 1.5 – 4.3, HFA 227: &gt; 16.1</td>
</tr>
<tr>
<td>Polyethylene glycol 300</td>
<td>n = 11-16</td>
<td>20 ≈ 4</td>
<td>HFA 134a: &gt; 50, HFA 227: &gt; 50</td>
</tr>
<tr>
<td>Polyethylene glycol 600</td>
<td>n = 20-25</td>
<td>20 ≈ 2</td>
<td>HFA 134a: &gt; 50, HFA 227: &gt; 50</td>
</tr>
<tr>
<td>Polyethylene glycol 1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brij 30</td>
<td>PEG-4 lauryl ether</td>
<td>9.7 ≈ 1.8</td>
<td>HFA 134a: 0.8 – 1.2, HFA 227: 0.03</td>
</tr>
<tr>
<td>Brij 35</td>
<td>PEG-23 lauryl ether</td>
<td>16.9 ≈ 0.08</td>
<td>HFA 134a: 0.03, HFA 227: 0.03</td>
</tr>
<tr>
<td>Brij 56</td>
<td>PEG-10 cetyl ether</td>
<td>12.9 ≈ 0.7 - 1</td>
<td>HFA 134a: 0.2, HFA 227: 0.2</td>
</tr>
<tr>
<td>Brij 76</td>
<td>PEG-2 stearyl ether</td>
<td>12.4 ≈ 0.7</td>
<td>HFA 134a: 0.3, HFA 227: 0.3</td>
</tr>
<tr>
<td>Brij 97</td>
<td>PEG-10 oleyl ether</td>
<td>12.4 ≈ 4</td>
<td>HFA 134a: 0.3, HFA 227: 0.3</td>
</tr>
<tr>
<td>Polysorbate (Tween)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG-20: w+x+y+z = 20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tween 20</td>
<td>PEG-20 sorbitan monolaurate</td>
<td>16.7 ≈ 0.1</td>
<td>HFA 134a: 1.4 – 3.5</td>
</tr>
</tbody>
</table>

PEG-20: sorbitan monolaurate
R = CH₂(CH₂)₃CH₃
Table 3.3: Solubility of Select Surfactants in HFAs (continued)

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Chemical Structure</th>
<th>Hydrophilic-Lipophilic Balance (HLB)</th>
<th>Apparent Solubility (% w/w) in*:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HFA 134a</td>
</tr>
<tr>
<td>Tween 60</td>
<td>PEG-20 sorbitan monostearate R = CH₂(CH₂)₁₅CH₃</td>
<td>14.9</td>
<td>≈ 0.1</td>
</tr>
<tr>
<td>Tween 80</td>
<td>PEG-20 sorbitan monooleate R = CH₂(CH₂)₆CH = CH(CH₂)₂CH₃</td>
<td>15.0</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td></td>
<td>Polypropylene glycol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Chemical structure image]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPG 2000</td>
<td>n = 26</td>
<td>≈ 2</td>
</tr>
<tr>
<td></td>
<td>Block polymer with ethylene oxide (PEG) and propylene oxide (PPO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Chemical structure image]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pluronic 10-R5</td>
<td>a = 9, b = 22</td>
<td>12-18</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Pluronic 17-R2</td>
<td>a = 15, b = 10</td>
<td>1 – 7</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Pluronic 17-R4</td>
<td>a = 15, b = 26</td>
<td>7 – 12</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>Pluronic 25-R4</td>
<td>a = 22, b = 38</td>
<td>7 - 12</td>
<td>≈ 2</td>
</tr>
<tr>
<td>Pluronic F-68</td>
<td>n = 80, m = 30</td>
<td>&gt; 24</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pluronic F-127</td>
<td>n = 106, m = 69</td>
<td>18 – 23</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pluronic L-43</td>
<td>n = 6, m = 21</td>
<td>7 – 12</td>
<td>≈ 3</td>
</tr>
<tr>
<td>Pluronic L-44 NF</td>
<td>n = 9, m = 21</td>
<td>12 – 18</td>
<td>≈ 2</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Chemical Structure</td>
<td>Hydrophilic-Lipophilic Balance (HLB)</td>
<td>Apparent Solubility (% w/w) in*: HFA 134a</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------</td>
<td>-------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Pluronic L-62</td>
<td>n = 5, m = 30</td>
<td>1 - 7</td>
<td>≈ 2</td>
</tr>
<tr>
<td>Pluronic L-64</td>
<td>n = 13, m = 30</td>
<td>12 - 18</td>
<td>≈ 1</td>
</tr>
<tr>
<td>Pluronic L-101</td>
<td>n = 4, m = 56</td>
<td>1 - 7</td>
<td>≈ 0.1 – 0.2</td>
</tr>
</tbody>
</table>

**Miscellaneous Surfactants**

- **Lecithin**
  - Chemical Structure: ![Lecithin structure](image)
  - HLB: 7.0
  - Apparent Solubility: < 0.01

- **Oleic acid**
  - Chemical Structure: ![Oleic acid structure](image)
  - HLB: 1.0
  - Apparent Solubility: < 0.02

- **Polyvinylpyrrolidone K25**
  - Chemical Structure: ![Polyvinylpyrrolidone K25 structure](image)
  - HLB: > 0.1

- **Polyvinylalcohol**
  - Chemical Structure: ![Polyvinylalcohol structure](image)
  - HLB: > 0.1

- **Oligolactic acid**
  - Chemical Structure: ![Oligolactic acid structure](image)
  - HLB: ≈ 2.7
Table 3.3: Solubility of Select Surfactants in HFAs (continued)

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Chemical Structure</th>
<th>Hydrophilic-Lipophilic Balance (HLB)</th>
<th>Apparent Solubility (% w/w) in*:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerosol OT (sodium dioctyl sulfosuccinate)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td></td>
<td>HFA 134a  HFA 227</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.01  &lt; 0.02</td>
</tr>
</tbody>
</table>

* If a range of values are presented for solubility, the HFA-surfactant system appeared to produce a single phase at the stated concentrations of the surfactant. All solubility values presented were carried out between 19.5 and 25°C at saturated pressure. Data in this table is compiled from BASF Corp. Product Information; Griffin, 1955; Alexandridis and Hatton, 1995; Vervaet and Byron, 1999; da Rocha et al., 2011; and Ridder et al., 2005 (57,253,255-258).
Several novel surfactant excipients that function as dispersion aids for HFA suspension pMDI formulations have also been explored. For instance, OLA, presented previously as a method to increase drug solubility, is similar to polylactic acid except that it is generally shorter than most polylactic acid chains (OLA generally consists of only 5 to 20 repeating units) and the terminal alcohol can be modified by acetylation (259). In addition to its application as an excipient in solution pMDI formulations, it has been shown to function as a suspension aid. The head group of OLA interacts with the drug and the tail interacts with HFA, thus permitting a surfactant-like effect in stabilizing the suspension formulation (207). Furthermore, it has been shown to enable improved through life medication delivery compared with conventional suspension pMDI formulations. Interestingly, OLAs have been presented to modify drug release by forming in situ microspheres for a variety of drugs including steroids, 5-lipoxygenase inhibitors, and immune response modifiers (260).

More common excipients have also been investigated as suspending aids in HFA propellants. PEG at 0.05 to 0.5% (w/w) with 0.001% (w/w) PVP has been shown to decrease interparticulate cohesive forces between albuterol sulfate drug particles suspended in a model propellant (261). This effect was inversely dependent on the molecular weight of PEG and increased with increasing concentration of PEG. Hydrophilic counterions, such as functionalized polyethers, can be used to stabilize suspension formulations depending on the physicochemical properties of the drug and the amount of the hydrophilic counterion used (208). Examples of such include carboxylic acid functionalized PEGs and glycine functionalized PEGs (209). For instance, it was
found that the addition of glycine functionalized PEG to a pirbuterol acetate formulation in HFA 134a with ethanol increased the time of flocculation compared with a formulation without PEG. Wu and da Rocha (262) explored the use of polylactic acid-PEG-polylactic acid (PLA-PEG-PLA) to disperse albuterol base in HFA 227 and showed that the concentration, molecular weight, length of the surfactant tail, and the ratio between number of PLA and PEG have a large impact on the drug’s cohesive forces. PLA-PEG-PLA microspheres have also been shown to modify drug release. Rogueda showed that 1H,1H,2H,2H-perfluoroctan-1-ol and methyl-PEG-1,2-distearoyl-phosphatidylethanolamine conjugate decrease adhesion of drug particles to the headspace and also retard phase separation time (263). Glaxo Group Ltd. has also shown that other novel surfactants can also be utilized in HFA formulations for the aforementioned purposes (264,265) (see Figure 3.7). Propylene glycol diesters (Miglyol 840) and triglyceride esters (Miglyol 812) of medium-chain fatty acids may also be utilized as surfactants and have been shown to decrease discharge pressure upon actuation, which may positively influence oropharyngeal drug deposition from pMDIs (266). Furthermore, volatile mono- and sesquiterpene hydrocarbon oils, such as citral, menthol, eucalyptus oil, cinnamaldehyde, and cineole (267) are being investigated stabilizers for suspension pMDI formulations (268). Interestingly, cineole along with n-heptane (267) has been shown to improve suspension quality of a peptide nanoparticle, engineered by the mechanism developed by Tan et al. (239), as described under the subheading “Particle Preparation for pMDI Formulations” within this chapter. Other excipients have also been explored, which includes diethylene glycol monoethyl ether, polyoxyethylene 20 sorbitan
monolaurate, polyoxyethylene 20 sorbitan monooleate, propoxylated PEG, and polyoxyethylene lauryl ether (269,270). These excipients have been found to have favorable solubility in HFAs 134a and 227. It is postulated that surfactants with elevated HLB can be functional in HFA 227 as suspension stabilizers, while all others studied by Byron and Blondino (130,131) are primarily functional in HFA 134a. It should be noted that many of these aforementioned excipients have yet to be used clinically and none of these excipients are in current marketed products.

As an alternative to surfactants, surface-modified nanoparticle excipients (271) can be utilized to modulate interparticulate interactions of drug particles in suspension pMDI formulations. These surface-modified nanoparticles are spherical with 5 to 10nm diameters and function to eliminate flocculation of drug particles, leading to improved dosing reproducibility. The core of the nanoparticle can be composed of amorphous silica or iron oxide and the functionalized surface is designed to be hydrophilic to enable compatibility with HFA. Since these particles are extremely small, a large number of nonaggregating nanoparticles can be used in the formulation. They provide a steric barrier, preventing drug particles from interacting with each other, thereby eliminating flocculation. Some examples of surface modification investigated for pMDI formulations include magnesium stearate (226), glycerol monostearate (226), and crosslinked chitosan-PEG 1000 (272). Furthermore, the gravitational settling or creaming rate of the drug is decreased since the drug is not permitted to flocculate. Similarly, the principle to provide a steric barrier to prevent drug particles from flocculating is also used in the following approaches: (1) formulating an in situ precipitation of the drug creating a micro-
suspension or nanosuspension complexes of the drug with hydroxypropyl-β-CD (273,274) or acylated-β-CD (210), PEG and/or ethanol in HFA; or (2) trapping HFA-philic (i.e., PEG) moieties (275) at the surface of polar drug particles using a modified emulsification-diffusion method.

Two innovative approaches have been taken to formulate polar drugs in dispersion by creating microenvironments that are aqueous with the drug enclosed in a “shell” that is HFA-philic. One approach is to use suspended core-shell particles in HFA, where the particles are made by emulsification diffusion (276). The shell consists of HFA-philic oligolactide grafts attached to short chitosan backbone, while the active drug moiety is found within the particle core and is protected by the shell. This approach has been used for albuterol sulfate and bovine serum albumin in HFA 227. The experiments revealed improved dispersion stability and aerosol characteristics (i.e., FPF and residual MMAD) compared to conventional formulations. A similar approach is to formulate drugs in water-in-oil (reverse) microemulsions, where the emulsions create an aqueous microenvironment within the propellant system that enables the delivery of water-soluble compounds. For instance, Selvam et al. and Chokshi et al. utilized various ethylene oxide-propylene oxide-ethylene oxide (EOₙ-PO₃₀-EOₙ) polymers to form reverse aqueous microemulsions in HFAs 134a and 227 (277,278). It was found that PO-based amphiphiles can reduce the tension of the propellant-water interface, thus permitting the formation of reverse aggregates, which can be utilized to deliver polar solutes via pMDIs. Others have formed reverse emulsions using fluorine moieties, such as perfluoroalkyl bromide with perfluoroalkylated dimorpholinophosphate (a fluorinated surfactant) (279)
or polar fluorinated nonionic oxyethylene glycol with ethanol, propanol, or pentanol as a cosolvent (280). It was found in the latter case that in order to successfully form microemulsions in HFA 134a, the surfactant had to possess a short fluorocarbon tail and/or a relatively long ethylene oxide head group. However, the amount of surfactant required to get reasonable water incorporation into the formulation adversely affects the drug delivery since it leads to decreased volatility which results in a coarser aerosol and increased oropharyngeal deposition (280). Thus, while reverse microemulsions in HFA appear to be an appealing mode for delivering polar drugs, their utility can be limited due to poor delivery efficiency and detrimental interaction between the device and formulation.
**Figure 3.7:** Structures of novel surfactants from Glaxo Group Ltd. Adapted from Looker et al., 2003 (264, 265).
Another consideration for the stability of suspensions is the effect of low levels of water in the formulation. For instance, an accelerated stability study of isoproterenol sulfate and atropine methylbromide HFA pMDIs at 40°C/75% relative humidity compared to 40°C/ambient humidity for 3 months reveals that at higher levels of humidity, the emitted doses were not uniform and the FPF was significantly reduced; however, moisture ingress can be limited with selected sealing gasket materials and controlled manufacturing conditions (281,282). However, the inclusion of water does not always have a detrimental effect on the suspension HFA formulation. In fact, in certain situations, adding a minute amount (< 0.18% (w/w) of water (283)), in excess to the amount of water that would nominally be in the formulation (i.e., water ingress by process or storage of the pMDI) has been found to improve the redispersibility of the formulation (284). For instance, 0.015% (w/w) water was added to a BDP monohydrate formulation resulting in a formulation that formed a weakly flocculated suspension, which was readily redispersed upon shaking (285).

5.3. PulmoSpheres®

The PulmoSpheres® technology relies on creating suspensions of lipid porous microspheres, which allows the propellant to permeate within the particles creating particles with an effective density that is virtually identical to the propellant regardless of the formulation temperature (23). By decreasing the density differential between the suspended drug particles and the continuous phase of pMDIs, particle settling or creaming is greatly reduced resulting in improved formulation stability. Furthermore, the
larger geometric size of PulmoSpheres®, results in an overall decrease in surface area of particles compared to conventional formulations (244). This reduces the subsequent contact area for particle-particle interactions, thereby reducing the probability of agglomeration. It is believed that this is due to a decreased van der Waals potential between particles, which depends on the difference in polarizability of the particles and the propellant. Since PulmoSpheres® are hollow porous particles, the incorporation of the propellant into the particles generates particles with similar polarizability as the propellant, which reduces the van der Waals potential between particles.

PulmoSpheres® for inhalation are manufactured in one of three ways: (1) the drug can be dissolved along with the lipid in the feed stock (23); (2) the drug can be suspended as crystals in the aqueous phase of the spray drying feed stock (286); or (3) creating excipient-only lipid particles (22). In the case of the suspended drug particles, the drug particles can in fact be partially dissolved, yielding a mixed phase feed stock (22,286). While the PulmoSphere® technology affords benefits over conventional formulations of suspension pMDIs, the spray drying process may not readily be utilized for compounds with low glass transition temperatures (e.g., glycopyrrolate), measureable propellant solubility (e.g., mometasone furoate), or detectable chemical lability (i.e., proteins and peptides). The excipient-only case overcomes challenges associated with drug stability during the spray drying process. In this case, the lipid microsphere excipient particles are combined with crystalline drug during preparation of the pMDI formulation (22). This approach greatly simplifies the process required to manufacture the PulmoSphere® particles.
Cromolyn sodium, albuterol sulfate, and formoterol fumarate PulmoSpheres\textsuperscript{\textregistered} have been effectively made with spray drying. While micronization leads to a broad range of particle size distributions and little control over morphology and density, engineering the drug into PulmoSpheres\textsuperscript{\textregistered} provides the opportunity to control these factors. PulmoSpheres\textsuperscript{\textregistered} can be engineered to enable delivery of a broad range of drug concentrations (10µg of formoterol fumarate to 1mg of cromolyn sodium) with decreased rate of phase separation and particle aggregation over a period of hours compared to commercial Intal\textsuperscript{\textregistered} CFC (a cromolyn sodium formulation) and Proventil\textsuperscript{\textregistered} HFA (an albuterol sulfate formulation) formulations (23). Furthermore, albuterol sulfate was formulated in $^{99m}$Tc-radiolabeled PulmoSphere\textsuperscript{\textregistered} particles in HFA 134a and was compared to Ventolin\textsuperscript{\textregistered} HFA (an albuterol sulfate formulation) in nine subjects using gamma scintigraphy. It was found that the lung deposition was doubled for the PulmoSphere\textsuperscript{\textregistered} formulation compared with the commercial product and oropharyngeal deposition was significantly reduced. In addition, distearoylphosphatidylcholine (DSPC)-coated budesonide microcrystals dispersed in HFA 134a were found to have residual MMADs of 3.2 to 3.4µm and did not present “loss of prime” concerns or variability in dose delivery over the course of the life of the vial (287). These proof-of-concept studies demonstrate potential advantages of PulmoSphere\textsuperscript{\textregistered} formulations over conventional suspension pMDI formulations. While, no PulmoSphere\textsuperscript{\textregistered} pMDI formulations have been approved, Tobi\textsuperscript{\textregistered} Podhale\textsuperscript{\textregistered}, a dry powder inhaler PulmoSphere\textsuperscript{\textregistered} tobramycin formulation, was approved in Europe in 2010 (288).
5.4. Excipients Used as Bulking Agents

Inherently, suspension pMDI formulations exhibit some degree of variable dosing behavior. Variability in dose delivery for suspension formulations can be caused by, among other things, (1) variable drug concentration because of drug deposition on the canister or valve surfaces; and (2) variable sampling of the formulation by the valve because of flocculation and creaming/settling (289). This behavior is especially apparent for low-dose formulations. One method to overcome dosing variability is to use bulking agents along with ethanol in the formulation (53,289). These bulking agents can be made of saccharides (e.g., lactose, maltose), amino acids (e.g., glycine, leucine) and salts (e.g., sodium chloride); however, most research has been conducted with α-lactose monohydrate (290,291). Whereas most suspension formulation approaches seek to reduce particle flocculation, this approach actually improves dosing reproducibility by greatly enhancing flocculation. Submicron bulking excipients are especially useful for forming a stable drug-excipient coflocculated matrix, which improves dosing reproducibility by minimizing the ability of the drug to migrate into and out of the valve metering volume (53). The underlying mechanism of how submicron lactose can be utilized as a bulking agent relies on the low sedimentation and high tendency of the submicron lactose to flocculate (271). Thus, the resulting effect is a suspension with a loosely flocculated matrix that houses the micronized drug and decreases the mobility of the drug in the formulation and can easily be redispersed upon shaking the vial. By minimizing the mobility of the drug particles, the bulking excipients minimize segregation of the drug in the formulation and thus ensure that the drug is, on the macroscopic level, uniformly
distributed in the canister. This allows for consistent sampling of the formulation by the valve. While submicron-sized lactose has received the most attention as a bulking agent, larger sized lactose (greater than 1μm in diameter) can also decrease drug adherence to the canister walls and valves while also increasing resistance to moisture ingress (292).

Submicron-sized lactose has been used to stabilize a micronized formoterol fumarate HFA suspension leading to long-term stability at room temperature and decreased dosing variability over the life of the pMDI while preventing loss of prime issues (53). L-leucine particles (38 to 125μm) have been used to stabilize albuterol sulfate suspensions and fluticasone propionate in HFA formulations (293,294). HFA formulations of albuterol sulfate and fluticasone propionate both had fewer irreversible drug agglomerates and increased FPFs when L-leucine was incorporated into formulation. A preferred process for making suspended bulking excipients is high pressure homogenization of a slurry of the micronized bulking agent in ethanol, until the desired size of the bulking agent is achieved (289). The slurry is then mixed with other components of the formulation to achieve the desired concentration of the drug and bulking agent. Formulations containing bulking excipient with particles with sizes between 100 and 200nm and excipient/drug ratios between 0.1:1 and 25:1 have been shown to result in stable pMDI suspensions (290). Lactose was found to have stronger cohesive effects with a model drug, sibenadet hydrochloride, compared with mannitol, resulting in more consistent FPF over the life of the inhaler; this suggests that the drug-excipient aggregation behavior plays a key role in the bulking agent’s utility (295).
6. Combination Drug pMDI Products

Frequently, there are therapeutic advantages with simultaneously administering two or three drugs in the same dose (i.e., combination drug product) because of synergistic effects of the different drugs (296). Combination therapies facilitate improved medication therapy adherence among patients. Chronic lung disease guidelines recommend treating severe COPD with a combination of inhaled medications, including long-acting β-agonists (LABA) and corticosteroids (CS). Furthermore, some evidence-based medicine suggests that combining these with a long-acting muscarinic antagonist (LAMA) will afford improved quality of life for patients due to complementary pharmacologic activities of these drugs (22,296).

There are several approaches used to formulate combination pMDI products. One such method currently being investigated involves tailored particle engineering by cocrystallizing two or more drugs (297). In this approach, a solution containing the drugs dissolved at the desired ratio is atomized and the droplets are collected in a crystallization vessel containing an antisolvent, while ultrasonic waves are utilized to induce nucleation and crystal growth. The solvent is then evaporated and micrometer-sized crystals are collected and delivered as suspension pMDIs. For this method, coformulating two physicochemically dissimilar drugs is especially challenging since the solubility of LABAs, LAMAs, and CSs can differ significantly relative to each other for a given solvent, thus making it difficult to find an appropriate solvent system and antisolvent for the crystallization technique. Alternatively, two or more drugs can be spray dried,
creating microparticles that contain both (or more) drugs. In this approach, the resulting particle may consist of crystalline, partially crystalline, and/or amorphous solids. Finally, two or three of the drugs can be formulated in an HFA system as a solution formulation. To formulate ipratropium, formoterol, and budesonide in HFA, the drugs were dissolved in the system using ethanol (26). The resulting formulation delivered 5µg ipratropium bromide, 2.25µg formoterol fumarate, and 80µg budesonide. The residual particle MMAD and GSD and FPF were identical for all three drugs. In addition, it is expected that the residual MMAD increases and the FPF decreases with the increase in nonvolatile concentration.

The most common approach being used in combination pMDIs is to develop suspension formulations in which the two drugs are both in the form of micronized, suspended drug particles. Combination suspension formulation approaches that have been used in marketed combination pMDI products include: (1) excipient-free suspensions (e.g., Advair® HFA, fluticasone propionate and salmeterol as a xinafoate salt); (2) using HFA soluble polymers, such as PEG and PVP as suspension stabilizers (e.g., Symbicort®, budesonide and formoterol fumarate dihydrate); or 3) using cosolvents, such as ethanol, to dissolve sufficient oleic acid to formulate a stable suspension (e.g., Dulera®, formoterol fumarate and mometasone furoate) (22).

In the aforementioned marketed approaches, the coformulation effect must be considered. When formulating a combination product of two drugs, the residual APSDs of the two drugs in the formulation are frequently different from each other. Moreover, this effect is generally dose dependent of the individual components of the pMDI
formulation, resulting in differing FPFs for the drugs in the combination product (22). For instance, Advair® HFA (available in 44/21, 110/21 and 220/21μg/actuation of fluticasone propionate/salmeterol in the form of a xinafoate salt) has a FPF of 48-52% for fluticasone propionate for the three strengths of fluticasone (44 to 220μg/actuation) and 63-75% for a fixed dose of salmeterol xinafoate. Whereas, fluticasone propionate, as monotherapy from Flovent®, at a dose range of 44 to 220μg/actuation yields a FPF of 41-50%. Thus, dose proportionality may not be achieved as a ratio of lung dose to the labeled dose as the individual strengths of the drugs in the combination pMDI increases.

Considerations of chemical interactions need to also be made when formulating a combination formulation. For instance, the interparticulate interactions for the two drugs found in Advair® and Symbicort® were found to be quite different, based on atomic force microscopy and Raman spectroscopy (298). It was found that budesonide and formoterol appeared as discrete particulates, whereas salmeterol and fluticasone appeared agglomerated once aerosolized and deposited on a cascade impactor plate. It was proposed that the drugs in Symbicort® interact with each other through weak van der Waals forces, while the drugs in Advair® interact with each other on a chemical level. The flocculation seen with the drugs in Advair® can potentially lead to a decrease in FPF, as the flocculates inherently have a larger aerodynamic diameter than that found for the individual drugs.

Pearl Therapeutics has enabled consistent aerosol performance of inhaled medication, regardless of if the drug(s) is/are emitted from a single-, double-, or triple-therapy product, thereby eluding the traditional coformulation effect (22,299). This
technology relies on the incorporation of drug-free microparticles into the suspension pMDI formulation. The phospholipid microparticles are made by spray drying from an aqueous emulsion containing perfluorooctyl bromide as the organic phase and DSPC and calcium chloride dispersed in the aqueous phase. Water and perfluorooctyl bromide are removed during the spray drying process resulting in microparticles of DSPC with calcium chloride. The microparticles are optimized for aerodynamic properties while designed to be ideal cosuspending agents for conventional drug crystals within suspension pMDIs. They are designed to have relatively large geometric particle size which maximizes the contact surface area for micronized drug particles, and the microparticles are porous thereby reducing the particle density, hence reducing the aerodynamic particle diameter. This technology involves cosuspending micronized drug crystals with the previously mentioned microparticles in HFA propellants, where the drug crystals are irreversibly associated with the porous DSPC and calcium chloride particles (299). Overall, this technology potentially offers the ability to match in vitro performance regardless of if the drug is delivered alone or in combination with other drugs.

The Pearl technology platform has been utilized for a variety of agents (22). It has been successfully utilized to formulate combinations of up to three drugs in a formulation, including a triple therapy of CS, LABA, and LAMA. For the triple therapy suspension pMDI, the FPF and the MMAD of the drug components assessed in the combination and as single components were comparable despite the 10-fold difference in dose between the drugs. The approach was found to be useful for pMDI suspension drug strengths ranging from 1 to 100µg/actuation. The technology has shown a linear
relationship between labeled dose and fine particle mass for glycopyrrolate suspension pMDI with doses ranging from 0.3 to 18µg/actuation (300). Within this range, the formulation was found to be stable in a 6-week temperature cycling study (between -5°C and 40°C) and in a 3-month accelerated stability study (at 40°C with 75% relative humidity).
7. Conclusions

Drug delivery via pMDIs has been a longstanding therapeutic modality for the treatment of respiratory diseases, such as asthma and COPD. Over the past two decades, pMDI formulation approaches have been reexamined primarily as a result of the transition from CFC to HFA propellants. The development efforts have led to not only new methods for formulating solution and suspension formulations, but they have also led to an increased understanding of critical formulation (and device) variables that influence the consistency and efficiency of the drug delivery. For example, while drug or excipient solubility in HFA systems may be enhanced by increasing ethanol concentration, this has a detrimental effect on atomization and droplet evaporation and thus has limited potential to increase the fine particle dose that can be delivered. It has also been found that the stability and dosing uniformity of suspension formulations have been improved through the use of a variety of surfactants, bulking agents, and phospholipid microparticles. Other formulation approaches, such as engineered drug-excipient particles or engineered excipient particles, are likely to expand the range of drugs that can be delivered from pMDIs and may enable sustained drug delivery. Expansion into new therapeutic areas, combination products, increased access to medication in developing markets and increasing cost pressures in developed markets will ensure that pMDIs will remain a mainstay in the treatment of pulmonary diseases for many years to come.
CHAPTER 4

METHODS FOR DETERMINING AERODYNAMIC PARTICLE SIZE DISTRIBUTION

Summary

Aerodynamic particle size distribution (APSD) is defined as a lognormal distribution of diameters of spherical particles with unit density having the same terminal settling velocity as the particles of interest. The APSD can be determined using a variety of particle sizing techniques, including cascade impactors, laser diffraction, time-of-flight, and microscopy. Among these techniques, particle sizing by cascade impactors is preferred, because it differentiates the APSDs of each active pharmaceutical ingredient (API) and nonvolatile excipient found within the formulation. In this chapter, cascade impactor theory is discussed thoroughly with the aid of Stokes’ equation. In addition, the Andersen Cascade Impactor (ACI) and Next Generation Impactor (NGI) are compared and an example of managing data from cascade impactor testing is also presented.
1. Definition of Aerodynamic Particle Size Distribution (APSD)

Aerodynamic particle size distribution (APSD) is of primary interest for inhalation researchers since it can be used as a metric to assess quality control between and within manufactured batches and in vivo drug delivery efficiency (301). APSD is a lognormal distribution of aerodynamic diameters. Aerodynamic diameter is defined as the diameter of a spherical particle with unit density having the same terminal settling velocity as the particle of interest. The aerodynamic diameter can be calculated from the particle of interest, by determining the volume-equivalent diameter and Stokes’ diameter, as shown in Figure 4.1 (302). The volume-equivalent diameter is the diameter of a sphere having the same volume as the irregularly shaped particle; it is utilized to determine the terminal settling velocity of the particle. The shape factor is the ratio of the actual drag force on the irregularly shaped particle relative to the drag force acting on a volume-equivalent particle. Since nonspherical particles are subject to larger drag forces as compared to their volume-equivalent spheres, they settle more slowly (302). The volume-equivalent sphere is not practical to discuss since it is difficult to experimentally determine. Thus, the Stokes’ particle is typically used in its place. The Stokes’ particle has a Stokes’ diameter, which is the diameter of a sphere with the same terminal settling velocity and density as the particle of interest. For spherical particles, the volume-equivalent diameter is equal to the Stokes’ diameter. The Stokes’ diameter can then be converted to the aerodynamic diameter using the equation presented in Figure 4.1.
The APSD is characterized by the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The MMAD is the aerodynamic diameter at which 50% of the aerosolized mass lies below (or above) the stated diameter. The GSD is a measure of the spread of data. The GSD for a given distribution is calculated using Equation 4.1, where $D_x$ is the diameter corresponding to the $x^{th}$-percentile within the lognormal distribution. A GSD of 1 implies that all of the particles within the sample have the same diameter and the sample is said to be monodispersed. A polydispersed sample has a GSD greater than 1, and the diameters of the particles lie within a given distribution and do not have the same diameters as each other. As a reference, a GSD of 2 implies that the diameter at the 84.1 percentile is four times the diameter at the 15.9 percentile within the distribution. Similarly, a GSD of 1.6 implies that the diameter at the 84.1 percentile is 2.56 times the diameter at the 15.9 percentile within the distribution.

\[
GSD = \frac{D_{50}}{D_{15.87}} = \frac{D_{84.13}}{D_{50}} = \sqrt{\frac{D_{84.13}}{D_{15.87}}} \quad \text{(Equation 4.1)}
\]
**Equations:**

\[
X = \frac{F_D}{F_{ve}} \\
V_t = \frac{\text{D}_{ve} \rho g C_c(D_{ve})}{18Xn} \\
C_c(D_x) = 1 + \frac{\lambda}{D_x} \left(2.34 + 1.05e^{-0.39D_x}\right) \\
D_{st} = \left(\frac{18V_n}{\rho g C_c(D_{st})}\right)^{1/2} = D_{ve} \left(\frac{C_c(D_{ve})}{XC_c(D_{st})}\right)^{1/2} \\
D_a = \left(\frac{18V_n}{\rho_o g C_c(D_a)}\right)^{1/2} = D_{st} \left(\frac{\rho}{\rho_o}\right)^{1/2} \left(\frac{C_c(D_{st})}{XC_c(D_a)}\right)^{1/2}
\]

**Symbols:**

- \(X\): Shape factor
- \(F_D\): Drag force on particle of interest
- \(F_{ve}\): Drag force on volume-equivalent particle
- \(V_t\): Terminal settling velocity
- \(D_{ve}\): Volume-equivalent diameter
- \(\rho\): Density of particle
- \(\rho_o\): Unit density
- \(g\): Gravitational acceleration
- \(C_c(D_x)\): Cunningham slip correction factor of \(D_x\)
- \(n\): Viscosity of air
- \(D_{st}\): Stokes’ diameter
- \(D_a\): Aerodynamic diameter
- \(\lambda\): Mean free path

**Figure 4.1:** Calculating aerodynamic diameter, \(D_a\), from an irregularly shaped particle. In this example, the irregularly shaped particle is a cube with a side length of 3.86\(\mu m\). The equations utilized for these calculations are also presented. For the calculations presented here, the Cunningham slip correction was assumed to be 1, since the diameters discussed are significantly greater than the mean free path of air molecules (\(\approx 65nm\)) (302).
2. Methods for Determining APSD

A multitude of methods have been developed to determine the APSD for an inhalation product: cascade impactors, laser diffraction, time-of-flight, and microscopy. While all of these methods are described briefly below, much attention is given to cascade impactors, since they are the instrument of choice for particle size characterization for aerosolized medications (301).

2.1. Cascade Impactors

Cascade impactors take advantage of impaction that permits segregation of particles into bins based on particle inertia, which is a function of the particle density, shape, and velocity. For all cascade impactors, an aerosol is passed through a nozzle and the output jet of aerosol particles in air is directed at a flat impaction (i.e., collection) plate, as seen in Figure 4.2. Many cascade impactors have a series of impaction plates. The plate deflects the air flow to form a 90° bend in the streamlines. The particles whose inertia exceeds a certain value are unable to follow the streamlines and result in impaction on the plate (301). Particles with less inertia remain airborne and can follow the airflow through the cascade impactor. Since the volumetric air flow through cascade impactors remain constant and the diameters of the nozzles in subsequent stages get smaller, the velocity of air through the nozzles increases at each stage, which permits collection of smaller particles as they achieve sufficient inertia to break away from the airflow, as presented in Figure 4.2 (B) (303,304). Aerosolized particles remain in the air
flow until a given particle’s inertia overcomes the air flow, at which point it deposits on the impaction plate. Particles that have sufficiently low inertia such that they are not collected on any impaction plate are eventually collected by a filter, downstream from the collection plates.

The Stokes’ number (Stk, see Equation 4.2), also known as the impaction parameter, is utilized to determine if a given particle with a known diameter and density, will impact on the collection plate (302). The Stokes’ number is the ratio of the stop distance to the diameter of the nozzle (D_n). The stopping distance is a function of the relaxation time of the particle (\tau), density (\rho) and diameter (D_p) of the particle, viscosity of the air (n), and the air flow velocity at the exit of the nozzle (U). As particle mass decreases, the Stokes’ number also decreases. A small Stokes’ number (i.e., Stk < 1) implies that the particle will adopt the air velocity very quickly; a large Stokes’ number (i.e., Stk > 1) implies that the aerosol particle will not readily adopt the air velocity and will follow its own trajectory leading to impaction on a collection plate.

\[
\text{Stk} = \frac{2\tau U}{D_n} = \frac{\rho D_p^2 U C_c(D_p)}{9 n D_n} \quad \text{(Equation 4.2)}
\]
Figure 4.2: Schematic of a generic cascade impactor where (A) depicts the air flow through the nozzle of the cascade impactor; and (B) depicts the flow of aerosolized particles through the cascade impactor.
The size at which a given impaction plate collects 50% of the mass entering is termed as the effective cutoff diameter, and it defines the calibration of the stage (i.e., the cutpoint) (301). The aerodynamic diameter for a given collection plate \(D_{a50}\) can be determined by Equation 4.3, which is a rearrangement of Equation 4.2, where \(\text{Stk}_{50}\) is the Stokes’ number at the corresponding diameter, \(N_n\) is the number of nozzles on the collection plate, and \(Q\) is the volumetric flow rate. Equation 4.3 is only valid if the nozzles are circular, which is the case for the two most commonly used cascade impactors in the pharmaceutical industry. A typical collection efficiency curves for an impaction plate is diagrammed in Figure 4.3, where the midway point of the curve at 50% defines the effective cutoff diameter. It is desired to have sharp cutpoints, such that all particles less than a given size are not collected, while those greater than that size are collected on the impactor plates. In reality, however, a small fraction of particles that are smaller than the effective cutoff diameter get collected while some larger particles continue onto subsequent stages. Cascade impactors that have relatively sharp cutpoints are desired, since these cutpoints define the sizes of particles collected on an impaction plate and affect the accuracy of calculated APSD.

\[
D_{a50} = \sqrt[\frac{27\text{Stk}_{50}\pi\pi D_n N_n}{4\rho QC_c(D_{a50})}}
\]

(Equation 4.3)

Particle sizing with the use of cascade impactors is preferred over any other particle sizing technique for pharmaceutical aerosols. While cascade impactor
experiments can be time and resource intensive, they afford the benefit of differentiating between multiple active pharmaceutical ingredients (API) and other components in a formulation (304,305). The most commonly used cascade impactors in the pharmaceutical industry are the Andersen Cascade Impactor (ACI) and the Next Generation Impactor (NGI), depicted in Figures 4.4 and 4.5, respectively. The ACI is an eight-stage vertical cascade impactor, while the NGI is a seven-stage impactor oriented horizontally. While the NGI is a newer and more expensive cascade impactor, it affords the following benefits compared to the ACI: (1) faster manual cycle time; (2) flexibility of operating at multiple flow rates without additional impactor stages; and (3) steeper stage efficiency curves (i.e., smaller GSD about the effective cutoff diameter) with minimal stage overlap (see Figure 4.6). Examples of other cascade impactors include the Marple-Miller Impactor, Multistage Liquid Impinger, Twin Stage Liquid Impinger, and the Micro-Orifice Uniform Deposit Impactor. Some of these alternative cascade impactors, including the NGI, offer gravimetric analysis, which permits avoiding the most time-consuming element of conventional cascade impactor testing (i.e., drug recovery and chemical analysis), but costs the researcher the ability to differentiate between drugs or drug and excipient within a given formulation (306).
Figure 4.3: Collection efficiency curve for an impaction plate, with an effective cutoff aerodynamic diameter of 5µm. The black line depicts the actual collection efficiency curve, while the blue line presents the ideal collection efficiency curve.
Figure 4.4: Schematic of the Andersen Cascade Impactor (ACI). The cutpoints for each stage are based on operation at 28.3L/min.
Figure 4.5: Schematic of the Next Generation Impactor (NGI). The cutpoints for each stage are based on operation at 30L/min.
**Figure 4.6:** Effective cutoff diameters and collection efficiency curves for (A) ACI operated at 28.3L/min, and (B) NGI operated at 30L/min. The vertical black dashed lines represent the cutpoints for stages 0 to 7 for the ACI and 1 to 7 for the NGI. The data in these graphs are presented as percentages and the area under each curve represents 100% of aerosolized particles with aerodynamic diameters equivalent to the corresponding cutpoint. Thus, the height of the peak increases as the width of the peak decreases. Wider peaks represent impaction plates with less defined cutpoints that have shallow efficiency curves and larger GSDs. The collection efficiency curves presented this way highlight the degree of overlap in particle size collection for a series of impaction plates. Data for this figure were originally published by Thermo-Electron (republished by Dunbar and Mitchell), and Marple et al. (307-309).
2.2. Laser Diffraction

Particle sizing by laser diffraction utilizes diffraction patterns of laser beams as they pass through an object ranging from nanometers to millimeters in diameter to determine a geometric diameter. For particles larger than 50µm in diameter, the Fraunhofer diffraction theory is used to determine particle size (310). The theory states that the intensity of light scattering by a particle is directly proportional to particle size, and the angle of the light beam is inversely proportional to particle size (306). Compared to small particles, large particles scatter relatively high intensity light at small angles relative to the laser beam; the scatter light intensity is then used to calculate a volume-equivalent diameter. For particles less than 50µm in diameter, Mie theory of light scattering is used to determine the particle size (310). Mie theory requires knowledge of optical properties of the sample and dispersant. While the refractive index of most dispersants are recorded in literature, the optical properties of the sample may need to be determined iteratively based on goodness-of-fit of modeled and actual data. Examples of particle sizing instruments that utilize laser diffraction include Malvern Spraytec, Malvern Zetasizer, Malvern Mastersizer, Shimadzu Particle Sizer (SALD series), and Sympatec Helos.

2.3. Time-of-Flight

Time-of-flight (ToF) technology provides real-time measurements of APSD. It involves accelerating particles in a nozzle. The lag between particle and gas velocities depends on the aerodynamic properties of the particle (311). The transit time of
accelerated particles between two laser beams is measured by a digital clock and stored in a multichannel accumulator (311). These times are then compared to a calibration curve, which relates aerodynamic diameter to each channel number, providing the APSD for the sample. Examples of particle sizing instruments that utilize the ToF technology include the TSI Aerodynamic Particle Sizer Spectrometer and TSI Aerosizer.

2.4. Microscopy

Microscopic evaluation is typically not utilized as a standard mode of particle sizing aerosolized particles due to the variability among users and techniques utilized and difficulty in sampling sufficient particles to determine the APSD (306,312). It is typically utilized to visually distinguish API from other nonvolatile excipients and examine morphology of residual particles. The slides are typically prepared by actuating the device and collecting the aerosolized particles on a microscope slide at some distance from the device. Alternatively, microscopy may also be utilized in conjunction with cascade impactors using filters in place of microscope slides (306). Typically, microscopy is utilized to identify non-drug and/or non-excipient particles that are inadvertently introduced into the product during manufacturing.
3. Data Analysis from Cascade Impactors

The primary benefit of using laser diffraction, ToF, or microscopy to determine the APSD is that these methods directly provide the particle size distribution, either geometric or aerodynamic, without any additional data manipulation or calculations. With cascade impactors, gravimetric or chemical analysis (typically by high performance liquid chromatography, HPLC) needs to be completed to determine the mass of API on each collection plate (see Figure 4.7). Thereafter, the data is fitted with a discrete or cumulative lognormal distribution to determine the MMAD and GSD for the aerosolized drug. The aerodynamic diameters versus cumulative percentage of mass less than the stated diameter can be plotted on a log-probability plot to determine the MMAD and GSD as depicted in Figure 4.7; alternatively, the data can be fitted by computer programs such as Chimera Technologies’ DistFit or MMAD Calculator (available at www.mmadcalculator.com) to determine the APSD.
**Figure 4.7:** Management of data derived from cascade impactor testing. In this case, the model data presented was derived experimentally from one ACI run at 28.3 L/min. The particle size data for determining the APSD can only be derived from the drug deposition within the cascade impactor, thus the mass of drug deposited on the stem, actuator, inlet, and jet are ignored for this analysis. The data can be handled as discrete mass or cumulative mass data. Graphs for both approaches are depicted with associated comments. Data points are labeled with the corresponding plate in red. Determining the MMAD and GSD can be accomplished by graphing the cumulative mass data on log-probability plot and fitting the data with a linear “best fit” line. The MMAD is the diameter at which the best fit line crossed 50% cumulative mass (red lines). Similarly, the GSD can be calculated based on Equation 4.1 using the green lines on the log-probability plot.

<table>
<thead>
<tr>
<th>ACI Part</th>
<th>Drug Recovered (µg/actuation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stem</td>
<td>2.38</td>
</tr>
<tr>
<td>Actuator</td>
<td>10.96</td>
</tr>
<tr>
<td>Inlet</td>
<td>12.12</td>
</tr>
<tr>
<td>Jet</td>
<td>0.18</td>
</tr>
<tr>
<td>Plate 0</td>
<td>0.26</td>
</tr>
<tr>
<td>Plate 1</td>
<td>0.12</td>
</tr>
<tr>
<td>Plate 2</td>
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<tr>
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<tr>
<td>Plate 4</td>
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</tr>
<tr>
<td>Plate 5</td>
<td>7.49</td>
</tr>
<tr>
<td>Plate 6</td>
<td>6.60</td>
</tr>
<tr>
<td>Plate 7</td>
<td>3.28</td>
</tr>
<tr>
<td>Filter</td>
<td>3.38</td>
</tr>
</tbody>
</table>

**Left of Purple Line:**
Mass of Drug on Plate 6 to Filter (F) = 13.26 µg

**Right of Purple Line:**
Mass of Drug on Plate 0 to Plate 5 = 9.73 µg
SECTION 2
DETAILS OF A SIMULATION MODEL FOR AERODYNAMIC PARTICLE SIZE DISTRIBUTIONS

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CHAPTER 5

DESCRIPTION OF THE SIMULATION ALGORITHM

Some excerpts are from: Modeling pMDI Delivery: A Priori Predictions, Empirical Models and Experiments

Published by: Stephen W. Stein, Poonam Sheth, Chris Karayiannis, Herbert Chiou, and Paul B. Myrdal


Summary

Predicting aerosol delivery from pressurized metered dose inhalers (pMDIs) can be accomplished using simple empirical equations derived from experiments or using a more complex a priori computational approach using fluid dynamics. In this chapter, an intermediate approach is described, which is rooted in the first principles of aerosol formation and aerosol evolution and deposition. This approach effectively simulates the aerodynamic particle size distribution (APSD) for a system with suspended drug/excipient and/or dissolved drug/excipient. It requires the user to define the formulation and the density of each component within the formulation and determine the size distribution of the initial droplets. Thereafter, individual droplets are modeled one at a time using random sampling from within user-specified distributions to determine the size of the initial droplet and the size of individual drug particles within a simulated atomized droplet. The number of suspended particles that each droplet contains is
determined by randomly selecting from within a Poisson distribution, which utilizes the number of particles per unit volume (PPUV) and then calculates the probability of having some number of suspended particles within a droplet. From this, the composition of the residual particle, which is deposited in the lungs, can be determined and the APSD of the formulation can be predicted. Details for each step of this Monte Carlo simulation are presented.
1. Introduction to Modeling (248)

Aerosol delivery from pressurized metered dose inhalers (pMDIs) is a complex process involving the discharge and atomization of a high pressure propellant-based formulation, rapid evaporation of the volatile formulation components, and significant fluid turbulence in the plume. While the underlying physics and thermodynamics of pMDI delivery have been investigated in significant detail (75,77), the ability to predict pMDI delivery is still limited. Several approaches have been evaluated for predicting aerosol delivery from pMDIs including simple empirical equations derived from experiments to more complex a priori computational approaches for solving aspects of the delivery process (e.g., computational fluid dynamics (CFD) for predicting droplet motion). In this chapter, an intermediate approach is described that predicts pMDI drug delivery based upon mathematical and statistical equations utilizing formulation data and empirical estimates of the size distribution of the initial atomized droplets. This approach can be used to predict pMDI delivery for multiple formulation configurations and has been demonstrated to effectively predict delivery from a wide variety of formulations including solutions, suspensions, combinations with one drug in solution and one in suspension, and novel solution formulations containing suspended excipient particles.

1.1. The Current State of the Art in Modeling pMDI Delivery

The simplest approach for modeling pMDI delivery involves the use of empirical models developed from experiments. Empirical equations have been developed for
predicting the MMAD as a function of dissolved nonvolatile concentration (84,204); the fine particle fraction as a function of nozzle diameter, valve size, and ethanol concentration (84,204); and the initial droplet diameter as a function of atomization conditions (75) or nozzle diameter, valve size, and ethanol concentration (204). While these models have proved to be useful for understanding the behavior of current systems, these approaches cannot be extrapolated to predict delivery for novel configurations and thus have limited application for identifying new innovations.

Despite increased understanding of the metering and atomization process in pMDIs, the ability to predict pMDI delivery a priori is still limited. Figure 5.1 describes the information required to predict pMDI delivery a priori. Pressurized MDI delivery can be considered to be divided into two stages: (1) “aerosol generation” and (2) “aerosol evolution and deposition”. In order to model the “aerosol generation” stage, mass transport equations are solved after separating the multi-phase formulation flow into three regimes: metering chamber flow, expansion chamber flow, and actuator nozzle flow (75,77). Accurate predictions of the time-resolved velocity and mass flow exiting the nozzle have been obtained using this approach, but have relied on empirical estimates of the initial droplet size (75,77) and thus are not true a priori predictions. Recently, alternative modeling approaches have been proposed to describe droplet breakup (313,314), but these have not yet been validated with experimental data to ensure that they accurately predict initial droplet distributions. Simulating the primary and secondary breakup of a simple liquid jet in air extends the limits of current computational power and two-phase flow theory (315). In addition, the presence of surfactant or suspended drug
may influence atomization, which further complicates predictions. Thus, while aspects of
the aerosol formation process can be effectively modeled, there are still significant
limitations preventing *a priori* prediction of the breakup of the formulation into droplets.

The “aerosol evolution and deposition” stage can currently be more readily
modeled *a priori* using existing CFD and related capabilities. However, extensive detail
on initial conditions (often not fully understood) are required. Complicating factors
include the fact that evaporation kinetics of the propellant(s) and cosolvent (if present)
are significantly influenced by evaporative cooling (316), the presence of dissolved
surfactant or drug, and the temperature and vapor concentration in the plume (317).

Droplet cooling may lead to water condensation and hygroscopic growth of residual
particles may occur in the humid airways. In addition, knowledge of drug particle shape
and packing are needed to predict aerodynamic behavior of residual particles containing
more than one suspended drug particle. Currently, aspects of “aerosol evolution and
deposition” stage can be predicted effectively (e.g., particle motion using CFD), but
complete prediction is not realistic due to computational limitations and insufficient
understanding of aspects of the process (e.g., dissolved surfactant or drug effects on
evaporation). Despite these limitations, CFD combined with empirical initial droplet size
estimates can provide useful predictions of aspects of pMDI delivery (318). However, the
time and expertise required for CFD modeling have prevented its widespread utilization.
Figure 5.1: Schematic representation of modeling of pMDI delivery from first principles (248).
1.2. A New Approach for Modeling the APSD Delivered from pMDIs

In this chapter, a new model is described for predicting the aerodynamic particle size distribution (APSD) delivered from pMDIs. The basis of this model is an algorithm that predicts the residual delivered aerosol based upon the formulation parameters, size of the input drug, and empirical data describing the initial size of the atomized droplets. This model expands on previous theoretical work (318-320) for predicting delivery from suspension pMDIs. However, it does not limit the analysis to monodispersed suspended drug particles, but allows for dissolved or suspended excipients, and a dissolved drug to be included in the model suspension formulation. Because the model can theoretically calculate the residual size distribution for a range of formulation types, it may be more useful than simple empirical equations and is much simpler to use than CFD or other computationally intensive models. The goal of this model is to provide a simple approach for rapidly studying the influence of formulation and hardware modifications on the APSD delivered from pMDIs.
2. Algorithm of Model

The Monte Carlo simulation utilized to model APSD from a variety of pMDI formulations is based on understanding the changes in atomized droplets as the volatile and semi-volatile components of the formulation evaporate to form residual particles. Thus, for thorough understanding of the logic utilized to model APSDs, it is imperative to revisit the atomization process for solution and suspension pMDIs, which was initially presented in Chapter 3.

2.1. Process Being Modeled

The model described henceforth seeks to model the droplet evolution process, presented in Figure 5.2, from effective initial droplets, which are the aerosolized droplets that form at the exit of the mouthpiece, to residual particles, which are devoid of propellant and any semi-volatile excipient and may deposit in the human lungs. Solution pMDI formulations contain dissolved drug(s), propellant, and other dissolved excipients, such as a cosolvent (commonly ethanol) or a surfactant (such as oleic acid) (321). Atomized droplets from solution formulations contain a representative amount of each component as that found in the bulk formulation. Over time, the propellant and some of the cosolvent evaporates; these droplets are termed “intermediate droplets.” Upon further evaporation of the cosolvent, “dry” spherical residual particles are formed, which are devoid of any volatile or semi-volatile excipients. These particles contain the dissolved drug and any other nonvolatile excipient in the formulation. Based on the size of the
initial droplets (mass median diameter of initial droplets, \( \text{MMD}_{\text{initial}} \)), it is possible to determine the residual particle size for dissolved drug (mass median aerodynamic diameter of residual particles, \( \text{MMAD}_R \)) in solution pMDIs (see Equation 5.1), which is dependent on the densities of the formulation (\( \rho_{\text{form}} \), see Equation 5.2) and the residual particles (\( \rho_R \), see Equation 5.3), and the weight fraction of nonvolatile concentration (\( C_{\text{NV}} \)) (204). The density of the formulation is calculated as the inverse of the sum of weight fraction concentration of a component \( i \) (\( C_i \)) divided by its density (\( \rho_i \)). The residual particle density is calculated using the weight fraction concentrations of the dissolved drug (\( C_{\text{soln}} \)) and dissolved nonvolatile excipient (\( C_{\text{excipient}} \)) and their respective densities (\( \rho_{\text{soln}} \) and \( \rho_{\text{excipient}} \)). Suspension pMDI formulations contain propellant, suspended drug(s) or excipient(s), and dissolved drug(s) or excipient(s). The droplet evolution process for suspension pMDI formulations is fairly similar to that of solution formulations, except for the contents of the initial droplet. For suspension formulations, the initial droplet may contain a varying number of suspended drug/excipient particles (i.e., 0, 1, 2, 3, etc.) along with a proportional amount of dissolved drug/excipients as that found in the bulk formulation. Given that each droplet may contain varying number of suspended drug particles, it is not surprising that the residual particles may be of different sizes and shapes depending on the number and size of each suspended drug/excipient within the particle.

\[
\text{MMAD}_R = (\rho_{\text{form}} \times C_{\text{NV}})^{1/3} \times \rho_R^{1/6} \times \text{MMD}_{\text{initial}}
\]  
(Equation 5.1)
\[ \rho_{\text{form}} = \left( \sum_{i=0}^{n} \frac{C_i}{\rho_i} \right)^{-1} \]  
(Equation 5.2)

\[ \rho_R = \frac{C_{\text{soln}} + C_{\text{excipient}}}{C_{\text{soln}} + C_{\text{excipient}}} \frac{\rho_{\text{soln}}}{\rho_{\text{excipient}}} \]  
Equation 5.3

2.2. Brief Overview of Model (248)

The algorithm for the Monte Carlo simulation used to model the process described in Figure 5.2 is presented in Figure 5.3. This simulation model is built in Microsoft Visual Basics for Applications and embedded in Microsoft Excel as a macroinstruction, which may be readily copied and used on multiple computers with either Windows or Mac operating systems. While this model can be utilized for a suspended excipient with a dissolved drug, for simplicity, the following discussion is based on assuming the suspended material is the drug.
Figure 5.2: Atomized pMDI droplet evolution model (316).
Initially, formulation information including concentration (% w/w), the micronized drug APSD, and the true density of each component and the size distribution of the initial droplets is defined by the user. Once the formulation information and initial atomized droplet size distribution are inputted, individual droplets are modeled one at a time using Steps 1 to 5 in Figure 5.3. The initial droplet size of a single droplet to be modeled is determined by selecting the droplet size in a statistically randomized fashion based on the input size distribution of the initial droplets (Step 1). Once the size of a given droplet is known, the number of suspended drug particles contained in the droplet is determined (Step 2). In order to do this statistical determination, the number of suspended particles in the formulation per unit volume (PPUV, #/mL) must be calculated using the input size distribution of the micronized suspended drug (mass median diameter, MMD\textsubscript{susp}, in µm), the mass of drug in the formulation (C\textsubscript{susp}, in g/mL), and Equation 5.4, which is modified from a previous study (4), where PPUV also depends on the geometric standard deviation (GSD\textsubscript{susp}) and density (ρ\textsubscript{susp}) of the suspended micronized material. Based on the droplet size and PPUV, the probability of having some number of suspended drug particles in the droplet can be determined using the Poisson statistical distribution function (318,319). A random number generator then selects the number of drug particles in the droplet based on these probabilities.

\[
PPUV = \frac{6C_{\text{susp}}6^{4.5}ln^2GSD_{\text{susp}}}{\rho_{\text{susp}}\pi(0.001MMD_{\text{susp}})^3}
\]  
(Equation 5.4)
**Figure 5.3:** Algorithm for simulation of suspension pMDIs.
The size of any suspended drug particles in the droplet is then determined by selecting drug particle sizes from the input size distribution of the bulk drug powder (provided by the user) in a statistically random fashion. The total volume of suspended drug particles is limited such that it cannot exceed the volume of the droplet (although this limit is rarely reached). Once the volume of the drug particles is known (Step 3), the mass and volume of dissolved drug and/or nonvolatile excipient (e.g., surfactant) is calculated based on the formulation details provided by the user (Step 4). Thus, by Step 4, the mass and volume of suspended drug particles, nonvolatile excipient, and solubilized drug in the droplet are known. From the information obtained in Step 4, the composition of the residual particle that remains after the propellant and cosolvent (if present) evaporate is determined. This information is used to calculate the aerodynamic diameter of the residual particle (Step 5). For residual particles with more than one drug particle, the shape factor was calculated using data from literature (322,323) using simplifying assumptions that the shape factor is independent of suspended particle size. For agglomerates with more than four drug particles, the particles were assumed to have a packing density factor of 0.741 – the packing density of closely packed spherical particles (323).

For a given pMDI configuration to be simulated, the algorithm in Figure 5.3 was executed until at least 10,000 droplets containing drug were obtained in order to provide statistically meaningful estimates of the size distribution (324). For most simulations (except those that had an extremely low percentage of droplets containing suspended drug particles and thus took much longer to model), at least 30,000 drug containing
droplets were modeled. An overall size distribution was calculated from all of the simulated droplets, using a statistical software that allows for fitting lognormal distributions.
3. Details of the Model

Each step outlined in the algorithm (Figure 5.3) is discussed in detail in this section. The discussion for each section includes detailed equations for the operation of the step as well as an example of the calculation for a simulation with 1.03% (w/w) albuterol sulfate, a model suspension drug, and 0.08% beclomethasone dipropionate, a model dissolved drug, in 8.1% (w/w) ethanol with HFA 134a. The micronized drug size for albuterol is 1.55µm MMD, with a GSD of 1.59. Table 5.1 presents the definitions for all the symbols utilized in the equations presented in this section.

3.1. Inputs

The inputs for this simulation program includes the formulation details (concentration, % w/w; and density, g/cm$^3$ (i.e., g/cc), of each component in the formulation), the raw micronized suspended drug’s particle size distribution, the initial droplets’ size distribution, and the number of droplets to simulate as presented in Figure 5.4. For the example presented in Figure 5.4, the formulation contains 1.03% (w/w) suspended drug (albuterol sulfate, $\rho_{\text{susp}} = 1.3g/cm^3$), 0.08% (w/w) dissolved drug (beclomethasone dipropionate, $\rho_{\text{soln}} = 1.25g/cm^3$), 8.1% (w/w) ethanol ($\rho_{\text{EtOH}} = 0.789g/cm^3$), and 90.79% HFA 134a ($\rho_{\text{HFA}} = 1.21g/cm^3$). For the purpose of further calculations, the concentration of each component found in the formulation is converted from % (w/w) to weight fraction.
The micronized APSD can be determined through some of the particle sizing techniques presented in Chapter 4. The raw micronized drug APSD can be entered in as the MMAD or MMD and the GSD. In the example in Figure 5.4, the model suspended drug has a MMAD\textsubscript{susp} of 1.77\(\mu\)m and a GSD (\(\sigma_g\), or GSD\textsubscript{susp}) of 1.59. The MMD of the suspended drug (MMD\textsubscript{susp}) can be calculated using Equations 5.5 and 5.6 with the help of the Solver function in Excel. For extremely small particles, the assumption of the Stokes’ law that the relative velocity of the gas at the surface of a small spherical particle is zero is not met (302). Thus, small particles settle faster than that predicted by Stokes’ law, because there is “slip” at the surface of the particles. The Cunningham slip correction of any particle with a diameter of \(D_x\) (Cc\((D_x)\)) is utilized to account for the noncontinuum effects on drag forces for small particles, whose size approaches the mean free path of the gas. Thus, the Cunningham slip correction has a significant impact in calculating the MMAD\textsubscript{susp} for micronized drug that is significantly smaller than 1\(\mu\)m (see Figure 5.5).

\[
\text{MMD}_{\text{susp}} = \sqrt[3]{\frac{\text{MMAD}_{\text{susp}}^2 \times \text{Cc}(\text{MMAD}_{\text{susp}})}{\rho_{\text{susp}} \times \text{Cc}(\text{MMAD}_{\text{susp}})}} 
\text{ (Equation 5.5)}
\]

\[
\text{Cc}(D_x) = 1 + \frac{1}{D_x} (0.1659 + 0.528e^{-8.33D_x}) 
\text{ (Equation 5.6)}
\]
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_g$</td>
<td>Geometric standard deviation</td>
<td>unitless</td>
</tr>
<tr>
<td>$\rho$</td>
<td>True density</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_0$</td>
<td>Unit density</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_C$</td>
<td>Calculated density of a cluster</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_{EtOH}$</td>
<td>True density of ethanol</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_{form}$</td>
<td>Calculated density of formulation</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_{HFA}$</td>
<td>True density of propellant</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_R$</td>
<td>Calculated density of residual particle</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_{soln}$</td>
<td>True density of dissolved drug or excipient</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\rho_{susp}$</td>
<td>True density of suspended drug or excipient</td>
<td>g/mL or g/cm$^3$</td>
</tr>
<tr>
<td>$\chi$</td>
<td>Shape factor</td>
<td>unitless</td>
</tr>
<tr>
<td>$C$</td>
<td>Concentration</td>
<td>weight fraction</td>
</tr>
<tr>
<td>$C_{EtOH}$</td>
<td>Concentration of ethanol</td>
<td>weight fraction</td>
</tr>
<tr>
<td>$C_{HFA}$</td>
<td>Concentration of propellant</td>
<td>weight fraction</td>
</tr>
<tr>
<td>$C_{soln}$</td>
<td>Concentration of dissolved drug or excipient</td>
<td>weight fraction</td>
</tr>
<tr>
<td>$C_{susp}$</td>
<td>Concentration of suspended drug or excipient</td>
<td>weight fraction</td>
</tr>
<tr>
<td>$Cc(D_X)$</td>
<td>Cunningham slip correction factor for diameter, $D_X$</td>
<td>unitless</td>
</tr>
<tr>
<td>CMD</td>
<td>Count median diameter</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>CMD$_{initial}$</td>
<td>Count median diameter of initial droplets</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>CMD$_{susp}$</td>
<td>Count median diameter of micronized suspended drug or excipient</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>$D_A$</td>
<td>Aerodynamic diameter</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>$D_c$</td>
<td>Diameter of a cluster</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>$D_{initial}$</td>
<td>Physical diameter of initial droplet</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>$D_{susp,i}$</td>
<td>Diameter of suspended drug particle, $i$</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>$D_X$</td>
<td>Some diameter</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>GSD</td>
<td>Geometric standard deviation</td>
<td>unitless</td>
</tr>
<tr>
<td>GSD$_{initial}$</td>
<td>Geometric standard deviation of initially atomized droplets</td>
<td>unitless</td>
</tr>
<tr>
<td>GSD$_{susp}$</td>
<td>Geometric standard deviation of micronized suspended drug or excipient</td>
<td>unitless</td>
</tr>
<tr>
<td>$M$</td>
<td>Average value for Poisson distribution</td>
<td>unitless</td>
</tr>
<tr>
<td>$M_R$</td>
<td>Mass of residual particle</td>
<td>g</td>
</tr>
<tr>
<td>$M_{soln}$</td>
<td>Mass of dissolved drug or excipient in a droplet</td>
<td>g</td>
</tr>
<tr>
<td>$M_{susp}$</td>
<td>Mass of suspended drug or excipient in a droplet</td>
<td>g</td>
</tr>
<tr>
<td>MMAD</td>
<td>Mass median aerodynamic diameter</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>MMAD$_{susp}$</td>
<td>Mass median aerodynamic diameter of suspended drug or excipient</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>MMD</td>
<td>Mass median diameter</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>MMD$_{susp}$</td>
<td>Mass median diameter of suspended drug or excipient</td>
<td>$\mu$m</td>
</tr>
<tr>
<td>OD</td>
<td>Actuator orifice diameter</td>
<td>mm</td>
</tr>
<tr>
<td>$P(I)$</td>
<td>Probability of having $I$</td>
<td>fraction</td>
</tr>
<tr>
<td>PPUV</td>
<td>Suspended drug particles per unit volume of the formulation</td>
<td>#/mL</td>
</tr>
<tr>
<td>$I$</td>
<td>Number of drug particles within a droplet</td>
<td>#</td>
</tr>
</tbody>
</table>
Table 5.1: List of Symbols in Equations Presented in Chapter 5, Section 3 (continued)

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>Volume</td>
<td>cm³</td>
</tr>
<tr>
<td>V_{liquid}</td>
<td>Difference in volumes of initial droplet and suspended drug or excipient</td>
<td>cm³</td>
</tr>
<tr>
<td>V_R</td>
<td>Volume of residual particle</td>
<td>cm³</td>
</tr>
<tr>
<td>V_{soln}</td>
<td>Volume of dissolved drug or excipient in droplet</td>
<td>cm³</td>
</tr>
<tr>
<td>V_{sup}</td>
<td>Volume of suspended drug or excipient in droplet</td>
<td>cm³</td>
</tr>
<tr>
<td>V_{void}</td>
<td>Volume of void space in residual particle</td>
<td>cm³</td>
</tr>
<tr>
<td>VS</td>
<td>Metering valve size</td>
<td>µL</td>
</tr>
</tbody>
</table>
**Figure 5.4**: Screen shot of the user interface with input variables.
Figure 5.5: Cunningham slip correction factor.
The effective initial atomized droplet size distribution is also one of the parameters inputted by the user. This can be determined experimentally using phase-Doppler particle analysis (325) or by including a dissolved drug in the formulation and calculating the initial droplet distribution based on measurements of the residual particle distribution (204). Alternatively, empirical equations can be used which take into account the formulation and hardware configurations (75,204). One such equation was used to determine the mass median diameter of the initial droplet (MMD_{initial}) for the example presented in Figure 5.4 (see Equation 5.7), where the valve size (VS) is 50μL and the actuator orifice diameter (OD) is 0.3mm, resulting in an MMD_{initial} of 10.66μm. The GSD (σ_g, or GSD_{initial}) was determined to be 1.8 based on previous studies (204).

Many times, the user inputted parameters are not known accurately due to limitations in experimentally measuring these variables. The tolerance for each inputted variable will be discussed in great detail in Chapter 6.

Finally, the number of droplets to simulate must also be entered prior to the start of the simulation. Increasing the number of droplets simulated increases the precision of the simulated APSD estimation, as presented by Stein (326) and in Figure 5.6. In the example presented above, 10,000 droplets will be simulated. The number of droplets to simulate can be between 1 and 65,501 for Excel 2003 and between 1 and 1,048,541 for Excel 2007 and newer versions.
**Figure 5.6:** Effect of number of droplets simulated on the APSD estimation for suspended drug. Six simulations were completed with a given number of droplets. The average MMAD for the residual particles is presented in red.
Step 1: Determine Size of Initial Atomized Droplets

Once the user has provided the above information, each atomized droplet is simulated individually until sufficient droplets have been modeled. The first step requires determining the geometric size of the initial atomized droplet in a statistically random fashion from within the user-defined lognormal droplet distribution. In order to do this, the MMD\text{initial} must be converted to the count median diameter (CMD\text{I}), using the Hatch-Choate equation for converting MMD to CMD (see Equation 5.8) (302). While the concept of mass-weighted distribution is useful in the discussion of drug delivery, it gives a misleading impression in the discussion of particle size since, for a polydispersed aerosol, a large amount of mass is carried by a small number of drug particles. The CMD is the median physical diameter of a distribution. Since the initial droplets are assumed to be lognormally distributed, converting the MMD\text{initial} to the CMD\text{initial} does not change the GSD\text{I}. The mass-weighted and count-weighted probability density functions for the example presented in Section 3.1 are diagramed in Figure 5.7, where the count-weighted probability density function is subsequently converted to a cumulative probability function.

\[
\text{CMD} = \text{MMD} \times e^{-3\ln^{2}\text{GSD}}
\]  

(Equation 5.8)
A uniform 0 to 1 random number generator is used to determine the size of the atomized droplet. The random number, R, corresponds to a cumulative probability value, where an R-value close to 0 results in the selection of a very small droplet, an R-value close to 1 results in the selection of a very large atomized droplet, and an R-value of 0.5 corresponds to the median droplet (which, for this example, is 3.78µm). For the first droplet simulated, in the example, the R-value of 0.78 was recovered, which corresponds to an initial droplet size of 7.914µm.
Figure 5.7: Mass- and count-weighted distribution for initial atomized droplets with an MMD\textsubscript{initial} of 10.66µm and GSD\textsubscript{initial} of 1.8. For the first droplet simulated, the R-value is 0.78, which corresponds to an initial droplet size of 7.914µm (as presented by the red dashed line on the graph on the bottom).
3.3. Step 2: Determine Number of Suspended Drug Particles in Droplet

The number of suspended drug particles in an atomized droplet is determined using the Poisson distribution (see Equation 5.9), where P(I) is the probability of I number of drug particles in a droplet and M is the product of volume of the initial droplet (assumed to be a sphere, determined using Equation 5.10) and number of particles per unit volume, (PPUV, determined using Equation 5.4, which can also be written as Equation 5.11), which gives the average number of drug particles in a droplet of a specific size. It is assumed that M is known and constant for a given droplet and that each droplet’s contents are independent of other droplets. In addition, the cumulative probability of the Poisson distribution is determined by a uniformly distributed random number, R, between 0 and 1, which in turn determines I.

\[
P(I) = \frac{e^{-M} \times M^I}{I!} \quad \text{(Equation 5.9)}
\]

\[
V = \frac{1}{6} \pi D_{\text{initial}}^3 \quad \text{(Equation 5.10)}
\]

\[
\text{PPUV} = \frac{6 \times C_{\text{susp}} \times e^{4.5\ln^2 GSD_{\text{susp}}} \times \rho_{\text{form}}}{\pi \times (0.0001 \times MMD_{\text{susp}})^3 \times \rho_{\text{susp}}} \quad \text{(Equation 5.11)}
\]

For the example presented in this chapter, the PPUV for the formulation is 1.241 \times 10^{10} \text{ particles/mL} and the volume of the first droplet simulated is 2.596 \times 10^{-10} \text{ cm}^3,
which results in \( M \) equal to 3.222 and a Poisson cumulative probability function as displayed in Figure 5.8. For the first droplet, the \( R \)-value selected in a statistically random fashion corresponds to an \( I \)-value of 4. Thus, the first droplet with a diameter of 7.914\( \mu \)m will contain four suspended drug particles. The \( M \)-value may change with subsequent simulated droplets. The effect of changing the \( M \)-value for the Poisson distribution for initially atomized droplets with diameters of 6.914\( \mu \)m (\( M = 2.15 \)) and 8.914\( \mu \)m (\( M = 4.60 \)) is presented in Figure 5.9. Increasing the atomized droplet size while fixing the PPUV results in decreasing the steepness of the Poisson cumulative distribution function, thereby indicating that droplets with a relatively large diameter can contain a greater number of suspended drug particles than droplets with a smaller diameter. Similarly, increasing the PPUV would also increase the \( M \)-value, resulting in an increased propensity for droplets to contain a greater number of drug particles.
Figure 5.8: Poisson distribution for a droplet with $M = 3.22$. The probability density function, in navy blue dotted line is presented on the left axis, with the cumulative distribution function in bold red line is presented on the right axis. For the example presented in this chapter, the $R$-value for the first droplet is 0.793, which corresponds to four suspended drug particles within the atomized droplet.
**Figure 5.9:** Poisson distribution functions for droplets with diameters of 6.914\(\mu\)m (top) and 8.914\(\mu\)m (bottom).
3.4. Step 3: Determine Volume and Mass of Suspended Drug Particles in Droplet

Now that the number of drug particles contained within a particular droplet is known, it is possible to determine the diameter, volume, and mass of each suspended drug particle. To determine the diameter of a given suspended drug particle, the raw micronized drug MMD, MMD\textsubscript{susp}, is converted to a count-weighted distribution, CMD\textsubscript{susp}, using Equation 5.8. The CMD\textsubscript{susp} is then converted to a cumulative probability function and a statistically random number, R, is selected between 0 and 1, which corresponds to the diameter for a given suspended drug particle, similar to how an initial droplet diameter is selected from within the user-defined distribution (as presented in Section 3.2, Step 1 of the algorithm). This function is done iteratively until all of the drug particles have been assigned a diameter. Thereafter, the volume of each suspended drug particle is calculated based on the statistically random selection of diameters and the assumption that the drug particle is spherical. Finally, for this step, the mass of the suspended drug particles is determined using Equation 5.12.

\[
M_{\text{susp}} = \rho_{\text{susp}} \times \left( \sum_{l=1}^{n} \frac{\pi}{6} \times D_{\text{susp}}^3 \right)
\]  
(Equation 5.12)

Based on the Poisson distribution, it was determined that the first atomized droplet contains four suspended drug particles. Figure 5.10 presents the R-values randomly selected for the four suspended drug particles and the resulting diameters of the
4 drug particles. The volume of the drug particles ($V_{\text{susp}}$) is $1.923 \times 10^{-12}\text{cm}^3$ and the mass of the four particles ($M_{\text{susp}}$) is $2.500 \times 10^{-12}\text{g}$.

If the volume of the suspended drug particles is greater than that of the simulated droplet, the volume of the suspended drug particles is assumed to be equal to that of the simulated droplet. This rule is termed as the “volume exclusion rule,” and it will be evaluated in more detail in Chapter 7.
**Figure 5.10:** Example of statistical selection of the size of the suspended drug particles contained within an atomized droplet.
3.5. Step 4: Determine Volume and Mass of Dissolved Drug or Excipient in Droplet

Up through Step 3, in Figure 5.3, the composition of the formulation, size of initial droplet, number of suspended drug particles contained within the droplet, and the total volume and mass of the suspended drug particles within the droplet has been quantified. The atomized droplet contains some volume occupied by the suspended drug particles and the remaining volume ($V_{\text{liquid}}$) contains the propellant, cosolvent, and dissolved drug or excipients at relative concentrations as that found in the bulk formulation. Thus, the mass and volume of the dissolved drug or excipient can be calculated using Equations 5.13 and 5.14, where $C_{\text{soln}}$, $M_{\text{soln}}$, $V_{\text{soln}}$, and $\rho_{\text{soln}}$ are defined as the concentration (weight fraction), mass (g), volume (cm$^3$), and density (g/cm$^3$) of the component(s) in solution, respectively, which may be dissolved drug and/or nonvolatile dissolved excipients. In the case of the example developed though this section, the volume of the liquid is $2.577 \times 10^{-19}$ cm$^3$, thus the resulting volume of dissolved beclomethasone dipropionate is $1.926 \times 10^{-13}$ cm$^3$, which is equivalent to $2.407 \times 10^{-13}$ g.

$$M_{\text{soln}} = C_{\text{soln}} \times \rho_{\text{soln}} \times (V_{\text{initial}} - V_{\text{susp}})$$  \hspace{2cm} (Equation 5.13)

$$V_{\text{soln}} = \frac{M_{\text{soln}}}{\rho_{\text{soln}}}$$  \hspace{2cm} (Equation 5.14)
3.6. Step 5: Determine Aerodynamic Diameter of Residual Particle

The aerodynamic diameter ($D_A$) for each residual particle is calculated using the volume equivalent diameter and the density of the residual particle (see Figure 5.11). Furthermore, based on the number of drug particles in a given droplet, a correction factor, known as a shape factor ($\chi$), and packing density are considered. The shape factor accounts for the deviation from a spherical residual particle if greater than one drug particle is within that droplet; these values can be found in Table 5.2. Previous work on shape factors and their effect on drag resistance has been done by YS Cheng et al. and CN Davis (322,323). YS Cheng’s group measured the dynamic shape factor parallel to air flow experimentally by using various sized monodispersed polystyrene latex spheres in an aqueous suspension by nebulization. However, due to the experimental limitation of the testing methods, they only reported the shape factors for up to and including four particles. On the contrary, CN Davis developed a theoretical model for determining shape factor, which is utilized in this model for droplets containing five or more drug particles. In addition, the packing density, a factor of 0.741, is also utilized; it accounts for the difference in residual particle density based on void volume that is not occupied by the suspended drug particles. The shape factor is assumed to be one if the volume of the dissolved drug exceeds the void volume of the aggregate of suspended drug particles for a given residual particle.
Table 5.2: Shape Factors Utilized in Calculating Aerodynamic Diameters

<table>
<thead>
<tr>
<th>Number of Drug Particles</th>
<th>Shape Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.022</td>
</tr>
<tr>
<td>3</td>
<td>1.08</td>
</tr>
<tr>
<td>4</td>
<td>1.12</td>
</tr>
<tr>
<td>5</td>
<td>1.07</td>
</tr>
<tr>
<td>6</td>
<td>1.05</td>
</tr>
<tr>
<td>7</td>
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<td>1.1</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
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<tr>
<td>10</td>
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<td>1.14</td>
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<td>13</td>
<td>1.12</td>
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<td>1.13</td>
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<td>15</td>
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<td>18</td>
<td>1.14</td>
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<tr>
<td>19</td>
<td>1.14</td>
</tr>
<tr>
<td>20</td>
<td>1.13</td>
</tr>
<tr>
<td>21</td>
<td>1.11</td>
</tr>
<tr>
<td>≥22</td>
<td>1.1</td>
</tr>
</tbody>
</table>
Figure 5.11: Flow chart and equations for calculating aerodynamic diameter for residual particles.
For the example developed in this section, the $V_{\text{susp}}$ was calculated as $1.923 \times 10^{-12}\text{cm}^3$ and the $V_{\text{void}}$ was determined to be $4.981 \times 10^{-13}\text{cm}^3$, which is greater than $V_{\text{soln}}$ ($1.926 \times 10^{-13}\text{cm}^3$). Thus, the right branch of Figure 5.11 was used to determine the diameter ($D_c$) and density ($\rho_c$) of the cluster, which was later utilized to determine the $D_A$, in an iterative fashion using Solver function in Visual Basics and 1.12 as the X. The $D_A$ of this residual particle was calculated to be 1.713$\mu$m.

3.7. Calculate Aerodynamic Particle Size Distribution from Simulation

Once sufficient droplets have been simulated, data from the output table, presented as Table 5.3, can be used to summarize the aerosolized mass data into twenty bins based on 5% intervals for the range of aerodynamic diameters simulated. To determine the APSD of the dissolved drug, “the mass of dissolved drug” column is utilized for the mass versus aerodynamic diameter data. To determine the APSD of the suspended drug, the “mass of suspended drug particles” data is utilized. The APSD can be determined by (1) plotting cumulative aerosolized mass for the dissolved or suspended drug versus aerodynamic diameter, as presented in Figure 5.12, to determine the diameter corresponding to the 50th-percentile and the GSD; (2) using lognormal statistical data fitting software; or (3) using online data fitting programs such as that available at www.mmadcalculator.com.
### Table 5.3: Output Table from Simulation for Example Presented in Chapter 5

<table>
<thead>
<tr>
<th>Diameter of Droplet (µm)</th>
<th>Droplet Volume (cm(^3))</th>
<th>Number of Suspended Drug Particles in Droplet</th>
<th>Volume of Suspended Drug Particles (cm(^3))</th>
<th>Mass of Suspended Drug Particles (g)</th>
<th>Mass of Dissolved Drug (g)</th>
<th>Volume of Dissolved Drug (cm(^3))</th>
<th>Mass Of Residual Particle (g)</th>
<th>Aerodynamic Diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.914</td>
<td>2.596E-10</td>
<td>4</td>
<td>1.923E-12</td>
<td>2.500E-12</td>
<td>2.407E-13</td>
<td>1.926E-13</td>
<td>2.741E-12</td>
<td>1.713</td>
</tr>
<tr>
<td>1.704</td>
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<td>2.423E-15</td>
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<td>0</td>
<td>0</td>
<td>5.191E-15</td>
<td>4.153E-15</td>
<td>5.191E-15</td>
<td>0.223</td>
</tr>
<tr>
<td>2.621</td>
<td>9.425E-12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.807E-15</td>
<td>7.046E-15</td>
<td>8.807E-15</td>
<td>0.266</td>
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<tr>
<td>2.520</td>
<td>8.378E-12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>7.829E-15</td>
<td>6.26E-15</td>
<td>7.829E-15</td>
<td>0.256</td>
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<tr>
<td>1.447</td>
<td>1.587E-12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.483E-15</td>
<td>1.187E-15</td>
<td>1.483E-15</td>
<td>0.147</td>
</tr>
<tr>
<td>1.480</td>
<td>1.69E-12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.586E-15</td>
<td>1.268E-15</td>
<td>1.586E-15</td>
<td>0.150</td>
</tr>
<tr>
<td>7.751</td>
<td>2.438E-10</td>
<td>7</td>
<td>2.743E-12</td>
<td>3.566E-12</td>
<td>2.252E-13</td>
<td>1.802E-13</td>
<td>3.791E-12</td>
<td>1.871</td>
</tr>
<tr>
<td>6.321</td>
<td>1.322E-10</td>
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<td>0</td>
<td>0</td>
<td>1.235E-13</td>
<td>9.887E-14</td>
<td>1.235E-13</td>
<td>0.641</td>
</tr>
<tr>
<td>7.973</td>
<td>2.653E-10</td>
<td>2</td>
<td>1.027E-12</td>
<td>1.335E-12</td>
<td>2.470E-13</td>
<td>1.976E-13</td>
<td>1.582E-12</td>
<td>1.493</td>
</tr>
<tr>
<td>3.865</td>
<td>3.023E-11</td>
<td>1</td>
<td>2.787E-14</td>
<td>3.624E-14</td>
<td>2.822E-14</td>
<td>2.258E-14</td>
<td>6.446E-14</td>
<td>0.518</td>
</tr>
</tbody>
</table>
Figure 5.12: The APSD of simulated (Sim) beclomethasone dipropionate (BDP, blue) and albuterol sulfate (AS, pink) for the example presented in this chapter. The red line indicates the aerodynamic diameter corresponding to the 50th-percentile, which is the mass median aerodynamic diameter for the distribution. The geometric standard deviation can also be determined from this graph, based on the methods described in Chapter 4.
CHAPTER 6
TOLERANCE OF INPUT PARAMETERS FOR SIMULATION MODEL

Summary

The inputted variables for the simulation model described in Chapter 5 include details of the initially atomized droplet size distribution and formulation. It is especially important to provide accurate details about the formulation, such as the concentration and density of each component and the particle size distribution of the suspended micronized material, in order improve the precision of the simulated aerodynamic particle size distribution (APSD). While many of these variables are extensively discussed in Section 3 (Chapters 8 to 11) of this dissertation, some of the variables are discussed in this chapter, with the intent of highlighting the extent to which some of these variables can be changed while having minimal impact on the resulting APSD. Of the properties evaluated, herein, it was found that minor changes in concentration of cosolvent and density of suspended material have the greatest impact in determining the APSD of dissolved and/or suspended drugs and/or excipients.
1. List of Input Variables

A primary assumption of the simulation model presented in Chapter 5 is that the inputted formulation information and initial droplet size distribution is precise for the pressurized metered dose inhaler (pMDI) formulation being modeled. In reality, however, it is difficult to provide an accurate account of the formulation and initial droplet parameters. Knowledge of the tolerance, defined as the permissible amount of variation, for a specific parameter provides users with the confidence that reasonable estimates of input parameters does not significantly change the simulated aerodynamic particle size distribution (APSD) for a given pMDI. This chapter and Section 3 of this dissertation further evaluate the user-defined variables needed to successfully simulate droplets from a suspension pMDI based on what was briefly introduced in Chapter 5. All of the input variables for the simulation model are listed in Table 6.1, along with additional chapters to review for more detail on each variable. Only select variables will be discussed in this chapter.
Table 6.1: List of Input Variables for Simulating the APSD of Suspension pMDIs

<table>
<thead>
<tr>
<th>Input (User-defined) Variables</th>
<th>Chapters for More Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Droplet Size Distribution</strong></td>
<td></td>
</tr>
<tr>
<td>Initial droplet mass median diameter (MMD)</td>
<td>Chapters 9 and 10</td>
</tr>
<tr>
<td>Initial droplet geometric standard deviation (GSD)</td>
<td>Chapter 9</td>
</tr>
<tr>
<td><strong>Volatile Propellant</strong></td>
<td></td>
</tr>
<tr>
<td>Propellant concentration</td>
<td>Chapter 6</td>
</tr>
<tr>
<td>Propellant density</td>
<td>Chapter 6</td>
</tr>
<tr>
<td><strong>Semi-volatile Cosolvent</strong></td>
<td></td>
</tr>
<tr>
<td>Cosolvent concentration</td>
<td>Chapter 6</td>
</tr>
<tr>
<td>Cosolvent density</td>
<td>Chapter 6</td>
</tr>
<tr>
<td><strong>Nonvolatile dissolved drug or excipient</strong></td>
<td></td>
</tr>
<tr>
<td>Dissolved drug or excipient concentration</td>
<td>Chapters 6 and 11</td>
</tr>
<tr>
<td>Dissolved drug or excipient density</td>
<td>Chapter 6</td>
</tr>
<tr>
<td><strong>Nonvolatile suspended drug or excipient</strong></td>
<td></td>
</tr>
<tr>
<td>Suspended drug or excipient concentration</td>
<td>Chapters 8, 9, 10, and 11</td>
</tr>
<tr>
<td>Suspended drug or excipient density</td>
<td>Chapter 6</td>
</tr>
<tr>
<td>Suspended drug or excipient mass median diameter (MMD)</td>
<td>Chapters 8, 9, 10, and 11</td>
</tr>
<tr>
<td>Suspended drug or excipient geometric standard deviation (GSD)</td>
<td>Chapter 6</td>
</tr>
</tbody>
</table>
2. Properties of Volatile and Semi-volatile Components

For the simulation program presented in Chapter 5, the volatile and semi-volatile components include the propellant(s) and cosolvent(s). Both of these components affect the atomization process, as described in Chapter 3, and impact the size of the initial droplets. Typically, decreasing the vapor pressure of the system leads to an increase in the effective initial droplet, which impacts the residual APSD for dissolved and suspended drug from pMDIs, as described in Chapters 9 and 10. For the purpose of this simulation model, the concentration (as % w/w) and density of the propellant(s) and the cosolvent(s) are used primarily to determine the inputted distribution of the initially atomized droplets (if an empirical approach is utilized by the user) or to determine the density of the formulation. The density of the formulation is utilized to determine the number of suspended drug particles per unit volume (PPUV) of formulation (see Equation 5.11). Increasing the density of the formulation leads to a proportional increase in the PPUV for the given formulation.

Since the concentration and density of volatile component(s) of a pMDI formulation is treated in the same manner in the simulation model as that of the semi-volatile component(s), only the effect of changing the concentration and density of a semi-volatile cosolvent is evaluated. The effects seen by modulating these two properties would be the same as using a different propellant and changing the concentration of the propellant. These effects are presented in Figures 6.1 and 6.2, for a formulation containing 0.4% (w/w) suspended or dissolved drug with a density of 1.2g/cm$^3$. As seen
in Figure 6.1, increasing the density of the cosolvent from 0.6 to 1.4g/cm³ has minimal impact on the simulated residual particle mass median aerodynamic diameter (MMAD) for formulations containing dissolved drug. However, increasing the concentration of the cosolvent from 0 to 16% (w/w) increases the residual particle MMAD by 0.35 ± 0.04µm, which is approximately 22% increase in MMAD with 16% cosolvent compared to formulations without cosolvent. This increase is related to the increase in initial droplet mass median diameter (MMD) with increase in cosolvent concentration.

The residual particle MMADs for suspension pMDIs not only exhibit dependence on the concentration of the cosolvent, but also, albeit to a minute extent, dependence on the density of the cosolvent, as presented in Figure 6.2. Increasing the concentration of cosolvent from 0 to 16% (w/w) increases the residual particle size by 0.17 ± 0.022µm, which is approximately 5.7% increase in MMAD. This increase in residual particle MMAD is less than that seen with increasing cosolvent concentration with solution pMDI formulations, indicating that suspension pMDI formulation APSD is less sensitive to changes in initial droplet size than that seen with solution formulations (as discussed in detail in Chapter 9). Increasing the density of the cosolvent from 0.6 to 1.4g/cm³ increases the residual particle MMAD by 0.0057µm (0.18%), 0.016µm (0.50%), 0.028µm (0.87%), and 0.053µm (1.7%) for formulations with 4%, 8%, 12%, and 16% (w/w) cosolvent, respectively. It is not surprising that increasing the density of the cosolvent has a greater impact on the residual particle MMAD for formulations with a relatively large amount of cosolvent. This occurs because increasing the proportion of the cosolvent allows the density of the cosolvent to have a greater impact on the density of
the formulation, thereby increasing the PPUV. Increasing the PPUV increases the propensity for simulated droplets to contain multiple suspended drug particles, which leads to increasing the overall residual particle MMAD for a given formulation.
Figure 6.1: The impact of changing cosolvent concentration and density on residual particle mass median aerodynamic diameter (MMAD) for dissolved drug. This formulation contains 1,1,1,2-tetrafluoroethane (HFA 134a) with 0.4% (w/w) dissolved drug with a density of 1.2g/cm³.
Figure 6.2: The impact of changing cosolvent concentration and density on residual particle mass median aerodynamic diameter (MMAD) for suspended drug. This formulation contains HFA 134a with 0.4% (w/w) suspended drug with a density of 1.2g/cm³ and micronized drug size of 2.5µm mass median diameter (MMD) (geometric standard deviation, GSD, of 1.4).
3. Dissolved Drug or Excipient Properties

The nonvolatile dissolved drug or excipient properties detailed by the user include the concentration and the density of the dissolved drug and/or nonvolatile excipient. The concentration and/or density of the dissolved drug or excipient play a role in determining the density of the formulation (used to calculate the PPUV), residual particle aerodynamic diameter, and dissolved drug APSD.

3.1. Concentration of Dissolved Drug or Excipient

A comparison of the simulated and experimental residual particle MMAD for 78 1,1,1,2-tetrafluoroethane (HFA 134a) solution formulations is depicted in Figure 6.3. The formulations modeled contained 0.01 to 6.7% (w/w) dissolved drug and/or nonvolatile excipient with 0 to 20% (w/w) ethanol, and an actuator orifice diameter of 0.14 to 0.42mm. These formulations contained cyclosporine, beclomethasone dipropionate, budesonide, ipratropium bromide, or celecoxib frequently with glycerol or polyethylene glycol 400. All formulations were fitted with 50µL metering valves. Equation 5.7 was utilized to calculate the initial droplet size distribution for the simulated residual MMAD values. The experimental residual MMAD determined by Aerodynamic Particle Sizer (APS) or the Andersen Cascade Impactor (ACI) have excellent agreement to the simulated data, with the data centered around the line of unity with a $R^2$ value of 0.95. The effect of the concentration of dissolved drug or excipient in combination
formulations that contain a drug or excipient in solution and suspension is discussed in detail in Chapter 11.

### 3.2. Density of Dissolved Drug or Excipient

The density of the dissolved drug or excipient is used to calculate the mass of the dissolved entity found in a simulated droplet, the aerodynamic diameter for a given droplet, and the PPUV for a formulation. Increasing the density of the dissolved nonvolatile drug or excipient increases the calculated mass of the dissolved entity found in a droplet, since the difference between the volumes of the initial droplet and the volume of suspended drug particles is used to calculate the volume and thereby the mass of the dissolved entity. Increasing the density of the dissolved drug or excipient increases the resulting APSD of the dissolved drug/excipient, as presented in Figure 6.4 for simulated pMDI solution formulations containing 0.4% (w/w) dissolved drug and 8% (w/w) ethanol in HFA 134a. For this example, doubling the density of the dissolved drug (from 0.8 to 1.6g/cm$^3$) increased the MMAD by 12.5% (from 1.692 to 1.903µm) without impacting the GSD (1.79 for a density of 0.8g/cm$^3$ and 1.77 for a density of 1.6g/cm$^3$).
Figure 6.3: A comparison of experimentally determined residual MMAD (x-axis) to the MMAD determined through simulations (y-axis) for solution pMDI formulations from data published in literature. Two of the studies involved APS measurements (Myrdal et al., 2004; Harris et al., 2006), and three of the studies involved cascade impactor measurements (Brambilla et al, 1999; Lewis et al, 2004; Haynes et al, 2005) (17,84,201,327,328).
Figure 6.4: APSD for solution formulations with varying density of dissolved drug. The formulations all consist of 0.4% (w/w) dissolved drug with 8% (w/w) ethanol in HFA 134a.
Similarly, increasing the density of the dissolved drug in a combination pMDI, containing one drug in solution and another in suspension, also increases the residual APSD of both drugs, as presented in Figure 6.5. Increasing the density from 0.8 to 1.6g/cm$^3$ increases the residual MMAD of the dissolved drug by 0.19µm (from 1.856 to 2.049µm) without significantly impacting the GSD. Changing the density of the dissolved drug also can impact the APSD of the suspended drug in a combination formulation by impacting the calculated PPUV. Increasing the density of the dissolved drug from 0.8 to 1.6g/cm$^3$ increases the density of the formulation by 0.3% (1.158 to 1.161g/cm$^3$), which changes the PPUV by 0.3% (from $1.117 \times 10^9$/mL to $1.120 \times 10^9$/mL). This increase in PPUV results in a minor increase in the simulated APSD of the suspended drug with increase in density of the dissolved drug in the combination solution/suspension formulation. The MMAD of the suspended drug in a formulation with the dissolved drug having a density of 0.8g/cm$^3$ is 3.430µm, which increases by 0.157µm when the dissolved drug density is doubled, which is a 4.58% increase in MMAD.
Figure 6.5: APSD for suspension formulation containing dissolved drug with varying density of the dissolved drug. The simulated formulations consist of 0.4% (w/w) dissolved drug and 0.2% (w/w) suspended drug with 8% (w/w) ethanol in HFA 134a. The micronized suspended drug has an MMD of 2.5µm with a GSD of 1.8 and a density of 1.2g/cm$^3$. 
4. Suspended Drug or Excipient Properties

The concentration, density, and micronized size distribution of the suspended drug or excipient has a significant impact on the APSD of suspension pMDIs. The effects of the concentration and size of the micronized drug on resulting MMAD and GSD of the residual particles from pMDIs that only contain the suspended drug in ethanol and HFA 134a are extensively discussed in Chapters 8, 9, and 10. Furthermore, the consequences of modulating the micronized size and concentration of the suspended drug or excipient in a combination formulation that contains a dissolved drug or excipient on residual APSD of the dissolved and suspended entities are discussed in Chapter 11. Thus, this section only evaluates the outcomes of changing the nonvolatile suspended material’s density and GSD on the resulting APSD.

4.1. Density of Suspended Drug or Excipient

The density of the suspended drug or excipient is utilized to determine the PPUV and the aerodynamic diameter for simulated droplets that contain suspended drug or excipient. Increasing the suspended drug or excipient density results in a net decrease in PPUV (see Table 6.2). In addition, increasing the density of the suspended material results in an increase in the calculated mass of the suspended drug or excipient particles for a given simulated droplet. This, in turn, results in an increase in the calculated aerodynamic diameter for that residual particle.
For formulations containing only suspended drug as the nonvolatile material in the formulation, increasing the suspended drug density from 0.8 to 1.6g/cm$^3$ increases the residual particle MMAD from 2.606 to 3.527µm, in a linear fashion ($R^2$ value of 0.99), as presented in Figure 6.6. This trend suggests that the impact of the density of the suspended drug or excipient on increasing the aerodynamic diameter for simulated residual particles has a greater impact on the residual particle APSD than that seen with the decrease in PPUV. Similar relationships between suspended drug residual particle APSD and suspended drug density are seen for combination pMDI formulations containing a suspended drug with a dissolved drug (presented by the blue shaded symbols in Figure 6.6). The APSD of dissolved drug in the combination pMDI does not appear to be impacted by the density of the suspended micronized material.
<table>
<thead>
<tr>
<th>Formulation Details</th>
<th>Density of Suspended Entity (g/cm³)</th>
<th>Suspended Particles per Unit Volume of Formulation (PPUV) (#/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4% (w/w) suspended material (MMD of 2.5µm, GSD of 1.8), 8% (w/w) ethanol in HFA 134a</td>
<td>0.8</td>
<td>3.35 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>2.68 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>2.24 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>1.92 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>1.68 × 10⁹</td>
</tr>
<tr>
<td>0.4% (w/w) suspended material (MMD of 2.5µm, GSD of 1.8), 0.2% (w/w) dissolved material (density of 1.2g/cm³), 8% (w/w) ethanol in HFA 134a</td>
<td>0.8</td>
<td>3.35 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
<td>2.68 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td>2.24 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>1.92 × 10⁹</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>1.68 × 10⁹</td>
</tr>
</tbody>
</table>
Figure 6.6: Residual particle MMAD as a function of suspended drug density for formulations detailed in Table 6.2.
4.2. GSD of Suspended Drug or Excipient

The GSD of the suspended drug or excipient is a measure of the spread of the particle sizes for the micronized material. A GSD of 1 implies that all of the micronized drug or excipient has the same diameter, while a GSD of 2 implies that the aerodynamic diameter corresponding to the 84.1 percentile on a log-probability plot of percentage of total aerosolized mass versus aerodynamic diameter is four times greater than the diameter corresponding to the 15.9 percentile (see Equation 4.1). The GSD of the micronized material plays a key role in determining the count median diameter (CMD) of the suspended material. The CMD for micronized material with a MMD of 2.5µm and GSD of 1.4 is 1.78µm, while that for material with the same MMD and GSD of 2.2 is 0.39µm. Upon examining Figure 6.7, it is clear that the micronized material with the larger GSD has a significantly greater proportion of smaller particles than that with the smaller GSD.

This effect manifests the changes seen in residual particle APSD as a function of raw micronized suspended material GSD, depicted in Figure 6.8. Increasing the GSD of the micronized suspended drug decreases the MMAD and increases the GSD of the resulting suspended drug APSD regardless of if the formulation contains a dissolved drug (Figure 6.8 (A) and (B)). For instance, increasing the micronized drug GSD from 1.4 to 2.2 decreased the MMAD by 4.8 and 5.1% for the formulations with and without dissolved drug and increased the GSD by 15.6 and 31.9% for the formulation with and without dissolved drug, respectively. The residual APSD for the dissolved component in
combination pMDI formulation was minimally affected by the increase in micronized suspended drug GSD (see Figure 6.8 (C)).
Figure 6.7: Size distribution of raw micronized material with a MMD of 2.5µm and a GSD of either 1.4 or 2.2. The CMD for these are 1.78 and 0.39µm for the micronized material with GSDs of 1.4 and 2.2, respectively.
Figure 6.8: APSD for a variety of formulations with varying micronized suspended drug GSD (1.4, red; 1.8, purple; 2.2, blue). The formulations presented are: (1) 0.4% (w/w) suspended drug (MMD of 2.5µm, GSD of 1.8, density of 1.2g/cm^3) with 8% (w/w) ethanol in HFA 134a; and (2) 0.4% (w/w) suspended drug (MMD of 2.5µm, GSD of 1.8, density of 1.2g/cm^3) and 0.2% (w/w) dissolved drug (density of 1.2g/cm^3) with 8% (w/w) ethanol in HFA 134a. The APSDs for formulation (1) is presented in (A). The APSD of the suspended component in formulation (2) is presented in (B), and the dissolved component in formulation (2) is presented in (C). The legend of each graph represents the residual particle MMAD and GSD (MMAD; GSD) for each distribution plotted.
CHAPTER 7

EVALUATION OF ASSUMPTIONS OF THE SIMULATION ALGORITHM

Summary

Assumptions are necessary in developing a model that is a simplification of the actual process. The model detailed in Chapter 5 relates the pressurized metered dose inhaler (pMDI) atomization process to aerosol drug disposition to predict the residual aerodynamic particle size distribution (APSD) for a given pMDI formulation. In doing so, it is presumed that the inputs for the system being modeled have been inputted accurately and that the pMDI hardware and formulation are ideal. These assumptions provide the constraints of the system and were discussed in Chapter 6 or will be discussed in Section 3 of this dissertation. Other assumptions included in this model help simplify the calculations for aerodynamic diameter; these assumptions are (1) the volume of the suspended drug or excipient particles for a given droplet cannot exceed the volume of the effective initial droplet (i.e., “volume exclusion rule”); (2) the volume not occupied by suspended drug or excipient particles is 25.9% of the volume of suspended drug or excipient particles in a cluster; and (3) the shape factor for agglomerates with some number of suspended particles is defined based on the number of suspended particles in the cluster. These assumptions were evaluated and found to have some effect on predicting APSD of dissolved and suspended drugs or excipients for pMDI formulations.
containing relatively large concentrations and/or relatively large raw micronized suspended drug or excipient size.
1. Why do Models have Assumptions?

A simulation model by definition is set of postulates, data, and inferences presented in a mathematical sequence describing some concepts and the relationships between them. In the research presented in this dissertation, the simulation model utilizes data and relationships derived from a multitude of scientists to relate the pressurized metered dose inhaler (pMDI) atomization process (i.e., the “aerosol formation” process from Chapter 5) to the aerosolized drug disposition (i.e., the “aerosol evaluation and deposition” process from Chapter 5). This model seeks to simplify reality in order to provide information that would otherwise have been difficult to gleam; thus, Dr. George E. P. Box was absolutely accurate when he stated that “essentially, all models are wrong, but some are useful” (329). As a simplification of reality, it is necessary to put constraints on a given model that delineate the situations in which the model is applicable; these constraints act as “domain assumptions” for a given model (330). For the model presented in this dissertation, many of the domain assumptions are in fact “heuristic assumptions,” which are rarely true in nature but are used in the model as placeholders with the intent to improve the model when a reasonable approach to mathematically represent the sub-process is developed (330). Furthermore, simplifications in postulates, data, and inference, are also assumptions that are necessary (and frequently, unavoidable) to build useful models; these assumptions are known as “negligibility assumptions.” While this terminology implies that the effects of these assumptions are inconsequential on the results of the model, they may be, in fact, more than negligible (330).
2. List of Assumptions

For the simulation model detailed in Chapter 5, the domain and heuristic assumptions are that the pMDI formulation details are defined by the user with great precision to the true values (as described in Chapter 6), and the pMDI hardware and formulation are ideal (as described in Chapters 2 and 3). Thus, it is assumed that all of the following are true:

1. The concentration of each component of the formulation is provided accurately.
2. The density of each component does not change during the formulation and atomized droplet evolution processes.
3. The density of each component is the actual density of the component in the formulation and residual particle.
4. The particle size distribution of the suspended drug or excipient is provided accurately and is lognormally distributed with one mode (i.e., no fines are present in the micronized material).
5. The micronized suspended material is spherical.
6. The initial atomized droplet particle size distribution is provided accurately.
7. There is no preferential deposition of drug or excipient on the canister or metering valve that changes the concentration or forms a concentration gradient of the drug or excipient in the formulation.
8. Changes in headspace in the canister do not impact the concentration of drugs or excipients.
9. There is no appreciable amount of leachables or extractables from the hardware components of the pMDIs.

10. There is no chemical interaction between the components of the formulation that leads to preferential attraction or repulsion on a molecular level.

11. The suspension is ideal, which implies that the suspended drug is homogeneously dispersed in the formulation and that there is no change in the particle size distribution of the micronized suspended drug as a function of Ostwald ripening.

12. Secondary droplet break-up or coalescence does not occur once the droplets are atomized.

The negligibility assumptions for this model include the volume exclusion rule, packing density for closely packed spheres, and the shape factor for clusters of suspended drug particles. These three assumptions are explained and evaluated in greater detail in Section 3 of this chapter.
3. Evaluation of Negligibility Assumption

For each of the negligibility assumptions, a description of the assumption is provided along with some simulated data for formulation containing 8% (w/w) ethanol in 1,1,1,2-tetrafluoroethane (HFA 134a), for illustrative purposes. The initial droplet was fixed at 9.14µm mass median diameter (MMD) with a geometric standard deviation (GSD) of 1.8. The suspended micronized drug had either 1 or 2.5µm MMD with a GSD of 1.8. For all of the simulations presented, at least 30,000 suspended drug containing droplets were simulated and the number of suspended particles per unit volume of formulation (PPUV, #/mL) was calculated using Equation 7.1 and presented in Table 7.1, where $C_{susp}$ is the weight fraction concentration of the suspended drug or excipient, $GSD_{susp}$ is the GSD of the suspended drug or excipient, $\rho_{form}$ is the density of the formulation (g/mL), $MMD_{susp}$ is the MMD (µm) of the suspended drug or excipient, and $\rho_{susp}$ is the density of the suspended drug or excipient. For this discussion, it is assumed that the suspended and dissolved nonvolatile entities in the formulation are drugs; however, the same discussion can be applied if either of the materials is an excipient.

$$PPUV = \frac{6 \times C_{susp} \times e^{4.5\ln^2(GSD_{susp})} \times \rho_{form}}{\pi \times (0.0001 \times MMD_{susp})^3 \times \rho_{susp}}$$

(Equation 7.1)
3.1. Volume Exclusion Rule

The volume exclusion rule is used to partially determine the total volume of suspended drug particles in an atomized droplet. The number of suspended drug particles is determined in a statistically random fashion from within an effective initial droplet-specific Poisson distribution, as presented in Section 3.3 in Chapter 5. Thereafter, each suspended drug particle is assigned a diameter in a statistically random manner from within the user-defined distribution of the micronized suspended drug particle size, which enables calculating the total volume of the initial droplet occupied by the suspended drug particles. If the volume of the suspended drug particles is greater than that of the simulated droplet, the volume of the suspended drug particles is assumed to be equal to that of the simulated droplet, given that it is physically impossible for the suspended drug particles to occupy more space than the volume of the initial droplet. This in turn would impact the aerodynamic particle size distributions (APSDs) of the drug in solution and in suspension.
### Table 7.1: Number of Suspended Drug Particle per Unit Volume (PPUV) for Example Formulations

<table>
<thead>
<tr>
<th>Formulation Number</th>
<th>Dissolved Drug Concentration (% w/w)</th>
<th>Suspended Drug Concentration (% w/w)</th>
<th>Suspended Drug MMD (µm)</th>
<th>PPUV (#/mL)</th>
<th>Simulated Droplets that Contain Suspended Drug Particles (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.04</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>0.04</td>
<td>1.0</td>
<td>$3.228 \times 10^9$</td>
<td>14.4</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>0.4</td>
<td>1.0</td>
<td>$3.229 \times 10^{10}$</td>
<td>49.2</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>0.04</td>
<td>2.5</td>
<td>$2.066 \times 10^8$</td>
<td>1.6</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>0.4</td>
<td>2.5</td>
<td>$2.067 \times 10^9$</td>
<td>10.5</td>
</tr>
<tr>
<td>7</td>
<td>0.04</td>
<td>0.04</td>
<td>1.0</td>
<td>$3.228 \times 10^9$</td>
<td>14.7</td>
</tr>
<tr>
<td>8</td>
<td>0.4</td>
<td>0.04</td>
<td>1.0</td>
<td>$3.229 \times 10^9$</td>
<td>14.5</td>
</tr>
<tr>
<td>9</td>
<td>0.04</td>
<td>0.04</td>
<td>2.5</td>
<td>$2.066 \times 10^8$</td>
<td>1.5</td>
</tr>
<tr>
<td>10</td>
<td>0.4</td>
<td>0.04</td>
<td>2.5</td>
<td>$2.066 \times 10^8$</td>
<td>1.5</td>
</tr>
<tr>
<td>11</td>
<td>0.04</td>
<td>0.4</td>
<td>1.0</td>
<td>$3.229 \times 10^{10}$</td>
<td>49.2</td>
</tr>
<tr>
<td>12</td>
<td>0.4</td>
<td>0.4</td>
<td>1.0</td>
<td>$3.229 \times 10^{10}$</td>
<td>49.9</td>
</tr>
<tr>
<td>13</td>
<td>0.04</td>
<td>0.4</td>
<td>2.5</td>
<td>$2.067 \times 10^9$</td>
<td>10.4</td>
</tr>
<tr>
<td>14</td>
<td>0.4</td>
<td>0.4</td>
<td>2.5</td>
<td>$2.067 \times 10^9$</td>
<td>10.5</td>
</tr>
</tbody>
</table>
Formulations 1 to 14, listed in Table 7.1, were simulated with 30,000 droplets each. Figure 7.1 presents the percentage of droplets that are affected by the volume exclusion rule. For these formulations, 0 to 11 droplets per simulation (regardless of if the droplet contains suspended drug particles) met the criteria for the volume exclusion rule, which is equal to an average of 0.011 ± 0.013% droplets simulated. This is equivalent to 0 to 138 droplets from a sample of suspended drug laden droplets, which is an average of 0.179 ± 0.18% of the simulated suspended drug laden droplets for a given formulation. Based on these results, it is evident that the criterion for volume exclusion is rarely met. Not surprisingly, Formulations 6, 13, and 14 are most affected by the volume exclusion criteria given that they have the largest micronized drug size and highest PPUV of the formulations simulated. Increasing the PPUV increases the likelihood that atomized droplets may contain multiple suspended drug particles, thereby allowing the volume of the suspended drug particles in a given atomized droplet to be sufficiently large that it may exceed the volume of the initial droplet. Increasing the size of the micronized drug further increases the volume of a cluster of suspended drug particles, since particles with a larger diameter occupy a greater volume than those with smaller diameters. However, since the volume exclusion rule does not impact a large percentage of droplets, the residual particle mass median aerodynamic diameter (MMAD) for the dissolved or suspended drug in Formulations 1 to 14 does not change significantly with omission of the volume exclusion rule (see Figure 7.2).
Figure 7.1: Percentage of simulated droplets that are affected by the volume exclusion rule for select formulations. The formulations are described in Table 7.1.
Figure 7.2: Residual particle MMAD for dissolved and suspended drug with and without the use of the volume exclusion rule for select formulations. The formulations are described in Table 7.1.
3.2. Packing Density for Closely Packed Spheres

The packing density, a factor of 0.741, is utilized in the final step of the simulation to determine the aerodynamic diameter of a given residual particle. It accounts for the difference in residual particle density based on void volume that is not occupied by the suspended drug particles within the residual particle. In other words, it is assumed that 74.1% of the volume of a cluster of suspended drug particles is occupied by the suspended material; the remainder volume, 25.9% of the cluster’s volume, is free to be occupied by air or dissolved drug or excipient. This value is derived from close packing of monodispersed hard spherical particles in a face-centered cubic structure from the study of crystallographic unit cells theory. In such a packing arrangement, each particle has eight neighbors and the packing efficiency is calculated as presented in Figure 7.3.
ΔABC is a right triangle formed on one face of a cube, thus the Pythagorean theorem can be applied to determine the length of the hypotenuse and the side of the cube:

\[ AC^2 = AB^2 + BC^2 \]

Given that \( AB = BC \) and \( AC \) is equal to the 4 times the radius of a spherical particle, \( r \),

\[ (4r)^2 = 2 \times AB^2 \]
\[ AB = 2r\sqrt{2} \]

Thus, the volume of the cube is,

\[ AB^3 = (2r\sqrt{2})^3 \]

There are a total of 4 spherical particles per cube, hence the volume occupied by the suspended drug particles is equal to

\[ 4 \times \frac{4}{3} \pi r^3 \]

The packing efficiency, \( PE \), is the ratio of the volume occupied by the spherical particles to the volume of the cube:

\[ PE = \frac{4 \times \frac{4}{3} \pi r^3}{(2r\sqrt{2})^3} = 74.1\% \]

**Figure 7.3:** Calculation of face-centered cubic packing efficiency for closely packed hard spheres.
There are multiple published models that allow for the estimation of the packing efficiency of randomly packed polydispersed particles (for example, see references (331-334)). Essentially, these models utilize one of two approaches: sequential addition models or collective rearrangement models (333). Sequential addition models are initiated with some number of spheres in the system. Each subsequent iteration of the simulation model adds a single sphere into the modeled system. Once each sphere is added, it is moved to a stable position, where it is in contact with two other spheres. Collective rearrangement models randomly generate and place spheres in a given domain, while allowing the spheres to overlap. The spheres are generated from within a given probability function; through a Monte Carlo simulation, they are separated by changing the sizes of the spheres to decrease the spheres’ overlap. Both of these approaches have obvious limitations. The sequential addition model typically leads to anisotropy (334) and relatively low packing densities compared to those derived experimentally (0.6225 to 0.6366 (333,335)), and the collective arrangement model unrealistically assumes that particles form a network of contact surfaces with other particles (333).

Through collective rearrangement simulations, a couple of studies have provided estimations of the packing density for lognormally distributed spheres with defined means and GSDs. Bezrukov et al. estimated that the volume fraction occupied by suspended particles with a mean diameter of 0.3µm and a GSD ranging from 1 to 2 could be between 0.620 to 0.715, with the majority of models estimating between 0.625 and 0.695 (334). Farr modeled the volume fractions to be between 0.6426 and 0.6931 (332). Not surprisingly, the volume fraction occupied by suspended particles is not especially
sensitive to the mean size of the particles, but it is extremely sensitive to the GSD of the particle distribution (334). The volume fraction occupied by suspended drug particles increases with increasing GSD. For instance, at a GSD of 1.2, the packing efficiency is modeled to be between 0.610 and 0.660 (334). Increasing the GSD to 1.4, increases the packing efficiency to 0.630 to 0.680. At a GSD of 1.8, the packing efficiency is estimated to be between 0.660 and 0.695. The association of volume fraction occupied by spherical particles and the GSD is also in agreement with the data presented by Yang et al. (336).

While simulation approaches to estimating the packing efficiency of lognormally distributed polydisperse particles exist, these methods are difficult to incorporate in the simulation model for determining the APSD from suspension pMDIs since it requires building a secondary Monte Carlo simulation within the existing model, which can significantly impact the usability of the current model (332). In order to evaluate how changing the packing efficiency impacts the overall APSD distribution, the results from simulations with packing efficiency of 0.620 were compared to the results from the existing program (see Figure 7.4). This value was determined since it is the lowest value estimated by the models developed by Bezrukov et al. (334), and it has the greatest deviation from the existing value of 0.741.

The value selected for the void volume has greatest impact in predicting APSD for formulations with relatively high suspended drug concentration and small micronized suspended drug, which effectively increases the PPUV. Formulations with relatively high PPUV result in an increased probability for simulating droplets that have multiple drug particles, which effectively increases the absolute void volume in a cluster of suspended
drug particles. Furthermore, modulating the void volume for solution formulation or for combination formulations with relatively high dissolved drug concentration compared to the suspended drug concentration has little to no impact on the resulting APSD because the residual particle size does not consider the void volume in a cluster of suspended drug particles if the volume of dissolved drug in the droplet exceeds the void volume (see Figure 5.11). Thus, Formulations 11 (0.04% dissolved drug with 0.4% 1.0µm suspended drug) and 13 (0.04% dissolved drug with 0.4% 2.5µm suspended drug) were simulated using packing efficiencies of 0.741 and 0.620 and compared to Formulations 7 (0.04% dissolved drug with 0.04% 1.0µm suspended drug) and 9 (0.04% dissolved drug with 0.04% 2.5µm suspended drug) from Table 7.1. Comparisons of the MMAD for the dissolved and suspended components for these formulations with both packing efficiencies are presented in Figure 7.4. Changing the packing efficiency from 0.741 to 0.620 resulted in a maximum decrease of 7.3% (0.22µm) in residual particle MMAD with an average change of 3.1% (0.06µm) for the formulations evaluated. Based on these results, it appears that the packing efficiency, and conversely, the void volume in an aggregate of suspended drug particles have minimal impact on the resulting residual MMAD for dissolved and suspended drugs.
Figure 7.4: The residual particle MMAD with packing efficiencies (PE) of 0.741 or 0.620 for Formulations 7, 9, 11 and 13 presented in Table 7.1.
3.3 Shape Factor for Agglomerates of Suspended Drug Particles

The shape factor accounts for the deviation in drag force from a spherical residual particle if greater than one drug particle is within that droplet; these values are then used to calculate the aerodynamic diameter, as presented in Chapters 4 and 5. The shape factor varies between 1 for residual particles that contain one suspended drug particle to a maximum of 1.14 for residual particles that contain 12, 18, or 19 suspended drug particles (322,323). The shape factors used in this simulation program are listed in Table 5.2 and presented in Figure 7.5. The shape factors for up to 4 suspended drug particles were determined experimentally using various sized monodispersed spheres in a nebulized system (322); the remainder of the shape factors utilized was determined through a theoretical model for monodispersed particles (323). In addition, the shape factor is assumed to be 1 for residual particles that have sufficient dissolved drug such that it exceeds the void space found in the cluster of suspended drug particles.
Figure 7.5: Dynamic shape factor as a function of number of suspended particles in an agglomerate used in the model described.
The current literature is lacking in experimental or simulated data predicting the shape factor for agglomerates of spherical particles that are polydispersed with a known GSD. In part, the difficulty in determining shape factors for such situations lies in the dynamic nature of shape factors. Shape factors are affected by the shape of the agglomerate, the size of the particles that make up the agglomerate, the orientation of the arrangement of particles within the agglomerate, the density of the agglomerate, the flow regime used during measurement/estimation of shape factor, and the pressure of the environment on the agglomerate (337-339). Thus, to evaluate the impact of shape factor on simulated APSD for a variety of suspension pMDI formulations, the shape factor was assumed to be either 1 or 1.26 for all agglomerates. A shape factor of 1 implies that the agglomerate, regardless of the number of drug particle within the cluster, does not impact the drag force of the particle. A shape factor of 1.26 was determined for a cluster of ten monodispersed polystyrene latex beads using a differential mobility analyzer and was the largest change in drag force (the drag force for the cluster is 26% greater than that for a sphere of equivalent volume as the cluster) experimentally determined by Zelenyuk et al. (337). The results for these simulations were then compared to the results of simulations that use the shape factors as presented in Figure 7.5.

Like void volume, modulating the shape factor has the greatest impact in predicting APSD from formulations with relatively high PPUV, which results in a propensity of having more droplets with two or more suspended drug particles compared to formulations with low PPUV. In addition, solution formulations and combination formulations with relatively high dissolved drug concentration compared to the
suspended drug concentration are minimally affected (if at all) except for modulating the shape factor. This is true because the shape factor is assumed to be 1 if the residual particle’s dissolved drug volume exceeds the void volume for the cluster. This discussion is further reflected in Figures 7.6 and 7.7, which present the effect of changing shape factors from the current model (dynamic shape factor) to either 1 (open symbols) or 1.26 (filled symbols) for all aggregates, regardless of the number of drug particles within the cluster, on the two drugs in Formulations 7, 9, 11, and 13 from Table 7.1. Increasing the value of the shape factor means that the resulting irregularly shaped particle has a greater drag force than a spherical particle with the same volume. Thus, the particle behaves like a smaller particle aerodynamically. For the formulations presented in Figures 7.6 and 7.7, using a shape factor of 1 results in the largest estimation of residual MMAD for the dissolved and suspended components and a shape factor of 1.26 results in the smallest estimated value. The dynamic shape factor, presented on the x-axis of both of the figures, typically results in an estimation similar to that found with a shape factor of 1.

Changing the shape factor between 1 and 1.26 appears to have a greater effect in predicting of the residual particle MMAD for the dissolved component for formulations with high concentration of suspended drug (or excipient) than with lower concentration of suspended drug (or excipient), as seen in Figure 7.6. For instance, theoretically changing the shape factor from 1 to 1.26 decreases the resulting MMAD for formulations containing 0.4% (w/w) suspended drug by a maximum of 0.22µm, but only by 0.02µm for formulations containing 0.04% (w/w) suspended drug. In addition, changing the theoretical shape factor has a more pronounced effect in predicting the residual APSD of
the suspended component of a combination pMDI, especially in the case where the micronized suspended material is relatively large (see Figure 7.7). Increasing the shape factor from 1 to 1.26 resulted in a decrease in suspended residual particle MMAD by 16.4% (0.50µm), 10.0% (0.28µm), 11.0% (0.21µm), and 4.5% (0.07µm), respectively for Formulations 13, 9, 11, and 7.
Figure 7.6: The effect of changing shape factor on the residual MMAD for the dissolved drug in a pMDI formulation with suspended drug. Open symbols denote a shape factor of 1. Filled symbols denote a shape factor of 1.26. These formulations are described in Table 7.1.
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CHAPTER 8
A MODEL FOR PREDICTING SIZE DISTRIBUTIONS DELIVERED FROM PRESSURIZED METERED DOSE INHALERS WITH SUSPENDED DRUG

Published by: Stephen W. Stein, Poonam Sheth, and Paul B. Myrdal


Summary

A new model has been developed for predicting size distributions delivered from pressurized metered dose inhalers (pMDIs) that contain suspended drug particles. This model enables the residual particle size distribution to be predicted for a broad range of formulations. It expands on previous models by allowing for polydisperse micronized input drug, dissolved drug, and dissolved excipient to be included in the formulation. The model indicates that for most pMDI configurations, the majority of droplets contain no drug or a single drug particle and the residual particle size distribution delivered from the pMDI is essentially equivalent to the size distribution of the micronized drug used in the formulation. However, for pMDIs with a high drug concentration or that use small micronized drug particles, there can be a substantial fraction of the droplets that contain multiple drug particles. The residual particle size distribution obtained from these pMDIs can be substantially larger than the size distribution of the micronized drug. Excellent agreement was observed between size distributions predicted using this model and those obtained from experimental cascade impactor measurements ($R^2 = 0.97$), thus
demonstrating the ability of the model to accurately predict the size distributions obtained from suspension pMDIs.
1. Introduction

1.1. Background

For over half a century pressurized metered dose inhalers (pMDIs) have been widely used in treatments for lung diseases such as asthma and chronic obstructive pulmonary disease. More recently, the utility of pMDIs has been investigated for the treatment of lung cancer and for systemic delivery of insulin and other peptides (201,340-342). Pressurized MDIs use propellants to atomize precise amounts of formulation into droplets that are capable of being delivered to the lung. The chlorofluorocarbon (CFC) propellants used in early pMDIs have been replaced by non-ozone depleting hydrofluoroalkane (HFA) propellants (177,343,344). The drug contained in the formulation can be dissolved in the formulation, producing a solution, or can be dispersed in the formulation, producing a suspension. In addition to a high pressure propellant and drug, pMDI formulations may also contain cosolvents, such as ethanol, or other excipients. These excipients may be surfactants, polymers, or micronized excipients that may function in providing physical stability to a suspension formulation, modifying the size of residual drug particles, or providing sustained drug release (260,289,345).

The ability of a pMDI to deliver drug to the lung is largely dependent on the residual aerodynamic particle sizes of the atomized droplets. The particle sizes of pMDI aerosols are often lognormally distributed, thus the aerodynamic particle size distribution (APSD) of the aerosolized particles can be described using the mass median diameter (MMD) or mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Generally, particles less than approximately 5μm MMAD are capable
of penetrating into the lung with smaller particles having the best chance to penetrate into the deep lung (34). The ideal aerodynamic particle size for delivery of drugs to the lung is subject to much debate and depends on the desired location in the respiratory tract for delivery of the particular drug (346-348).

For solution pMDIs, the size of residual particles delivered to the patient is a function of the initial droplet size and the concentration of nonvolatile components (i.e., drug and/or excipient) in the formulation (204,327). During the actuation of the device, the high pressure propellant acts as an energy source to dispense the formulation from the device and atomize the formulation into a polydisperse distribution of small droplets. The atomized droplet size distribution is lognormal in nature and generally has a GSD of approximately 1.6 to 1.8 (204). The initial MMD of the atomized droplets vary in size depending on the propellant, cosolvent, valve size, and actuator orifice diameter but is typically around 8 to 12μm for HFA 134a-based pMDIs (204). Once atomized, these initial droplets undergo rapid evaporation of the propellant and cosolvent, if present. After the evaporation is completed, the residual particles from a solution pMDI are nearly spherical and contain drug and any nonvolatile excipient present in the formulation (204,349). Since the drug is dissolved in a homogeneous solution prior to atomization, the size of each residual particle is proportional to the initial size of its respective atomized droplet. Thus, larger initial droplets result in larger residual particles and smaller initial droplets result in smaller residual particles.

The formation of the residual particles from suspension pMDIs is more complex than from solution pMDIs and is illustrated in Figure 8.1. As is the case with solution
pMDIs, the suspension formulation is atomized into droplets with a range of initial droplet diameters which depends on the formulation and device. The initial droplets contain propellant, cosolvent, any dissolved nonvolatile excipients (e.g., surfactant), and varying number of suspended drug particles. The formulation can also contain dissolved drug, but this is not typical. Some droplets contain no drug particles, as depicted by droplets A and B in Figure 8.1, while others contain 1, 2, or even more drug particles as depicted by droplets C to E in Figure 8.1. The number of drug particles contained within the droplets depends on the size of the micronized drug, the concentration of the drug in the formulation, and the size of the initial droplet. The aerodynamic size of the residual particles depends on the number of suspended drug particles contained in a given droplet, the size of these suspended drug particles, the shape of the residual particle, and the mass of nonvolatile components contained in the droplet. The shape of the residual particles with greater than one drug particle can deviate from a perfect sphere, as presented by the residual particle in Figure 8.1 C. The shape factor and packing density, discussed in Section 2.1.6 of this chapter, allow for calculation of the aerodynamic diameter for these residual particles. The likelihood of any given droplet having one or more drug particles depends on the size of the atomized droplet and on the formulation and increases as the number of drug particles present per unit volume of formulation and the droplet volume increase.

The atomization of nebulized monodisperse suspensions was previously described by Raabe (350). In order to develop good calibration aerosols, Raabe developed an equation to estimate the amount of dilution of a formulation of monodisperse polystyrene
latex (PSL) particles is required in order to minimize the number of “multiplets” (i.e., residual particles containing more than one PSL particle). The delivery from suspension pMDIs has been modeled by Gonda (318) and Chan and Gonda (319) who built upon the work of Raabe to model delivery of monodisperse particles contained in polydisperse droplets. In reality, however, the delivery of drug from suspension pMDIs is more complicated than that modeled by Gonda since the drug particles are virtually always polydisperse and most suspension pMDIs include nonvolatile excipients that change the aerodynamic size of the residual particles.

1.2. Characterizing the Size Distribution of the Initial Droplets

One of the challenges in modeling both solution and suspension pMDI drug delivery is determining the size distribution of the initial droplet diameters. This is a critical input for predicting the residual aerosol size distribution delivered from either solution or suspension pMDIs. The initial droplet size distribution can be estimated theoretically, experimentally, or empirically through equations. Theoretical models have been developed for predicting the size distribution of droplets atomized from pMDIs using droplet breakup models (313). However, these models are computationally intensive and the ability of these models to accurately predict initial droplet sizes for highly volatile liquids such as propellants has not yet been demonstrated.
Figure 8.1: Droplet atomization process from suspension pMDIs. Some droplets can contain no drug particles, as depicted in (A) and (B), while others can contain 1, 2, or more drug particles as depicted in (C) to (E). The size of the residual particles depends on the size and number of drug particles contained within the droplet and the concentration of any nonvolatile excipient (usually surfactant) dissolved in the formulation.
Experimental measurement of the initial droplet distribution is also very challenging as a result of the extremely rapid changes in droplet size immediately after atomization due to evaporation of the highly volatile formulation. Phase-Doppler particle anemometry (PDPA) has been shown to provide useful insight into the size of the atomized droplets (76,96), but requires a high level of expertise to generate and analyze the data. Additional challenges include the small measurement volume for the technique and the challenge of measuring near to the exit of the actuator nozzle. Laser diffraction is another approach for experimentally characterizing droplet size distributions. In addition to the technical challenges described for the PDPA technique, laser diffraction has the challenge of beam steering caused by changes in the index of refraction of the air due to the high concentration of propellant vapor in the plume (351). Thus, while experimental approaches provide useful insight, they are limited in their ability to characterize the size distribution of the droplets just after atomization.

Another approach for determining the size distribution of initial droplets is to use theoretical equations describing the relationship between the size of the initial droplets and residual particles. For solution pMDIs, it is possible to estimate the initial droplet size distribution by measuring the size distribution of the residual particles after all of the volatile components of the formulation evaporate and then theoretically calculating the initial droplet sizes using Equation 8.1 (204). The MMD of the initial droplets (MMD_I) from a solution formulation can be readily predicted based on knowledge of the residual particle mass median diameter (MMD_R) and properties of the formulation – particularly the concentration of the nonvolatile components (C_{NV}, weight fraction) of the formulation.
– as described by Equation 8.1, where $\rho_I$ and $\rho_R$ are the densities of the initial droplets and the residual particles, respectively. The $\rho_I$ is the same as the density of the formulation, $\rho_{form}$. The GSD of the initial droplet distribution (GSD$_I$) and the residual particle distribution (GSD$_R$) is the same (204). An advantage of this approach is that it relies on measurement of the residual aerosol size distribution. The residual size distribution is much easier to measure than the initial droplet size distribution since the size is no longer changing when measured.

\[
\text{MMD}_I = \text{MMD}_R \times \left( \frac{\rho_I C_{NV}}{\rho_R} \right)^{-1/3} 
\]  
(Equation 8.1)

Previous research has been used to provide an empirical equation for predicting the initial droplet size distribution for 1,1,1,2-tetrafluoroethane (HFA 134a) solution pMDIs as a function of the ethanol concentration, the valve size, and the actuator orifice diameter as presented in Equation 8.2 (204), where MMD$_I$ is in $\mu$m, VS is the valve size ($\mu$L), $C_{\text{EtOH}}$ is the concentration of ethanol in the formulation (weight fraction), and OD is the actuator orifice diameter (mm). Equation 8.2 has been shown to provide accurate size distribution estimates for HFA 134a solution pMDIs for a variety of formulations, valves, and actuator configurations (204). It is not possible to generate a separate empirical equation for the initial droplet size distribution for suspension pMDIs since the presence of varying number of drug particles in each residual particle precludes the use of simple equations such as Equation 8.1.
1.3. Purpose

The objective of this research is to expand on the work of Raabe and Gonda to develop a computational model to describe the residual aerosol delivered from suspension pMDIs taking into account the polydispersity of the raw drug particles and atomized droplets and the inclusion of nonvolatile excipients in the formulation (318,319,350). This paper will apply the developed model to theoretically predict the residual particle size distribution from suspension pMDI formulations and the results will be compared to experimental measurements.

\[
\text{MMD}_1 = 6.90 + 0.0441(\text{VS}) + 23.6(C_{\text{EtOH}}) - 63.8(C_{\text{EtOH}})^2 + 24.7(C_{\text{EtOH}})(\text{OD}) - 0.129(C_{\text{EtOH}})(\text{VS})
\]  

(Equation 8.2)
2. Materials and Methods

2.1. Description of Theoretical Model

Figure 8.2 represents the algorithm that is used in this research to determine the residual particle size distribution delivered from pMDIs. The algorithm requires detailed formulation information, such as weight concentration (% w/w) of each component, the density of each component (g/cm\(^3\)), and the APSD of the raw micronized drug. In addition, the initial droplet size distribution must be provided. Once the formulation information is provided and the initial droplet size distribution is determined, Steps 1–5 in Figure 8.2 are used to predict, on a droplet-by-droplet basis, the size and composition of residual particles that results from each atomized droplet.

For each droplet to be modeled, the first step in the algorithm is to determine the initial droplet size. Since the overall distribution of atomized droplets is one of the inputs to the model, the size of any given atomized droplet must be determined by randomly sampling from the overall initial droplet size distribution. This “random sampling” is done by using a random number generator to generate a number between 0 and 1 and then finding the droplet size for the inverse cumulative distribution function that corresponds to this random number. Subsequently, the number of drug particles contained in the droplet can be determined. The Poisson statistical distribution is used to determine the probabilities of the droplet containing 0, 1, 2, and 3, etc., suspended drug particles. Once these probabilities are calculated, the number of suspended drug particles contained in the droplet is determined by randomly sampling from the Poisson
distribution in a manner similar to that used to sample the initial droplet diameter. After the number of drug particles in the droplet is known, the sizes of these drug particles are determined (Step 3) by a similar random sampling from the inverse cumulative distribution function of the micronized drug, which is known since the size distribution of the micronized drug is one of the inputs to the algorithm. If any dissolved drug or excipient is included in the formulation, the mass and volume of these are determined (Step 4) using simple calculations and the formulation information provided in the input stage. In Step 5, the aerodynamic diameter of the residual particle is calculated based on the mass and volume of drug and/or excipient determined in Step 4 and based on an estimation of the shape factor, which is based on the number of drug particles contained in the residual particle. The content of volatiles in the formulation (i.e., propellant and co-solvent) do not contribute to the size distribution of the residual particles, since it is assumed that the residual particles are “dry” and only contain dissolved and/or suspended nonvolatiles that were simulated in Steps 4 and 5 (93).
Figure 8.2: Algorithm for simulating residual particle aerodynamic size distributions from suspension or solution pMDIs. In this research, the model for determining residual particle distribution from suspension pMDIs has been explored in detail.
In order to obtain a meaningful estimate of the residual particle size distribution, Steps 1–5 must be repeated for many droplets. Previous work has indicated that at least 5000 drug containing droplets are required in order to obtain accurate size distribution measurements (326). For the simulations reported in this paper, the model was created in Microsoft Visual Basic® 6.5 and embedded into Microsoft Excel® 2007 (Redmond, Washington, USA) with enough droplets in order to obtain at least 10,000 drug containing droplets for each simulation. In the final step, titled “Output” in Figure 8.2, an overall residual APSD is calculated based on residual aerodynamic diameter and mass outputs from each droplet included in the simulation. This algorithm was described briefly elsewhere (248), but each step in the algorithm is described in detail in Sections 2.2.1 to 2.2, 3 to 3.4, and 4 of this chapter along with any assumptions made.

A benefit of the algorithm is that it accounts for many of the differences in properties of the suspended drug particles. The residual aerosol for suspension pMDIs is influenced by the particle size distribution of the micronized drug powder, the density of the drug particles, and even the solubility of the drug in the formulation. All of these factors are taken into account in the algorithm. In reality, it is usually necessary to have very low drug solubility in the formulation in order to develop a stable suspension pMDI product. Therefore, it is reasonable in most cases to ignore (as the simulations reported in this chapter do) the amount of drug dissolved in the formulation. Nevertheless, this algorithm provides the flexibility to model even complicated formulation scenarios.
2.1.1. Inputs: Estimate of the Initial Droplet Size Distribution

One of the inputs required for the model is the initial size distribution of the atomized droplets. Previous research has shown that the initial droplet size distribution is dependent on the cosolvent concentration (typically, ethanol) in a formulation, the actuator orifice diameter, and the valve size (204). For the simulations in this paper, Equation 8.2 was used to estimate the MMD$_I$. The units associated with Equation 8.2 are micrometers, so the droplet diameter was converted to centimeters in order to maintain consistency of units; centimeter–gram–second system of units was used in the program. The GSD$_I$ was assumed to be 1.60 for all of the simulations based on previous research (204). Equation 8.2 is an estimate of the initial droplet size distribution generated using solution pMDI formulations. In this paper it is being used to estimate the initial droplet size distribution for suspension pMDI formulations. Thus we are assuming that the presence of drug particles in the formulation does not sufficiently alter the atomization process to meaningfully change the size of the initial atomized droplets. It is difficult to experimentally verify this assumption due to the previously described challenges of experimentally measuring the initial droplet size distribution.

In order to predict the diameter of a given droplet from the initial droplet size distribution, the distribution must first be converted to a number-weighted size distribution. To do this, the initial droplet count median diameter (CMD$_I$) is calculated from the MMD$_I$ obtained, using Equation 8.2, by the Hatch–Choate equation (see Equation 8.3) (352).
2.1.2. Step 1 – Determine Size of the Initial Atomized Droplet

The diameter of the initial droplet is calculated using a lognormal cumulative distribution function, assuming that the distribution of initial droplets follows a lognormal distribution. To do this, a random number, R, is sampled from a uniform distribution between 0 and 1. The size of the initial droplet, $D_I$, is then set to the droplet diameter that corresponds to the value of R from the inverse cumulative distribution function using the “LOGINV” function in Excel. When the value of R is 0.5, then the diameter of the droplet would be equal to the median diameter from the lognormal distribution curve (i.e., the diameter would be equal to CMD$_1$). An R-value that is very close to 0 (i.e., 0.001) results in a very small initial droplet diameter and an R-value that is very close to 1 (i.e., 0.999) results in an initial droplet diameter that is on the large diameter “tail” of the lognormal size distribution described by CMD$_1$ and GSD$_1$. Once the diameter of the initial droplet is determined, the volume of the initial droplet can then be calculated using the basic geometrical equation describing the volume of a sphere (Equation 8.4), where $V_I$ is the volume, and $D_I$ is the diameter of a sphere, which is the value resulting from the lognormal cumulative distribution function.

$$ CMD_1 = MMD_1 \times e^{-3 \times 1n^2 GSD_1} \quad \text{(Equation 8.3)} $$

$$ V_I = \frac{1}{6} \pi D_I^3 \quad \text{(Equation 8.4)} $$
2.1.3. Step 2 – Determine Number of Suspended Particles in the Droplet

The likelihood that a droplet will contain one or more drug particles depends on volume of the droplet and the number of drug particles per unit volume of the formulation and can be described using the Poisson distribution statistical function. Large droplets have a higher probability of having one or more drug particles than small droplets. Similarly, droplets from formulations that contain a higher number of drug particles per volume of formulation are more likely to contain drug particles than are droplets of the same size for a formulation with fewer drug particles. In order to randomly determine the number of particles in a given droplet using a Poisson distribution, the number of particles per unit volume (PPUV, #/cm$^3$) in the formulation must first be calculated. To determine this, Equation 8.5 can be used, where $C_D$ is the concentration of the drug (weight fraction), $\rho_D$ is the drug particle density, and GSD$_D$ and MMD$_D$ are the geometric standard deviation and mass median diameter, respectively, of the micronized drug.

\[
PPUV = \frac{6 \times C_D \times \rho_D \times e^{4.81n^2GSD_D}}{\pi \times (0.0001 \times MMD_D)^3 \times \rho_D}
\]  
(Equation 8.5)

Once the number of particles per unit volume and the initial droplet diameter are known, the Poisson distribution can be used to determine the number of drug particles in the droplet. The Poisson distribution, as described by Equation 8.6, is a discrete distribution that presents the probability ($P(I)$) of a particular droplet containing some number of drug particles, $I$, given the average occurrence of the event, $M$ (318,350).
\[ P(I) = \frac{e^{-M} \times M^I}{I!} \] (Equation 8.6)

It is assumed that each droplet's contents are independent of other droplets. \( M \) is the product of volume of the initial droplet \( (V_1 \text{ from Equation 8.4}) \) and PPUV (Equation 8.5), giving the average number of drug particles in a droplet of a specific size. Once the \( M \) is known, Equation 8.6 is used to determine the fraction of the atomized droplets that contain 0, 1, 2, and 3, etc., suspended drug particles. The number of particles in the droplet is then determined using a random number generator to sample based on these probabilities. The value of \( M \) is calculated for each droplet in the simulation since the volume of each droplet differs. It is also assumed that the drug particles are uniformly distributed within the bulk formulation. In real suspension formulations, particles flocculate and even form irreversible aggregates. Loose flocculates contained in the formulation will likely break apart during the atomization process, but irreversible aggregates will cause some deviation from the assumption of uniform particle distribution in the formulation. The influence of suspension quality on suspension pMDI delivery is outside the scope of this investigation.

2.1.4. Step 3 – Determine the Size of the Suspended Drug Particles in the Droplet

The characterization of drug particles suspended in any given droplet can be calculated in a manner similar to that of initial droplets. The diameter of each drug particle is calculated by random sampling from the micronized drug particle size distribution that is provided as an input to the program. This sampling is done by using a
uniformly distributed random number generator to select a number between 0 and 1 and then using the Excel “LOGINV” function to calculate the inverse of the cumulative lognormal distribution function of drug particle size that corresponds to this random number. As with the initial droplet diameter determination, the number-weighted drug particle size distribution (CMD_D) and GSD_D is used in this step. This process is conducted independently for each drug particle in a given droplet. Using the diameter values obtained for each drug particle, and assuming that drug particles are spherical, the volume of each drug particle in a droplet can be calculated and summed to provide the total volume that the drug particles occupy in a droplet. If the volume of drug particles exceeds the volume of the initial droplet (an extremely unusual occurrence), then the volume of initial droplet is used in place of the volume of drug particles for further calculations. If the droplet has any drug particles, the mass of the drug particles can then be calculated by taking the product of the volume of the drug particles and density of the drug as presented in Equation 8.7, where M_D is the total mass of drug contained in the droplet, M_i is the mass of any given drug particle i, V_i is the volume of that drug particle, and \( \rho_D \) is the drug particle density, which is assumed to be the same for all of the drug particles.

\[
M_D = \sum_{i=1}^{n} M_i = \sum_{i=1}^{n} V_i \times \rho_D 
\quad \text{(Equation 8.7)}
\]
2.1.5. Step 4 – Determine Volume or Mass of Dissolved Drug or Excipient in Droplet

In this step, the volume and mass of dissolved drug or excipient are calculated based on the difference in volumes of the initial droplet (Step 1) and drug particles (Step 3) and the formulation density and excipient concentration. The volume of the liquid portion of the initial droplet is simply the difference of the total volume of the initial droplet and the volume of the drug particles in that droplet. The mass of the liquid can be determined by multiplying the volume of the liquid and density of the formulation, $\rho_{\text{form}}$, which is calculated as shown in Equation 8.8, where $C_i$ is the weight fraction of some component, $i$, and $\rho_i$ is the density of that component. The density of the formulation is the reciprocal of the sum of the ratio of the weight fraction to the density of the component for each ingredient in the formulation (204).

$$\rho_{\text{form}} = \left( \sum_{i=0}^{n} \frac{C_i}{\rho_i} \right)^{-1} \quad \text{(Equation 8.8)}$$

The mass of the dissolved drug and excipients is equal to the mass of the liquid portion of the initial droplet multiplied by the weight fraction of excipient in the formulation. The volume of the dissolved drug and excipients can then be determined by dividing the mass of the dissolved drug and excipients by its density.
2.1.6. **Step 5 – Determine Aerodynamic Diameter of Residual Particle**

The last step for a given droplet is to calculate the aerodynamic diameter for each drug laden residual particle based on its density \( \rho_R \), Equation 8.9) and volume equivalent diameter \( d_v \), Equation 8.10), where \( M_R \) is the mass of the residual (which is the sum of the mass of any dissolved excipient determined in Step 4 \( M_E \) and mass of drug particles determined in Step 3 \( M_D \) in the particle) and \( V_R \) is the volume of the residual (which is the sum of the volume of the excipient \( V_E \) and volume of the drug \( V_D \)).

\[
\rho_R = \frac{M_R}{V_R} = \frac{M_E + M_D}{V_E + V_D} \quad \text{(Equation 8.9)}
\]

\[
d_v = \left( \frac{6 \times V_R}{\pi} \right)^{1/3} \quad \text{(Equation 8.10)}
\]

Furthermore, for droplets containing two or more drug particles, a shape factor and packing density, are considered. The shape factor accounts for differences in the aerodynamic properties for spherical and nonspherical residual particles. Previous work to estimate shape factors has been done by Cheng et al. (322) and Davies (323). Cheng et al. measured the dynamic shape factor parallel to air flow experimentally by using various sized monodisperse PSL in aerosols from nebulized aqueous suspensions. However, due to the experimental limitation of the testing methods, they only obtained reasonable estimates of the shape factor for agglomerates of up to four particles. On the other hand, Davies developed a theoretical model for determining shape factor, which is
utilized in this paper for droplets containing five or more drug particles. The packing density, a factor of 0.741, accounts for the difference in residual particle density based on void volume that is not occupied by the drug particles. If the droplet contains four drug particles or less, Equations 8.9, 8.10, and 8.11 are used to calculate aerodynamic diameter of the residual particle (322). The value for shape factor used with Equations 8.9, 8.10, and 8.11 is taken to be 1.0, 1.0, 1.022, 1.08 and 1.12 for droplets containing 0, 1, 2, 3 and 4 drug particles, respectively (322). Note that for Equation 8.11 $\text{AD}_R$ is the aerodynamic diameter of the residual particle, and the shape factor is determined as described above based on the number of drug particles contained within the residual particle.

$$\text{AD}_R = d_v \times \left( \frac{\rho_R}{\text{shape factor}} \right)^{\frac{1}{2}} \quad \text{(Equation 8.11)}$$

If the droplet contains greater than four drug particles, Equations 8.12, 8.13 and 8.14 are used to calculate aerodynamic diameter of the residual particle (323). For droplets containing 5, 6, 7, 8 and 9 drug particles the shape factors are considered to be 1.07, 1.05, 1.08, 1.10 and 1.10, respectively as given by Davies (323). For droplets having 10–21 drug particles the shape factor stays relatively constant from 1.12 to 1.14 (323) and droplets having more than 21 drug particles the shape factor remains constant at 1.10. Note that $d_{\text{cluster}}$ is the volume equivalent diameter of the cluster and $\rho_{\text{cluster}}$ is the density of the cluster.
\[ d_{\text{cluster}} = \left( \frac{6 \times V_D}{0.741 \times \pi} \right)^{\frac{1}{3}} \]  
(Equation 8.12)

\[ \rho_{\text{cluster}} = \frac{M_D + M_E}{V_D} \times 0.741 \]  
(Equation 8.13)

\[ AD_R = d_{\text{cluster}} \times \left( \frac{\rho_{\text{cluster}}}{\text{shape factor}} \right)^{\frac{1}{2}} \]  
(Equation 8.14)

2.1.7. Output – Calculate Aerodynamic Particle Size Distribution from Simulation

Steps 1–5 are repeated until at least 10,000 residual particles containing drug are obtained. Since many of the atomized droplets do not contain any drug, more than 10,000 droplets are modeled. Once the sufficient drug containing residual particles are obtained, the simulation is stopped and the drug residual particle size distribution is calculated. This is done by sorting the droplets by aerodynamic particle size and summing the mass of drug particles for all of the droplets contained in each given size bin. The residual particles are sorted into 20 different size bins based on their aerodynamic diameter. Twenty bins were selected in order to provide adequate resolution of the residual particle size distribution. More or less bins could be selected if desired. The total mass of each formulation component contained in all of the residual particles is calculated for each size bin. In this way, the mass of drug in each of the size bins can be determined. This is used to calculate the aerodynamic particle size distribution of the drug delivered in the residual
aerosols. In a similar fashion, it would be possible to determine the aerodynamic particle size distribution of the dissolved excipient delivered in the residual aerosols, but this is usually not desired. A commercial fitting program (DISTFIT™, Chimera Technologies, Forest Lake, MN) is used to calculate the MMAD and GSD of the aerosol. For most formulations, the data is fitted using a monomodal lognormal distribution, as the residual particle distribution usually has only one mode. However, for complex formulations (i.e., combination formulations with two different drugs included in the formulation or formulations with both suspended and dissolved drug) this simplifying assumption may not be valid. A chi-square goodness-of-fit test was used to assess the lognormal distribution; an α-level of < 0.02 was considered indicate a good level of fit for the monomodal lognormal distribution.

2.2. Experimental Materials and Method

Albuterol sulfate micronized to varying particle sizes was provided by 3M Drug Delivery Systems (St. Paul, MN, USA) and Micron Technologies Ltd. (Dartford, Kent, UK). Valves and actuators were provided by 3M Drug Delivery Systems and pressure resistant glass vials were purchased from Research Products International Corporation (Mt. Prospect, IL, USA). HPLC-grade methanol and phosphoric acid were purchased from Sigma–Aldrich (St. Louis, MO, USA). 200 proof ethanol was purchased from Decon Labs (King of Prussia, PA, USA) and HFA 134a, from Atofina Chemicals Incorporated (Philadelphia, PA, USA).
2.2.1. Determining APSD of Micronized Drug

The particle size distribution of two of the lots of micronized albuterol sulfate used in the experimental formulations was measured using the Model 3321 Aerodynamic Particle Sizer Spectrometer™ (APS) in conjunction with the Model 3433 Small Scale Powder Disperser (both from TSI Inc., Shoreview, MN, USA). The first drug lot had an MMAD of 2.62μm and a GSD of 1.81. The second lot had an MMAD of 1.77μm and a GSD of 1.57.

The third drug lot was obtained by high shear homogenization of the first drug lot in 200 proof ethanol using a technique described elsewhere (289,290). After high shear homogenization, the particle size of the albuterol sulfate in the resultant ethanol slurry was measured using the Malvern Mastersizer 2000 particle size analyzer (Malvern Instruments Ltd., Malvern, Worcestershire, UK). Prior to the size measurement, the slurry was diluted by adding additional 200 proof ethanol in order to get the particle concentration in the appropriate range for the instrument. The size of the micronized drug in the slurry was measured to have an MMD of 1.06μm and a GSD of 1.57. Since micronized albuterol sulfate has a density of approximately 1.25g/cm³, the MMAD for this drug lot is approximately 1.22μm.

2.2.2. Formulation of pMDIs

Twelve suspension pMDIs, containing 0.01 to 1% (w/w) of varying sizes of micronized albuterol sulfate and approximately 8.5% (w/w) 200 proof ethanol in HFA 134a were prepared in pressure resistant glass vials (see Table 8.1). Once the glass vials
contained the desired amount of ethanol and micronized drug, a cold-transfer technique was used to fill the vials with HFA 134a. Each of the vials was immediately crimped with a 50μL valve using a small-scale bottle crimper. Vials were sonicated for 60 seconds to disperse the suspension.
Table 8.1: Pressurized MDI Formulations Used for Experimental Size Distribution Measurements with the ACI Along with the Number of Actuations Used During ACI Testing

<table>
<thead>
<tr>
<th>Micronized Drug Size (MMAD, µm; GSD)</th>
<th>Drug Concentration (% w/w)</th>
<th>Ethanol Concentration (% w/w)</th>
<th>Actuations (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.22; 1.57</td>
<td>0.0093</td>
<td>8.9</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>0.0883</td>
<td>8.7</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>0.215</td>
<td>8.7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>0.878</td>
<td>8.6</td>
<td>3</td>
</tr>
<tr>
<td>1.77; 1.57</td>
<td>0.0328</td>
<td>8.2</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>0.107</td>
<td>8.2</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>0.412</td>
<td>8.2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1.028</td>
<td>9.0</td>
<td>2</td>
</tr>
<tr>
<td>2.62; 1.81</td>
<td>0.0333</td>
<td>8.6</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>0.116</td>
<td>8.4</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>0.409</td>
<td>8.2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>1.096</td>
<td>8.7</td>
<td>2</td>
</tr>
</tbody>
</table>
2.2.3. **Andersen Cascade Impactor (ACI) Testing**

Prior to each run, the stages of the ACI were thoroughly rinsed with 50% (v/v) methanol:water followed by 100% methanol and dried in a stream of dry air. Once dry, the stages and the throat were coated with 50:50 methanol:Pluronic L10. QVAR® actuators, with an orifice diameter of 0.3mm, were used for all of the testing. For each experiment in the series, the sample vial was actuated three times in order to prime the valve; the stem of the valve was subsequently cleaned with the diluent (77:23 water:methanol). The valve stem and actuator were then dried and the vial was fitted to the clean actuator. The flow rate through the ACI was adjusted to 28.3L/min using a TSI Series 4000 flow meter (TSI Inc., Shoreview, MN, USA). Triplicate ACI analyses were done using each vial. In order to have sufficient drug on the stages of the ACI for accurate quantification of the drug, the number of actuations for each vial varied between 2 and 25 based on the concentration of the formulation (see Table 8.1). The valve stem, actuator, USP throat, stages 0 through 7, and the filter were rinsed with appropriate volumes of the diluent and the amount of drug present on each stage was determined by high performance liquid chromatography (HPLC).

2.2.4. **Analytical Assay**

The HPLC system consisted of a Waters 2690 Separations module coupled with a Waters 996 PDA. An Apollo C18 5μm 150mm × 4.6mm column, maintained at 30 ± 2°C, was used. 1% phosphoric acid:methanol (77:23 v/v) was used as the mobile phase at a flow rate of 0.75 mL/min with an injection volume of 40μL. The data was collected and
processed utilizing Millennium Version 3.20 with UV detection at 225nm. Quantitation was conducted based on peak area using a standard curve with a linear region between 0.250 and 250μg/mL albuterol sulfate. The total run time was 5 minutes per sample and the retention time for albuterol sulfate was 3.3 minutes. No leachable and extractable compounds were detected from the vials or bags used to rinse the ACI stages upon analysis of the HPLC data.

2.2.5. Determining APSD of Residual Particles

The HPLC results from the ACI test were used to determine the APSD of the drug delivered in the residual aerosols. DistFit was used to determine the MMAD and GSD of the aerosol and the aerosol was assumed to be a monomodal lognormal distribution. For the formulations described in Table 8.1, the residual particle size distributions all fit the monomodal lognormal distribution reasonably well. No size information is available for the portion of the drug that deposited on the valve stem, actuator, and USP inlet and these were, thus, not included in the APSD calculations.
3. Results and Discussion

3.1. Sample Output from Suspension pMDI Model

Simulations were made using the model shown in Figure 8.2 for a variety of pMDI formulation configurations. Sample output from two different configurations are shown in Table 8.2 and Table 8.3. Both of these tables show the first 23 droplets from separate simulations. The first two columns show the diameter and volume, respectively, of the initial droplet for each configuration. The volume and mass of the drug particles and surfactant in each droplet are shown in the fourth through seventh columns. Aerodynamic diameter is shown in the last column. Once the desired number of droplets have been simulated and the droplets are sorted according to their residual particle aerodynamic diameter, the information in column five (mass of drug particles) and the last column (aerodynamic diameter) are used to calculate the aerodynamic particle size distributions of the drug. Note that many of the droplets contain zero drug mass since they do not contain any suspended drug particles in the droplet.
Table 8.2: Output from the First 23 Droplets Simulated for a Given Formulation*

<table>
<thead>
<tr>
<th>Diameter of Droplet (µm)</th>
<th>Droplet Volume (cm³)</th>
<th># of Drug Particles in Droplet</th>
<th>Volume of Drug Particles (cm³)</th>
<th>Mass of Drug Particles (g)</th>
<th>Mass of Surfactant (g)</th>
<th>Volume of Surfactant (cm³)</th>
<th>Mass of Residual Particle (g)</th>
<th>Mass of Particle Aerodynamic Diameter (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.948</td>
<td>1.102E-10</td>
<td>0</td>
<td>0</td>
<td>2.535E-14</td>
<td>2.028E-14</td>
<td>2.535E-14</td>
<td>0.378</td>
<td></td>
</tr>
<tr>
<td>1.214</td>
<td>9.364E-13</td>
<td>0</td>
<td>0</td>
<td>2.154E-16</td>
<td>1.723E-16</td>
<td>2.154E-16</td>
<td>0.077</td>
<td></td>
</tr>
<tr>
<td>1.158</td>
<td>8.134E-13</td>
<td>0</td>
<td>0</td>
<td>1.871E-16</td>
<td>1.497E-16</td>
<td>1.871E-16</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td>5.482</td>
<td>8.628E-11</td>
<td>0</td>
<td>0</td>
<td>1.985E-14</td>
<td>1.588E-14</td>
<td>1.985E-14</td>
<td>0.349</td>
<td></td>
</tr>
<tr>
<td>2.989</td>
<td>1.399E-11</td>
<td>0</td>
<td>0</td>
<td>3.217E-15</td>
<td>2.574E-15</td>
<td>3.217E-15</td>
<td>0.190</td>
<td></td>
</tr>
<tr>
<td>2.750</td>
<td>1.089E-11</td>
<td>0</td>
<td>0</td>
<td>2.505E-15</td>
<td>2.004E-15</td>
<td>2.505E-15</td>
<td>0.175</td>
<td></td>
</tr>
<tr>
<td>3.574</td>
<td>2.390E-11</td>
<td>1</td>
<td>2.031E-12</td>
<td>3.046E-12</td>
<td>5.031E-15</td>
<td>4.025E-15</td>
<td>3.051E-12</td>
<td>1.925</td>
</tr>
<tr>
<td>8.211</td>
<td>2.899E-10</td>
<td>0</td>
<td>0</td>
<td>6.668E-14</td>
<td>5.334E-14</td>
<td>6.668E-14</td>
<td>0.522</td>
<td></td>
</tr>
<tr>
<td>2.159</td>
<td>5.273E-12</td>
<td>0</td>
<td>0</td>
<td>1.213E-15</td>
<td>9.703E-16</td>
<td>1.213E-15</td>
<td>0.137</td>
<td></td>
</tr>
<tr>
<td>3.247</td>
<td>1.793E-11</td>
<td>0</td>
<td>0</td>
<td>4.124E-15</td>
<td>3.300E-15</td>
<td>4.124E-15</td>
<td>0.207</td>
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</tr>
<tr>
<td>2.590</td>
<td>9.096E-12</td>
<td>0</td>
<td>0</td>
<td>2.092E-15</td>
<td>1.674E-15</td>
<td>2.092E-15</td>
<td>0.165</td>
<td></td>
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<tr>
<td>4.301</td>
<td>4.166E-11</td>
<td>0</td>
<td>0</td>
<td>9.582E-15</td>
<td>7.666E-15</td>
<td>9.582E-15</td>
<td>0.274</td>
<td></td>
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<tr>
<td>10.447</td>
<td>5.969E-10</td>
<td>1</td>
<td>1.327E-13</td>
<td>1.991E-13</td>
<td>1.373E-13</td>
<td>1.098E-13</td>
<td>3.363E-13</td>
<td>0.911</td>
</tr>
<tr>
<td>5.296</td>
<td>7.778E-11</td>
<td>0</td>
<td>0</td>
<td>1.789E-14</td>
<td>1.431E-14</td>
<td>1.789E-14</td>
<td>0.337</td>
<td></td>
</tr>
<tr>
<td>3.905</td>
<td>3.118E-11</td>
<td>0</td>
<td>0</td>
<td>7.172E-15</td>
<td>5.738E-15</td>
<td>7.172E-15</td>
<td>0.248</td>
<td></td>
</tr>
<tr>
<td>2.308</td>
<td>6.434E-12</td>
<td>0</td>
<td>0</td>
<td>1.480E-15</td>
<td>1.184E-15</td>
<td>1.480E-15</td>
<td>0.147</td>
<td></td>
</tr>
<tr>
<td>3.522</td>
<td>2.288E-11</td>
<td>0</td>
<td>0</td>
<td>5.263E-15</td>
<td>4.211E-15</td>
<td>5.263E-15</td>
<td>0.224</td>
<td></td>
</tr>
<tr>
<td>21.095</td>
<td>4.915E-09</td>
<td>11</td>
<td>5.188E-12</td>
<td>7.782E-12</td>
<td>1.130E-12</td>
<td>9.036E-13</td>
<td>8.911E-12</td>
<td>2.532</td>
</tr>
<tr>
<td>2.015</td>
<td>4.286E-12</td>
<td>0</td>
<td>0</td>
<td>9.859E-16</td>
<td>7.887E-16</td>
<td>9.859E-16</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>6.094</td>
<td>1.185E-10</td>
<td>0</td>
<td>0</td>
<td>2.726E-14</td>
<td>2.180E-14</td>
<td>2.726E-14</td>
<td>0.388</td>
<td></td>
</tr>
<tr>
<td>10.469</td>
<td>6.007E-10</td>
<td>0</td>
<td>0</td>
<td>1.382E-13</td>
<td>1.105E-13</td>
<td>1.382E-13</td>
<td>0.666</td>
<td></td>
</tr>
<tr>
<td>1.747</td>
<td>2.790E-12</td>
<td>0</td>
<td>0</td>
<td>6.418E-16</td>
<td>5.134E-16</td>
<td>6.418E-16</td>
<td>0.111</td>
<td></td>
</tr>
</tbody>
</table>

*Formulation with 0.4% (w/w) suspended drug with an MMAD of 2.5µm and GSD of 1.6, 8.5% (w/w) ethanol, 0.02% (w/w) oleic acid, 91.1% HFA 134a, 50µL valve, and actuator orifice diameter of 0.3mm.
Table 8.3: Output from the First 23 Droplets Simulated for Another Formulation*

<table>
<thead>
<tr>
<th>Diameter of Droplet (μm)</th>
<th>Droplet Volume (cm³)</th>
<th># of Drug Particles in Droplet</th>
<th>Volume of Drug Particles (cm³)</th>
<th>Mass of Drug Particles (g)</th>
<th>Mass of Surfactant (g)</th>
<th>Volume of Surfactant (cm³)</th>
<th>Mass Of Residual Particle (g)</th>
<th>Aerodynamic Diameter (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.400</td>
<td>4.461E-11</td>
<td>2</td>
<td>3.461E-14</td>
<td>5.192E-14</td>
<td>1.030E-14</td>
<td>1.151E-14</td>
<td>6.222E-14</td>
<td>0.511</td>
</tr>
<tr>
<td>3.387</td>
<td>2.034E-11</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4.703E-15</td>
<td>5.254E-15</td>
<td>4.703E-15</td>
<td>0.204</td>
</tr>
<tr>
<td>1.926</td>
<td>3.741E-12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.648E-16</td>
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*Formulation with 0.4% (w/w) suspended drug with an MMAD of 1.5μm and GSD of 1.6, 8.5% (w/w) ethanol, 0.02% (w/w) oleic acid, 91.1% HFA 134a, 50μL valve, and actuator orifice diameter of 0.3mm.
For the pMDI configuration in Table 8.2, two of the three droplets that did contain
drug particles had just a single drug particle, but the other droplet had 11 drug particles.
For the configuration in Table 8.2, the MMD₁ calculated and used in the simulation was
10.7μm based on Equation 8.2 and the details of the formulation, valve size, and actuator orifice. Most of the droplets are smaller than this (the CMD₁ for this configuration was
3.8μm). As expected based on the properties of the Poisson statistical distribution
function, larger droplets were more likely to contain one or more drug particles. The
largest droplet was the droplet that contained 11 drug particles. This droplet was
approximately eight times larger by volume than any of the other droplets in Table 8.2.
However, not all large droplets contain drug and some relatively small droplets do contain drug. For example, a droplet with an initial diameter of 3.6μm had a drug particle whereas a different droplet with an initial diameter of 8.2μm had no suspended drug particles. This seemingly unusual result is simply a result of the random sampling based on the Poisson distribution probabilities.

The difference in the size of the drug particles from the simulations can be seen in
Table 8.2 by the fact that the mass of drug particles in the two droplets containing a
single drug particle varied by more than a factor of 15. For the droplets containing no
drug particles, the final aerodynamic diameter is essentially proportional to the diameter
of the initial droplet. For the droplets containing drug, the final aerodynamic diameter is
primarily controlled by the mass of the drug particles. The droplet with the 11 drug
particles had the largest residual particle aerodynamic diameter (2.53μm).
Comparing the results in Table 8.2 and Table 8.3 illustrates the impact that the concentration of suspended drug particles has on the percentage of droplets that contain drug particles and the percentage of multiplets. The concentration of suspended drug particles per unit volume increases proportionally with increasing drug concentration in the formulation and increases according to the third power with decreasing input drug size. Thus, the formulation in Table 8.3 has approximately 4.6 times (i.e., 1.67 to the third power) as many suspended drug particles in the formulation as that represented in Table 8.2, since the input drug size for the formulation in Table 8.2 is 1.67 times larger than that for the formulation in Table 8.3. Not surprisingly, the formulation in Table 8.3 has more droplets which contain drug (seven compared to three) and more multiplets (five versus one) than the formulation in Table 8.2.

### 3.2. Factors Influencing Whether Droplets Contain Drug Particles

#### 3.2.1. Does the Droplet Contain any Drug?

Simulations were made on many formulations in order to gain insight into the number of atomized droplets that contain one or more drug particles. In order to do this, the drug concentration was varied from 0 to 1% (w/w) and the input drug MMAD was varied from 1 to 5μm. For all of the formulations, the input drug GSD was set to 1.6, the ethanol concentration to 8.5% (w/w), no surfactant was included, HFA 134a was the propellant, the valve size was set to 50μL, and the actuator orifice diameter to 0.3mm. Figure 8.3 shows the percentage of the atomized droplets that contain one or more drug
particles for these simulations. Both the drug concentration and the input drug size significantly influence the percentage of atomized droplets containing drug, but the influence is most significant for the input drug size. Most commercial suspension pMDI formulations have input drug with MMADs between about 2 and 5μm and concentrations less than about 0.5% (w/w) drug. For these formulations, less than about 30% of the atomized droplets contain drug. In many cases, less than 10% of the atomized droplets contain drug particles.
Figure 8.3: The percentage of atomized droplets containing one or more drug particles from simulations using different drug concentrations and input drug sizes.
3.2.2. How Many Drug Particles does a Droplet Contain?

Drug concentration and input drug size not only influence how many of the droplets contain drug particles, but they also significantly influence how many of the droplets are multiplets. Figure 8.4 illustrates this for four of the formulations used to create Figure 8.3. The majority of the droplets that do contain drug have a single drug particle. This is particularly true for simulated formulations that used an input drug MMAD of 3µm. For the formulation with an input drug size of 3µm and 0.1% (w/w) drug, 87% of the drug containing droplets had just a single drug particle, 9% contained two drug particles, and just 4% of the drug containing droplets had more than two drug particles. The formulation with an input drug MMAD of 1.0µm and 0.5% (w/w) drug had a far greater proportion of multiplets. For this formulation, only 31% of the droplets containing drug had a single drug particle compared to 69% which were multiplets. This formulation had many large multiples. Approximately 5.7% of the drug containing droplets had between 20 and 50 drug particles and about 2.3% of the droplets had more than 50 drug particles. While only about 8.0% of the drug containing droplets had more than 20 drug particles, these droplets contained 54% of the total drug particle mass and thus can significantly impact the overall residual aerosol size distribution. The residual particle sizes of the droplets containing many drug particles are smaller than one might anticipate. For example, one of the droplets in the simulation of the formulation with 0.5% of the 1.0µm MMAD input drug contained 606 drug particles in the droplet. Despite having 606 drug particles, the residual particle aerodynamic diameter was only 5.5µm. It should be noted that particle diameter is not additive for clusters of many drug
particles, but rather drug volume and mass are additive and particle diameter increases with drug mass to the one-third power. Additionally, most of the individual drug particles from an input size distribution with a mass median aerodynamic diameter of 1.0μm are substantially smaller than 1.0μm. As a result, some of these large multiplet particles end up being of an aerodynamic particle size capable of reaching the lung.
Figure 8.4: The percentage of the total droplets containing drug plotted as a function of the number of drug particles in the droplet shown for pMDI configurations with varying micronized drug size and concentration in % (w/w). For all four configurations simulated, the valve size used was 50μL, the orifice diameter was 0.3mm, the ethanol concentration was 8.5% (w/w), and the propellant was HFA 134a.
3.2.3. The Influence of Initial Droplet Size

The data from the full simulations represented in Table 8.2 and Table 8.3 was analyzed to understand the influence of initial droplet size on the likelihood that droplets have at least one drug particle (Figure 8.5) or have multiple drug particles (Figure 8.6). Larger droplets were much more likely to have suspended drug particles than smaller droplets (Figure 8.5). More of the droplets contained drug for the formulation with the smaller input drug size compared to the formulation with the larger input drug size due to the fact that more total drug particles were present in the formulation (Equation 8.5). Larger atomized droplets and formulations with smaller input drug size had the highest probability of having multiple drug particles (Figure 8.6). For the small fraction of droplets with initial diameters greater than 20μm, large agglomerates having many drug particles were obtained. These clusters contained on average 102 and 31 drug particles for the formulations with 1.5μm and 2.5μm input drug MMAD, respectively.
Figure 8.5: The percentage of atomized droplets containing at least one drug particle for the simulations shown in Table 8.2 and Table 8.3. Both formulations contain 0.4% (w/w) drug.
Figure 8.6: The average number of drug particles per droplet containing drug for the simulations shown in Table 8.2 and Table 8.3. Both formulations contained 0.4% (w/w) drug.
Figure 8.7: The residual particle size distribution of drug obtained from a simulation with 0.4% (w/w) suspended drug with an MMAD of 2.5μm and GSD of 1.6, 8.5% (w/w) ethanol, 0.02% (w/w) oleic acid, 91.1% HFA 134a, 50μL valve, and 0.3mm actuator orifice diameter.
3.3. Predicting Residual Particle Size Distributions for a Variety of Suspension pMDI Formulations

3.3.1. Example Residual Particle Size Distribution from a Simulation

The aerodynamic size distribution from the complete simulation that is partially shown in Table 8.2 was calculated using DistFit software and is shown in Figure 8.7 as a representative example of the size distribution results obtained using the model. The MMAD of the residual particles was estimated to be 2.92μm and the GSD was estimated to be 1.63. This simulation contained 10,000 drug containing droplets. The quality of the distribution is highly dependent on the number of drug containing droplets in the simulation and tends to be of poorer quality (i.e., they are more variable and deviate more from a lognormal distribution) when less than 10,000 drug containing droplets are included. The distribution shown in Figure 8.7 was representative of a typical distribution obtained from most of the simulations reported in this paper.

3.3.2. The Influence of Input Drug Size and Concentration on Residual Particle Size Distribution

Simulations were made for formulations with a wide range of input drug sizes and drug concentrations in the formulations. All of these simulations had 8.5% (w/w) ethanol, no surfactant, HFA 134a, and used 50μL valves and actuators with an orifice diameter of 0.3mm. The input drug sizes selected ranged from 0.5 to 2.62μm MMAD. Three of the input particle sizes (1.22, 1.77, 2.62μm MMAD) used in these simulations were selected
due to the fact that albuterol sulfate with these particle sizes was available for experimental testing to compare the simulations to actual experiments (see Section 3.4). The residual particle MMADs from these simulations are shown in Figure 8.8. The residual particle MMAD increases with increasing input drug size and drug concentration.
Figure 8.8: The MMAD obtained from simulations of formulations with varying drug concentrations and input drug size. All experiments assumed 50µL valves, actuators with an orifice diameter of 0.3mm, 8.5% (w/w) ethanol, no surfactant, and HFA 134a.
For the simulations using low drug concentrations, the residual particle MMAD is essentially the same as the MMAD of the input drug. This indicates that the number of multiplets is sufficiently low as to have a minimal impact on the residual particle size distribution. As the drug concentration in the formulation increases, the residual particle MMAD increases due to the increased number of multiplets. The drug concentration at which the residual particle MMAD begins to noticeably deviate from the input drug size is lower for the smaller input drug size. This is due to the fact that at a given drug concentration there are more particles per unit volume for the smaller input drug size. Thus, there are more multiplets at a given drug concentration when a smaller input drug size is used (see Figure 8.4, for example).

The difference that the input drug size has on the residual particle MMAD is less significant at higher drug concentrations. The relationship between input particle MMAD and residual particle MMAD is simple at low drug concentrations. However, the relationship is much more complex at higher drug concentrations. This can be seen by comparing the residual MMAD for formulations 1.0 and 2.25μm input drug. For formulations with drug concentrations of 0.0013% (w/w), the residual particle MMAD was 2.22 times higher (2.22μm compared to 1.00μm) for formulation with 2.25μm input drug. Thus, a 2.25-fold increase in input drug MMAD resulted in a 2.22-fold increase in residual particle MMAD. At the drug concentration of 1.0% (w/w), the 2.25-fold increase in input drug MMAD resulted only in a 1.29-fold increase in residual particle MMAD (3.09μm compared to 2.40μm).
There is some scatter in the simulations is due to the fact that these are random simulations with typically 10,000 drug containing droplets (up to 30,000 in some cases). Most pMDI products on the market, on the other hand, deliver tens to hundreds of millions of drug containing droplets (4). Simulation with larger sample sizes can be used to reduce the variability in the estimated residual particle MMAD (326), but increase computational requirements and thus reduce the number of simulations that can be run in a given amount of time.

3.4. Comparison of Simulated and Experimental Particle Size Distributions

Experimental measurements were made from pMDIs using the formulations described in Table 8.1 with QVAR® actuators and 50μL Spraymiser™ valves. The residual APSDs were measured using the ACI. The residual APSDs were also simulated for these same pMDI configurations. The pMDI configurations examined consisted of a range of different input drug sizes (MMADs from 1.22 to 2.62μm) and a broad range of drug concentrations (less than 0.01 to greater than 1%, w/w). Figure 8.9 shows a comparison of the experimental and simulated APSDs. There was good agreement between the MMAD values predicted in the simulations and those measured from the ACI (R² = 0.97) demonstrating the utility of the algorithm for predicting residual APSDs for a broad range of suspension pMDI configurations.
Figure 8.9: A comparison of the predicted residual particle MMAD to the MMAD obtained from experimental measurements using the ACI for 12 suspension pMDI configurations.
4. Conclusions

A model for predicting the aerodynamic particle size distributions delivered from a variety of pMDIs formulations was developed. This model expands on the models developed by Gonda (318) and Chan and Gonda (319) by allowing for polydisperse micronized input drug to be included in the simulation, dissolved drug and/or excipient to be included in the formulation, and the initial droplet size distribution used in the simulation to be estimated based on empirical equations for HFA 134a formulations (204). The model calculates the aerodynamic diameter of residual particles obtained from atomized droplets after evaporation of the volatile components of the pMDI formulation. Key inputs needed for this simulation are complete details of the formulation composition, the size distribution of any micronized drug(s) included in the formulation, and optionally the initial size distribution of the atomized droplets.

The model was used to evaluate drug delivery from suspension pMDIs. The model indicated that the majority of atomized droplets do not contain micronized drug particles in them. For these droplets, the residual particles contain only surfactant or any other nonvolatile excipient or drug dissolved in the formulation. Typically, less than 30% of the atomized droplets contain micronized drug; however, for many formulations, less than 10% of the atomized droplets contain drug. The percentage of droplets containing drug is sensitive to the drug concentration and very sensitive to the input drug size.

For typical suspension pMDI configurations (with micronized drug having an MMAD > 2μm and a drug concentration less than about 0.5%, w/w), the vast majority of
the atomized droplets that do contain micronized drug particles contain just a single drug particle. For example, less than 13% of the residual particles with drug were multiplets for a suspension pMDI containing 0.1% (w/w) of micronized drug with an MMAD of 3μm. The proportion of the multiplets increases for formulations with higher drug concentrations and smaller input drug sizes. For example, 69% of the residual particles with drug were multiplets for a suspension pMDI containing 0.5% (w/w) of micronized drug with an MMAD of 1μm. For suspension pMDIs that result in residual particles with few multiplets, the size distribution of the residual aerosol delivered to the patient is essentially equal to the size distribution of the micronized drug. On the other hand, suspension pMDIs containing smaller micronized drug and/or higher drug concentrations have a higher proportion of multiplets which in turn can result in a substantially larger MMAD of the residual aerosol compared to the MMAD of the micronized drug.

In order to demonstrate the utility of the model, size distributions predicted using the model for 12 different suspension pMDI configurations were compared to experimental cascade impactor measurements of the aerosol delivered from equivalent suspension pMDIs. The size of the micronized drug was varied from 1.22 to 2.62μm and a wide range of drug concentrations (less than 0.01 to greater than 1%, w/w) were used. On average, the model slightly overestimated the residual particle MMAD by about 6%. However, over this broad range of suspension pMDI configurations, the size distributions predicted by the model closely agreed with the experimental measurement ($R^2 = 0.97$). The close agreement between the predicted and experimentally measured residual particle size distributions demonstrates the utility of this model for predicting suspension pMDI
size distributions. In the future, additional work should be done to demonstrate the utility of this model for predicting the particle size distributions for more complex pMDI formulations such as formulations containing multiple suspended drugs or formulations with one suspended drug and one dissolved drug.
CHAPTER 9

THE INFLUENCE OF INITIAL DROPLET SIZE ON RESIDUAL PARTICLE SIZE FROM PRESSURIZED METERED DOSE INHALERS

Published by: Poonam Sheth, Stephen W. Stein, and Paul B. Myrdal


Summary

Pressurized metered dose inhalers (pMDIs) are widely used for the treatment of diseases of the lung, including asthma and chronic obstructive pulmonary disease. The mass median aerodynamic diameter of the residual particles (MMAD_R) delivered from a pMDI plays a key role in determining the amount and location of drug deposition in the lung and thereby the efficacy of the inhaler. The mass median diameter of the initial droplets (MMD_I), upon atomization of a formulation, is a significant factor influencing the final particle size. The purpose of this study was to evaluate the extent that MMD_I and initial droplet geometric standard deviation (GSD) influence the residual aerodynamic particle size distribution (APSD_R) of solution and suspension formulations. From 48 1,1,1,2-tetrafluoroethane (HFA 134a) solution pMDI configurations with varying ethanol concentrations, valve sizes, and actuator orifice diameters, it was experimentally found that the effective MMD_I ranged from 7.8 to 13.3μm. Subsequently, computational methods were utilized to determine the influence of MMD_I on MMAD_R, by modulating the MMD_I for solution and suspension pMDIs. For solution HFA 134a
formulations of 0.5% drug in 10% ethanol, varying the MMD$_I$ from 7.5 to 13.5µm increased the MMAD$_R$ from 1.4 to 2.5µm. For a suspension formulation with a representative particle size distribution of micronized drug (MMAD = 2.5µm, GSD = 1.8), the same increase in MMD$_I$ resulted in an increase in the MMAD$_R$ from 2.7 to only 3.3µm. Hence, the same increase in MMD$_I$ resulted in a 79% increase in MMAD$_R$ for the solution formulation compared to only a 22% increase for the suspension formulation. Similar trends were obtained for a range of drug concentrations and input micronized drug sizes. Thus, APSD$_R$ is more sensitive to changes in MMD$_I$ for solution formulations than suspension formulations; however, there are situations in which hypothetically small micronized drug in suspension (e.g., 500nm MMAD) could resemble trends observed for solution formulations. Furthermore, the relationship between APSD$_R$ and drug concentration and MMD$_I$ is predictable for solution pMDIs, but this is not as straightforward for suspension formulations. In addition, the MMAD$_R$ was relatively insensitive to changes in initial droplet GSD (from 1.6 to 2.0) and the solution and suspension pMDI residual particle GSDs were essentially identical to the initial droplet GSDs.
1. Introduction

Inhalation drug therapies are widely used for topical treatment of lung diseases, such as chronic obstructive pulmonary disease (COPD) and asthma. These drug delivery systems allow for treating pulmonary conditions, while limiting systemic adverse effects and include liquid nebulizers, dry powder inhalers, and pressurized metered dose inhalers (pMDIs). Pressurized MDIs are well accepted and highly utilized by patients across the globe, with the annual production of over a half-billion units and nearly one trillion pMDI doses inhaled by patients to date (20,152). Moreover, pMDIs are currently being investigated as a method for delivering drugs for systemic illnesses, thereby making drug delivery of these agents less invasive than some of the current delivery mechanisms (341,353,354).

Aerosol delivery from pMDIs is a complex process involving the discharge and atomization of a pressurized propellant-based formulation, rapid evaporation of the volatile components of the formulation, and significant fluid dynamics in the plume. Due to the post-atomization evaporation of the propellant and semi-volatile excipients, the residual particles that are formed are significantly smaller than the initially atomized droplets. The residual particles contain drug and any other nonvolatile excipients found in the formulation and are ideally of a size that readily deposits in the lung.

The particle size distribution of residual particles are often lognormally distributed and can be characterized by the mass median diameter (MMD) or mass median aerodynamic diameter (MMAD) and a geometric standard deviation (GSD). The
MMD or MMAD are the physical diameter or the aerodynamic diameter, respectively, for which half of the total aerosolized mass lies above the indicated diameter. In general, residual particles with aerodynamic diameters less than about 5μm are likely to deposit in the lung, with smaller particles having a better chance to penetrate in the deep lung. Residual particles with aerodynamic diameters less than about 0.5μm have decreased amount of impaction in the lung and are frequently exhaled (34). The GSD describes the spread of the distribution and is the ratio of the diameter corresponding to the 84th percentile to that of the 50th percentile on a log-probability plot. A monodispersed aerosolized distribution (i.e., all of the particles are of identical size) has a GSD of 1, and a polydisperse aerosolized distribution has a GSD greater than 1. Collectively, the residual particle MMAD (MMAD$_R$) and GSD can be used to describe the residual aerodynamic particle size distribution, APSD$_R$.

Pressurized MDIs can be formulated such that the drug is dissolved in the formulation, rendering a solution. The initially aerosolized droplets from pMDIs contain propellant, semi-volatile cosolvents, nonvolatile excipients and the drug. Since solution pMDI formulations are homogeneous, the APSD$_R$ is directly linked to the size of the aerosolized droplets present immediately after atomization, termed as initial droplets (see Figure 9.1). Thus, initial droplets with larger diameters have corresponding larger residual particles than those with smaller diameters. The initial droplet size distribution can be characterized by the MMD of the initial droplets, MMD$_I$. For solution formulations, the MMD$_I$ can be readily used to predict the MMAD$_R$ with the knowledge of the properties of the formulation – particularly the concentration of the nonvolatile
components \((C_{NV},\text{ weight fraction})\) of the formulation and the density of each component of the formulation – as described by Equation 9.1 (82), where \(\rho_I\) and \(\rho_R\) are the densities of the formulation and the residual particles, respectively. The densities of the formulation and of the residual particles required to solve Equation 9.1 can be calculated using Equations 9.2 and 9.3, respectively. Note that \(C\) corresponds to the weight fraction concentration of the component in the subscript and \(\rho\) corresponds to the density of the component mentioned in the subscript for Equations 9.2 and 9.3.

To solve for \(\text{MMAD}_R\), in Equation 9.1, the \(\text{MMD}_I\) must be known. Experimentally determining the \(\text{MMD}_I\) for a given pMDI configuration is especially challenging due to the rapid changes in droplet size immediately upon atomization. Phase-Doppler particle anemometry has been shown to produce useful insight into the size of atomized droplets (76,96). Alternatively, laser diffraction can also be used to experimentally characterize droplet size distributions. These techniques do not measure the size of the droplets immediately after atomization, but nevertheless provide valuable insight into initial droplet size. Unfortunately, both of these approaches require a high level of technical expertise and specialized equipment.

\[
\text{MMAD}_R = \text{MMD}_I \times (\rho_I \times C_{NV})^{1/3} \times \rho_R^{1/6} \quad \text{(Equation 9.1)}
\]

\[
\rho_I = \left(\frac{C_{\text{propellant}}}{\rho_{\text{propellant}}} + \frac{C_{\text{cosolvent}}}{\rho_{\text{cosolvent}}}\right)^{-1} \quad \text{(Equation 9.2)}
\]
Alternatively, pMDIs can be formulated such that solid drug is dispersed in the formulation, creating a suspension. Like solution formulations, predicting APSD$_R$ from suspension formulations also depends on the MMD$_I$. However, due to the heterogeneous nature of suspension formulations, many of the initial droplets do not contain drug and those that do contain suspended drug particles can have a varying number of drug particles (see Figure 9.1). Residual particles that contain more than one drug particle are termed as “multiplets”. As Raabe (350) and Gonda (318) previously presented, a cumulative Poisson distribution (see Equation 9.4) can be utilized to determine the probability that a given initial droplet will contain 0, 1, 2, 3, etc., suspended drug particles. The Poisson distribution is a function of the volume of the initial droplet and the number of suspended drug particles per unit volume (PPUV) in the formulation. It is a discrete distribution that presents the probability (P(I)) of a particular droplet containing some number, I, of drug particles given the average occurrence of the event, M; where M is the product of the volume of the droplet (which is influenced by the MMD$_I$) and the PPUV in the formulation. However, simply knowing a formulation-specific Poisson distribution is not sufficient for determining the APSD$_R$ of suspension pMDIs. Stein et al. (249) published a theoretical method to determine particle size distributions for suspension pMDIs, while accounting for polydispersity of the micronized drug and of the initial droplets. This method requires the user to define the distribution of the initial
droplets and properties of the formulation and then utilizes a simulation algorithm to determine the APSD_R of the suspended drug for that formulation.

\[ P(I) = \frac{e^{-M} \times M^I}{I!} \]  

(Equation 9.4)

Although the underlying principles of pMDI atomization have been investigated (75,76,96), predicting product performance for such devices is still a relatively complex process. Product performance of pMDIs is often characterized by APSD_R and quantification of the amount of drug that would be respirable (i.e., fine particle fraction, mass of drug with aerodynamic diameters of less than approximately 5μm). Frequently, formulation optimization is required to select formulations that provide desirable product performance. To do this, manufacturers need to make several test aerosols with varying formulations and conduct laborious cascade impactor testing to determine the APSD_R and fine particle fraction. Thus, being able to accurately predict residual size distributions would provide the benefit of decreasing the reliance on trial-and-error design for pMDIs. While it is known that MMD_I plays a critical role in determining the APSD_R of solution pMDIs, it is not known how significant of an impact the MMD_I has on the APSD_R of suspension pMDIs. The research presented herein seeks to quantify the effect of initial droplet diameter on the MMAD_R and compare and contrast that effect for 1,1,1,2-tetrafluoroethane (HFA 134a) solution and suspension pMDI formulations.
Figure 9.1: Depiction of droplet atomization from solution and suspension pMDIs. The initial droplets (which contain propellant, semi-volatile cosolvent, nonvolatile excipients and drug) undergo rapid evaporation of the propellant and the cosolvent, leaving only drug and nonvolatile excipients in the residual particle.
2. Experimental Methods

Oligolactic acid, valves, aluminum vials, and actuators were provided by 3M Drug Delivery Systems. 200 proof ethanol was purchased from Decon Labs (King of Prussia, PA, USA) and HFA 134a, from Atofina Chemicals Incorporated (Philadelphia, PA, USA).

2.1. Evaluated Solution Formulations

The pMDIs tested were formulated by the cold-transfer technique in aluminum cans and had nominally 0.4% (w/w) oligolactic acid ($\rho = 1.25\text{g/cm}^3$), as the model “drug”, with HFA 134a as the propellant system ($\rho = 1.21\text{g/cm}^3$). Oligolactic acid is an excipient used in pMDIs to enhance drug solubility, improve suspension quality, or form \textit{in situ} microspheres that can provide sustained release (259,260). In this case, it was used as a model drug due to its relatively high solubility in HFA 134a, which permits solution formulations in which the “drug” concentration could be varied independently from the cosolvent concentration. Ethanol was used as a cosolvent ($\rho = 0.789\text{g/cm}^3$) at concentrations of 1, 5, 10 and 20% (w/w). The vials were fitted with Spraymiser™ metering valves (25, 50 or 100μL). The vials were coupled to actuators with varying orifice diameters: 0.29, 0.36, 0.43 and 0.49mm. In all, 48 configurations were tested.
2.2. Determining APSD<sub>R</sub> and Calculating MMD<sub>I</sub> of Solution Formulations

It has been reported that APSD<sub>R</sub> measurements of solution pMDIs containing up to 20% (w/w) ethanol obtained through the Model 3321 Aerodynamic Particle Sizer (APS) spectrometer (TSI Inc., Shoreview, MN, USA) are correlated well with those acquired via cascade impactor testing and thus are an acceptable means to measure the particle size of pMDIs (355). Thus, the APSD<sub>R</sub> from pMDI solution formulations was determined using the Model 3321 APS. The Model 3306 Respirable Impactor Inlet (RI; also from TSI Inc.), which includes the United States Pharmacopeia (USP) inlet throat, was used to capture the aerosol in the pMDI plume and transfer the sample to the APS for APSD<sub>R</sub> measurements. Tests were conducted by actuating the pMDI into the USP inlet five times, over a span of a 60 second collection period. All configurations were tested in triplicate at a flow rate of 28.3L/min that was verified using a TSI Series 4000 flow meter (TSI Inc. Shoreview, MN, USA).

The MMAD<sub>R</sub> from the APS output was used to calculate MMD<sub>I</sub> based on the varying formulation components using Equation 9.5 and Equations 9.2 and 9.3 for the ρ<sub>I</sub> and ρ<sub>R</sub>. It should be noted that the MMD<sub>I</sub> that is calculated provides insight into the initial droplet size distribution of those droplets which penetrate through the USP inlet and are characterized by the ACI. The GSD of size distribution was also recorded. Additionally, valve delivery was calculated to confirm consistent functioning of the pMDI valves.
\[
MMD_I = \frac{\text{MMAD}_R}{\sqrt[3]{\rho_I} \times C_{\text{NV}} \times \sqrt[6]{\rho_R}} 
\] 
(Equation 9.5)

2.3. Computational Analysis

A theoretical Monte Carlo simulation model has been developed in Microsoft Visual Basic® 6.5 and embedded into Microsoft Excel 2010 (Redmond, WA, USA) to predict APSD\textsubscript{R} from HFA 134a pMDI formulations containing a single drug in solution or suspension with varying cosolvent concentration, orifice diameter, and valve size (248,249). The algorithm for this model is presented in Figure 9.2. To simulate the residual particle size of any given pMDI formulation, the user provides formulation details, and the size distributions of the initial droplets and micronized suspended drug (if applicable). Each atomized droplet is then simulated individually until sufficient drug laden residual particles are obtained to provide a representative size distribution estimate. For the data presented in this paper, each simulation consisted of 10,000 drug laden particles (326) and each formulation was simulated in triplicate. For any given droplet, a physical initial droplet diameter is randomly selected from the lognormal distribution provided by the user. If the pMDI only has dissolved drug, the mass of the drug within the simulated droplet is determined based on the weight fraction of the drug in the formulation. The density of the drug is utilized to determine the aerodynamic diameter of the resulting particle, assuming that the residual particle is spherical (349). For suspension formulations, once the volume of the droplet is calculated, a cumulative Poisson distribution is utilized to randomly determine the number of drug particles in the
droplet based on the droplet volume and number of suspended drug particles per unit volume, PPUV (see Equation 9.6), where $C_{\text{drug}}$ is the concentration of the suspended drug (weight fraction), $\rho_{\text{drug}}$ is the suspended drug particle density, and $\text{GSD}_{\text{drug}}$ and $\text{MMD}_{\text{drug}}$ are the geometric standard deviation and mass median diameter, respectively, of the micronized drug used in the formulation. The size of each drug particle within that droplet is then randomly selected based on the lognormal size distribution of the micronized drug. Thereafter, the aerodynamic diameter of the residual particle is calculated, while accounting for any excipient in solution and changes to the aerodynamic diameter as a factor of the number of drug particles contained within the residual particle (which may affect drag force of the residual particle). The size distribution of all of the residual particles simulated was then determined using Chimera Technologies’ DistFit™ (Forest Lake, MN, USA) with a $\chi^2$ goodness-of-fit limit of 0.02.

$$\text{PPUV (cm}^{-3}) = \frac{6 \times C_{\text{drug}} \times \rho_I \times e^{4.5 \ln^2 \text{GSD}_{\text{drug}}}}{\pi \times (0.0001 \times \text{MMD}_{\text{drug}})^3 \times \rho_{\text{drug}}}$$  \hspace{1cm} (Equation 9.6)
Figure 9.2: Schematic of the algorithm used to predict APSD\(_R\) for pMDIs through a Monte Carlo simulation model.
To better understand the sensitivity of the MMAD\textsubscript{R} on the effect of changing MMD\textsubscript{I} and initial droplet GSD, several theoretical formulations were simulated with a variety of solution and suspension pMDI configurations. MMD\textsubscript{I} values were selected to reflect the range of the MMD\textsubscript{I} found from the experimental APS data. Drug concentration ranged from 0.1 to 0.7% (w/w) ($\rho = 1.25$ g/cm$^3$) and ethanol concentration was fixed at 10% (w/w). The suspended micronized drug was assumed to have an input drug size distribution of 0.5 to 2.5\textmu m MMAD with a GSD of 1.8. The GSD of the initial droplet size distribution was assumed to be 1.8 for all simulations unless otherwise noted (82). For evaluating the effect of the GSD of initial droplet size distribution, the GSD was allowed to vary between 1.6 and 2.0, which resembles realistic GSDs for initial droplets obtained through the USP inlet (82).
3. Results and Discussion

3.1. Range of Initial Droplet Diameters

The MMAD<sub>R</sub> was measured for 48 solution pMDI configurations with ethanol concentrations ranging from 1 to 20% (w/w), orifice diameters ranging from 0.29 to 0.49 mm and valve size ranging from 25 to 100μL using the APS. Subsequently, the corresponding MMD<sub>I</sub> from each configuration's MMAD<sub>R</sub> was calculated using Equation 9.5 and is presented in Figure 9.3.

The MMD<sub>I</sub> ranged from 7.8 to 13.3μm for solution HFA 134a pMDI formulations containing 0.4% (w/w) drug with varying ethanol concentrations, metering valve sizes, and actuator orifice diameters (see Figure 9.3). The effective MMD<sub>I</sub> for pMDIs is influenced by varying formulation and device parameters. MMD<sub>I</sub> increases substantially with the increase of valve size and ethanol. The MMD<sub>I</sub> from pMDI configurations with 25μL valves are more sensitive to changes in ethanol concentration than the configurations with 100μL valves, as presented by the stark increase in MMD<sub>I</sub> for the configurations with 25μL valve as ethanol concentration increases from 1 to 20% (w/w) compared to the 100μL valve configurations. The spread in MMD<sub>I</sub> data for a given ethanol and valve size level is attributed to the effect of orifice diameter on the MMD<sub>I</sub>. At high ethanol concentrations, such as at 20% (w/w), MMD<sub>I</sub> was less sensitive to valve size and orifice diameter. At a given ethanol concentration, increasing orifice diameter from 0.29 to 0.49mm and valve size from 25 to 100μL resulted in an average increase in MMD<sub>I</sub> of approximately 34%. Additionally, for a given orifice diameter, initial droplet
size increased approximately 56% as a function of changing ethanol concentration (from 1 to 20% w/w) and valve size. Over the entire range of orifice diameters, valve sizes, and ethanol concentrations examined, the MMD$_i$ increased by approximately 70%.
Figure 9.3: $\text{MMD}_I$ calculated using Equations 9.2, 9.3, and 9.5, and experimental measurements of MMAD$_R$ for pMDIs with varying ethanol concentration (1–20% (w/w), as presented on the x-axis), valve size (25–100µL, as differentiated by the symbols) and actuator orifice diameters (0.29–0.49mm, attributing to the spread of the data for a given ethanol concentration and valve size). All of the formulations were solution formulations with 0.4% (w/w) drug concentration.
3.2. Effect of Initial Droplet Diameters on APSD$_R$ of Solution and Suspension Formulations

Based on the MMD$_I$ values derived for solution pMDIs through the APS measurements (see Figure 9.3), it was determined that the effective MMD$_I$ from commonly formulated pMDIs is typically between approximately 7 and 14μm. This range provides a representative distribution of initial droplet sizes for HFA 134a pMDI formulations with varied drug concentrations, cosolvent concentrations, valve sizes, and orifice diameters. To evaluate the effect of initial droplet diameters, simulations were done using three different MMD$_I$ values (7.5, 10.5, and 13.5μm) with varying drug concentrations for solution and suspension formulations. Figure 9.4 presents sample distributions from simulations using 0.5% drug in solution or suspension (with a micronized drug size of 2.5μm MMAD and GSD of 1.8) formulations for pMDI configurations in which the MMD$_I$ varied.
**Figure 9.4:** Example size distributions (from simulations) of three solution and three suspension formulations, each containing 0.5% drug (w/w) and 10% (w/w) ethanol. The suspension formulations were simulated with 2.5μm drug (GSD of 1.8) and an initial droplet GSD of 1.8. The intersection of the data curve with the red dashed line at 50% cumulative mass distribution represents the MMAD_R of the formulation.
From Figure 9.4, it is evident that MMD₁ has a greater influence on the MMADₐ for solution formulations compared to suspension formulations. The MMADₐ (represented by the point at which the data curve intersects the red dashed line at 50% cumulative mass distribution in Figure 9.4) for solution formulations ranged from 1.4 to 2.5μm and for suspension formulations, from 2.7 to 3.3μm (for an MMD₁ of 7.5 and 13.5μm, respectively). The MMADₐ for suspension formulations is higher in all cases than those from solution formulations. Interestingly, the amount that the MMADₐ increased with increasing MMD₁ for solution formulations was 1.1μm (an 80% increase) compared to 0.7μm (a 26% increase) for suspension formulations. Thus, for formulations containing 0.5% (w/w) drug, the increase in MMD₁ has greater effect on the resulting MMADₐ of solution formulations compared to suspension formulations.

Figures 9.5 and 9.6 show the result of simulations that illustrate the influence of MMD₁, drug concentration, and size of the suspended drug particles on the change in the residual MMADₐ relative to the MMADₐ obtained using either the smallest MMD₁ or the lowest drug concentration and micronized drug size as the formulation of interest. For all of the formulations, increasing MMD₁ and drug concentration resulted in increased MMADₐ. Furthermore, as the MMD₁ increases for solution formulations, MMADₐ increases linearly as anticipated by Equation 9.1 and is independent of the drug concentration (see Figure 9.5). For solution formulations, the change in MMADₐ with respect to drug concentration (see Figure 9.6) follows a cube-root function (82). Both of these graphs suggest that the change in MMADₐ for solution pMDI formulations with respect to changing MMD₁ is predictable using a simple equation (Equation 9.1).
Suspension pMDIs, with 0.5, 1.25, or 2.5μm MMAD micronized drug, exhibit a decreased relative change in MMAD$_R$ compared to solution pMDI formulations with changes in either MMD$_I$ or drug concentration.
Figure 9.5: The relative change in $\text{MMAD}_R$ with respect to changes in $\text{MMD}_I$ for simulations of solution and suspension pMDIs with 10% (w/w) ethanol and varying drug concentrations. The suspension formulations were simulated with 0.5, 1.25 or 2.5$\mu$m drug (all with a GSD of 1.8) and an initial droplet GSD of 1.8. The “Factor Change in $\text{MMAD}_R$” is defined as the $\text{MMAD}_R$ at a given $\text{MMD}_I$ and drug concentration divided by the $\text{MMAD}_R$ at the lowest $\text{MMD}_I$ value examined (i.e., 7.5$\mu$m) and the same drug concentration and micronized drug size.
**Figure 9.6:** Depicts the effective change in $\text{MMAD}_R$ with respect to change in drug concentration. Each formulation contained 10% (w/w) ethanol. The suspension formulations were simulated with 0.5, 1.25 or 2.5μm drug (all with a GSD of 1.8) and a MMD$_I$ GSD of 1.8. The “Factor Change in $\text{MMAD}_R$” is defined as the $\text{MMAD}_R$ at a given drug concentration and MMD$_I$ divided by the $\text{MMAD}_R$ at the lowest drug concentration examined (i.e., 0.1%) and the same MMD$_I$ as the configuration of interest.
Solution formulations are inherently homogeneous, such that increasing the MMD of each initial droplet will result in a proportional increase in the amount of drug in each initial droplet. Furthermore, increasing the drug concentration in solution pMDI formulations will render a proportional increase in the amount of drug within the initial droplet. As the volatile components in these initial droplets evaporate, the residual particle will consist only of the nonvolatile components of the formulation (in this case, only drug) and will result in an increase in the amount of drug within the residual particle. Consequently, MMAD is related to the mass of the nonvolatile component for the formulation, which in turn is directly proportional to the volume of the drug, in this case. Thus, the MMAD for solution pMDIs would increase as a cube-root function of the drug concentration.

For suspension formulations, the heterogeneous nature of the formulation leads to initial droplets containing a varying number of drug particles. Hence, the MMAD for suspension formulations will be influenced by portion of the droplets that are multiplets which in turn depends on MMD and PPUV (see Equation 9.6). The fraction of multiplets is the proportion of drug laden residual particles from suspension formulations containing two or more drug particles. As drug concentration increases, while all other variables are held constant, the fraction of multiplets and PPUV also increase. As MMD increases, the fraction of multiplets again increases even though the PPUV remains constant (see Table 9.1). The PPUV and MMD are key parameters in the Poisson distribution calculation (see Equation 9.4) and thus impact the number of drug particles within a droplet. Therefore, as the PPUV and MMD increase, the fraction of multiplets will also increase.

When the drug concentration in a suspension pMDI is sufficiently low, the PPUV will
also be low, rendering a residual \( \text{MMAD}_R \) that mimics the MMAD of the micronized drug (249) since very few of the atomized droplets contain more than one drug particle. However, with higher drug concentrations (which proportionally increases PPUV) and \( \text{MMD}_t \) values, more multiplets are formed which leads to a relative increase in \( \text{MMAD}_R \).

Furthermore, Equation 9.6 demonstrates that as the micronized drug size decreases, PPUV will increase. As PPUV increases, the atomized droplets will have a greater proportion of multiples which results in the \( \text{MMAD}_R \) being increasingly larger than the MMAD of the micronized drug. Figure 9.6 indicates that smaller suspended micronized drug have a greater change in relative \( \text{MMAD}_R \) with increasing \( \text{MMD}_t \) or increasing drug concentration compared to larger suspended micronized drug. Notably, suspended 0.5\( \mu \)m MMAD (GSD of 1.8) drug with 0.7\% (w/w) drug and a \( \text{MMD}_t \) of 13.5\( \mu \)m (GSD of 1.8) closely resembles a relative change in \( \text{MMAD}_R \) similar to that seen for a comparable solution pMDI formulation.

The impact of PPUV and the size of the atomized droplet diameter (\( \text{MMD}_t \)) on the percentage of multiplets for pMDI formulations with 2.5\( \mu \)m MMAD micronized drug are shown in Table 9.1. With a 7 fold increase of the drug concentration, from 0.1 to 0.7\%, the percentage of multiplets increases by 2.5 and 1.8 folds, for 7.5 and 13.5\( \mu \)m \( \text{MMD}_t \), respectively. The same increase in drug concentration proportionally increases the PPUV. In addition, there is a 2.3 (0.1\% w/w) and 1.7 (0.7\% w/w) times increase in percent multiplets for a 1.8 fold increase in \( \text{MMD}_t \). Hence, suspension pMDIs with relatively high drug concentration (and thus high PPUV) and relatively large \( \text{MMD}_t \) will have a relatively greater percent multiplets, which leads to the relative increase in the
MMAD$_R$. This rational is also applicable for the pMDI formulations presented in Figures 9.5 and 9.6 with 0.5 and 1.25μm MMAD micronized drug.

3.3. Effect of Initial Droplet GSD on APSD$_R$ of Solution and Suspension Formulations

While the increase in MMAD$_R$ is especially pronounced with increases in drug concentration and MMD$_I$, it is relatively insensitive to increases in initial droplet GSD for solution or suspension formulations (see Figure 9.7). In Figure 9.7, the unshaded symbols represent an initial droplet GSD of 1.6, the partially shaded symbols represent a GSD of 1.8, and the completely shaded symbols represent a GSD of 2.0. Suspension pMDIs with smaller initial droplet GSDs tended to have more multiplets which, surprisingly, results in a relatively small impact on the resulting MMAD$_R$. While modulating the initial droplet GSD did not significantly impact the MMAD$_R$, it did affect the residual particle GSD. The GSD of the residual particles for solution and suspension formulations were essentially identical to that of the initial droplet GSD for all of the configurations presented in Figure 9.7. For instance, suspension formulations with an initial droplet GSD of 1.6 had residual particles with an average ± standard deviation GSD of 1.60 ± 0.017, regardless of the MMD$_I$. Similar results were found for both formulation types and all initial droplet GSDs.
**Table 9.1:** Values of PPUV and Percent Multiplets for Various MMD₁ and Drug Concentrations for Suspension pMDI Formulations with 2.5µm MMAD Micronized Drug

<table>
<thead>
<tr>
<th>Drug Content (% w/w)</th>
<th>MMD₁ (µm) 10.51</th>
<th>7.50</th>
<th>13.50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PPUV (cm⁻³)</td>
<td>Multiplets (%)</td>
<td>PPUV (cm⁻³)</td>
</tr>
<tr>
<td>0.1</td>
<td>7.99 × 10⁸</td>
<td>12.92</td>
<td>7.99 × 10⁸</td>
</tr>
<tr>
<td>0.3</td>
<td>2.40 × 10⁹</td>
<td>22.24</td>
<td>2.40 × 10⁹</td>
</tr>
<tr>
<td>0.5</td>
<td>4.00 × 10⁹</td>
<td>27.91</td>
<td>4.00 × 10⁹</td>
</tr>
<tr>
<td>0.7</td>
<td>5.59 × 10⁹</td>
<td>31.71</td>
<td>5.59 × 10⁹</td>
</tr>
</tbody>
</table>
Figure 9.7: The influence of drug concentration, $MMD_I$ (as presented by the shape of the symbol), and initial droplet GSD (as presented by the shading of the symbol) on $MMAD_R$ for solution and suspension pMDIs with 10% ethanol and HFA 134a. All data were derived from simulations; the suspended micronized MMAD was 2.5μm (GSD = 1.8). Unshaded symbols indicate an initial droplet GSD of 1.6; partially shaded symbols, 1.8; and completely shaded symbols, 2.0.
For a larger initial droplet GSD for suspension pMDI formulations, more droplets need to be simulated to sample the same number of drug laden droplets compared to a smaller initial droplet GSD, as presented in Figure 9.8. In the case of the 1.6 and 2.0 initial droplet GSDs, each of the drug laden size distribution graphs presents a total of 10,000 droplets; however, four times as many droplets needed to be simulated to get the same number of drug containing droplets with an initial droplet GSD of 2.0 for an MMD$_I$ of 10.5μm compared to the GSD of 1.6. Of the drug laden droplets, since the initial droplet size distribution is wider with a GSD of 2.0 than that with a GSD of 1.6, the physical median diameter for a fixed MMD$_I$ is smaller, which is a property of the lognormal distribution and explained by Hatch and Choate (352). In addition, there are relatively more small and less large droplets in the distribution with a GSD of 2.0 than with 1.6. Furthermore, drug particles are more likely to be contained in larger droplets and the larger a droplet is the more likely it is to contain multiple drug particles. For a given MMD$_I$, a smaller GSD has significantly less small initial droplets and marginally more large droplets than a larger GSD, resulting in the larger GSD having a greater potential to contain droplets with single drug particles (i.e., “singlets”) and, conversely, less multiplets. However, the high number of residual particles containing singlets may off-set the impact of a greater proportion of multiplets among drug laden particles for droplets with higher initial droplet GSDs. Thus, with all else held constant, initial droplets with smaller GSDs have more multiplets, which minimally impacts MMAD$_R$ from suspension formulations.
Figure 9.8: Number-weighted size distribution for identical formulations with two different initial droplet GSDs. Each of the formulations contains 0.5% (w/w) suspended drug with 10% (w/w) ethanol in HFA 134a. The formulations were simulated with 2.5μm drug particles (GSD = 1.8). The MMD₁ for these formulations is 10.5μm with a GSD of 1.6 or 2.0. The graph presents the size distributions for all droplets, regardless of if they contain drug particles (i.e., overall distribution) and the distribution of those with drug particles (i.e., drug laden). A total of 10,000 drug laden particles were simulated for both configurations.
4. Conclusions

Experimentally, it was determined that initial droplet mass median diameter (MMD$_I$) ranges from 7.8 to 13.3μm for HFA 134a pressurized metered dose inhaler (pMDI) formulations with varying ethanol concentrations, metering valve sizes, and actuator orifice diameters. Using the experimental range of MMD$_I$ for potentially commercial pMDIs, computational simulations were conducted to gain a better insight on the influence of MMD$_I$ on residual particle mass median aerodynamic diameter (MMAD$_R$) for solution and suspension formulations. Identical changes in MMD$_I$ have a greater impact on the MMAD$_R$ of solution formulations than of suspension formulations, regardless of drug concentrations. Furthermore, the effect of increasing drug concentration and MMD$_I$ for solution formulations has a predictable effect on MMAD$_R$ which can readily be described by a cube-root function of the drug concentration, as presented by Equation 9.1. However, the MMAD$_R$ for suspension formulations is not as sensitive to changes in MMD$_I$ as solution formulations and is greatly dependent on other factors such as drug concentration, micronized drug size, and number of suspended drug particles per unit volume (PPUV), which all affect the fraction of residual particles containing multiple drug particles. Interestingly, the MMAD$_R$ for formulations with small suspended drug (i.e., 500nm MMAD) may be as sensitive to changes in drug concentration and MMD$_I$ as dissolved drug in the HFA 134a system. The initial droplet geometric standard deviation (GSD) of suspension formulations appears to have a significant impact on the percent of residual particles containing multiple drugs, but this
impact does not translate to a distinct change in the MMAD$_R$ for suspension formulations. No significant or predictable relationship is found with modulating initial droplet GSD and MMAD$_R$ for solution formulations. However, the residual particle GSD reflected the initial droplet GSD for both types of pMDI formulations.
CHAPTER 10

FACTORS INFLUENCING AERODYNAMIC PARTICLE SIZE DISTRIBUTION
OF SUSPENSION PRESSURIZED METERED DOSE INHALERS

Published by: Poonam Sheth, Stephen W. Stein, and Paul B. Myrdal


Summary

Pressurized metered dose inhalers (pMDIs) are frequently used for the treatment of asthma and chronic obstructive pulmonary disease. The aerodynamic particle size distribution (APSD) of the residual particles delivered from a pMDI plays a key role in determining the amount and region of drug deposition in the lung and thereby the efficacy of the inhaler. In this study, a simulation model that predicts the APSD of residual particles from suspension pMDIs was utilized to identify the primary determinants for APSD. These findings were then applied to better understand the effect of changing drug concentration and micronized drug size on experimentally observed APSDs determined through Andersen Cascade Impactor testing. The experimental formulations evaluated had micronized drug mass median aerodynamic diameters (MMAD) between 1.2 and 2.6µm and drug concentrations ranging from 0.01 to 1% (w/w) with 8.5% (w/w) ethanol in 1,1,1,2-tetrafluoroethane (HFA 134a). It was determined that the drug concentration, micronized drug size, and initially atomized droplet distribution have a significant impact in modulating the proportion of atomized
droplets that contain multiple suspended drug particles, which in turn increases the residual APSD. These factors were found to be predictive of the residual particle MMAD for experimental suspension HFA 134a formulations containing ethanol. The empirical algebraic model allows predicting the residual particle size for a variety of suspension formulations with an average error of 0.096µm (standard deviation of 0.1µm).
1. Introduction

Inhalation drug therapy is the primary modality of drug delivery for patients that suffer from asthma or chronic obstructive pulmonary disease (COPD). It allows for topical treatment of the lung, while minimizing systemic exposure of the drug. One of the widely utilized methods for delivering drugs to the lungs is through pressurized metered dose inhalers (pMDIs), which use pressurized propellant as the energy source to atomize formulation into droplets containing medications. In addition to pMDI formulations containing propellants and drugs, they may also contain cosolvents (e.g., ethanol) and/or dissolved excipients. The drug may be dissolved in the formulation, rendering a solution; or the micronized drug particles may be dispersed in the formulation, rendering a suspension.

The clinical efficacy from any pMDI depends on a variety of clinical and delivery system factors. While many clinical factors are independent of the device, developing a delivery system that can produce residual particles that can efficiently deposit in the patient’s lung is paramount to the success of the inhaler. One of the primary performance metrics evaluated for pharmaceutical aerosols is the residual aerodynamic particle size distribution (APSD) of the aerosolized drug product. The residual APSD is characterized by the residual mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD). The MMAD signifies the aerodynamic diameter at which half of the aerosolized drug mass lies below the stated diameter. Particles with an aerodynamic diameter of approximately 0.5 to 5µm have the highest probability of depositing in the lung, with the smaller particles having a greater probability to penetrate into the deep
lung. Particles with aerodynamic particles much larger than 5µm tend to impact in the oropharyngeal cavity (356). The larger the GSD value, the greater the spread of the aerodynamic diameters of the residual particles.

When a pMDI is actuated, the formulation exits a spray orifice and is broken up into many initial atomized droplets that contain a representative proportion of each excipient that is dissolved in the formulation. If the drug is in solution, the atomized droplets will also contain an identical proportion of drug as that found in the formulation. However, if the drug is suspended in the formulation, varying number of drug particles are found in a given droplet, with the concentration and size of the solid suspended drug and the size of the initial droplet influencing the number of drug particles in a given droplet (5). Given the volatile nature of the propellant, the propellant rapidly evaporates rendering an intermediate droplet that contains cosolvent, nonvolatile excipient, and the drug. The cosolvent also evaporates over the due course of droplet evolution leaving residual particles that constitute of only nonvolatile mass, which can deposit in the human lungs. These residual particles are significantly smaller than their corresponding initial droplets.

For formulations where the drug is in solution in the HFA-cosolvent system, each atomized droplet contains a proportional amount of drug as that found in the bulk formulation. Throughout the process of droplet evolution from initial droplets into residual particles, each residual particle will contain the same amount of drug as that found in its corresponding initial droplet. This amount of drug will contribute to the residual APSD. Thus, the residual particle size for solution pMDI formulations is
dependent on the size distribution of the initial droplets and the concentration of the drug. The residual APSD is readily estimated by Equation 10.1. Formulations with larger initial droplet sizes result in a larger residual APSD compared to those with smaller initial droplet sizes.

\[
\text{MMAD}_R = \text{MMD}_I \times (\rho_I \times C_{\text{NV}})^{1/3} \times \rho_R^{1/6}
\]

(Equation 10.1)

Where \(\text{MMAD}_R\) (\(\mu\text{m}\)) is the mass median aerodynamic diameter of the residual particles, \(\text{MMD}_I\) (\(\mu\text{m}\)) is the mass median diameter (MMD) of the initial droplets, \(C_{\text{NV}}\) (weight fraction) is the concentration of the nonvolatile components (e.g., dissolved drug and excipients) in the formulation, and \(\rho_I\) and \(\rho_R\) are the densities (\(\text{g/cm}^3\)) of the formulation and the residual particles, respectively.

The residual APSD from suspension pMDI formulations cannot be adequately described by a simple equation. Atomized droplets may contain some number (i.e., 0, 1, 2, 3, etc.) of different sized suspended drug particles. The probability that a given initial droplet will contain a certain number of drug particles can be described by a Poisson distribution (3,4). The Poisson distribution is a function of the volume of the initial droplet and the number of suspended drug particles per unit volume (PPUV) in the formulation. The PPUV increases with decreasing drug size and increasing drug concentration. Thus, it is expected that the residual APSD for suspension pMDI formulations is largely dependent on the size of the drug particles and the proportion of
droplets that contain multiple drug particles. However, a simple and empirical algebraic expression to describe this relationship for suspension pMDIs does not exist.

A useful model that does not require an arsenal of technical calculations and experimentation would greatly benefit the formulation development and quality control process for suspension pMDI manufacturing. It would allow for improved high throughput screening of plausible suspension pMDI products, decreased time and resource investment in current trial-and-error approach to evaluating test pMDIs, and better understanding of the link between pMDI device and formulation variables to product performance. The objective of this study is to thoroughly evaluate the dependency of various parameters (i.e., micronized drug particle size distribution, drug concentration, and initially atomized droplet size) that affect the residual APSD of suspension HFA 134a pMDIs through a previously published simulation model (248,249) along with experimental in vitro cascade impactor data. These factors are analyzed as they relate to intermediate factors such as the proportion of drug containing droplets that contain multiple suspended drug particles and PPUV. The results presented herein will provide the understanding necessary to facilitate suspension pMDI formulation and device design.
2. Experimental Methods

2.1. Computational Algorithm

A Monte Carlo simulation model has been developed in Microsoft Visual Basic® 6.5 and embedded into Microsoft Excel 2007 (Redmond, WA, USA) to predict residual APSD from hydrofluoroalkane pMDI formulations containing a single drug in suspension with varying cosolvent concentration, actuator orifice diameter, and metering valve size (248,249). The algorithm for this model is presented in Figure 10.1. To simulate the residual particle size of any given pMDI formulation, the user provides formulation details and the size distributions of the initial atomized droplets and micronized drug. For the simulations presented in this paper, Equation 10.2 was used to calculate the initial droplet MMD (204), based on knowledge of the formulation and device parameters. Each atomized droplet is then simulated individually until sufficient drug containing residual particles (at least 10,000 particles) are obtained to provide a representative size distribution estimate (326). For any given droplet, a physical initial droplet diameter is randomly selected from the lognormal distribution determined from Equation 10.2 with a GSD of 1.8 (204). Once the volume of the droplet is calculated, a cumulative Poisson distribution is utilized to randomly determine the number of drug particles in the droplet based on the droplet volume and PPUV (see Equation 10.3). The size of each drug particle within that droplet is then randomly selected based on the lognormal size distribution of the micronized drug. Thereafter, the aerodynamic diameter of the residual particle is calculated as a factor of the number, volume, and density of drug particles.
contained within the residual particle. The size distribution of all of the residual particles simulated is then determined using statistical software as presented in Section 2.7.

\[
MMD_i = 6.90 + 0.0441(VS) + 23.6(C_{EtOH}) - 63.8(C_{EtOH})^2 + 24.7(C_{EtOH} \times OD) - 0.129(C_{EtOH} \times VS)
\]  
(Equation 10.2)

Where VS (µL) is the metering valve size, \(C_{EtOH}\) (weight fraction) is the concentration of the ethanol in the formulation, and OD (mm) is the actuator orifice diameter.

\[
PPUV = \frac{6 \times C_{drug} \times \rho_i \times e^{4.5 \ln^2 GSD_{drug}}}{\pi \times (0.0001 \times MMD_{drug})^3 \times \rho_{drug}}
\]  
(Equation 10.3)

Where PPUV (cm\(^3\)) is the number of suspended drug particles per unit volume, \(C_{drug}\) (weight fraction) is the concentration of the drug, \(\rho_{drug}\) (g/cm\(^3\)) is the drug particle density, and \(GSD_{drug}\) and \(MMD_{drug}\) (µm) are the geometric standard deviation and mass median diameter, respectively, of the micronized drug used in the formulation.
**Figure 10.1:** Monte Carlo simulation algorithm utilized to model suspension pMDI formulations. Steps 1 to 4 are repeated until sufficient initial droplets are simulated. Particle size distribution is abbreviated as PSD. All other abbreviations can be found in text.
The Poisson distribution is a discrete distribution that describes the probability that a given droplet, of a defined size, will contain some number of drug particles. It accounts for the size of the simulated initial droplet and the PPUV, to determine the probability that the droplet will have a given number of drug particles. Using a uniform 0 to 1 random number generator (R) and the droplet-specific cumulative Poisson distribution, a specific number of drug particles are found to be contained in the droplet being simulated based on the R-value, which denotes the probability of the fraction less than within the Poisson distribution. If the R-value is close to one, the droplet will contain a relatively larger number of drug particles; if the value is close to zero, the droplet will contain very few or no drug particles.

One way of characterizing the residual particle distribution, other than using the MMAD and GSD, is to evaluate the proportion of drug containing particles that contain one or multiple drug particles. Atomized particles that do not contain drug do not contribute mass or size to the APSD of the drug and can therefore be ignored in this analysis. Residual drug containing particles that contain only one drug particle are termed as “singlets,” while those that contain more than one drug particle are termed as “multiplets.” Since the sum of the percentage of singlets and multiplets always equals 100, generally only one of values will be provided for a given simulation.

2.2. Simulated APSD – Description of Configurations Evaluated

To better understand the sensitivity of the residual MMAD on the effect of changing micronized drug MMAD, drug concentration, and initial droplet MMD, several
theoretical formulations were simulated with a variety of HFA 134a suspension pMDI configurations. For all simulations, unless otherwise noted, the initial droplet MMD was 10.7µm (which corresponds with the initial MMD predicted from Equation 10.2 using a 50µL valve size and 0.3mm actuator orifice diameter), with a GSD of 1.8 (204). The model drug concentration ranged from 0.002 to 4% (w/w) with micronized drug size varying from 0.5 to 3µm MMAD ($\rho_{\text{drug}} = 1.25g/cm^3$). The ethanol concentration was fixed at 8% (w/w).

2.3. Materials

Micronized albuterol sulfate of varying particle sizes were provided by 3M Drug Delivery Systems (St. Paul, MN, USA) and Micron Technologies Limited (Dartfort, Kent, UK). Metering valves, actuators, and Pluronic L10 (BASF Corp., Florham Park, NJ, USA) were provided by 3M Drug Delivery Systems. Pressure resistant glass vials were purchased from Research Products International Corporation (Mt. Prospect, IL, USA). 200 proof ethanol was purchased from Decon Labs (King of Prussia, PA, USA) and HFA 134a, from Atofina Chemicals Incorporated (Philadelphia, PA, USA). HPLC-grade methanol and phosphoric acid were purchased from Sigma-Aldrich (St. Louis, MO, USA).

2.4. Evaluated Experimental Formulations

The particle size distribution of two of the lots of micronized albuterol sulfate that were used in the subsequent formulations were determined using the Model 3321
Aerodynamic Particle Sizer Spectrometer™ (APS) with the Model 3433 Small Scale Powder Disperser (both from TSI Inc., Shoreview, MN, USA). The two lots evaluated had a micronized MMAD of 2.62µm (GSD of 1.81) and 1.77µm (GSD of 1.57). A third drug lot was obtained by high shear homogenization of the first drug lot in 200 proof ethanol using a technique described by Jinks (289) and James et al. (357). The particle size of this lot was determined to have a size distribution of 1.22µm MMAD (GSD of 1.57) using the Malvern Mastersizer 2000 (Malvern Instruments Ltd., Malvern, Worcestershire, UK)

A total of 12 suspension pMDI formulations containing albuterol sulfate 0.01 to 1% (w/w) with varying sizes of the drug and a nominal 8.5% (w/w) 200 proof ethanol in HFA 134a were prepared in pressure resistant glass vials fitted with 50µL Spraymiser™ metering valves. Once the vials contained the desired weight of drug and ethanol, HFA 134a was filled using a cold-transfer technique. Each of the vials was crimped with a valve using a small-scale bottle crimper. Prior to using the vials, the vials were sonicated for approximately one minute to disperse the suspension.

2.5. Andersen Cascade Impactor (ACI) Testing

Before beginning each ACI test, the stages of the ACI were rinsed with 50% methanol in water, followed by 100% methanol and air dried. Once dry, the stages and throat were coated with 50:50 methanol:Pluronic L10 and the methanol was allowed to evaporate in order to prevent particle bounce. QVAR® actuators (orifice diameter of 0.29mm) were used for all tests. For each vial, the vial was actuated three times to prime
the valve, and the stem of the valve was subsequently rinsed with the diluent, 77:23 water:methanol. Once the valve stem was dry, it was fitted with a clean actuator. The air flow through the ACI was adjusted to 28.3L/min and was verified using a TSI Series 4000 flow meter (TSI Inc., Shoreview, MN, USA). Each vial was tested in triplicate and the number of actuations for each test varied between 2 and 25, based on the drug concentration of the vial used. The valve stem, actuator, USP throat, stages 0 to 7, and the filter were rinsed with appropriate volumes of the diluent. The amount of drug deposited on each part was determined by high performance liquid chromatography (HPLC).

2.6. Analytical Assay

The HPLC system consisted of a Waters 2690 Separations Module coupled to a Waters 996 Photodiode Array Detector (both from Waters, Milford, MA, USA). An Apollo C18 5µm 150mm × 4.6mm column was used. 40µL of the sample was injected onto the column and the mobile phase used for the separation was 0.1% phosphoric acid:methanol (77:23 v/v) at a flow rate of 0.75mL/min. The data was collected and processed using Millennium Version 3.20 with UV detection at λ<sub>max</sub> of albuterol sulfate (225nm). Quantitation was conducted based on peak area using a linear standard curve between 0.250 and 250µg/mL albuterol sulfate. The retention time for the drug was 3.3min. No leachable or extractable compounds from vials or bags used to rinse the ACI stages were detected upon analysis of the HPLC data.
2.7. Statistical Analysis

Residual APSDs were determined using Chimera Technologies’ DistFit (Forest Lake, MN, USA), a data fitting program. Data from simulations and experimental tests were assumed to have a monomodal lognormal distribution. For simulated data, the aerodynamic diameters and corresponding mass for the 10,000 droplets simulated were grouped into 20 bins. These data were then inputted into DistFit to determine the MMAD and GSD of the aerosol. For each ACI run, the residual APSD of the albuterol sulfate was determined based off of HPLC results. The cumulative drug mass percentage recovered in the ACI on each stage was included in the particle size analysis. A $\chi^2$ goodness-of-fit test with a p-value < 0.02 was assumed to yield a reasonable lognormal fit for the data.

Multiple linear regressions presented in this paper were performed using Stata Corporation’s Stata 10.0 (College Station, TX, USA). An a priori p-value of 0.05 was used to delineate statistical significance. Adjusted R$^2$ values have been reported for any multiple linear regression models with more than one independent variable.
3. Results

3.1. Factors Influencing the Fraction of Atomized Droplets that Contain Drug Particles

For a single actuation of a pMDI, 700,000 to 300,000,000 droplets can be atomized depending on the formulation and hardware configuration (4). However, for a suspension pMDI formulation, only some of the atomized droplets contain drug particles. The size and concentration of the micronized drug in a suspension pMDI formulation are two important factors that influence the number of atomized droplets that contain drug particles. Figures 10.2 and 10.3 present simulated data for representative HFA 134a suspension formulations with varying concentration of drug and 8% (w/w) ethanol; the data in Figure 10.2 is for a micronized suspended drug size of 1.5μm MMAD (GSD of 2.0), while Figure 10.3 represents a 2.5μm MMAD (GSD of 2.0) distribution.
**Figure 10.2:** Approximate occurrence of residual particles containing 0, 1, or more than 1 drug particle (left y-axis) and residual MMAD (right y-axis) with respect to drug concentration for micronized suspended drug with a MMAD of 1.5μm (GSD of 2.0) for an HFA 134a formulation containing 8% (w/w) ethanol and no other excipients.
Figure 10.3: Approximate occurrence of residual particles containing 0, 1, or more than 1 drug particle (left y-axis) and residual MMAD (right y-axis) with respect to drug concentration for micronized suspended drug with a MMAD of 2.5μm (GSD of 2.0) for an HFA 134a formulation containing 8% (w/w) ethanol and no other excipients.
For all of the micronized drug sizes or concentrations examined, a significant portion of atomized droplets do not contain any drug particles, as represented by the column on the left for each drug concentration (i.e., the dark blue columns) on the bar charts (see Figures 10.2 and 10.3). For example, for formulations with 2.5μm MMAD drug, the percentage of atomized droplets that did not contain drug particles ranged from 58% (at a drug concentration of 1% (w/w)) to 89% (at a drug concentration of 0.1% (w/w)). Formulations with 1.5μm MMAD micronized drug had fewer “empty” droplets (i.e., droplets without suspended drug particles) compared to formulations with 2.5μm MMAD micronized drug; although, 30 to 71% of the simulated droplets did not contain drug for the 1.5μm MMAD micronized drug depending on drug concentration of the formulations examined. In addition, of the droplets that contain drug particles, many have only one drug particle, but some droplets contain multiple drug particles.

The number of atomized droplets that contain drug particles is directly related to the number of drug particles per unit volume (PPUV) in the formulation. Increasing the drug concentration or decreasing the size of the micronized drug results in an increased PPUV, which correspondingly increases the number of atomized droplets containing drug. The percentage of atomized droplets that contain suspended drug particles for the formulations presented in Figures 10.2 and 10.3 can be determined by summing the middle and right bars for each drug concentration series or simply subtracting the percentage of atomized droplets that do not contain drug particles from 100%. Increasing the suspended drug concentration from 0.1 to 1% (w/w) increased the percentage of drug
containing droplets from 29 to 70% for 1.5μm MMAD (see Figure 10.2) and 11 to 42% for 2.5μm MMAD drug formulation (see Figure 10.3).

In addition to the drug concentration and micronized drug size, the initial droplet size also influences the proportion of atomized droplets that contain suspended drug particles. Figure 10.4 presents the percentage of aerosolized droplets that contain micronized drug for three different initial droplet sizes using a 2.5μm MMAD model micronized drug (GSD of 2.0) and a range of drug concentrations (0.1 to 1% w/w) from an HFA 134a system with 8% (w/w) ethanol. Atomized droplets with larger initial droplet MMDs and higher drug concentrations tend have more drug containing droplets than droplets with smaller initial droplet MMDs and lower drug concentrations as presented by Figure 10.4 and further evaluated by Sheth et al. (5). Increasing the simulated initial droplet MMD from 9.1 to 12.3μm results in increasing the proportion of drug containing droplets in a sample of atomized droplets from 11.2 to 15.3% and from 41.6 to 50.8% for formulations with 0.1 and 1% (w/w) 2.5μm MMAD drug, respectively.
Figure 10.4: Proportion of atomized droplets containing suspended drug particles for formulations with 0.1 to 1% (w/w) drug for an HFA 134a formulation containing 8% (w/w) ethanol. Three different sizes of initial droplet sizes were evaluated: 9.1, 10.7 and 12.3μm (GSD of 1.8). The MMAD of the suspended micronized drug is 2.5μm (GSD of 2.0). No other excipients were included in the simulated formulation.
3.2. Factors Influencing the Fraction of Multiplets

Factors that influence the proportion of atomized droplets from a pMDI suspension formulation that contain suspended drug particles, also influence the proportion of drug containing atomized droplets that contain single or multiple drug particles. Thus, the micronized drug size and concentration, and the initial droplet size distribution influence percentage of singlets and multiplets in samples of drug containing droplets.

3.2.1. The Influence of Micronized Drug Size and Concentration on the Proportion of Multiplets

Increasing the micronized drug size for a given drug concentration results in an increase in the occurrence of singlets and a significant decrease in multiplets among a sample of drug containing droplets. For instance, for formulations with 0.1% (w/w) suspended 1.5µm MMAD micronized drug, 15.3% of atomized droplets contain a single drug particle and 13.7% contain more than one drug particle, as determined from simulations (see Figure 10.2). This can also be expressed as 53% singlets and 47% multiplets among a sample of drug containing droplets for this formulation. Similarly, for formulations containing 0.1% (w/w) suspended 2.5µm MMAD micronized drug, 8.2% of atomized droplets contain a single drug particle and 3.1% of atomized droplets contain more than one drug particle, which equals to 73% singlets and 27% multiplets (see Figure 10.3). Thus, increasing the micronized drug size from 1.5 to 2.5µm MMAD results in far fewer multiplets being present which, as will be discussed later, has a significant
influence on the MMAD of the residual aerosol. Similarly, the proportion of droplets containing multiple drug particles starkly increases with increasing drug concentration. In particular, Figures 10.2 and 10.3 show that the number of droplets containing greater than 4 drug particles dramatically increases with increasing drug concentration or decreasing micronized drug particle size. For example, with 0.1% (w/w) 2.5µm MMAD micronized drug, there are only 0.5% of drug containing particles that contain more than 4 drug particles; increasing the concentration to 1% (w/w), leads to increasing the percentage of drug containing particles with more than 4 drug particles to 9.0% (an 18.2 fold increase).

Similar trends are seen with a wide variety of formulations with a fixed initial droplet size distribution. Figure 10.5 presents a contour plot for percentage of multiplets as a factor of micronized drug size and drug concentration for HFA 134a formulations with 8% (w/w) ethanol. A total of 60 simulations were conducted to define the design space presented in Figure 10.5. As previously described, changes in the drug concentration and MMAD of the micronized drug have a systematic effect on the percent of multiplets. For instance, for simulations at 0.1% (w/w) drug concentration, there are approximately 81 and 16% multiplets, for 0.5 and 3µm MMAD micronized drug, respectively. The percent of multiplets is also impacted by the drug concentration to a lesser extent than micronized drug size. This is due to the fact that the number of suspended drug particles in the formulation (PPUV, see Equation 10.3) is proportional to the drug concentration to the first power, but inversely proportional to the MMAD of the drug to the third power.
Figure 10.5: Percentage of simulated aerosolized droplets that contain two or more drug particles in a sample of only drug containing particles as a function of the drug concentration and the MMAD of the micronized drug. All simulations contained micronized drug with a GSD of 1.8, 8% (w/w) ethanol in HFA 134a; no other excipients were included in the simulations.
3.2.2. Effect of Initial Droplet Size Distribution on Percentage of Multiplets

The initially atomized droplets from a pMDI are not entirely uniform in physical size; actually, these droplets follow a lognormal distribution with a given mass median diameter (MMD) and GSD (204). For the simulated data presented in this paper, the MMD of the initial droplet was empirically estimated using Equation 10.2 and the GSD was assumed to be 1.8 for the USP inlet based on the research conducted by Stein and Myrdal (204). Increasing the initial droplet MMD results in a greater propensity of having larger initial droplets within the initial droplet distribution compared to smaller initial droplet MMD.

Simulations were done in order to assess how the initial droplet size influences the proportion of multiplets in the aerosol. The initial droplet MMD can be varied based on device parameters (i.e., metering valve size and actuator orifice diameter) and formulation (i.e., concentration of cosolvent), as presented in Equation 10.2. For the simulations presented in Figure 10.6, the valve size and orifice diameters were varied while the ethanol concentration was fixed at 8% (w/w) to modulate the initial droplet MMD while the formulation was fixed with 0.4% (w/w) suspended drug (having either 1.0 or 2.5µm MMAD). With the increase in initial droplet MMD, there is a significant decrease in percent singlets and increase in percent multiplets. For instance, for a formulation containing 1.0µm MMAD micronized drug, the percentage of drug containing droplets that contained only one drug particle decreased from 37.8 to 20.7% as the initial droplet MMD is increased from 8.0 to 13.0µm. Moreover, with the increase in initial droplet size, the percentage of droplets that contain a large number of drug
particles greatly increased. This is true for both formulations, but is especially evident for formulations with smaller micronized drug particle size. For example, 29.4% of drug containing atomized droplets from a 0.4% suspended formulation containing 1.0µm MMAD micronized drug with 13.0µm initial droplet MMD have more than 9 drug particles; whereas only 11.9% for the same drug size with 8.0µm initial droplet have more than 9 drug particles. These percentages decrease starkly when the micronized drug is changed to 2.5µm MMAD: 4.2% for the 13.0µm and 1.0% for the 8.0µm initial droplet MMD.
Figure 10.6: Percentage of drug containing atomized droplets that contain some number of drug particles for 0.4% (w/w) suspended drug, with 8% ethanol in HFA 134a with varying initial droplet MMD. The purple bars represent 2.5µm MMAD (GSD of 1.8) micronized drug with an initial droplet MMD of 8 or 13µm (GSD of 1.8). The green bars represent 1.0µm MMAD (GSD of 1.8) micronized drug with an initial droplet MMD of 8 or 13µm (GSD of 1.8).
3.3. Relationship Between Proportion of Multiplets and the Residual MMAD

The residual particle MMAD is influenced both by the size of the micronized drug as well as the relative proportion of multiplets in the aerosol. The residual MMAD for any pMDI suspension formulation, containing no additional nonvolatile excipient, is a property of the distribution of drug containing particles. Many of the atomized droplets do not contain suspended drug particles; as a result, these droplets do not contribute to the residual size of the suspended drug. For dilute formulations, most of the droplets containing suspended drug particles are singlets. Thus, the residual MMAD mimics the MMAD of the micronized drug. However, with the increase in concentration or decrease in micronized drug size, more drug containing droplets will have multiple drug particles, which effectively results in the residual MMAD deviating more significantly from the MMAD of the micronized drug. For a given input drug size and initial droplet MMD, the ratio of residual MMAD to the micronized drug MMAD as a function of drug concentration increases in a predictable manner, as presented in Figure 10.7. At low concentrations, the ratio is approximately 1 for all three drug sizes modeled. This indicates that in relatively dilute formulations, the residual MMAD is nearly identical to that of the micronized drug MMAD. However, as the drug concentration increases, the residual MMAD also increases since more multiplets are obtained. This increase is much more dramatic for formulations with smaller micronized drug sizes since many more micronized drug particles are present in the formulation, thus increasing the likelihood of having more droplets containing multiple drug particles.
Figure 10.7: A comparison of the ratio of the residual particle MMAD to the micronized drug MMAD for various sized micronized drug at different concentrations. All simulations were conducted with 8% ethanol in HFA 134a, with no additional excipients.
In addition to the concentration and size of the micronized drug, the initial droplet size distribution also has an impact on the resulting residual MMAD. Figure 10.6 presents data for two different micronized suspended drugs at a concentration of 0.4% (w/w) with two different initial droplet MMDs. The residual particle sizes for the four formulations depicted in Figure 10.6 increased with increasing initial droplet MMD. For instance, for the 1.0µm MMAD micronized drug, the residual MMAD was 1.6µm for a configuration with initial droplet MMD of 8.0µm; the residual MMAD increased to 2.4µm when the initial droplet MMD was increased to 13.0µm. Similar trend was seen for the 2.5µm MMAD micronized drug: increasing the initial droplet MMD from 8.0 to 13.0µm, resulted in increasing the residual MMAD from 2.8 to 3.2µm. The increase in residual MMAD with increasing initial droplet MMD can be primarily attributed to the corresponding increase in percentage of multiplets. For instance, increasing the initial droplet MMD by 5µm increased the percentage of multiplets from 26.7% for 8µm to 44.6% for 13µm initial droplet MMD for the formulations with 2.5µm micronized drug. This led to an overall increase in residual MMAD by 0.42µm. For a larger variety of suspended pMDI formulations (with micronized drug MMAD of 0.5 to 3µm and drug concentrations ranging from 0.004 to 1% (w/w), data not shown), increasing the initial droplet MMD from 8.6 to 13.2µm resulted in increasing the residual MMAD for all micronized drug sizes and drug concentrations.
3.4. Relationship Between Particles per unit Volume (PPUV) and Percentage of Multiplets on Residual MMAD

Interestingly, when the percentage of multiplets among drug containing droplets or the ratio of the MMADs of the residual particle to that of the micronized drug is compared to the PPUV, the data from simulations with varying micronized drug size (0.5 to 3μm MMAD) and varying drug concentration (0.1 to 1.2% w/w) all lie on the same curve, as seen in Figure 10.8. The unshaded symbols in Figure 10.8 correspond to the percentage of multiplets (on the left y-axis) and the shaded symbols correspond to the relative change in residual MMAD as a factor of the MMAD of the micronized drug (on the right y-axis). For a ten-fold change in drug concentration, from 0.1% to 1% (w/w), with a fixed initial droplet MMD, the PPUV for all micronized drug sizes increase by a factor of 10 (see Equation 10.3). The PPUV for the 2.5μm MMAD micronized drug ranged from $7.6 \times 10^8$ to $7.6 \times 10^9$ cm$^{-3}$ for 0.1 and 1% drug concentration, respectively. For the same range of drug concentrations, the PPUV for the 1.0μm drug was much larger and ranged from $1.2 \times 10^{10}$ to $1.2 \times 10^{11}$ cm$^{-3}$. With a ten-fold increase in the PPUV, the percent multiplets for the 1.0μm MMAD micronized drug increased by 26.9% (from 55.7% to 82.5%), and the relative MMAD increased by 60% (from ratio of 1.5 to 2.4). For the 2.5μm MMAD drug, the same increase in the PPUV yielded a similar increase in absolute percentage of multiplets (from 21.2 to 49.1%, for $7.6 \times 10^8$ and $7.6 \times 10^9$ cm$^{-3}$ PPUV, respectively) and a significantly lower change in the relative MMAD (21% increase, from ratio of 1.1 to 1.3) compared to that of the 1.0μm drug.
Figure 10.8: Depicts the percentage of multiplets (on the left y-axis) with the ratio of residual drug MMAD to the MMAD of the micronized drug (on the right y-axis) for a given number of particles per unit volume, PPUV. The various symbols refer to different micronized drug size (all with GSD of 1.8). Unshaded symbols correspond to the percentage of multiplets axis. Shaded symbols correspond to the MMAD ratio. All simulated formulations contained drug concentration between 0.1 and 1.2% (w/w), 8% ethanol in HFA 134a, with no additional excipients.
Increasing the drug size leads to decreasing the PPUV, decreasing the percentage of multiplets, and decreasing the relative MMAD, as seen by the short segments of each series for a given curve in Figure 10.8. When the PPUV is low for a formulation, the percentage of multiplets is also low. The percent of multiplets for the given initial size distribution can be modeled by Equation 10.4. In addition, as evidenced with the data presented in Figure 10.7, the ratio of the MMADs of the residual particle to the micronized drug is nearly 1 for formulations with low percentage of multiplets. However, with the increase in percentage of multiplets, the PPUV and the MMAD ratio also increase. In fact, the relative change in residual MMAD as a factor of the size of the micronized drug, for an initial droplet MMD of 10.7µm with GSD of 1.8, can be modeled by Equation 10.5. Increasing the initial droplet MMD from 10.7µm would yield a greater proportion of multiplets than what is modeled by Equation 10.4 and a greater ratio of residual MMAD to micronized drug MMAD than what is modeled by Equation 10.5.

\[
\text{Multiplets} = -0.544 \ln^2(\text{PPUV} \times 10^{-8}) + 17.23 \ln(\text{PPUV} \times 10^{-8}) - 14.422
\]

\[R^2 = 0.99\]

Where Multiplets is the percentage of multiplets for formulations with an initial droplet MMD of 10.7µm and PPUV (cm\(^{-3}\)) is the number of drug particles per unit volume in the formulation, which can be calculated from Equation 10.3.
\[
\frac{\text{MMAD}_R}{\text{MMAD}_{\text{Drug}}} = 0.0615 \ln^2(\text{PPUV} \times 10^{-8}) - 0.201 \ln(\text{PPUV} \times 10^{-8}) + 1
\]

\[R^2 = 0.98\]

Where \(\text{MMAD}_R\) is the residual MMAD of the formulation and \(\text{MMAD}_{\text{Drug}}\) is the micronized drug MMAD, which collectively provide the relative increase in residual MMAD as a factor of the micronized drug size. The PPUV \((\text{cm}^{-3})\) can be calculated from Equation 10.3.

### 3.5. Comparison of Simulated Data with Experimental Data

While the above results and conclusions were determined through a simulation model developed by Stein et al. (248,249), similar trends are seen with experimental cascade impactor testing using the USP inlet. With dilute drug concentrations, the residual MMAD closely mimics that of the micronized drug. For instance, the average residual MMAD (for the lowest concentration, \((\text{w/w})\)) for each of the micronized drug sizes experimentally evaluated are \(1.47 \pm 0.04\mu\text{m} (0.010\%)\), \(1.73 \pm 0.005\mu\text{m} (0.033\%)\), and \(2.55 \pm 0.03\mu\text{m} (0.033\%)\) for the 1.22, 1.77, and 2.62\(\mu\text{m}\) MMAD micronized drug, respectively. As the drug concentration increased, the ratio of the MMAD of the residual particle to that of the micronized drug also substantially increased, indicating that the residual particle MMAD increased. When compared to simulated data, the residual MMADs of these formulations varied by a maximum of 8.8%, which corresponds to an
absolute difference of 0.22μm; the average (± standard deviation) difference is 4.03% (± 4.66%), which corresponds to 0.096μm (± 0.088μm). When comparing the experimental residual MMAD to the percentage of multiplets (determined through simulations), it is evident that the increase in the residual MMAD is closely associated with the increase in the percentage of multiplets.

Furthermore, the calculated PPUV was used to calculate the relative increase in residual MMAD as a function of the micronized drug size for formulations containing nominal 8% (w/w) ethanol in HFA 134a (see Equation 10.5, above) and was compared to the experimental values. This theoretical ratio predicted the experimental ratio of residual MMAD to micronized drug MMAD with modest accuracy, with an absolute error being between 0.002 and 0.27 (average of 0.085). Equation 10.5 was further utilized to predict the residual MMAD for twelve experimental formulations. The experimental and predicted residual MMADs were well correlated with an R² of 0.907, with an absolute difference of 0.010 and 0.39μm between the two MMAD values. Of note, Equation 5 was developed based on simulated formulations containing 8% (w/w) ethanol; however, the experimental formulations contained an average of 8.5 ± 0.3% ethanol. Not surprisingly, Equation 10.5 under-predicts the residual MMAD for most of these formulations, since it assumes that the initial droplet size is smaller than if it was calculated using Equation 10.2 with the experimental ethanol concentration.

Since Equation 10.5 does not effectively predict residual MMAD from formulations with varying calculated initial droplet MMDs, a multiple linear regression model was developed to further expand the range of formulations that may be evaluated.
Equation 10.6 was found to be a reasonable empirical model with each variable having a p-value < 0.05 and an overall p-value < 0.001 with an adjusted $R^2$ of 0.94. The residual MMAD from suspension pMDI formulations is highly dependent on the micronized drug size and concentration, and initial droplet size, which all play a key role in determining the number of multiplets among a sample of drug containing droplets. The resulting residual MMAD from Equation 10.6 was compared to experimental residual MMAD values derived from Andersen Cascade measurements, as depicted in Figure 10.9. Experimental residual MMADs were well correlated to Equation 10.6, with an $R^2$ of 0.95 about the line of unity, suggesting that with the knowledge of the values for the parameters in Equation 10.6, one can effectively correlate the residual MMAD from HFA 134a suspension pMDI formulations with only one drug and no other excipients.

$$\text{MMAD}_R = 0.768(\text{MMAD}_{\text{Drug}}) + 0.0759(\text{MMD}_I) + 88.6C_{\text{Drug}} \quad \text{(Equation 10.6)}$$

$$+ \frac{7.25}{\text{MMAD}^3_{\text{Drug}}} - 0.4$$

$$R^2 = 0.94$$

Where $\text{MMAD}_R$ ($\mu$m) is the residual MMAD from a suspension HFA 134a pMDI formulation, $\text{MMAD}_{\text{Drug}}$ ($\mu$m) is the micronized drug MMAD, $\text{MMD}_I$ ($\mu$m) is the initial droplet MMD (calculated from Equation 10.2), $C_{\text{Drug}}$ (weight fraction) is the concentration of the suspended drug.
Figure 10.9: A comparison of experimental residual MMAD values derived by Andersen Cascade Impactor measurements to those values derived from Equation 10.6. The red dotted diagonal represents the line of unity. The model micronized drug MMAD varied from 1.22 to 2.62µm (with varying micronized drug GSD). All formulations contained varying concentrations of drug with a nominal 8.5% (w/w) ethanol and HFA 134a. All of the aerosol vials were fitted with 50µL Spraymiser™ valves with 0.3mm actuator orifice diameters.
4. Discussion

The relationships evaluated in this chapter can be explained by considering the determinants of residual particle size for suspension pMDI formulations. Many of the atomized droplets do not contain drug; hence, they do not have an impact on the residual particle size. The residual particle MMAD is only dependent on atomized droplets that contained at least one drug particle. The primary determinants of the aerodynamic diameter of a given simulated residual particle are the size and the number of the drug particles within that droplet and the size of the droplet. As more atomized drug containing droplets for a given formulation contain multiple drug particles, the larger the residual MMAD will be.

The Poisson distribution is utilized to determine the number of drug particles within each simulated atomized droplet, thus it also determines the percentage of multiplets among drug containing droplets. The Poisson distribution changes for each initially atomized droplet, based on the average value of having a given number of drug particles within a droplet. This average value is defined as the product of the initial droplet volume, and the particles per unit volume (PPUV) for the formulation. The initial droplet volume is a function of the initial droplet MMD. The PPUV is a calculated value and increases with increasing drug concentration and decreasing micronized drug volume. The micronized drug volume is a function of the micronized drug MMAD. This leads to a high PPUV for high concentration formulations with small micronized drug.

Equation 10.6 was developed to predict the residual MMAD from suspension pMDIs with ethanol in HFA 134a. It was found that the micronized drug MMAD and
concentration, and initial droplet MMD (which is modulated by metering valve size, actuator orifice diameter, and cosolvent concentration and calculated from Equation 10.2) are significant predictors for the residual MMAD. Interestingly, all of these variables are determinants for the percentage of multiplets in a sample of drug containing droplets. With the increase in PPUV of the formulation (a function of micronized drug concentration and size) and initial droplet volume, the residual particle MMAD increases. Furthermore, at dilute concentrations, when the PPUV is relatively low, the residual particle size mimics that of the micronized size of the drug. At high drug concentrations, the micronized size of the drug continues to play a critical role in determining the residual MMAD, but the relationship between micronized drug size and residual particle size is not direct. At high concentrations of smaller micronized drug, the resulting residual particle MMAD is primarily determined by the number of multiplets and the size of the drug particle aggregates. For high concentration formulations with larger micronized drug size, the deviation of the resulting residual particle MMAD from the MMAD of the micronized drug is not substantial. For such formulations it is physically less possible to fit multiple drug particles into a given atomized droplet, thus the resulting residual particle MMAD is primarily determined by the number and size of singlets, which can be thought of as the lack of substantial percentage of multiplets.
5. Conclusions

Overall, the study presented herein shows that residual particle MMAD from single drug containing suspension HFA 134a formulations can be empirically predicted for a variety of micronized drug size using basic arithmetic operations. The residual particle MMAD is highly dependent on the micronized drug size and concentration, and the initial droplet MMD. The initial droplet MMD for such formulations can be calculated with knowledge of the metering valve size, actuator orifice diameter, and ethanol concentration. Increases in drug concentration, micronized drug size, and initial droplet MMD leads to an increase in residual particle MMAD. Furthermore, increase in drug concentration and initial droplet MMD leads to a substantial increase in the ratio of the residual particle MMAD to the micronized drug MMAD. This effect is especially pronounced for high concentration formulations with relatively small micronized drug MMAD.
CHAPTER 11
UNDERSTANDING AND MODELING AERODYNAMIC PARTICLE SIZE DISTRIBUTION OF SUSPENSION PRESSURIZED METERED DOSE INHALERS CONTAINING DISSOLVED DRUG OR EXCIPIENT

Parts of this chapter have been prepared for a manuscript authored by Poonam Sheth, Usir S. Younis, Stephen W. Stein, Erik Mogalian, and Paul B. Myrdal

Summary

The pressurized metered dose inhalers (pMDIs) formulations described herein may contain a dissolved drug or excipient in combination with a suspended drug or excipient. When formulating such products, it is important to be cognizant of the impact an additional nonvolatile entity may have on the drug’s aerodynamic particle size distribution (APSD). Through experimental analyses of a variety of combination pMDIs and the aid of a simulation model, a more thorough understanding of such formulations is presented. Variables, such as the dissolved entity’s concentration, suspended entity’s micronized size, and suspended entity’s concentration are identified as key variables that impact the APSD of the dissolved and suspended drug(s) or excipient(s). Through the data presented in this chapter, it is possible to better understand the product performance of more complex suspension formulations and define formulation parameters with quality as the end goal.
1. Introduction

Inhalation drug therapies are widely used for treating lung conditions such as asthma and chronic obstructive pulmonary disease (COPD). These delivery systems allow for treating pulmonary diseases while limiting systemic adverse effects. One of the modalities of delivering drugs to the lung is via the pressurized metered dose inhaler (pMDI). The first pMDI was produced in the mid-1950’s by Riker Laboratories (now, 3M Pharmaceuticals) (3). These devices are now well accepted and highly utilized with global annual production of over half-billion units (152) and sales increasing by 24 million units from 2007 to 2010 (total sales of 277 million in 2010) (358).

Current therapeutic guidelines for the treatment of asthma and COPD suggest patients use drugs from different drug classes on a regular basis to effectively treat their conditions. The National Heart, Lung, and Blood Institute’s (NHLBI’s) Guidelines for the Diagnosis and Management of Asthma (359) recommends that patients use long-acting β-agonists along with inhaled corticosteroids to manage their moderately severe chronic condition. If the condition progressively worsens, a triple therapy is suggested with the aforementioned drug classes and an anticholinergic agent. The addition of multiple inhaled drug therapies to a patient’s medication regimen frequently adds confusion and increased chances of poor medication regimen adherence. Thus, being able to combine therapies in one pMDI affords great benefits to patients. Despite these advantages, combining various drugs in one system complicates the formulation process due to differences in solubility and effective doses.
1.1. Dual Drug Combination pMDIs

When formulating two or more drugs in one pMDI device, a “coformulation effect” must be considered. A combination inhaler product of two drugs may have different product performance than if both drugs were formulated separately at doses identical to that present in the combination inhaler product. Furthermore, if the drug concentration of one of the drugs in a dual drug combination pMDI is altered, it may non-linearly impact the product performance, especially aerodynamic particle size distribution (APSD) of the second drug in the combination (22). More often than not, product performances for the two drugs in a combination formulation differ from each other. Moreover, this effect is generally dose-dependent of the individual components of the pMDI formulation, resulting in differing product performance for both drugs with change in the concentration of either drug (22).

1.2. Importance of APSD

Initially atomized droplets from pMDIs are relatively large and contain propellant, cosolvent, dissolved excipients, and drug(s) in solution and/or suspension. These droplets are lognormally distributed (249) and undergo a dynamic transformation with the evaporation of the propellant and cosolvent, leading to lognormally distributed residual particles of nonvolatile matter that can deposit in the human lungs. The ability of a pMDI to deliver drug to the lung is largely dependent on the residual aerodynamic particle size distribution (APSD). APSD is characterized by mass median aerodynamic diameter (MMAD) and geometric standard distribution (GSD). An aerodynamic diameter
of a particle is defined as the diameter of a spherical particle with unit density that has the same settling velocity as the particle of interest. The mass median diameter (MMD) is the physical diameter at which half of the aerosolized mass lies above the indicated diameter; MMD can be converted to MMAD by multiplying by the density of the droplet. The GSD represents the spread of the lognormal distribution of the particles, where a GSD of 1 indicates a sample of monodispersed particles and a GSD greater than 1 indicates polydisperse particles.

Particles with aerodynamic diameters of less than approximately 5μm are more likely to penetrate into the lung (34). Along with clinical factors, formulation parameters (e.g., amount of cosolvent, nonvolatiles, and propellant), device parameters (e.g., valve size and orifice diameter), and variability in micronized drug lot (i.e., MMD and GSD of input suspended drug) have a significant impact on APSD and thereby the success of an aerosolized product. The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) has focused on APSD as it pertains to quality control of pMDIs and other inhaled medications (35-37). These papers highlight the correlation of APSD to drug deposition in the lung and further present the necessity to determine and understand APSD with faster, higher throughput methods than by cascade impactors.

1.3. Value of Modeling APSD and Study Objectives

The atomization of nebulized monodisperse suspensions was first investigated by Raabe (350). Subsequently, the delivery from suspension pMDIs has been modeled by Gonda (318) and Chan and Gonda (319) who built upon the work of Raabe to model
delivery of monodisperse particles contained in polydisperse droplets. In reality, the delivery of drug from suspension pMDIs is more complicated than that modeled by Gonda and Chan, since the drug particles are virtually always polydisperse and most suspension pMDIs include nonvolatile excipients that modify the APSD. Some of the principles used by Raabe (350), Chan, and Gonda (318,319) can be applied to modeling polydispersed micronized drug in a suspension pMDI formulation with polydispersed droplets. A current simulation model (248,249) effectively simulates the APSD for a single drug suspended in 1,1,1,2-tetrafluoroethane (HFA 134a) with ethanol.

A useful model that predicts APSD from dual drug pMDIs and does not require an arsenal of technical calculations and experimentation would benefit the formulation and quality control process for pMDI manufacturing. It would facilitate the formulation process by allowing for improved high throughput screening of plausible dual component pMDI products and decreased time and resource investment in current trial-and-error approach to evaluating test pMDIs. Furthermore, it may provide guidance in defining the design space for potentially successful pMDI products with two nonvolatile components, where one is in solution and the other is in suspension.

The study, described herein, seeks to expand on the model developed by Stein et al. by including a dissolved drug in the suspension pMDI and provide a better understanding of how APSD of the dissolved or suspended entity is modified by changing the concentration of either drug or changing the size of the suspended drug. Furthermore, the model’s application can be broadened to include predicting APSD for any type of nonvolatile component in solution and suspension in the HFA 134a-ethanol
system. For instance, the model can be extended to evaluate formulations such as (1) suspended excipient with dissolved drug, such as that presented in Stein’s patent (38); or (2) suspended drug with dissolved excipient, such as that seen in Proventil® HFA formulation. From a quality control standpoint, such a model would provide better understanding of the sensitivity of various device and formulation components to product performance, which permits a priori evaluation of batch-to-batch variation. While such a model is extremely useful in decreasing the time required to find or perfect a potential pMDI product, it will not eliminate the need for rigorous in vitro testing of pMDI products, since the model presents a best-case scenario.
2. Materials and Methods

2.1. Experimental Materials and Method

Micronized albuterol sulfate of varying particle sizes was provided by 3M Drug Delivery Systems (St. Paul, MN, USA) and Micron Technologies Ltd. (Dartford, Kent, UK). Beclomethasone dipropionate, micronized lactose monohydrate of varying particle sizes, flunisolide hemihydrate, oleic acid, valves, and actuators were provided by 3M Drug Delivery Systems. Lactose monohydrate serves as a model suspended drug for this study. Pressure resistant glass vials were purchased from Research Products International Corp. (Mt. Prospect, IL, USA). HPLC-grade methanol and phosphoric acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). 200 proof ethanol was purchased from Decon Labs (King of Prussia, PA, USA), and HFA 134a from Atofina Chemicals Inc. (Philadelphia, PA, UA).

2.1.1. Determining the APSD of Micronized Drug

The particle size distribution of two lots of micronized albuterol sulfate used in the experimental formulations was measured using the Model 3321 Aerodynamic Particle Sizer Spectrometer™ (APS) in conjunction with the Model 3433 Small Scale Powder Disperser (both from TSI Inc., Shoreview, MN, USA). The first lot had an MMD of 2.30µm and a GSD of 1.81. The second lot had an MMD of 1.55µm and a GSD of 1.57. A third lot of albuterol sulfate was obtained by high shear homogenization of the first drug lot in 200 proof ethanol using a technique described by Jinks (289) and James et al.
After high shear homogenization, the particle size of the albuterol sulfate in the slurry was measured using the Malvern Mastersizer 2000 particle size analyzer (Malvern Instruments Ltd., Malvern, Worcestershire, UK). The MMD was determined to be 1.06µm with a GSD of 1.57.

In addition, the Malvern Mastersizer 2000 was also used to determine the size of two lots of lactose monohydrate. The first lot has a MMD of 2.12µm with a GSD of 1.60. The second lot was prepared by high shear homogenization using an Avestin EmulsiFlex-C50 (Avestin Europe GmbH, Mannheim, Germany), as described elsewhere (38). The MMD of the homogenized lot was 1.06µm with a GSD of 1.60.

2.1.2. Formulation of pMDIs

33 pMDIs containing 0 to 1.4% (w/w) of varying sizes of suspended, micronized albuterol sulfate or lactose monohydrate, 0 to 0.3% (w/w) dissolved drug (beclomethasone dipropionate or flunisolide hemihydrate), and 0 to 0.03% oleic acid with approximately 8.2% (w/w) 200 proof ethanol in HFA 134a were prepared in pressure resistant glass vials (see Table 11.1). Once the glass vials contained the desired amount of ethanol and drugs, a cold-transfer technique was used to fill the vials with HFA 134a. Each vial was immediately crimped with a 50µL Spraymiser™ metering valve using a small-scale bottle crimper. Vials were sonicated for 60 seconds to disperse the suspension.
Table 11.1: Pressurized MDI Formulations Used for Experimental APSD Measurements with the ACI

<table>
<thead>
<tr>
<th>Suspended Drug* and Concentration (% w/w) (MMD, GSD)</th>
<th>Dissolved Drug* and Concentration (% w/w)</th>
<th>Oleic Acid Concentration (% w/w)</th>
<th>Ethanol Concentration (% w/w)</th>
<th>Number of Actuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS, 0.0093% (1.06µm, 1.57)</td>
<td>BDP, 0.084%</td>
<td>8.1%</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>AS, 0.215% (1.06µm, 1.57)</td>
<td>BDP, 0.167%</td>
<td>8.0%</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>AS, 0.878% (1.06µm, 1.57)</td>
<td>BDP, 0.253%</td>
<td>8.4%</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>AS, 0.030% (1.55µm, 1.57)</td>
<td>FH, 0.166%</td>
<td>0.019%</td>
<td>8.0%</td>
<td></td>
</tr>
<tr>
<td>AS, 0.410% (1.55µm, 1.57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS, 1.028% (1.55µm, 1.57)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS, 0.052% (2.30µm, 1.81)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS, 0.409% (2.30µm, 1.81)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS, 1.096% (2.30µm, 1.81)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS, 0.032% (1.55µm, 1.57)</td>
<td>BDP, 0.076%</td>
<td>8.2%</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>AS, 0.019% (1.55µm, 1.57)</td>
<td>BDP, 0.249%</td>
<td>8.4%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>AS, 0.532% (1.55µm, 1.57)</td>
<td>BDP, 0.090%</td>
<td>8.2%</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>AS, 0.407% (1.55µm, 1.57)</td>
<td>BDP, 0.302%</td>
<td>8.0%</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>AS, 0.982% (1.55µm, 1.57)</td>
<td>BDP, 0.079%</td>
<td>8.3%</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>AS, 1.039% (1.55µm, 1.57)</td>
<td>BDP, 0.306%</td>
<td>8.4%</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>AS, 0.028% (2.30µm, 1.81)</td>
<td>BDP, 0.071%</td>
<td>8.0%</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>AS, 0.038% (2.30µm, 1.81)</td>
<td>BDP, 0.282%</td>
<td>8.3%</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>AS, 0.672% (2.30µm, 1.81)</td>
<td>BDP, 0.068%</td>
<td>8.1%</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>AS, 0.728% (2.30µm, 1.81)</td>
<td>BDP, 0.260%</td>
<td>8.0%</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>AS, 1.238% (2.30µm, 1.81)</td>
<td>BDP, 0.073%</td>
<td>8.0%</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>AS, 1.356% (2.30µm, 1.81)</td>
<td>BDP, 0.268%</td>
<td>8.0%</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>LM, 0.973% (1.06µm, 1.60)</td>
<td>BDP, 0.080%</td>
<td>9.9%</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>LM, 1.003% (2.12µm, 1.60)</td>
<td>BDP, 0.085%</td>
<td>8.0%</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>AS, 0.402% (1.06µm, 1.57)</td>
<td>BDP, 0.084%</td>
<td>0.018%</td>
<td>8.0%</td>
<td></td>
</tr>
<tr>
<td>AS, 0.126% (1.06µm, 1.57)</td>
<td>FH, 0.171%</td>
<td>0.017%</td>
<td>8.1%</td>
<td></td>
</tr>
<tr>
<td>AS, 0.397% (1.70µm, 1.60)</td>
<td>BDP, 0.083%</td>
<td>0.030%</td>
<td>7.9%</td>
<td></td>
</tr>
<tr>
<td>AS, 0.121% (1.70µm, 1.60)</td>
<td>FH, 0.169%</td>
<td>0.020%</td>
<td>8.0%</td>
<td></td>
</tr>
<tr>
<td>LM, 0.101% (1.06µm, 1.60)</td>
<td>FH, 0.169%</td>
<td>0.021%</td>
<td>8.0%</td>
<td></td>
</tr>
<tr>
<td>LM, 0.987% (2.12µm, 1.60)</td>
<td>FH, 0.164%</td>
<td>0.019%</td>
<td>7.9%</td>
<td></td>
</tr>
</tbody>
</table>

* AS: albuterol sulfate, LM: lactose monohydrate, BDP: beclomethasone dipropionate, FH: flunisolide hemihydrate
2.1.3. Andersen Cascade Impactor (ACI) Testing

Prior to each run, the stages of the ACI were thoroughly rinsed with 50% (v/v) methanol:water followed by 100% methanol and dried. Once dry, the stages and the USP inlet were coated with 50:50 methanol:Pluronic L10 and the methanol was allowed to evaporate. QVAR® actuators (orifice diameter of 0.3mm) were used for all testing. For each experiment in the series, the sample vial was actuated three times in order to prime the valve; the stem of the valve was subsequently cleaned with the diluent (75:25 methanol:water). The valve stem was then dried and the vial was fitted with a clean actuator. The flow rate through the ACI was adjusted to 28.3L/min and verified using a TSI Series 4000 flow meter (TSI Inc., Shoreview, MN, USA). Each pMDI vial was tested in triplicate. In order to obtain accurate analytical quantification of the drug, the number of actuations varied between 2 and 25, based on the concentration of both drugs in the formulation, producing sufficient drug collection on each stage of the ACI (see Table 11.1). The valve stem, actuator, USP inlet, jet, stages 0 to 7 of the ACI, and the filter were rinsed with known volumes of the diluent and the amount of drug present for each component was quantified by high performance liquid chromatography (HPLC).

2.1.4. Analytical Assay

The HPLC system consisted of a Waters 2690 Separation module coupled with a Waters 996 Photodiode Array ultraviolet detector (both from Waters Corp., Milford, MA, USA). An Apollo C18 5µm 150mm × 4.6mm column, maintained at 30 ± 2°C was used. A gradient separation method was utilized to characterize beclomethasone dipropionate
and albuterol sulfate. For this method, 50µL injection volume was utilized and the initial mobile phase composition was 65% (v/v) methanol:0.1% phosphoric acid in water at a flow rate of 0.85mL/min. After 3.5min, the mobile phase linearly changed over 30 seconds to 80% (v/v) methanol:0.1% phosphoric acid with a flow rate of 1.5mL/min. The data was collected and processed using Waters Empower Pro 2 chromatography data software. The total run time for this method was 12min. Albuterol sulfate eluted at 1.6min and was detected at 225nm; beclomethasone dipropionate eluted at 8.2min and was detected at 238nm. Flunisolide hemihydrate was quantified using Supelcosil LC-18 5µm 150mm × 4.6mm column. The mobile phase for this isocratic method was 90% (v/v) methanol:0.1% phosphoric acid in water at a flow rate of 1.5mL/min. Flunisolide hemihydrate was detected at 238nm. Quantification was conducted based on peak area using a five-point standard curve. Lactose monohydrate was not quantified using the HPLC. No leachable and extractable compounds were detected from the vials or bag used to rinse the ACI stages upon analysis of the HPLC data.

2.1.5. Determining APSD of Residual Particles

The HPLC results from the ACI test were used to determine the APSD of the drug delivered in the residual aerosols. Chimera Technologies, Inc.’s DistFit 2009.01 (Forest Lake, MN, USA) was used to determine the MMAD and GSD of the residual particles; the data were fitted with monomodal and bimodal lognormal distributions based on whether the drug was in suspension or in solution with the ethanol-HFA 134a system. No
size information is available for the portion of the drug that deposited on the valve stem, actuator, and USP inlet; thus, these were not included in the APSD calculations.

2.2. Theoretical Framework

A Monte Carlo simulation model previously established to estimate the APSD of residual particles for pMDIs containing a propellant, ethanol, and a single active pharmaceutical ingredient (API) in suspension (248,249) has been modified to include an additional entity in solution, as depicted in Figure 11.1. The highlighted sections of Figure 11.1 in light red represent the modification to the model in order to incorporate the additional drug in solution; these modifications are discussed in detail in Section 2.2.1 of this chapter. This figure consists of two panels; the top panel depicts the physical atomization process while the bottom panel explains how this process is modeled. For simplicity, the discussion in this chapter is generally presented from the perspective that the nonvolatile entities are drugs; however, the same discussion would be applicable if the entities were nonvolatile excipients. When a pMDI is actuated, the formulation exits the actuator spray orifice and is broken up into many initial atomized droplets that contain a representative proportion of each excipient as that found in the formulation. If the drug is in solution, the atomized droplets will also contain an identical proportion of drug found in the formulation. However, if the drug is suspended in the formulation, varying number of drug particles can be found in each droplet. Most marketed pMDI products deliver tens to hundreds of millions of suspended drug containing droplets per actuation (4). Over time, the propellant and some of the cosolvent evaporates given their
volatile nature, rendering an intermediate droplet that contains some cosolvent, dissolved drug, and/or suspended drug. The cosolvent will completely evaporate over the due course of droplet evolution leaving residual particles that constitute of only nonvolatile mass, which can deposit in the human lungs. These residual particles are significantly smaller than their corresponding initial droplets.

While the base model is described in great detail by Stein et al. (248,249), it is briefly discussed here. The original model enables the prediction of APSD from a suspension formulation, while expanding on previous models by allowing for polydispersed micronized suspended drug and initial droplets. The key inputs for the original model are density and concentration of each component of the formulation, the micronized drug size distribution for the suspended component, and the size distribution of the initially atomized droplets. The latter can be estimated using the equations provided by Stein and Myrdal (204). Typically, for HFA 134a formulations tested using the USP inlet, the initial droplet MMD is between 8 and 13µm (5) and the GSD is approximately 1.8 (204). For the purposes of the experiments described herein, the initial droplet MMD was assumed to be 9.14µm with a GSD of 1.8, based on calculations using Equation 11.1 (where MMD_I is the initial droplet MMD, MMAD_R is the residual particle MMAD, C_NV (weight fraction) is the concentration of the dissolved nonvolatile component, and ρ_I and ρ_R are the densities of the formulation and the residual particles, respectively) with 8% (w/w) ethanol, 0.083% (w/w) model dissolved drug (ρ = 1.25g/cm³) in HFA 134a (residual particle MMAD of 0.94µm). Since the nonvolatile
component is a small fraction of the formulation, small changes in the nonvolatile concentration is not expected to significantly modify the initial droplet size distribution.

\[
MMD_I = \frac{\text{MMAD}_R}{(\rho_I \times C_{NV})^{1/3} \times \rho_R^{1/6}}
\]  
(Equation 11.1)

Once the user inputs the above information, each atomized droplet is simulated individually. The size of a given atomized droplet is determined from the user-defined distribution. Thereafter, the number of drug particles contained within the droplet is determined. The likelihood that a droplet will contain one or more suspended drug particles depends on volume of the droplet and the number of suspended drug particles per unit volume of the formulation (PPUV, see Equation 11.2, where PPUV (cm\(^3\)) is the number of suspended drug particles per unit volume of formulation, \(C_{\text{drug}}\) (weight fraction) is the concentration of the suspended drug, \(\rho_{\text{drug}}\) is the suspended drug particle density, \(\rho_I\) is the formulation density, and GSD\(_{\text{drug}}\) and MMD\(_{\text{drug}}\) (µm) are the geometric standard deviation and mass median diameter, respectively, of the micronized drug used in the formulation). It can be described using the Poisson distribution function. The Poisson distribution is used to randomly determine the number of suspended particles in a given droplet based on the PPUV in the formulation and a given droplet’s volume. Large droplets have a higher probability of having one or more drug particles than small droplets. Similarly, droplets from formulations that contain a higher PPUV are more likely to contain drug particles than are droplets of the same size for a formulation with
fewer PPUV. Thus, pMDIs with a high drug concentration or ones that use small micronized drug can have a substantial fraction of the drug laden droplets that contain multiple drugs, termed as “multiplets,” and a smaller fraction of drug laden droplets that contain single suspended drug particle, termed as “singlets.”

\[
\text{PPUV} = \frac{6 \times C_{\text{drug}} \times e^{4.5 \ln^2 GSD_{\text{drug}}} \times \rho_l}{\pi \times (0.0001 \times \text{MMD}_{\text{drug}})^3 \times \rho_{\text{drug}}}
\]  
(Equation 11.2)

Finally, each suspended drug particle is randomly assigned a diameter based on the particle size distribution of the micronized material, which was entered by the user. This information, in conjunction with the suspended drug density, is used to determine the volume and mass of each residual particle. Once sufficient drug laden particles are simulated, the APSD for the suspended drug can be determined by fitting a lognormal distribution to the mass versus aerodynamic diameter of residual particles data. For the simulations presented in this chapter, at least 30,000 drug laden particles were simulated (326).
Figure 11.1: Depiction of the physical process of atomization (top panel) compared to the simulation algorithm (bottom panel). The brackets towards the top of the “Simulated Process” panel indicate the relationship between each simulation step and its corresponding physical process. Sections highlighted in light red denote the modifications to the model described by Stein et al. (248, 249).
2.2.1. Modification of Theoretical Model

The modifications to the simulated model are presented by the light red highlights in Figure 11.1. Atomized droplets from a combination pMDI formulation containing a drug in suspension and a drug in solution may contain only dissolved drug or dissolved and suspended drugs with ethanol and the propellant. These droplets will evaporate over time, rendering residual particles containing only dissolved drug or both dissolved and suspended drugs, with a varying number of suspended drug particles. To account for the additional entity in the formulation, the user must input the concentration and density of the dissolved drug prior to using the model to determine the APSD of the suspended or dissolved component.

If the simulated total volume of the suspended drug particles exceeds the volume of the initial droplet (for any given atomized droplet), it is then assumed that the volume of the suspended drug particles is equal to that of the volume of the initial droplet, as discussed in Chapters 5 and 7. If the simulated total volume of the suspended drug particles is less than the volume of the initial droplet, it is assumed that the remainder of the volume of the initial droplet is occupied by the propellant, cosolvent, and dissolved drug at proportions equal to that found in the bulk formulation. Based on the relative composition of the formulation, the volume and the mass of the dissolved drug contained within a given initial droplet can be determined (see Equations 11.3 and 11.4, where $M_{\text{soln}}$ (g) is the mass of drug in solution, $\rho_I$ and $\rho_{\text{soln}}$ (g/cm$^3$) are the densities of the formulation and dissolved drug, $C_{\text{soln}}$ (weight fraction) is the concentration of the dissolved drug in the formulation, and $V_I$ and $V_{\text{susp}}$ (cm$^3$) are the volumes of the initial atomized droplet and
suspended drug particles within the droplet, respectively). By summing the mass of the suspended and dissolved drugs for each particle, the mass of the residual droplet can be calculated, which then determines the mass-equivalent diameter for a given residual particle (see Figure 11.2). Thereafter, the aerodynamic diameter of the residual particle is computed, while accounting for changes to the aerodynamic diameter as a factor of the number of suspended drug particles contained within the residual particle, using the shape factor (possibly affecting drag force of the residual particle).

Once sufficient initial droplets are simulated, the mass of suspended or dissolved drug, and aerodynamic diameter for each droplet is utilized to determine the APSD for the suspended or dissolved drug. Since aerosolized particles are lognormally distributed (302), the data are fitted with a monomodal or bimodal lognormal distribution using DistFit. Ideally, a monomodal distribution would result for the drug in suspension in a pMDI formulation with suspended and dissolved drug. The dissolved drug distributions from dual product pMDI formulations are expected to be bimodal, where one mode represents the APSD for the dissolved drug from droplets without any suspended drug and the other, for dissolved drug from droplets containing both drugs.

\[
M_{\text{soln}} = \rho_l \times C_{\text{soln}} \times (V_l - V_{\text{susp}}) \quad \text{(Equation 11.3)}
\]

\[
V_{\text{soln}} = \frac{M_{\text{soln}}}{\rho_{\text{soln}}} \quad \text{(Equation 11.4)}
\]
**Figure 11.2:** Calculation of aerodynamic diameter for residual particles, where the subscripted variables are defined in the legend. In addition, \( V \) (cm\(^3\)) is the volume, \( M \) (g) is the mass, \( D \) (cm) is the diameter, and \( \rho \) (g/cm\(^3\)) is the density of the item in the subscription. Additional variables are defined as follows: \( \chi \) is the shape factor, \( Cc(X) \) is the Cunningham slip correction factor for variable \( X \), and \( \rho_0 \) (g/cm\(^3\)) is unit density. For more information, see Chapter 5.
3. Results and Discussion

3.1. Factors Affecting Suspended Component APSD

Similar to the results and discussion presented in Chapters 8 and 10, the suspended component’s APSD in a combination formulations containing a dissolved and suspended drug or excipient is most affected by the micronized drug or excipient size and concentration. For a given size of micronized albuterol sulfate at a given beclomethasone dipropionate concentration, increasing the suspended component’s concentration results in an increase in the resulting MMAD of the suspended entity, as seen in the examples presented in Table 11.2. This trend is expected based on the multiplets discussion in Chapter 10: increasing the drug concentration results in an increase in the percentage of droplets containing multiple suspended particles, which results in increasing the residual MMAD relative to the raw micronized drug MMAD. Furthermore, increasing the size of the micronized albuterol sulfate, while fixing all other variables, also leads to an increase in residual particle MMAD. This phenomenon is also detailed in Chapter 10 and relies on (1) the micronized drug MMAD limiting how small the residual MMAD can be for relatively dilute formulations; and (2) decreasing the percentage of multiplets with increasing micronized drug size limits the proportion of aggregates that form with atomization of the given formulation.
<table>
<thead>
<tr>
<th>Albuterol Sulfate Micronized Size (MMAD) and Concentration (% w/w)</th>
<th>Beclomethasone Dipropionate Concentration (% w/w)</th>
<th>Suspension Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>MMAD (µm)</td>
<td>GSD</td>
</tr>
<tr>
<td>1.77µm, 0.03%</td>
<td>0%</td>
<td>1.76</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>2.02</td>
</tr>
<tr>
<td>1.77µm, 0.4%</td>
<td>0%</td>
<td>2.15</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>2.33</td>
</tr>
<tr>
<td>2.62µm, 0.03%</td>
<td>0%</td>
<td>2.35</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>2.63</td>
</tr>
<tr>
<td>2.62µm, 0.4%</td>
<td>0%</td>
<td>2.81</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
<td>2.77</td>
</tr>
</tbody>
</table>
Table 11.2 also presents that fixing the suspended drug concentration and micronized drug size while modulating the dissolved drug can affect the resulting residual MMAD of the suspended entity. Additional examples of these effects can be seen in Figure 11.3. Through these examples, it is evident that for formulations with low concentrations of suspended drug, increasing the dissolved drug concentration can affect the resulting residual MMAD of the suspended material. For instance, increasing the beclomethasone dipropionate concentration from 0% to 0.08% for formulations containing approximately 0.05% albuterol sulfate (micronized MMAD of 2.62µm), slightly increased the residual suspended MMAD from 2.35µm (GSD 1.74) to 2.38µm (GSD 1.71). Further increase in beclomethasone dipropionate concentration to 0.3% resulted in a substantial increase in residual MMAD of the suspended drug (MMAD of 2.63µm, GSD 1.66). Similarly, for the formulations containing 0.03% albuterol sulfate (micronized MMAD of 1.77µm), the residual particle MMAD changed as a function of beclomethasone dipropionate concentration: 1.68µm (GSD 1.60), 1.78µm (GSD 1.65), and 2.02µm (GSD 1.53) for combination formulations containing 0%, 0.08% and 0.3% beclomethasone dipropionate. Increasing the albuterol sulfate concentration relative to the beclomethasone dipropionate concentration for a given micronized drug size results in a diminishing effect of the dissolved drug on the residual suspended drug’s MMAD. For instance, Figure 11.3 (B) presents that the addition of up to 0.3% beclomethasone dipropionate to a 1% albuterol sulfate formulation does not impact the resulting suspended drug’s APSD, with all three formulations having MMAD of approximately 2.5µm (GSD 1.61).
The effects seen in Table 11.2 and Figure 11.3 can be explained by the propensity for atomized droplets to contain multiple suspended particles. In general, for concentrated suspension formulations most of the atomized droplets contain suspended particles. Furthermore, a large proportion of those atomized droplets contain multiple suspended particles. With the increased propensity of residual particles comprising of aggregates of suspended particles, the effect of additional dissolved nonvolatile on the suspended entity’s APSD is diminished. This may occur due to: (1) the fraction of the total mass occupied by the suspended entity is much greater than that occupied by the dissolved entity for a given residual particle; (2) the fraction of the volume occupied by the suspended entity is much greater than that occupied by the dissolved entity for a given residual particle since the dissolved entity can mostly fit in the void spaces of the aggregate of suspended particles; and (3) the addition of the dissolved entity does not significantly impact the volume or mass of relatively large residual particles containing aggregates of suspended particles. For dilute suspension formulations, the addition of the nonvolatile component can significantly alter the mass and volume of the residual particles containing suspended particles thereby affecting the APSD of the suspended component.
Figure 11.3: Residual APSDs of suspended albuterol sulfate (AS) for six formulations, some of which contain dissolved beclomethasone dipropionate (BDP). All formulations contain 8% ethanol with HFA 134a.
Through simulations, it was noted that the effect of the dissolved drug concentration on the residual MMAD of the suspended drug is also dependent on the raw micronized drug size, as presented in Figure 11.4. Through the comparison of the contour plots for 1.0µm and 2.5µm raw micronized drug MMAD, it is evident that changing the dissolved drug component from 0 to 0.8% has a marginally greater impact on the suspended drug MMAD for the smaller micronized drug than the larger micronized drug. This effect can be explained by a similar argument as that presented above. For instance, for the formulations presented in Figure 11.4 (A), increasing the dissolved nonvolatile concentration from 0 to 0.8% (w/w) for a formulation containing 0.6% (w/w) 1.0µm MMAD suspended drug or excipient decreased the proportion of droplets containing the model suspended entity (83.0% and 72.4%). A similar trend is seen with the 2.5µm MMAD model suspended entity, where an increase in dissolved nonvolatile concentration from 0 to 0.8% results in a decrease in atomized droplets that contain the suspended drug (24.2% and 23.7%), albeit to a lesser extent than that seen with the 1.0µm MMAD configurations. Given that the majority of the atomized droplets for the smaller micronized model suspended entity contain suspended drug particles, and of those droplets 63.1 to 82.3% (for 0 and 0.8% dissolved nonvolatile) of droplets contain multiple suspended drug particles, the resulting suspended entity’s MMAD substantially increases as a result of a large proportion of atomized droplets containing aggregates of suspended particles as a function of the concentration of the dissolved nonvolatile. Conversely, for the larger micronized MMAD, not only is there substantially less atomized droplets that contain suspended particles, but those that do contain suspended
particles predominantly only contain a single particle (52.8 to 71.3%). Thus the driving force for the minute increase in suspended entity residual MMAD as a function of the concentration of the dissolved nonvolatile is due to the additional mass and volume contributed to residual particles with additional dissolved nonvolatile content.
Figure 11.4: Residual APSD of model suspended component with micronized MMAD of (A) 1.0µm and (B) 2.5µm (GSD of 1.8) as a function of suspended and dissolved component concentrations.*Note that the APSD is of the suspended component in a combination pMDI formulation containing dissolved and suspended nonvolatiles.
3.2. Factors Affecting Solution Component APSD

Recall from Chapter 6 that the dissolved drug or excipient concentration and initial droplet diameter are the primary determinants for the APSD of solution pMDIs. The residual APSD of solution pMDIs follows a monomodal lognormal distribution. In contrast, the residual APSD of the dissolved component of combination pMDIs follows a bimodal lognormal distribution, as explained in Figure 11.5. All of the aerosolized droplets from combination pMDIs contain the dissolved nonvolatile drug or excipient. Aerosolized droplets that do not contain suspended particles contain a representative amount of the dissolved nonvolatile as the formulation. For droplets that do contain suspended particles, the remainder of the volume of initial droplets is occupied by a representative concentration of dissolved nonvolatile as the formulation. Both types of aerosolized droplets contribute to the overall APSD of the nonvolatile dissolved component, theoretically resulting in a bimodal lognormal distribution. Many times, due to the formulation variables subsequently discussed, it is difficult to resolve the two modes; thus, a monomodal distribution is frequently fitted to these formulations. These monomodal distributions typically have relatively large GSDs, which are greater than those seen with the suspension counterpart.
Figure 11.5: Depiction of why the dissolved entity of a combination formulation theoretically exhibits a bimodal distribution.
For instance, Figure 11.6 presents the monomodal distribution of a solution formulation containing 0.08% beclomethasone dipropionate and a bimodal distribution of 0.08% beclomethasone dipropionate with 1% suspended albuterol sulfate (micronized drug MMAD 1.77µm). As a solution formulation, with reasonable Chi-square goodness-of-fit, the beclomethasone dipropionate solution formulation has a residual MMAD of 1.03µm with a GSD of 1.56. The combination formulation exhibits two modes for the beclomethasone dipropionate residual APSD: 1.42µm MMAD (GSD 2.46) and 2.40µm MMAD (GSD 1.53). The smaller mode is predominantly representative of aerosolized particles that do not contain suspended drug particles. However, this distribution has a larger MMAD and GSD than that seen with the 0.08% beclomethasone dipropionate formulations since it is difficult to experimentally resolve the two modes. The larger mode (2.40µm MMAD (GSD 1.53)) has a similar distribution to that seen for albuterol sulfate in a 1% albuterol sulfate suspension formulation with a micronized drug size of 1.77µm containing 0.08% beclomethasone dipropionate (2.45µm MMAD (GSD 1.60)).
Figure 11.6: Residual APSDs of a beclomethasone dipropionate (BDP) solution formulation and beclomethasone dipropionate in a combination formulation containing albuterol sulfate (AS). The micronized MMAD of albuterol sulfate is 1.77µm. These formulations also contain 8% (w/w) ethanol with HFA 134a.
Simulations present an alternative way to understand the bimodal distribution phenomenon. Figure 11.7 presents the ACI profiles for dissolved flunisolide hemihydrate and 8% ethanol formulations in HFA 134a. One of the formulations contains 0.019% oleic acid and 0.166% flunisolide hemihydrate (presented as black bars) and the other formulation contains 0.019% oleic acid, 0.164% flunisolide hemihydrate, and 0.987% 2.12µm MMD lactose monohydrate (presented as blue bars). In general, the ACI profile for the solution pMDI formulation has a greater deposition of flunisolide hemihydrate on the lower stages of the ACI (plate 5 and lower), which corresponds to a relatively small residual MMAD. For the formulations that contain suspended lactose, more of the total mass of flunisolide hemihydrate (blue filled and unfilled bars) is deposited on the upper stages of the ACI (plate 5 and greater). Predominantly the mass of flunisolide hemihydrate collected on plates 0 to 5 is primarily contributed by atomized droplets that contained suspended lactose monohydrate and dissolved flunisolide hemihydrate (blue filled bars). On the lower stages, it is clear that the flunisolide hemihydrate mass is associated with droplets that do not contain suspended particles. In addition, Figure 11.7 also presents that the simulated GSD of the dissolved drug in a combination formulation is larger than that seen with a simple simulated solution pMDI formulation.
Figure 11.7: Simulated APSD of dissolved drug in the following formulations: (A) 0.019% oleic acid, 0.166% flunisolide hemihydrate with 8% ethanol and (B) 0.019% oleic acid, 0.164% flunisolide hemihydrate, 0.987% 2.12µm MMD lactose monohydrate with 8% ethanol. The mass predicted on each stage of the ACI is based on the total mass recovered in the ACI through experiments.
Similar to solution pMDI formulations, the solution component’s APSD in a combination formulation is affected by the dissolved nonvolatile entity’s concentration. For instance, increasing the concentration of beclomethasone dipropionate from 0.08% (unfilled blue circles) to 0.3% (filled blue circles) results in an increase in residual MMAD of the beclomethasone in the combination formulation with albuterol sulfate (see Figure 11.8). The MMAD of 0.08% beclomethasone dipropionate in a solution pMDI is 0.87µm and increases to 1.16µm for the 0.3% beclomethasone dipropionate formulation. For the formulations containing albuterol sulfate, increasing the beclomethasone dipropionate concentration from 0.08% to 0.3% resulted in 0.16 to 0.47µm (average 0.27µm) increase in the dissolved component’s MMAD.

The effect of modulating the dissolved component’s concentration has a minimal effect on the resulting dissolved drug MMAD for formulations that contain a high concentration of suspended component. For instance, the MMAD differences between the 0.3% and 0.08% beclomethasone dipropionate formulations for the 1% albuterol sulfate (micronized MMD 1.55µm) is 0.16µm and for the 1% albuterol sulfate (micronized MMD 2.30µm) is 0.17µm. Conversely, the effect of modulating the dissolved component’s concentration has a significant effect on the resulting MMAD for formulations that contain a low to moderate concentration of suspended component. For instance, the MMAD differences between the 0.3% and 0.08% beclomethasone dipropionate formulations for the 0.4% albuterol sulfate (micronized MMD 1.55µm) is 0.47µm and for the 0.4% albuterol sulfate (micronized MMD 2.30µm) is 0.28µm. These effects can be explained by considering the number of suspended particles per unit
volume (PPUV) for these formulations (see Table 11.3). Recall from Chapter 10 that increasing the PPUV results in increasing the proportion of atomized droplets that contain suspended particles and the proportion of suspended drug or excipient containing droplets that can contain multiple particles. With an increase in the proportion of atomized droplets that contain multiple suspended particles, there is a corresponding increase in the absolute void volume in these aggregates. Thus, at low concentrations of suspended drug, the atomized droplets predominantly contain no or one suspended drug particle, which do not have the void volume as seen with residual particles containing multiple suspended particles. Thus at low concentrations of suspended drug, the addition of dissolved drug to the formulation significantly contributes mass and volume to residual droplets that evolved from droplets without suspended drug particles and droplets with a single drug particle. At relatively high concentrations of suspended drug, the atomized droplets predominantly contain aggregates of suspended drug particles. These aggregates are fairly large and porous. They have void volumes that are equivalent to nearly 26% of the volume of the suspended particles, which can be occupied by the dissolved drug or excipient. Thus, significant changes in the dissolved drug concentrations do not contribute significantly to the volume or mass of relatively large residual particles containing multiple suspended drug particles due to the porous nature of these residual particles and the probability of the dissolved drug occupying the space between suspended particles in the aggregates.
Figure 11.8: The MMAD of beclomethasone dipropionate (BDP) in combination pMDI formulations with albuterol sulfate (AS). The concentrations of beclomethasone dipropionate are 0.08% (unfilled blue circles) and 0.3% (filled blue circles) with varying albuterol sulfate concentration and micronized sizes (expressed as MMMD) with 8% ethanol in HFA 134a. The ratio of the MMAD of beclomethasone dipropionate 0.3% to 0.08% for a given suspension composition is presented on the right axis (denoted by unfilled black triangles).
Table 11.3: PPUV for Formulations Presented in Figure 11.8

<table>
<thead>
<tr>
<th>Suspended Component of Formulation (% w/w, micronized MMD)</th>
<th>Suspended Particles Per Unit Volume (PPUV, mL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.08% (w/w) BDP</td>
</tr>
<tr>
<td>0% AS</td>
<td>0</td>
</tr>
<tr>
<td>0.03% AS, 1.55µm</td>
<td>7.26 × 10⁸</td>
</tr>
<tr>
<td>0.4% AS, 1.55µm</td>
<td>6.16 × 10⁹</td>
</tr>
<tr>
<td>1% AS, 1.55µm</td>
<td>2.22 × 10¹⁰</td>
</tr>
<tr>
<td>0.03% AS, 2.30µm</td>
<td>1.96 × 10⁸</td>
</tr>
<tr>
<td>0.4% AS, 2.30µm</td>
<td>4.66 × 10⁹</td>
</tr>
<tr>
<td>1% AS, 2.30µm</td>
<td>8.60 × 10⁹</td>
</tr>
</tbody>
</table>

Where the suspended component is albuterol sulfate (AS) and the dissolved component is beclomethasone dipropionate (BDP).
3.3. Comparison of Experimental and Simulated APSD

The model utilized to explain some of the results in Sections 3.1 and 3.2 of this chapter has proven to be useful in gaining insight of factors that modulate combination pMDI formulations that contain dissolved and suspended drugs or excipients. As examples, Figures 11.9 and 11.10 illustrate the theoretical (i.e., simulated) and experimental APSD of various dissolved (beclomethasone dipropionate or flunisolide hemihydrate) and suspended components (albuterol sulfate or lactose monohydrate) in combination pMDIs. For the formulations evaluated, there was close agreement between the theoretical and experimental APSD. As presented in Figure 11.11, there was reasonable correlation between the MMAD values predicted in the simulations and those measured from the ACI ($R^2 = 0.91$) demonstrating the utility of the algorithm for predicting residual APSDs for a broad range of pMDI configurations (see Table 11.1).
**Figure 11.9**: Simulated (Sim) and experimental (ACI) APSDs of the dissolved component for a variety of formulations containing beclomethasone dipropionate (BDP), flunisolide hemihydrate (FH), and lactose monohydrate (LM). All of the formulations contained a nominal 8% ethanol with HFA 134a, and a metering valve size of 50µL with a QVAR® actuator.
Figure 11.10: Simualted (Sim) and experimental (ACI) APSDs of the suspended component for a variety of formulations containing albuterol sulfate (AS) and flunisolide hemihydrate (FH). Both of the formulations contained a nominal 8% ethanol with HFA 134a, and a metering valve size of 50µL with a QVAR® actuator.
**Figure 11.11:** Comparison of experimental residual particle MMAD to simulated residual particle MMAD for the formulations detailed in Table 11.1. All vials were fitted with 50µL Spraymiser™ valves and QVAR® actuators. The formulations include 8% (w/w) ethanol in HFA 134a.
4. Conclusions

Combination drug therapy or formulations with nonvolatile excipients presents a variety of benefits for patients suffering from chronic lung disease. However, the formulation of such pMDIs requires an understanding of how the addition of a dissolved or suspended drug or excipient affects the overall APSD of the residual particles. In general, increasing the concentration of either dissolved or suspended drug or excipient, or decreasing the size of the micronized suspended drug or excipient will result in a relative increase in the solution and suspension residual particle size, which depends on the overall bulk characteristics of the atomized droplets as summarized in Figure 11.12. The algorithm presented in this chapter serves as a satisfactory model in predicting the effective residual MMAD for dissolved and suspended drug(s) or excipient(s) in combination products.
**Figure 11.12:** Summary of relationships between formulation variables and resulting APSD for dissolved and suspended entities in combination formulations. Conclusions made based on simulations and experimental analyses. Abbreviations used in this figure: mass (M), volume (V), increase (↑), no change (↔), aerodynamic particle size of solution component (APSD$_{soln}$), and aerodynamic particle size of suspension component (APSD$_{susp}$).
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FUTURE OUTLOOK

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CHAPTER 12

SIMULATION MODEL SUMMARY AND EXPANSION

Summary

The previous chapters have extensively discussed a simulation model that effectively estimates the residual aerodynamic particle size distribution (APSD) from a variety of pressurized metered dose inhalers (pMDIs) containing any practical combination of dissolved or suspended drug or excipient in an ethanol and 1,1,1,2-tetrafluorethane (HFA 134a) system. This model may be utilized to evaluate batch-to-batch variations for quality control purposes or aid in a priori designs of pMDIs. However, the current model has some limitations that can be addressed by the expansions presented in this chapter. These improvements include: (1) modeling the APSD for alternative propellant systems; (2) modeling the APSD for formulations that contain two different suspended drugs or excipients; and (3) modeling the percentage of throat deposition and respirable mass for any pMDI formulation. Plausible approaches for incorporating these expansions are also discussed.
1. Scope of Presented Model

The formulation process of dual drug pressurized metered dose inhalers (pMDIs) can be lengthy and empirical. The addition of one drug in the formulation may non-linearly impact the product performance of the second drug in the formulation; this requires iterative testing of a series of pMDIs in order to identify a formulation with the most potential for success. One of the primary attributes used to characterize the product performance of inhaled medications is the residual aerodynamic particle size distribution (APSD) of the aerosolized drug(s). Aerosolized particles with aerodynamic diameters of less than approximately 5μm are likely to penetrate into the lung (34), thus delivering the drug to the site of action. Along with clinical factors, formulation (i.e., concentration of propellant, cosolvent, drugs, and excipients; solubility of the drugs; density of the nonvolatile components; and raw micronized size of suspended drug or excipient) and device parameters (i.e., metering valve size and actuator orifice diameter) have a significant impact on APSD and thereby the success of an aerosolized product.

The APSD can be experimentally determined using cascade impactor testing. Alternatively, a computational model using the principles of statistics and physical chemistry may be used to predict the APSD generated by pMDIs based on formulation, device, and raw drug substance considerations. Unlike its predecessors (318,319,350), the model described in Section 2 of this dissertation, and further validated in Section 3, permits modeling APSD for formulations with polydispersed atomized droplets and polydispersed raw micronized suspended material. It effectively models the APSD of
suspension pMDIs that contain suspended drug or excipient and/or dissolved drug or excipient with a cosolvent (typically, ethanol) and a propellant. For validation purposes, only 1,1,1,2-tetrafluoroethane (HFA 134a) was used. It requires the user to define the formulation and the density of each component within the formulation and determine the size distribution of the initial droplets. Once the user has entered the formulation variables, individual droplets are modeled one at a time using random sampling from within user-specified distributions to determine the size of the initial droplet and the size of individual drug particles. The number of suspended particles that each droplet contains is determined by randomly selecting from within a Poisson distribution, which utilizes the number of suspended particles per unit volume of the formulation (PPUV) and calculates the probability of having some number of suspended particles within a droplet. From this, the composition of the residual particle, including the volume and mass of the dissolved and suspended drug(s) or excipient(s), can be determined and the APSD of the aerosolized nonvolatile entities can be predicted.

This model effectively estimates the APSD of dissolved and suspended entities in single and dual component pMDIs and it does not require an arsenal of technical calculations, which benefits the formulation and quality control process for pMDI manufacturing. It facilitates the formulation process by allowing for improved high throughput screening of plausible pMDI products and decreased time and resource investment in current trial-and-error approach used to evaluate test pMDIs. Furthermore, it may provide guidance in defining the design space for potentially successful pMDI products with up to two nonvolatile components, where one is in solution and the other is
in suspension. From a quality control standpoint, this model would provide better understanding of the sensitivity of various device and formulation components on product performance, permitting a priori evaluation of batch-to-batch variation. While such a model is extremely useful in decreasing the time required to find or perfect a potential pMDI product, it will not eliminate the need for rigorous in vitro testing of pMDI products, since the model presents a best case scenario.

The simulation models can be effectively utilized to better understand formulations with (1) a single drug in solution; (2) a single drug in suspension; or (3) a dual component system, where a suspended drug or excipient is combined with a dissolved drug or excipient in a single pMDI formulation. The following illustrations present summary relationships between the key variables that determine APSD based on simulations. These illustrations can be utilized to understand the sensitivity of APSD on a variety of variables and define plausible formulations that may provide desired APSDs. Figure 12.1 presents the effect of different dissolved drug and ethanol concentrations on residual APSD. The ethanol concentration effectively modulates the initial droplet mass median diameter (MMD), such that increasing the ethanol concentration increases the initial droplet in a quadratic manner (see Equation 5.7). For solution pMDI formulations, the drug concentration has a greater impact than the ethanol concentration in modulating the residual MMAD. The impact of changing the initial droplet MMD (effectively, ethanol concentration) has a greater effect on the residual MMAD of formulations with a higher drug concentration compared to those with a lower drug concentration. From Equation 9.1, it is known that the residual MMAD of solution pMDI formulations is
directly proportional to the product of the initial droplet MMD and the cube-root of the dissolved nonvolatile concentration.

For suspensions, the micronized drug concentration, micronized drug size, and ethanol concentration determine residual MMAD. Figure 12.2, presents the relationships between these variables. Increasing the drug concentration and the micronized drug size at a fixed ethanol concentration increases the residual MMAD for relatively simple suspension formulations, with the impact of micronized drug size being greater than the drug concentration. Increasing the ethanol concentration does not have a large affect the residual MMAD except at relatively high ethanol concentrations with a concentrated suspension formulation regardless of micronized drug size, as presented in Chapters 9 and 10 and in Figure 12.2.
Figure 12.1: Simulated effect of dissolved drug concentration and ethanol concentration on the resulting residual MMAD of the dissolved drug. The density of the model drug is assumed to be 1.25 g/cm$^3$. Equation 5.7 was utilized to calculate the initial droplet MMD with a valve size of 50µL and an actuator orifice diameter of 0.3mm.
Figure 12.2: Effect of various formulation variables on the resulting residual suspension APSD. The density of the model drug is assumed to be 1.25g/cm³ and the GSD of the micronized drug is assumed to be 1.8. Equation 5.7 was utilized to calculate the initial droplet MMD with a valve size of 50µL and an actuator orifice diameter of 0.3mm. Top row presents difference between 4 and 8% ethanol; middle row presents difference between 1.5 and 2.5µm MMAD micronized drug; bottom row presents difference between 0.1 and 0.4% suspended drug concentration.
For complex pMDI formulations containing two components with one in solution and another in suspension, the dissolved and suspended component concentrations, micronized component size, and ethanol concentration have an impact on the resulting residual MMAD of the solution and suspension components, as presented in Figure 12.3. Like simple solution and suspension formulations, increasing ethanol concentration has a greater impact on the MMAD of dissolved drug compared to a suspended drug in a combination formulation. In addition, increasing ethanol concentration from 0 to 20% has a greater impact on the residual MMAD of both components in formulations with relatively high concentrations of dissolved drug compared to suspended drug. For a fixed ethanol concentration, increasing the raw micronized size and concentration of the suspended component typically results in an increase in the residual MMAD of the suspended component for formulations with relatively low concentrations of the dissolved drug. For a higher drug concentration with fixed ethanol concentration, increasing the concentration of the suspended component may result in a decrease in residual MMAD for smaller micronized raw drug due to a larger number of atomized droplets containing multiple suspended drug particles compared to the formulation with the larger micronized raw drug. Furthermore, a substantial increase in dissolved nonvolatile concentration relative to the suspended component concentration results in an increase in the residual MMAD of the suspended component. The residual MMAD of the dissolved nonvolatile component is dependent on the concentration and micronized size of the suspended component. Increasing the concentration of the dissolved or suspended nonvolatile component for a fixed ethanol concentration and micronized drug size results
in an increase in residual MMAD of the dissolved component, as seen in Figure 12.3. With all other variables fixed, increasing the micronized component size for formulations with relatively low concentrations of the micronized drug (as compared to the dissolved drug) results in a decrease in the residual MMAD of the dissolved component. The increase in residual MMAD of the dissolved nonvolatile component effectively mirrors the changes seen in the proportion of atomized droplets that do not contain suspended particles and the suspended component containing droplets that have multiple suspended particles (i.e., multiplets). For instance, increasing the concentration or decreasing the micronized size of the suspended component results in an increase in droplets that contain suspended particles and in the percentage of multiplets. Decreasing the number of droplets that do not contain suspended drug particles results in an effective increase in the droplets that contain both suspended and dissolved drugs. This in turn serves as the driving force in increasing the residual MMAD of the dissolved component. Increase in the proportion of aggregates of suspended particles aerosolized from combination formulations further increases the residual MMAD of the dissolved component since the dissolved component in the droplets with aggregates of suspended drug particles have larger Stokes’ diameters than that seen with droplets that do not contain suspended particles or those that contain only one suspended particle.
Figure 12.3: Effect of various formulation variables on the resulting residual suspension and dissolved APSD and types of atomized droplets from combination pMDIs. The densities of the model drugs are assumed to be 1.25g/cm³ and the GSD of the micronized drug is assumed to be 1.8. Equation 5.7 was utilized to calculate the initial droplet MMD with a valve size of 50μL and an actuator orifice diameter of 0.3mm. The formulations contained 8% (w/w) ethanol and 0.5% (w/w) model suspended drug with HFA 134a, unless otherwise noted.
Figure 12.3: (continued) Effect of various formulation variables on the resulting residual suspension and dissolved APSD and types of atomized droplets from combination pMDIs. The densities of the model drugs are assumed to be 1.25 g/cm³ and the GSD of the micronized drug is assumed to be 1.8. Equation 5.7 was utilized to calculate the initial droplet MMD with a valve size of 50 µL and an actuator orifice diameter of 0.3 mm. The formulations contained 8% (w/w) ethanol and 0.5% (w/w) model suspended drug with HFA 134a, unless otherwise noted.
**Figure 12.3:** (continued) Effect of various formulation variables on the resulting residual suspension and dissolved APSD and types of atomized droplets from combination pMDIs. The densities of the model drugs are assumed to be 1.25g/cm³ and the GSD of the micronized drug is assumed to be 1.8. Equation 5.7 was utilized to calculate the initial droplet MMD with a valve size of 50µL and an actuator orifice diameter of 0.3mm. The formulations contained 8% (w/w) ethanol and 0.5% (w/w) model suspended drug with HFA 134a, unless otherwise noted.
2. Future Expansion of Suspension Pressurized Metered Dose Inhaler Simulation Model

While the model presented is versatile in predicting residual APSD from a variety of formulations, it can be improved by allowing for estimation of the residual APSD from pMDIs with different propellant (or propellant blends) and pMDIs with two different suspended drugs. Furthermore, the residual APSD is not the only in vitro metric that predicts the success of a pMDI. Additional performance metrics, such as the amount of drug that deposits in the throat (or the inlet of a cascade impactor) and in the respirable region of the lung is of great importance in determining the efficacy and adverse effects of medications delivered via pMDIs and would be valuable information to have beforehand when screening plausible formulations or evaluating batch-to-batch variations for quality control of manufactured pMDIs.

2.1. Different Propellant Systems

Propellants provide the energy to atomize the pMDI formulation. As discussed in Chapter 3, the choice of propellant plays a key role in the drug delivery efficiency of the device. Vapor pressure is the primary property that determines the speed and rate of evaporation (155,316). Upon exit from the valve and actuator orifice, the high vapor pressure formulation’s ejection is linked to shear-thinning, where large droplets are broken into smaller droplets as they interact with relatively stagnant air (155,360). This may lead to a decrease in resulting APSD and inlet drug deposition, and an increased
drug deposition on the device and respirable dose (155). In addition, the propellant is also the main determinant of the initial droplet diameter emitted from the device (76,155,316). Equation 12.1 presents a proportionality relationship determined between vapor pressure and the emitted initial droplet MMD, $MMD_i$, where $p_\infty$ is the ambient pressure and $p_{ec}$ is the pressure in the expansion chamber of the actuator (362). Based on this relationship, it is evident that increasing the vapor pressure of the formulation increases the pressure in the expansion chamber, which results in decreasing the initial droplet MMD.

$$MMD_i \propto \left( \frac{p_\infty}{p_{ec} - p_\infty} \right)^{0.46}$$

(Equation 12.1)

Of the two propellants available for pMDI formulation, HFA 134a has a greater vapor pressure and lower boiling point than 1,1,1,2,3,3,3-heptafluoropropane (HFA 227). The vapor pressure of HFA 134a is 83.0 psi at 20°C with a boiling point of -25.8°C (57,155). The vapor pressure of HFA 227 is 56.6 psi at 20°C with a boiling point of -17.3°C (57,155,361). Thus, it is expected that the initial droplet MMD for HFA 227 formulations will be greater than that seen with HFA 134a for similar hardware and formulation configurations, especially with formulations with low cosolvent concentrations (see Figure 12.4). However, unlike HFA 134a, there is limited published experimental data with solution pMDI formulations containing HFA 227, which prevents researchers from developing an empirical relationship between formulation and hardware variables and initial droplet diameter (similar to Equation 5.7 for HFA 134a (204)). Table 12.1 presents experimental residual particle sizes for HFA 227 solution pMDI
formulations with varying ethanol and dissolved nonvolatile concentrations. The residual particle MMADs for these formulations were determined using either the TSI Aerodynamic Particle Sizer (APS) or the Andersen Cascade Impactor (ACI). The initial droplet MMD was calculated using the experimental residual particle MMAD and Equation 9.5. The data presented in Table 12.1 is presented graphically in Figure 12.4. For these HFA 227 formulations, the smallest initial droplet MMD is 8.06µm (5% ethanol with 0.08% dissolved nonvolatile) and the largest MMD is 13.72µm (15% ethanol with 1.04% dissolved nonvolatile). The initial droplet size is generally between 9.5 and 11µm, with the average being a MMD of 9.93 ± 1.17µm. However, this data set is too small to determine an empirical relationship between initial droplet MMD and formulation and hardware parameters.
Table 12.1: HFA 227 Solution pMDI Formulations with Residual Particle MMAD and Calculated Initial Droplet MMD

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Dissolved Nonvolatile Entity</th>
<th>Dissolved Nonvolatile Entity Concentration (% w/w)</th>
<th>Experimental Residual Particle MMAD (µm)</th>
<th>Calculated Initial Droplet MMD* (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>0</td>
<td>0.1</td>
<td>1.35</td>
<td>11.46</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>0</td>
<td>1</td>
<td>2.58</td>
<td>10.14</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>0</td>
<td>1.5</td>
<td>2.74</td>
<td>9.39</td>
</tr>
<tr>
<td>(204) APS</td>
<td>Oligolactic acid</td>
<td>0</td>
<td>0.45</td>
<td>2.04</td>
<td>10.48</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>3</td>
<td>0.1</td>
<td>1.17</td>
<td>9.98</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>3</td>
<td>1</td>
<td>2.32</td>
<td>9.19</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>3</td>
<td>1.5</td>
<td>2.92</td>
<td>10.09</td>
</tr>
<tr>
<td>(202) APS</td>
<td>Beclomethasone dipropionate</td>
<td>5</td>
<td>0.08</td>
<td>0.87</td>
<td>8.06</td>
</tr>
<tr>
<td>(202) ACI</td>
<td>Beclomethasone dipropionate</td>
<td>5</td>
<td>0.08</td>
<td>0.96</td>
<td>8.92</td>
</tr>
<tr>
<td>(204) APS</td>
<td>Oligolactic acid</td>
<td>5</td>
<td>0.45</td>
<td>2.05</td>
<td>10.68</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
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<td>0.1</td>
<td>1.14</td>
<td>9.84</td>
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<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
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<td>1</td>
<td>2.39</td>
<td>9.55</td>
</tr>
<tr>
<td>Reference</td>
<td>Method</td>
<td>Dissolved Nonvolatile Entity</td>
<td>Ethanol Concentration (% w/w)</td>
<td>Dissolved Nonvolatile Concentration (% w/w)</td>
<td>Experimental Residual Particle MMAD (µm)</td>
</tr>
<tr>
<td>-----------</td>
<td>--------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>6</td>
<td>1.5</td>
<td>2.83</td>
<td>9.86</td>
</tr>
<tr>
<td>(202) APS</td>
<td>Beclomethasone dipropionate</td>
<td>10</td>
<td>0.08</td>
<td>0.93</td>
<td>8.70</td>
</tr>
<tr>
<td>(202) ACI</td>
<td>Beclomethasone dipropionate</td>
<td>10</td>
<td>0.08</td>
<td>1.05</td>
<td>9.87</td>
</tr>
<tr>
<td>(202) ACI</td>
<td>Beclomethasone dipropionate</td>
<td>10</td>
<td>0.4</td>
<td>1.65</td>
<td>9.08</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>10</td>
<td>0.1</td>
<td>1.18</td>
<td>10.30</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>10</td>
<td>1</td>
<td>2.60</td>
<td>10.50</td>
</tr>
<tr>
<td>(201) APS</td>
<td>Cyclosporine</td>
<td>10</td>
<td>1.5</td>
<td>2.93</td>
<td>10.32</td>
</tr>
<tr>
<td>(204) APS</td>
<td>Oligolactic acid</td>
<td>10</td>
<td>0.45</td>
<td>1.95</td>
<td>10.29</td>
</tr>
<tr>
<td>(327) ACI</td>
<td>Beclomethasone dipropionate, Glycerol</td>
<td>13</td>
<td>1.385</td>
<td>3.50</td>
<td>12.75</td>
</tr>
<tr>
<td>(202) APS</td>
<td>Beclomethasone dipropionate</td>
<td>15</td>
<td>0.08</td>
<td>1.01</td>
<td>9.65</td>
</tr>
<tr>
<td>(202) ACI</td>
<td>Beclomethasone dipropionate</td>
<td>15</td>
<td>0.08</td>
<td>1.00</td>
<td>9.53</td>
</tr>
<tr>
<td>(202) APS</td>
<td>Beclomethasone dipropionate</td>
<td>15</td>
<td>0.4</td>
<td>1.67</td>
<td>9.31</td>
</tr>
</tbody>
</table>
Table 12.1: HFA 227 Solution pMDI Formulations with Residual Particle MMAD and Calculated Initial Droplet MMD (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Method</th>
<th>Dissolved Nonvolatile Entity</th>
<th>Ethanol Concentration (% w/w)</th>
<th>Dissolved Nonvolatile Concentration (% w/w)</th>
<th>Experimental Residual Particle MMAD (µm)</th>
<th>Calculated Initial Droplet MMD* (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(202)</td>
<td>ACI</td>
<td>Beclomethasone dipropionate</td>
<td>15</td>
<td>0.4</td>
<td>1.62</td>
<td>9.03</td>
</tr>
<tr>
<td>(327)</td>
<td>ACI</td>
<td>Ipratropium bromide, Glycerol</td>
<td>15</td>
<td>1.037</td>
<td>3.40</td>
<td>13.72</td>
</tr>
<tr>
<td>(202)</td>
<td>APS</td>
<td>Beclomethasone dipropionate</td>
<td>20</td>
<td>0.08</td>
<td>1.10</td>
<td>10.60</td>
</tr>
<tr>
<td>(202)</td>
<td>ACI</td>
<td>Beclomethasone dipropionate</td>
<td>20</td>
<td>0.08</td>
<td>0.94</td>
<td>9.02</td>
</tr>
<tr>
<td>(202)</td>
<td>APS</td>
<td>Beclomethasone dipropionate</td>
<td>20</td>
<td>0.4</td>
<td>1.58</td>
<td>8.92</td>
</tr>
<tr>
<td>(202)</td>
<td>ACI</td>
<td>Beclomethasone dipropionate</td>
<td>20</td>
<td>0.4</td>
<td>1.52</td>
<td>8.56</td>
</tr>
</tbody>
</table>

The residual particle MMAD was determined by the TSI Aerodynamic Particle Sizer (APS) or the Andersen Cascade Impactor (ACI).

* Calculated using Equation 9.5.
Figure 12.4: Calculated initial droplet MMD as a function of ethanol concentration and dissolved nonvolatile concentration (% NVC) for a variety of HFA 227 solution pMDI formulations (filled circles) and HFA 134a formulations (unshaded circles). The HFA 227 formulations are detailed in Table 12.1. The HFA 134a formulations were presented in Figure 6.3.
An alternative approach to determining the initial droplet distribution of HFA 227 is to utilize empirical relationships between residual particle MMAD for a dissolved nonvolatile component and formulation and hardware parameters, and then calculate the resulting initial droplet MMD. Ivey et al. (362) presented an empirical relationship between residual particle MMAD (in meters) and the surface tension of propellant in air ($\sigma_{pa}$), vapor pressure of the HFA-ethanol system ($p_{mc}$), density of the particle ($\rho_p$), unit density ($\rho_o$), and concentration of the dissolved nonvolatile component ($C_{nv}$, w/w) (see Equation 12.2 and Table 12.2), where all units are presented in International System (SI) of units. However, for this approach, the formulations listed in Table 12.1 exhibit acceptable correlation for residual particle MMAD estimations but no relationship for initial droplet MMD estimations (see Figure 12.5).

$$\text{MMAD} = 416 \times \frac{\sigma_{pa}}{p_{mc}} \times \sqrt[3]{\frac{C_{nv} \times \rho_p}{\rho_o}}$$  (Equation 12.2)
Table 12.2: Values for $\sigma_{pa}$ and $p_{mc}$ in Equation 12.2 (362)

<table>
<thead>
<tr>
<th>Property</th>
<th>HFA 134a</th>
<th>HFA 227</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\sigma_{pa}$</td>
<td>$0.06021747\left(1 - \frac{T}{374.2}\right)^{1.26}$</td>
<td>$0.0504773\left(1 - \frac{T}{376.0}\right)^{1.26}$</td>
</tr>
<tr>
<td>As a function of temperature (T) in Kelvin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$p_{mc}$</td>
<td>$5.72 \times 10^5 - 2.8 \times 10^5 \times X_{\text{EIOH}}$</td>
<td>$3.90 \times 10^5 - 2.7 \times 10^5 \times X_{\text{EIOH}}$</td>
</tr>
<tr>
<td>As a function of mass fraction of ethanol ($X_{\text{EIOH}}$)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 12.5: Estimated residual particle MMAD and initial droplet MMD from Equations 9.5 and 12.2, and Table 12.2 compared to experimental values presented in Table 12.1 (362).
2.2. Dual Suspension Formulations

Current therapeutic guidelines recommend chronic use of medications, such as inhaled corticosteroids, to prevent exacerbations of chronic obstructive pulmonary disease and asthma (359). Should exacerbations occur, short-acting β-agonists are used to temporarily relieve symptoms and considerations are made to add additional inhaled medications, such as long-acting β-agonists or anticholinergic agents, to the patient’s therapeutic regimen. The addition of multiple inhalers to an individual’s medication therapy can lead to confusion and poor adherence. Thus, there is great interest in developing dual drug pMDIs. The current marketed FDA-approved pMDIs that contain two drugs are Advair® HFA (fluticasone propionate and salmeterol xinafoate), Dulera® (mometasone furoate and formoterol fumarate dihydrate), and Symbicort® (budesonide and formoterol fumarate dihydrate). All of these formulations have both drugs in suspension. Similar to formulations that contain a suspended and dissolved entity, the addition of one suspended drug in the formulation may non-linearly impact the product performance of the second suspended drug in the formulation. Thus to avoid iterative testing of a series of pMDIs in order to identify a dual suspended drug formulation with potential for success, a model is required.

Figure 12.6 presents the pseudocode for modeling the APSD of two suspended entities, drug(s) and/or excipient(s), in a propellant-cosolvent system which may include a dissolved drug or excipient. Atomized droplets from suspension pMDIs that contain two suspended entities (i.e., “dual suspension” pMDIs) may consist of either suspended entity (differentiated by color in Figure 12.6), both suspended entities, or no suspended
particles. In addition, these droplets also contain propellant, cosolvent, and dissolved nonvolatile excipients or drugs. Over time, the propellant and cosolvent evaporate, rendering residual particles. From such formulations, up to three distinct APSDs can be found, corresponding to the first suspended, second suspended, and dissolved entities. To model this process, the user must input the concentration, density, and micronized material distribution of the second suspended entity in addition to the user-defined variables listed in Chapters 5 and 6. Thereafter, each atomized droplet can be simulated individually based on the inputted initial droplet distribution. In order the determine the number of suspended particles for each droplet, a Poisson distribution is utilized for each type of suspended drug, which is a function of the PPUV of the first or second suspended entity. Thereafter, the volume of each type of suspended entity is calculated. If the total volume of both suspended entities exceeds the volume of the initial droplet, the Poisson distribution is utilized to statistically randomly reassign the number of first and second type of suspended particles within the given droplet until the total volume of suspended particles is less than the volume of the initial droplet. Thereafter, the volumes and/or masses of both types of suspended particles are utilized to determine if the volume and mass of the nonvolatile dissolved drug or excipient (if present) and the resulting aerodynamic diameter for the simulated droplet. Once sufficient droplets are simulated, the APSD of all nonvolatile entities can be determined, as presented in Chapter 5.

The pseudocode presented in Figure 12.6 was utilized to simulate three suspension pMDI formulations that contained 8% (w/w) ethanol in HFA 134a without any dissolved drug or excipients. The formulations are detailed in Table 12.3. Increasing
the total concentration of suspended drug or decreasing the size of suspended drug increases the likelihood that the simulated atomized droplet contains one or more suspended drug particles, which is consistent with the previously established relationships between suspended drug concentration and micronized drug size and PPUV (see Chapter 10). In the case with dual suspension formulations (i.e., Formulation 3), the PPUV for each suspended drug plays a role in determining the number of atomized droplets that contain the given suspended drug. For instance, the PPUV for the first drug (MMD 2.23µm) is $8.7 \times 10^8$/mL, which is nearly two orders less than that for the second drug (MMD 0.89µm). Among a sample of suspended drug containing droplets, 20.2% of the droplets contain the first drug, while 96.5% of droplets contain the second drug, despite having both drugs at the same concentration in the formulation (0.2% w/w). For this formulation, 16.64% of suspended drug laden droplets contained both types of drug particles; 3.51% of suspended drug laden droplets contained only the first suspended drug (due to the lower PPUV); and 79.85% of suspended drug laden droplets contained only the second drug (due to the significantly greater PPUV). The total PPUV for Formulation 3 is $1.46 \times 10^{10}$/mL, which is greater than that seen with Formulations 1 and 2, which provides insight as to why a greater proportion of atomized droplets contained suspended drug particles.
**Pseudocode for Modifying Model**

**New User Defined Variables:**
- Concentration of second suspended drug/exipient
- Density of second suspended drug/exipient
- Micronized particle size distribution of second suspended drug/exipient

**Modifications to the Monte Carlo Simulation:**
- Calculate the count median diameter of the second suspended drug/exipient
- Use the properties of the second suspended drug/exipient to determine the density of the formulation
- Calculate PPUV
  - Determine PPUV of first suspended drug/exipient (PPUV1)
  - Determine PPUV of second suspended drug/exipient (PPUV2)
- Determine number of suspended drug particles of each type within a simulated droplet
  - Do
    - Determine Poisson Distribution (Initial droplet volume, PPUV1)
    - Statistically randomly determine number of suspended drug particles for the first suspended drug/exipient
    - Determine the volume of first type of suspended drug/exipient particles (Vsusp1)
    - Determine Poisson Distribution (Initial droplet volume, PPUV2)
    - Statistically randomly determine number of suspended drug particles for the second suspended drug/exipient
    - Determine the volume of second type of suspended drug/exipient particles (Vsusp2)
  - Loop while [initial droplet volume < (Vsusp1 + Vsusp2)]
- Calculate the mass for drug particles for the first type of suspended drug/exipient (Msusp1) and the second type of suspended drug/exipient (Msusp2)
- Calculate the volume and mass of dissolved drug(s) or nonvolatile excipient(s) using Vsusp1 and Vsusp2 (Msoln)
- Calculate aerodynamic diameter (AD) using mass of first type of suspended drug/exipient particles, second type of suspended drug/exipient particles, and volume of dissolved drug(s) or nonvolatile excipient(s)

**Modifications to the Output from the Simulation:**
- Utilize the following to determine the residual particle aerodynamic size distributions for drugs/exipients:
  - Dissolved drug/exipient: Msoln versus AD
  - First suspended drug/exipient: Msusp1 versus AD
  - Second suspended drug/exipient: Msusp2 versus AD

---

**Process to Model**

**Figure 12.6:** Pseudocode and simplification of process to model APSD for pMDI formulations that contain two suspended entities. The text in green and purple refer to the first and second suspended drug or excipient, respectively, and refer to the colors of the suspended particles found in the “Process to Model” panel.
**Table 12.3: Details of Simulated Formulations Containing up to Two Suspended Model Drugs**

<table>
<thead>
<tr>
<th>Formulation*</th>
<th>Overall % of Droplets that Contain Suspended Drug</th>
<th>First Suspended Drug (MMD: 2.23µm, GSD: 1.6)</th>
<th>Second Suspended Drug (MMD: 0.89µm, GSD: 1.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Concentration of Suspended Drug (% w/w)</td>
<td>Concentration of Suspended Drug (% w/w)</td>
<td>% of Droplets that are Suspended Drug Laden and Contain First Suspended Drug</td>
</tr>
<tr>
<td>1</td>
<td>10.65</td>
<td>0.2</td>
<td>8.67 × 10^8</td>
</tr>
<tr>
<td>2</td>
<td>52.73</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>54.30</td>
<td>0.2</td>
<td>8.67 × 10^8</td>
</tr>
</tbody>
</table>

* All formulations contained 8% (w/w) ethanol in HFA 134a. The initial droplet size MMD was assumed to be 10.66µm (GSD of 1.7).
Figure 12.7 presents a comparison of the residual particle mass versus residual aerodynamic diameter for the droplets simulated for the three formulations presented in Table 12.3. As expected, an increase in residual particle mass leads to an increase in aerodynamic diameter for all three formulations. In addition, there is increased variability in the predicted aerodynamic diameter for a given particle in Formulation 1, which is similar to that seen with Formulation 3, but much less than that seen with Formulation 2. As an example, for residual particles with similar mass \((9.51 \times 10^{-11} \text{g} \text{ and } 9.69 \times 10^{-11} \text{g})\), there is a maximum 11% difference in the resulting aerodynamic diameter \((5.30 \mu\text{m} \text{ and } 5.88 \mu\text{m})\), which can be attributed to the differences in the number of drug particles contained within the droplet (1 and 20 particles, respectively) and the associated shape factors and void volumes. The APSD for both of the suspended drugs for all three formulations are presented in Figure 12.8. The MMAD (GSD) for the first suspended drug from Formulation 1 is \(2.789 \mu\text{m} (1.54)\) and for the second suspended drug from Formulation 2 is \(1.602 \mu\text{m} (1.55)\). The MMAD (GSD) for the first and second suspended drugs in Formulation 3 are \(2.919 \mu\text{m} (1.49)\) and \(1.773 \mu\text{m} (1.67)\), respectively. It is not surprising that the residual APSD for both drugs is affected by the presence of the other suspended drug, given the “coformulation effect” discussed in Chapter 3 and the data presented in Figure 12.7. Further research needs to be conducted on how the fraction of droplets containing multiple suspended drug particles affects the resulting APSD of suspended drugs (or excipients) in dual suspension pMDI formulations. In addition, this model needs to be validated with experimental data.
**Figure 12.7:** Mass of residual particle versus residual particle aerodynamic diameter for formulations detailed in Table 12.3.
Figure 12.8: Residual APSD of suspended drugs found in Formulations 1 to 3 in Table 12.3.
2.3. Estimating Additional Performance Metrics

The success of pMDIs depends on the clinical factors (e.g., patient’s disease state, education on using the device, inhalation rate) and manufacturing variables. Quality design of the product can ensure that various formulation and device variables interact with each other to yield acceptable product performance, which can be determined through \textit{in vitro} experiments. A robust pMDI should deliver a consistent amount of drug with a consistent drug particle size distribution with each actuation. Of the delivered drug, some proportion of the aerosolized drug deposits in the upper airways (e.g., oral cavity, pharynx), and is not respirable. The percentage of aerosolized dose that deposits in the oropharyngeal cavity is characterized and termed as “throat deposition.” The amount of aerosolized drug that deposits in the throat is dependent primarily on the lifetime of droplets, which is a function of the volatility and concentration of the cosolvent. The slower the aerosolized droplets evaporate and the longer they remain at a larger droplet size, the more likely they are to deposit in the oropharynx by impaction or turbulent deposition (97). Furthermore, the fraction and mass of the delivered dose that can penetrate into the lung, known as fine particle fraction (FPF) and fine particle dose (FPD), is frequently characterized in order to express the amount of drug from a pMDI that correlates to the mass of the drug that clinically deposits in the lung. Particles with aerodynamic diameters of less than approximately 5μm are more likely to penetrate into the lung (34). Thus the FPD is the mass of the particles in the delivered dose with aerodynamic diameters of less than 5μm in one actuation; the FPD can be expressed as the FPF, which is the FPD divided by the cumulative mass of the aerosolized drug.
Increasing the vapor pressure of the cosolvent or decreasing the cosolvent concentration is expected to decrease throat deposition and increase the respirable dose (155). A potential modification to the current simulation model has been presented in Figure 12.9 to enable calculating the throat deposition and the FPD based on the user-defined variables (detailed in Chapter 5), cosolvent properties, and simulated APSD.
**Figure 12.9:** Algorithm for methods to determine the ex-valve dose, throat deposition, and fine particle mass for a pMDI formulation.
To determine the FPF, the fraction of the aerosol depositing in the throat must first be determined. The percentage of aerosolized droplets as a function of initial droplet size that are collected in the United States Pharmacopeia (USP) inlet was experimentally determined to be a function of the evaporation rate of droplets from the cosolvent-propellant system, as presented in Figure 12.10. Increasing the ethanol concentration from 8 to 20% effectively increases the evaporation time of the formulation and results in a decrease in collection of atomized droplets for a given initial droplet size. This results in increased drug deposition in the inlet with 20% ethanol formulations compared to that seen with 8% ethanol formulations.
**Figure 12.10:** The collection of drug in the USP inlet (i.e., collection efficiency) as a function of effective initial atomized droplets for a variety of formulations. Each formulation contains 0.3% (w/w) dissolved drug (beclomethasone dipropionate) in 8 or 20% (w/w) ethanol with HFA 134a or HFA 227. Inlet collection efficiency curves were determined by (1) using Equation 9.5 to determine the initial droplet diameters, with the Andersen Cascade Impactor particle size range for each stage as the residual MMAD; and (2) calculating collection efficiency (%) as $100 \times (1 - \frac{\text{Drug}_{\text{inlet}}}{\text{Drug}_{\text{LVC}}})$, where $\text{Drug}_{\text{inlet}}$ and $\text{Drug}_{\text{LVC}}$ is the mass of drug per actuation collected on a given stage of the cascade impactor for the inlet and large volume chamber, respectively (363,364).
A decrease in evaporation rate with the addition of a cosolvent is associated with an increase in droplet lifetime. Initial atomized droplets from pMDIs contain mostly the propellant and cosolvent. The evaporation of both of these entities can be thought of as a two-step process, as presented in Figure 12.11, where the propellant evaporates first resulting in the intermediate droplet, followed by the evaporation of the cosolvent. As the propellant and cosolvent evaporate, the temperature of the droplet decreases due to the latent heat associated with evaporation, which may significantly affect the evaporation rate of solvents with higher latent heats of evaporation (316). While in reality the propellant and cosolvent evaporate simultaneously, it is reasonable to model the evaporation as a two-step process since the cosolvent evaporation will be negligible when the droplet is at the wet bulb temperature of the propellant.

Based on the model of droplet formation and aerosol maturation presented in Figure 12.11, the droplet lifetime can be calculated. The droplet lifetime is calculated for Phase I and Phase II, independent of each other, as presented in Figure 12.11 and Table 12.4 (302,316). For Phase I, the droplet lifetime is calculated by integrating the evaporation rate equation over the interval of initial droplet diameter to intermediate droplet diameter, using Equations 12.3 to 12.6, where Equation 12.6 is plugged into Equation 12.5. For Phase II, the droplet lifetime is calculated over a range of diameters ranging from the intermediate diameter to the residual particle size. Equations 12.7 to 12.9 are substituted into Equation 12.5 and solved iteratively to determine the time for evaporation of the propellant or cosolvent. Equation 12.7 represents the effect of evaporation on droplet temperature: as the droplet is cooled by the heat required for
evaporation, it decreases the vapor pressure of the solvent at the droplet surface, resulting in a decrease in the rate of evaporation. Equation 12.8 presents a form of the Kelvin equation, where the Kelvin ratio is the ratio of the vapor pressure of the solvent at the droplet surface to the vapor pressure of the bulk solvent (302). Decreasing the Kelvin ratio to less than 1 implies that the mass balance of the droplet with the environment results in droplet evaporation. As a result of this relationship, it is clear that smaller droplets evaporate more rapidly than larger droplets. Finally, the bracketed portion of Equation 12.6 represents the Fuchs correction factor for droplet diameters less than 1µm (302). Since the evaporation rate of droplets is controlled by the rate at which vapors can diffuse away from the droplet, it is imperative to consider the mean free path of the solvent vapor (see Equation 12.9) for small droplets. The total droplet lifetime for a given formulation can be calculated by adding the results of Equation 12.5 for Phase I and Phase II. This calculated droplet lifetime represents the time for the initial droplet to evaporate to the residual particle in still air, if no other forces are acting on it (302).
### Table 12.4: Variables for Equations 12.3 to 12.9

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMDD&lt;sub&gt;I&lt;/sub&gt;</td>
<td>Initial droplet mass median diameter (µm for Equation 12.3; convert to m for Equation 12.5)</td>
</tr>
<tr>
<td>ρ&lt;sub&gt;I&lt;/sub&gt;</td>
<td>Density of initial droplet (g/cm&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
<tr>
<td>C&lt;sub&gt;NV&lt;/sub&gt;</td>
<td>Concentration of nonvolatile (weight fraction)</td>
</tr>
<tr>
<td>ρ&lt;sub&gt;R&lt;/sub&gt;</td>
<td>Density of residual particle (g/cm&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
<tr>
<td>MMAD&lt;sub&gt;R&lt;/sub&gt;</td>
<td>Residual particle mass median aerodynamic diameter (µm for Equation 12.3; convert to m for Equation 12.5)</td>
</tr>
<tr>
<td>MMDD&lt;sub&gt;int&lt;/sub&gt;</td>
<td>Intermediate droplet mass median diameter (µm for Equation 12.3; convert to m for Equation 12.5)</td>
</tr>
<tr>
<td>C&lt;sub&gt;CS&lt;/sub&gt;</td>
<td>Concentration of cosolvent (weight fraction)</td>
</tr>
<tr>
<td>ρ&lt;sub&gt;int&lt;/sub&gt;</td>
<td>Density of intermediate droplet (g/cm&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
<tr>
<td>C&lt;sub&gt;HFA&lt;/sub&gt;</td>
<td>Concentration of propellant (weight fraction)</td>
</tr>
<tr>
<td>ρ&lt;sub&gt;HFA&lt;/sub&gt;</td>
<td>Density of propellant (g/cm&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
<tr>
<td>ρ&lt;sub&gt;CS&lt;/sub&gt;</td>
<td>Density of cosolvent (g/cm&lt;sup&gt;3&lt;/sup&gt;)</td>
</tr>
<tr>
<td>D&lt;sub&gt;D&lt;/sub&gt;</td>
<td>Droplet diameter</td>
</tr>
<tr>
<td>t</td>
<td>Time</td>
</tr>
<tr>
<td>D&lt;sub&gt;HFA&lt;/sub&gt;</td>
<td>Diffusion coefficient of propellant vapor in air</td>
</tr>
<tr>
<td>M&lt;sub&gt;HFA&lt;/sub&gt;</td>
<td>Molecular weight of propellant</td>
</tr>
<tr>
<td>D&lt;sub&gt;CS&lt;/sub&gt;</td>
<td>Diffusion coefficient of cosolvent vapor in air</td>
</tr>
<tr>
<td>M&lt;sub&gt;CS&lt;/sub&gt;</td>
<td>Molecular weight of cosolvent</td>
</tr>
<tr>
<td>T&lt;sub&gt;D&lt;/sub&gt;</td>
<td>Temperature of droplet (calculate using Equation 12.7)</td>
</tr>
<tr>
<td>T&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>Ambient temperature</td>
</tr>
<tr>
<td>p&lt;sub&gt;D&lt;/sub&gt;</td>
<td>Vapor pressure of solvent at droplet surface (calculate using Equation 12.8)</td>
</tr>
<tr>
<td>R</td>
<td>Gas constant</td>
</tr>
<tr>
<td>λ&lt;sub&gt;∞&lt;/sub&gt;</td>
<td>Mean free path of solvent gas molecule in air (calculate using Equation 12.9)</td>
</tr>
<tr>
<td>H&lt;sub&gt;HFA&lt;/sub&gt;</td>
<td>Latent heat of evaporation of propellant</td>
</tr>
<tr>
<td>H&lt;sub&gt;CS&lt;/sub&gt;</td>
<td>Latent heat of evaporation of cosolvent</td>
</tr>
<tr>
<td>k&lt;sub&gt;V,HFA&lt;/sub&gt;</td>
<td>Thermal conductivity of propellant vapor</td>
</tr>
<tr>
<td>k&lt;sub&gt;V,CS&lt;/sub&gt;</td>
<td>Thermal conductivity of cosolvent vapor</td>
</tr>
<tr>
<td>r&lt;sub&gt;am&lt;/sub&gt;</td>
<td>Collision radius of an “air molecule”</td>
</tr>
<tr>
<td>r&lt;sub&gt;m,HFA&lt;/sub&gt;</td>
<td>Collision radius of a propellant molecule</td>
</tr>
<tr>
<td>r&lt;sub&gt;m,CS&lt;/sub&gt;</td>
<td>Collision radius of a cosolvent molecule</td>
</tr>
<tr>
<td>N</td>
<td>Number of gas molecules per unit volume of air</td>
</tr>
</tbody>
</table>

* Use SI units unless otherwise noted.
**Phase I: Droplet Formation**

\[
MMD_I = \frac{(\rho_I \times C_{NV})^{1/3} \times \rho_R^{1/6}}{MMAD_R}
\]

\[
\rho_I = \left(\frac{C_{HFA}}{\rho_{HFA}} + \frac{C_{CS}}{\rho_{CS}}\right)^{-1}
\]

\[
\int_{MMD_I}^{MMD} f(D_D) \, dD_D = \int_0^t f(t) \, dt
\]

\[
\frac{dD_D}{dt} = -\frac{4D_{HFA}M_{HFA}P_D}{R\rho_{HFA}D_D T_D} \times \left[2\lambda + D_D \over D_D + 5.33 \left(\frac{\lambda^2}{D_D}\right) + 3.42\lambda\right]
\]

\[
T_\infty - T_D = \frac{D_{HFA}M_{HFA}H_{HFA}P_D}{R_kV_{HFA}T_D}
\]

\[
p_D = \rho_{HFA} \times \exp\left(\frac{4Y_{HFA}M_{HFA}}{R \rho_{HFA}D_D T_D}\right)
\]

\[
\lambda = \left[\sqrt{2N\pi(r_{am} + r_{m,HFA})}\right]^{-1}
\]

**Phase II: Aerosol Maturation**

\[
MMD_{Int} = MMD_I \times \left[\frac{\rho_I \times (C_{NV} + C_{CS})^{1/3}}{\rho_{Int}}\right]
\]

\[
\rho_{Int} = (C_{NV} + C_{CS}) \times \left(\frac{C_{NV}}{\rho_R} + \frac{C_{CS}}{\rho_{CS}}\right)^{-1}
\]

\[
\int_{MMD_{Int}}^{MMD} f(D_D) \, dD_D = \int_0^t f(t) \, dt
\]

\[
\frac{dD_D}{dt} = -\frac{4D_{CS}M_{CS}P_D}{R\rho_{CS}D_D T_D} \times \left[2\lambda + D_D \over D_D + 5.33 \left(\frac{\lambda^2}{D_D}\right) + 3.42\lambda\right]
\]

\[
T_\infty - T_D = \frac{D_{CS}M_{CS}H_{CS}P_D}{R_kV_{CS}T_D}
\]

\[
p_D = \rho_{CS} \times \exp\left(\frac{4Y_{CS}M_{CS}}{R \rho_{CS}D_D T_D}\right)
\]

\[
\lambda = \left[\sqrt{2N\pi(r_{am} + r_{m,CS})}\right]^{-1}
\]

**Figure 12.11:** Calculating droplet lifetime for two phases of evaporation. The symbols for the equations are defined in Table 12.4.
Table 12.5: Physical Properties for a Variety of Solvents

<table>
<thead>
<tr>
<th>Solvent or Cosolvent Property (Units)</th>
<th>HFA 134a</th>
<th>HFA 227</th>
<th>Water</th>
<th>Ethanol</th>
<th>Methyl Acetate</th>
<th>Ethyl Acetate</th>
<th>Butyl Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion coefficient of vapor ($D_v$) (m$^2$/s)</td>
<td>$9.7017 \times 10^{-6}$</td>
<td>$8.0000 \times 10^{-6}$</td>
<td>$2.6674 \times 10^{-5}$</td>
<td>$1.1979 \times 10^{-5}$</td>
<td>$9.60116 \times 10^{-6}$</td>
<td>$8.47348 \times 10^{-6}$</td>
<td>$7.03312 \times 10^{-6}$</td>
</tr>
<tr>
<td>Molecular weight (M) (kg/mol)</td>
<td>0.10203</td>
<td>0.17003</td>
<td>0.01802</td>
<td>0.04607</td>
<td>0.074048</td>
<td>0.088104</td>
<td>0.116156</td>
</tr>
<tr>
<td>Density of solvent ($\rho$)* (kg/m$^3$)</td>
<td>1466.4373</td>
<td>1642.6268</td>
<td>998.7010</td>
<td>807.2349</td>
<td>983.9725</td>
<td>933.7182</td>
<td>890.1319</td>
</tr>
<tr>
<td>Saturated vapor pressure ($p$)* (Pa)</td>
<td>8119.536</td>
<td>5182.070</td>
<td>1423.602</td>
<td>1319.337</td>
<td>2847.340</td>
<td>1976.006</td>
<td>648.162</td>
</tr>
<tr>
<td>Latent heat of vaporization ($H$)* (J/kg)</td>
<td>235584</td>
<td>146523</td>
<td>2460053</td>
<td>959240</td>
<td>469397</td>
<td>426578</td>
<td>381526</td>
</tr>
<tr>
<td>Thermal conductivity of gas ($k_v$) (W/(m × K))</td>
<td>0.01352</td>
<td>0.007432</td>
<td>0.01858</td>
<td>0.01452</td>
<td>0.01147</td>
<td>0.01028</td>
<td>0.009804</td>
</tr>
<tr>
<td>Surface tension* (N/m)</td>
<td>0.020202</td>
<td>0.017218</td>
<td>0.076141</td>
<td>0.026898</td>
<td>0.030043</td>
<td>0.027084</td>
<td>0.02627</td>
</tr>
<tr>
<td>Average radius of molecule ($r_m$) (m)</td>
<td>$3.271 \times 10^{-10}$</td>
<td>$3.695 \times 10^{-10}$</td>
<td>$1.966 \times 10^{-10}$</td>
<td>$2.902 \times 10^{-10}$</td>
<td>$3.217 \times 10^{-10}$</td>
<td>$3.455 \times 10^{-10}$</td>
<td>$3.806 \times 10^{-10}$</td>
</tr>
<tr>
<td>Droplet temperature ($T_D$) (K)</td>
<td>214.483</td>
<td>215.345</td>
<td>285.336</td>
<td>271.700</td>
<td>253.719</td>
<td>265.244</td>
<td>284.285</td>
</tr>
<tr>
<td>Vapor Pressure at 20°C (Pa)</td>
<td>572000</td>
<td>390470</td>
<td>2338</td>
<td>6317</td>
<td>21516</td>
<td>9134</td>
<td>1128</td>
</tr>
</tbody>
</table>

Data from (172,316,365)
*Values at temperature of $T_D$
For illustrative purposes, the evaporation time for droplets between 0.8 and 10µm in diameter containing pure propellant or cosolvent were calculated using the equations in Figure 12.11 and are presented in Figure 12.12. The values for calculating the curves in Figure 12.12 are listed in Table 12.5. In general, increasing the size of the droplet or the latent heat of vaporization or decreasing the vapor pressure results in a decrease in droplet evaporation time, as seen for the solvents in Figure 12.12. For droplets with diameters of 10µm, it takes 0.28, 2.17, 3.30, 6.14, 11.18, and 52.38 times longer for HFA 227, methyl acetate, ethyl acetate, ethanol, butyl acetate, and water droplets, respectively, to evaporate completely compared to HFA 134a droplets. These differences between solvents remain fairly constant as droplet sizes decrease.
Figure 12.12: Evaporation time for a variety of solvents as a function of droplet diameter.
Given that the concentration of the cosolvent has a very strong relationship with amount of aerosolized drug depositing in the throat and reaching the respirable region of the lung, as presented by Gupta et al. (200), it is reasonable to associate these performance parameters with droplet evaporation time (or droplet lifetime) in hopes of predicting percentage of drug depositing in the throat and on stages 3 to filter of the Andersen Cascade Impactor (i.e., aerodynamic diameters $\leq 4.7\mu$m), ex-valve. Table 12.5 presents the droplet lifetime for four formulations containing 0.3% (w/w) dissolved drug, with 8% (w/w) cosolvent in HFA 134a. Increasing droplet lifetime typically resulted in increasing throat deposition and decreasing respirable mass. Figure 12.13 presents the correlation between droplet evaporation time and respirable mass and throat deposition for the data presented in Table 12.10, and by Stein and Myrdal in 2006 (316). The data presented in Figure 12.13 (B) was determined using the TSI Model 3306 Impactor Inlet and Model 3321 Aerodynamic Particle Size Spectrometer, with a variety of cosolvents and 1% (w/w) dissolved nonvolatile material (316). While the relationships presented in Figure 12.13 (A) and 12.13 (B) differ, in both circumstances it is clear that there is a strong dependence of throat deposition and respirable mass on droplet lifetime. Based on these observations, it is reasonable to further explore the relationship between throat deposition and respirable mass and their dependence on droplet evaporation rate, instrumentation utilized, and nonvolatile component concentration, which may provide insight on predicting alternative product performance parameters for a variety of pMDI formulations.
**Table 12.6: Results from Theoretical and Experimental Assessment of pMDIs Using Novel Cosolvents**

<table>
<thead>
<tr>
<th>Cosolvent</th>
<th>Cosolvent Density (g/cm³)</th>
<th>Residual Particle MMAD* (µm)</th>
<th>Initial Droplet MMD (µm)</th>
<th>Intermediate Droplet MMD (µm)</th>
<th>Droplet Lifetime (s)</th>
<th>Respirable Mass* (% Ex-Valve)</th>
<th>Throat Deposition* (% Ex-Valve)</th>
<th>Cosolvent Vapor Pressure at 20°C (Pa)</th>
<th>Wet Bulb Temperature Change (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl Acetate</td>
<td>0.934</td>
<td>1.412</td>
<td>8.967</td>
<td>4.239</td>
<td>0.00464</td>
<td>67.46</td>
<td>12.24</td>
<td>21516</td>
<td>39.3</td>
</tr>
<tr>
<td>Ethyl Acetate</td>
<td>0.901</td>
<td>1.533</td>
<td>9.605</td>
<td>4.556</td>
<td>0.00618</td>
<td>63.63</td>
<td>17.14</td>
<td>9134</td>
<td>27.8</td>
</tr>
<tr>
<td>Ethanol</td>
<td>0.789</td>
<td>1.267</td>
<td>7.879</td>
<td>3.982</td>
<td>0.00645</td>
<td>59.04</td>
<td>24.12</td>
<td>6317</td>
<td>21.3</td>
</tr>
<tr>
<td>Butyl Acetate</td>
<td>0.882</td>
<td>1.414</td>
<td>8.848</td>
<td>4.241</td>
<td>0.01051</td>
<td>47.52</td>
<td>32.58</td>
<td>1128</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Each formulation contained 0.3% (w/w) dissolved drug with 8% (w/w) cosolvent in HFA 134a.
Figure 12.13: Relationship between droplet evaporation time and throat deposition and respirable mass. The data presented in (A) represents the data in Table 12.6. The data in (B) represents the data determined by Stein and Myrdal using the TSI Model 3306 Impactor Inlet and Model 3321 Aerodynamic Particle Size Spectrometer (316).
3. Conclusions

Through this study, it has been possible to use the principles of statistics, physical chemistry, and aerosol science to effectively model the residual aerodynamic particle size distributions (APSD) for a variety of pressurized metered dose inhaler (pMDI) formulations containing nonvolatile dissolved and/or suspended drug or excipient in a propellant-ethanol system with excellent correlation to data derived from Andersen Cascade Impactor testing. This enables researchers to design formulations and select pMDI hardware components while considering the impact of a variety of variables on the overall APSD of each nonvolatile component. This model provides the base for future studies that simulate and evaluate (1) pMDIs containing alternative propellants or blends of propellants; (2) pMDIs containing two suspended entities, each with their own micronized drug particle size distribution; and (3) other performance predictors, such as percentage of dose that deposits in the throat and in the respirable regions of the lung.
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