PREDICTION OF MELTING POINT LOWERING IN EUTECTIC MIXTURES

By

Bandar Aldhubiab

_____

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF PHARMACEUTICAL SCIENCES

In Partial Fulfillment of the Requirements

For the degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2010

THE UNIVERSITY OF ARIZONA
GRADUATE COLLEGE

As members of the Dissertation Committee, we certify that we have read the dissertation prepared by Bandar Aldhubiab

entitled Prediction of the melting point lowering in the eutectic mixture

and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy

_____ Date: May 11 2010
Dr. Samuel H Yalkowsky

_____ _____ Date: May 11 2010
Dr. Michael Mayersohn

_____ Date: May 11 2010
Dr. Paul Myrdal

_____ Date:

_____ Date:

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

_____ Date: May 11 2010
Dissertation Director: Dr. Samuel H Yalkowsky

STATEMENT BY AUTHOR

This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at The University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this thesis are allowable without special permission provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of Graduate College when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED:__BANDAR ALDHUBIAB_____

ACKNOWLEDGEMENTS

I would first like to thank my advisor, Dr. Samuel H. Yalkowsky. Throughout my doctoral degree, he taught me behavioral and technical skills, enhanced my critical thinking, and provided guidance for my scientific writings and presentations. Besides always being there for me as an academic advisor, he has also acted as a philosophical advisor and life coach.

In further appreciation, I would like to express my sincerest thanks to Dr. Mayersohn, Dr. Myrdal, and Dr. Murphy for offering their valuable time to serve on my committee. Their involvement and feedback are truly appreciated.

My thanks continues to my lab mates, Dr. Duoli Guo, Dr. Katherine Chu, and Dr. Parijat Jain for their ongoing support during my PhD degree. I will also not forget Abdull-qadir Khan for helping me finish my experiments. These individuals never hesitated to help me and I consider them like family.

I have deepest gratitude toward my father and mother who have taught me the basics of life. Their teachings have played an important role in my education. I learned from my father to persevere to achieve my goals. He also encouraged me throughout my graduate studies.

Finally, I would like to thank my lovely wife, Asma, without her support, this would not have been possible. I would also like to thank my best friend and neighbor, Dr. Khalid Alghanem, for being there for me, especially for my last year of study. I am grateful for the valuable advice that he gave me.

DEDICATION

TO MY FAMILY

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Three solution models: ideal, regular, and quasi- regular, were used to predict the melting point of eutectic mixtures containing Polyethylene Glycol (PEG) 400 and PEG 4000 with nine poorly water- soluble drugs: 1-naphthoic acid, estrone, griseofulvin, indomethacin, phenobarbital, paracetamol, salicylic acid, salicylamide and naproxen. PEG 400 was physically mixed with drug at different weight percentages to determine the melting points of the pure drugs and the melting point depression using Differential Scanning Calorimetry (DSC). The PEG 4000 eutectic mixtures were processed by the solvent evaporation method. In both the PEG 400 and PEG 4000 study, the quasi-regular solution model accounted for the most realistic conditions of entropy and enthalpy of the mixtures compared to ideal and regular solution models.

CHAPTER I: INTRODUCTION TO PEG 400 EUTECTIC MIXTURES

Over the last fifty years, many techniques have been used to increase the water solubility and dissolution rate of poorly water-soluble drugs. These involve alteration of the vehicle or alteration of the crystallinity of the drug. Crystallinity modification can be accomplished by particle size reduction, crystal form alteration, or eutectic formation[1-4]. Eutectic mixtures are typically formed by combining the drug with carrier substance which weakens the crystal structure of the drug by acting as an impurity or a solvent. The use of a water-soluble polymer as a carrier substance, further enhances the dissolution rate. The reduction of the drug's crystal quality is evidenced by the lowering of its melting point[5]. This discussion attempts to better understand the lowering of the melting point in eutectic formation. The diagram below (Figure 1) represents the different phases of the eutectic system.

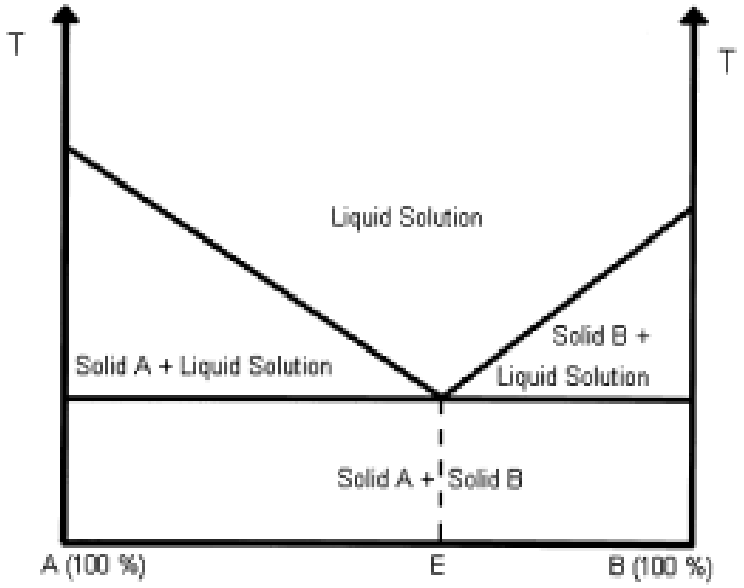

Figure 1. a typical phase diagram illustrating a eutectic mixture. [5]

This diagram illustrates the different phases of a mixture of compound A and B at different proportions and at different temperatures. When compound B is dispersed in compound A, the melting temperature of the mixture will continue to decrease until it reaches the eutectic point E, at which the melting temperatures of compound A and B have reached a minimum. At the eutectic temperature, compound A and B are completely miscible and just below this temperature, both compounds crystallize simultaneously. The same relationship applies when adding compound A to compound B [5].

1.1. Background (Methods)

Several methods have been proposed for making eutectic mixtures. The 'melting' method involves the joining of a carrier and a drug through a heating and mixing process. The carrier (e.g. solid polymer) is heated until it becomes liquid, at which point, the drug is added and the two are mixed. The mixture is then cooled until it becomes solid, and then milled until the mixture takes the form of fine particles[6, 7] .

The Solvent Evaporation Method involves dissolving the drug and the polymer in an organic solvent followed by removal of the solvent by evaporation or spray drying[3, 8] .

The Co-precipitation Method involves dissolving both drug and the polymer in a suitable organic solvent and changing the environment in to precipitate the drug and the polymer. This is often accomplished by changing the pH. Then, the solvent is filtered or

evaporated[9]. The Kneading Method is a form of solvent evaporation that involves mixing the polymer with an organic solvent. The paste is mixed with the drug and then dried at a temperature that is appropriate[10].

Nazzal et al. recently proposed another method that involves mixing a semisolid carrier with a solid drug. The results of this experiment with thermo-analysis suggest that semisolid carriers and solid drugs can be combined to form eutectic mixtures to increase drug absorption[11].

1.2. Carriers (Polymers)

Two main solid polymers have been used as carriers depending on their molecular size. Polyethylene Glycol (PEG) is the most common polymer that has been used in enhancing the solubility of poorly water-soluble drugs[12-20]. Its molecular weight ranges from 200 to 20000. PEGs that are below a 600 molecular weight are liquid and those with molecular weights higher than 1000 are solid. The smaller molecular weight PEGs are not preferable because of their toxicity. The larger molecular weight PEGs have a very low solubilization power due to the slow releasing of the drug from the folded polymer. The larger polymer also has a slower dissolution rate than the smaller one because of its molecular size.

Moreover, drug molecules tend to disperse more easily in a smaller polymer because of its comparable size, than in the larger ones. The study by Ford et al. shows that the dissolution rate of a drug decreases with higher molecular weight polymers as compared to lower molecular weight polymers[21].

CHAPTER II: THEORY

Three solution models (ideal, regular, and quasi-regular) can be used to characterize the entropy and enthalpy of melting of drug-polymer eutectic mixtures. Each of these were used to estimate the melting temperatures of several concentrations of the nine drugs in mixture with PEG.

2.1. Ideal Solution Model:

The ideal solubility of solid solute *u* is the solubility that it would have in an ideal solvent. An ideal solvent is one in which there is no volume or enthalpy change upon mixing and one in which the entropy of mixing is ideal, i.e., the mixture is completely random. This ideal solubility is described by the integrated form of the Clausius-Clapeyron equation[22, 23]:

$$R \cdot \ln X_u^{ideal} = -\Delta S_m \cdot \frac{(T_{mix} - T)}{T} + \Delta Cp_m \cdot \frac{(T_{mix} - T)}{T} - \Delta Cp_m \cdot \ln \frac{T_{mix}}{T} \qquad (1)$$

where X_u^{ideal} is the mole fraction of the solute in an ideal solvent, R is the universal gas constant, T is the applied temperature, T_{mix} is the melting point of the mixture, ΔS_m is the entropy of melting of the pure drug, and ΔCp_m is its differential heat capacity of melting. This equation is used to determine the mole fraction of the solute in the ideal solvent at different temperatures. It can also be used to find the melting temperature for different

concentrations of an ideal solute. Note that when X_u is1, T_{mix} is equal to T_m, the melting point of the pure drug.

Because of the lack of differential heat capacity data, it is customary to approximate its value. The most common approximations are those of van't Hoff and Hildebrand. The former assumes that $\Delta Cp_m = 0$, while the latter assumes that $\Delta Cp_m = \Delta S_m$. Wu and Yalkowsky (2009) have recently shown that since the numerical value of $\ln(T_{mix}/T)$ is very close to that of $(T_{mix}-T)/T$ there is little difference between the two approximations[24]. The use of the van't Hoff approximation results in the following simplification of equation[23, 25, 26]:

$$R \cdot \ln X_u^{ideal} = -\Delta S_m \cdot \frac{(T_{mix} - T)}{T} \qquad (2)$$

If the solute's mole fraction, entropy of melting and melting point are known, then the melting temperature of the mixture, T_{mix} can be calculated. For mole fraction solubility up to 0.5, the melting point of eutectic mixtures can be predicted by rearranging the Van't Hoff equation 2 to give[23]:

$$T_{mix} = \frac{T_m \cdot \Delta S_m}{\Delta S_m - R \cdot \ln X_u} \qquad (3)$$

At equilibrium, the melting point of the pure compound is directly related to the enthalpy

and entropy of melting:

$$T_m = \frac{\Delta H_m}{\Delta S_m} \tag{4}$$

By replacing ΔS_m with $\frac{\Delta H_m}{T_m}$, Equation 3 becomes:

$$T_{mix} = \frac{T_m \cdot \Delta H_m}{\Delta H_m - R \cdot T_m \cdot \ln X_u} \tag{5}$$

2.2. Regular Solution Model:

The previous equations assume that the enthalpy and entropy of mixing are ideal and that volume change of mixing is zero. Unfortunately, this is not always the case. When non-ideal mixing occurs, an activity coefficient is used to account for the deviations from ideality. The activity, or the behavior of the solute molecule in the solvent is defined by the following[22]:

$$a = X \cdot \gamma \tag{6}$$

where *a* is the activity, γ is the activity coefficient, and X is the mole fraction of the solute. Taking the natural logarithm of Equation 9, we get:

$$\ln a = \ln X + \ln \gamma \tag{7}$$

In the case of ideal solutions, γ =1.

By combining Equations 2 and 7, we get[22]:

$$\ln X_u = -\Delta S_m \cdot \frac{(T_m - T_{mix})}{T_{mix}} - \ln \gamma_u \tag{8}$$

The activity coefficient can be calculated using Scatchard, Hildebrand and Wood's equation that directly relates the activity coefficient to the volume of the solute[22]:

$$\ln \gamma_u = (E_u + E_v - 2E_{uv}) \frac{V_u \Phi_v^{\,2}}{RT_{mix}} \tag{9}$$

Where E_u is the energy required to separate a pure solute molecule, E_v is the energy required to separate a pure solvent molecule and E_{uv} is the energy gained when they are mixed, and Φ_v is the volume fraction of the solvent.

The energy required to separate a molecule of the pure solute from a bulk phase can be given by this equation[23]:

$$E_u = CED_u \cdot V_u \tag{10}$$

Where V_u is the molar volume of the solute, and CED_u the cohesive energy density of a pure solute.

To make a hole in the pure solvent large enough to accommodate a solute molecule[23]

$$E_v = CED_v \cdot V_u \tag{11}$$

The energy gained for the mixing of the two will be[23]:

$$E_{uv} = -2CED_{uv} \cdot V_u \tag{12}$$

By adding all three equations we get[23]:

$$\Delta E_{mix} = (CED_u + CED_v - 2CED_{uv})V_u \tag{13}$$

The following is an important proposal by Scatchard (1933) and Hilderbrand (1929) for estimating the cohesive energy density of the mixture[23](Yalkowsky 1999):

$$CED_{uv} = \sqrt{CED_u \cdot CED_v} \tag{14}$$

This is called the geometric mean approximation. By substituting CED_{uv} from Equation 18 into Equation17, we obtain[23]:

$$\Delta E_{mix} = \left(\sqrt{CED_u} - \sqrt{CED_v}\right)^2 V_u \tag{15}$$

The solubility parameter δ is defined as the square root of the cohesive energy density

$$\delta = \sqrt{CED} \tag{16}$$

Incorporating Equation 20 into Equation 19 gives[23]:

$$\Delta E_{mix} = (\delta_u - \delta_v)^2 V_u \Phi_v^{\ 2} \tag{17}$$

where δ_u is the solubility parameter of the solute, and δ_v is the solubility parameter of the solvent.

By incorporating Equation 17 into Equation 9, the activity coefficient becomes[22]:

$$\ln \gamma_u = (\delta_u - \delta_v)^2 \frac{V_u \Phi_v^{\ 2}}{RT_{mix}} \tag{18}$$

By substituting ln γ of Equation 18 into Equation 8 we obtain the regular solution theory for similarly sized molecular volumes:

$$\ln X_u = \left(\frac{\Delta S_u^m}{R}\right) \cdot \left(\frac{T_{mix} - T_m}{T_{mix}}\right) + \frac{V_u \cdot (\delta_u - \delta_v)^2 \cdot \Phi_v{}^2}{RT_{mix}} \quad (19)$$

To solve for T_{mix}, Equation 19 is rearranged to:

$$T_{mix} = \frac{T_m \cdot \Delta S_m - V_u \cdot (\delta_u - \delta_v)^2 \cdot \Phi_v{}^2}{\Delta S_m - R \ln X_u} \quad (20)$$

Based on Equation 20, the predicted temperature to melt a solute:solvent mixture, T_{mix}, accounts for non-ideal enthalpy of mixing. The regular solution theory assumes that no hydrogen bonds or ionic bonds are formed and that non-ideal mixing occurs due to London forces. Like the ideal solubility equation, regular solution theory assumes entropy of mixing is ideal.

2.3. Quasi-Regular Solution Model:

The regular solution theory assumes ideal entropy of mixing. However, we know that this is not always the case, especially in polymeric solvent systems. Flory and Huggins (1944) developed a statistical model to calculate the entropy of mixing for polymer solutions. They assumed that the mixture is divided into equal sized boxes occupied by the polymer segments and solute molecule. Based on these assumptions, the equation to calculate the entropy of mixing is [22]:

$$\Delta S_{mix} = -R(n_u \ln \Phi_u + n_v \ln \Phi_v) \tag{21}$$

where n_u is the number of moles of the solute, n_v is the number of moles of the solvent, Φ_u is the volume fraction of the solute, and Φ_v is the volume fraction of the polymeric solvent molecule containing N segments. By combining the non-ideal enthalpy of mixing (Eqn. 18) and the non-ideal entropy of mixing (Eqn. 21) in the overall free energy of mixing equation and differentiating with respect to n_u, the new activity coefficient of the solute in the polymer is[22]:

$$\ln \gamma = \ln \Phi_u + \left(1 - \frac{1}{N}\right) \cdot \Phi_v + (\delta_u - \delta_v)^2 \frac{V_u \cdot \Phi_v^{\,2}}{R \cdot T_{mix}} \tag{22}$$

where N is the number of segments in each polymer molecule.

Combining Equation 22 and Equation 8 gives:

$$\ln X_u = \left(\frac{\Delta S_u^m}{R}\right) \cdot \left(\frac{T_{mix} - T_m}{T_{mix}}\right) + \frac{V_u \cdot (\delta_u - \delta_v)^2 \cdot \Phi_v^{\,2}}{R T_{mix}} + \ln \Phi_u + \left(1 - \frac{1}{N}\right) \cdot \Phi_v \tag{23}$$

To solve for T_{mix}, Equation 23 is rearranged to:

$$T_{mix} = \frac{T_m \cdot \Delta S_m - V_u \cdot (\delta_u - \delta_v)^2 \cdot \Phi_v{}^2}{\Delta S_m - R \ln X_u + R\left(\ln \Phi_u + \left(1 - \frac{1}{N}\right) \cdot \Phi_v \right)} \quad (24)$$

Equation 24 is the quasi-regular solution model for predicting the melting point of the drug-polymer mixture. This equation accounts for the non-ideal entropy of mixing as well as the non-ideal enthalpy of mixing between the drug and polymer.

CHAPTER III: EXPERIMENTAL SECTION

3.1. Materials:

1-Naphthoic acid, indomethacin, estrone, griseofulvin, naproxen, paracetamol, salicylamide, salicylic acid, and PEG 400 were obtained from Sigma Aldrich. Phenobarbital was purchased from Mallinckrodt.

3.2. Methods:

Drug- PEG 400 mixtures with drug loading ranging from 50% to 100% drug (w/w %) were physically mixed using a mortar and pestle. The melting temperatures, T_{mix}, were experimentally obtained using the Differential Scanning Calorimetry (DSC). A 5-10 mg sample of each mixture was weighed into an aluminum hermetic pan that is covered with a vent hole. Samples were run on a DSC Q1000 from TA Instruments with a heating rate of 5 °C /min and purged with dried nitrogen gas at a flow rate of 40 ml/min. Duplicates were determined for each drug-polymer composition. All of the samples were run above the melting point of the pure drug by 10-20 °C. The DSC was calibrated using Indium. The TA Instrument software program reports the melting temperature and the enthalpy of melting of the mixture.

For some samples, parallel measurements of weight loss were performed using a TGA Q50 Thermogravimetric Analyzers from TA Instruments. The heating rate was 5 °C/min and samples were purged with 60 ml/min nitrogen gas. The DSC plot, which

shows the melting point of the mixture, and the TGA graph, which shows the point at which weight loss occurs, are overlaid in order to distinguish between drug melting and evaporation. Hot-stage microscopy was also used to confirm the melting temperature of the eutectic mixtures.

3.3. Physical Properties:

Table 1 summarizes the physical properties. (solubility parameter, δ, melting point, T_m, enthalpy of melting, ΔH_m , molecular weight, MW, and the logarithm of the octanol/water partition coefficient, log K_{ow}) of the 9 drugs studied

Table 1. List of Physical Properties

Drug	δ $(J/cm^3)^{1/2}$	T_m (°C)	ΔHm (KJ/mol)	MW (g/mol)	log K_{ow}
1-Naphthoic acid	18.2	161	21.79	172	3.1
Estrone	20.2	253	39.99	270	3.13
Griseofulvin	21.0[27]	219	42.55	352	2.18
Indomethacin	24.5[28, 29]	160	36.82	358	4.27
Naproxen	23.4[28, 29]	154	31.01	230	3.18
Phenobarbital	27.0[27]	176	24.85	232	1.47
Paracetamol	30.0[28, 29]	169	26.15	151	0.46
Salicylamide	29.6[28, 29]	140	24.87	137	1.28
Salicylic acid	31.3[28, 29]	159	26.15	151	2.26

CHAPTER IV: RESULTS AND DISCUSSION

4.1. Assigning a value of N for PEG-400:

In order to assign a value of N for PEG-400, equation 28 was solved for integral numbers of methylene and ether groups, using an average of 14 cm^3/group. The calculated melting points were compared to the experimental values. The average absolute error (AAE) for the 9 drugs is shown as a function of N in Figure 1. It is clear that an N of around 14 gives the best fit.

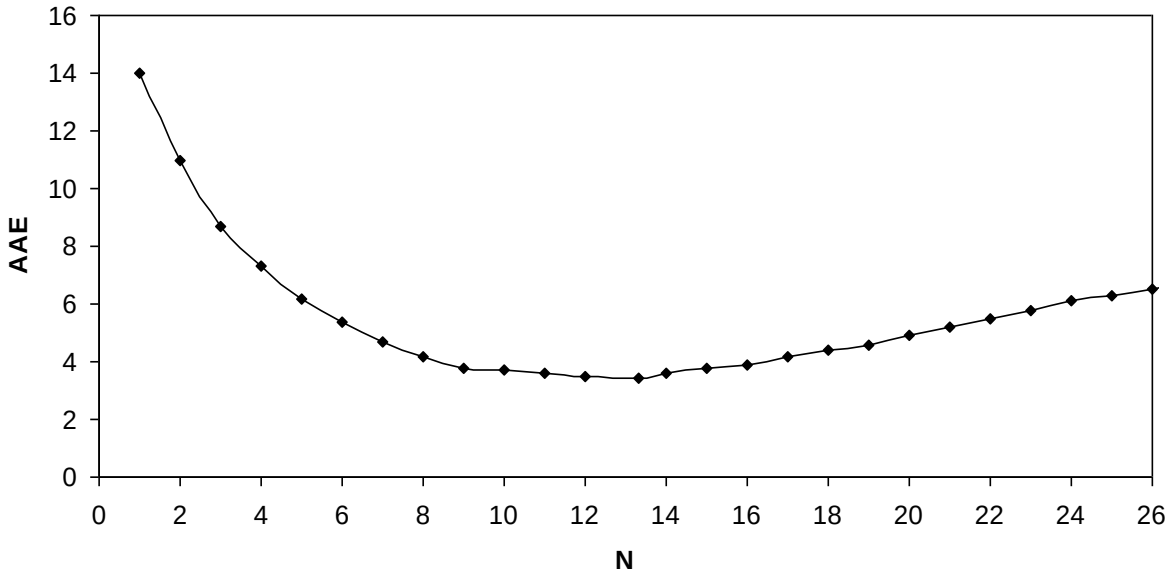

Figure 2. Dependence of average absolute error of Tmix at 50% drug load for 9 drugs on the effective number of repeating segments of PEG-400.

4.2. Eutectic diagram:

Representative plots are shown in Figures 3 – 11. For some drugs, a melting point was not observed when the polymer load was increased to greater than 50%. The samples themselves were clear liquid mixtures at room temperature and the DSC confirmed that the drug was completely dissolved in PEG 400. For this reason, the highest fraction of PEG 400 evaluated was 50%. In all cases, the results show that the melting point depression of the drug-polymer eutectic mixture is roughly proportional to the amount of PEG 400 added. The polymer acted as an impurity which weakens the crystal lattice and lowers the melting point. Theoretically, a eutectic point should be observed.

The melting points of the nine drugs and their eutectic mixtures at 50 w/w% (drug-polymer) are presented in columns 2 and 3 of Table 2. Their corresponding melting point predictions and the associated errors from the ideal, regular, and quasi-regular solution models are also included in the table. The observed melting temperatures are plotted as dcircle in Figures 3 – 11 for 50 to 100% drug load of indomethacin, salicylamide, and salicylic acid.

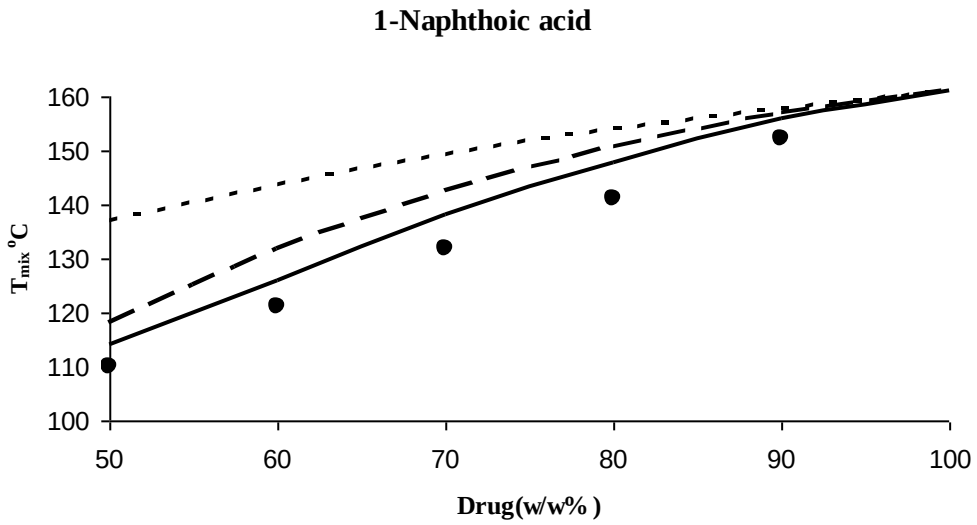

Figure 3. **T_{mix} of 1-Naphthoic acid and PEG 400**

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

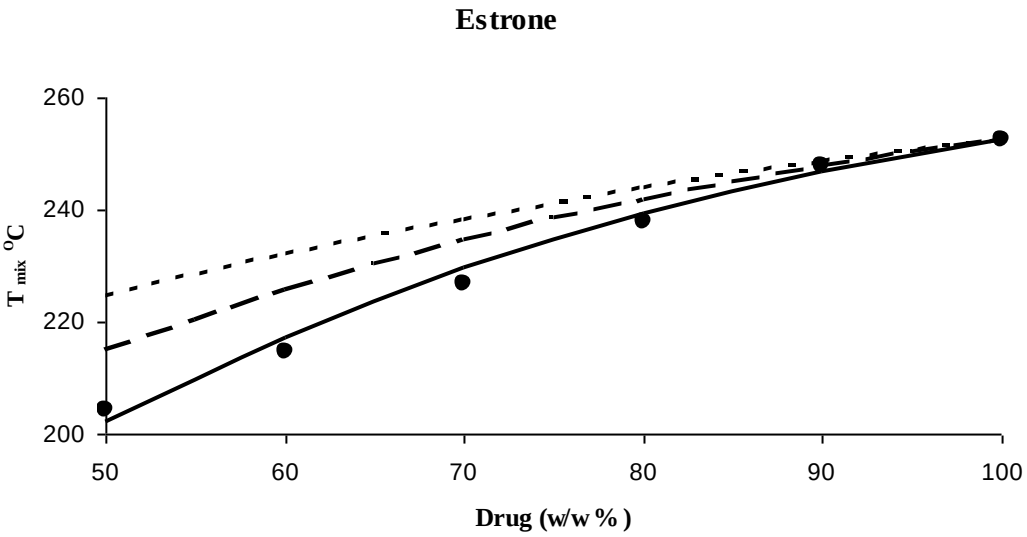

Figure 4. **T_{mix} of Estrone and PEG 400**

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

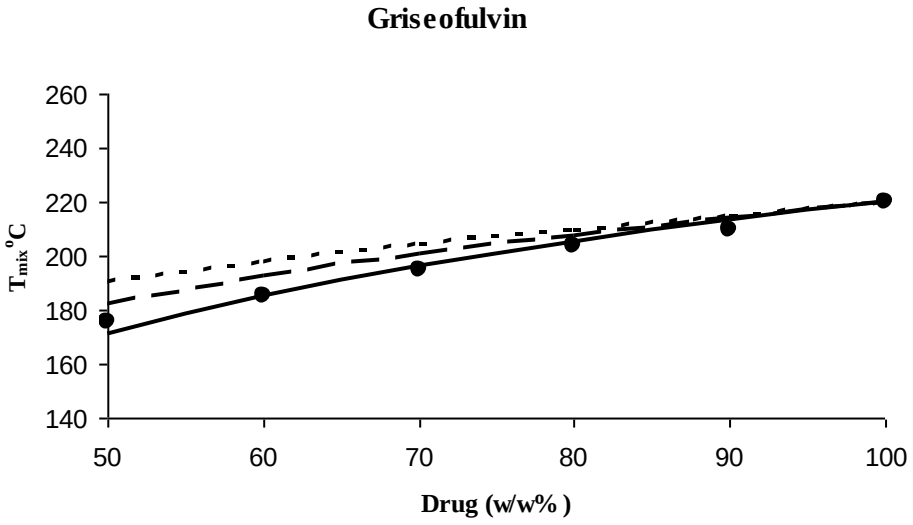

Figure 5. T_{mix} of Griseofulvin and PEG 400

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

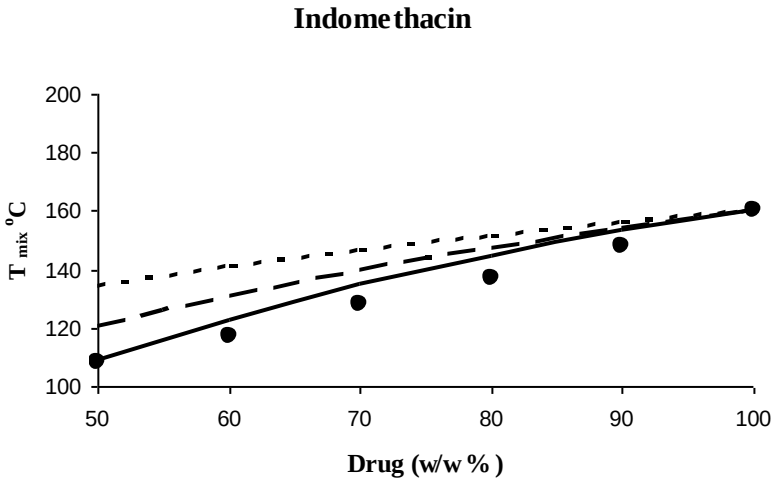

Figure 6. T_{mix} of Indomethacin and PEG 400.

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

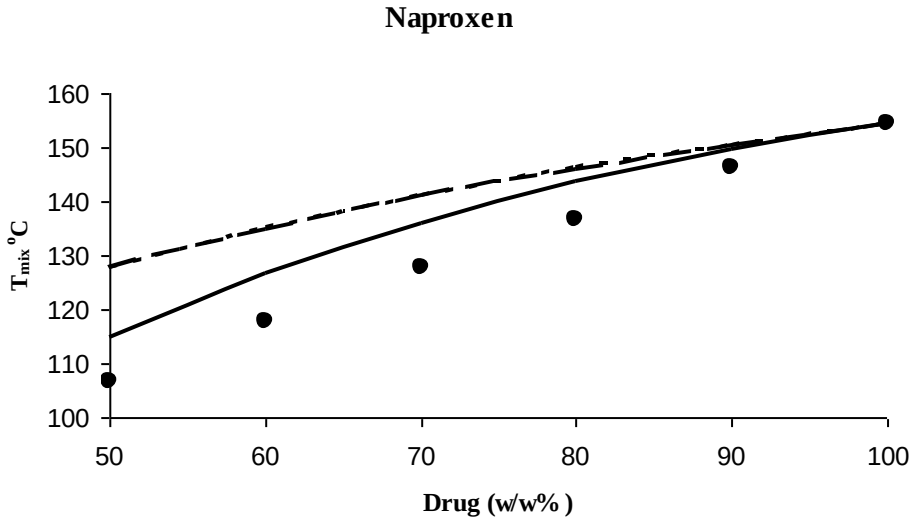

Figure 7. T_{mix} of Naproxen and PEG 400

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

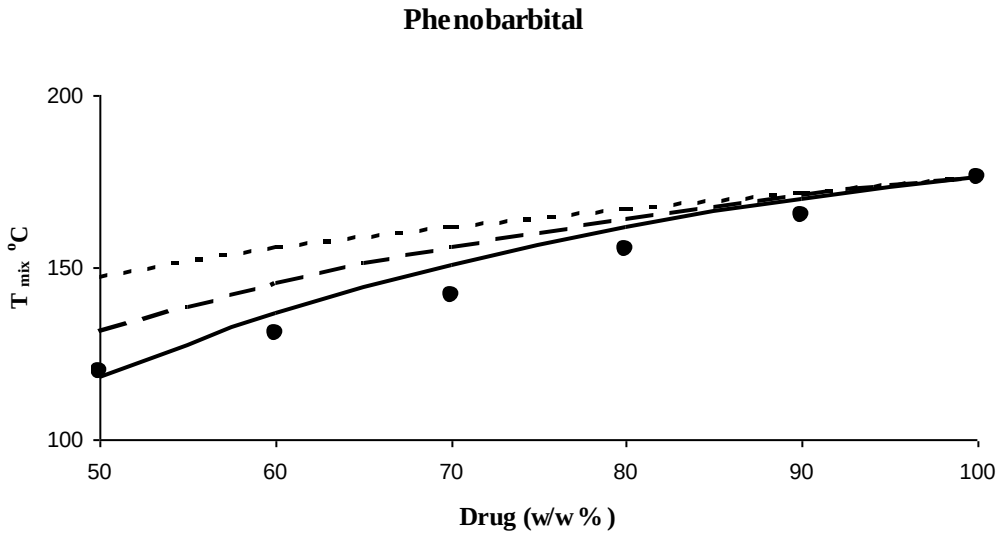

Figure 8. T_{mix} of Phenobarbital and PEG 400

Observed, •; ideal, (- - -) ; regular, (━ ━); quasi-regular, (▬)

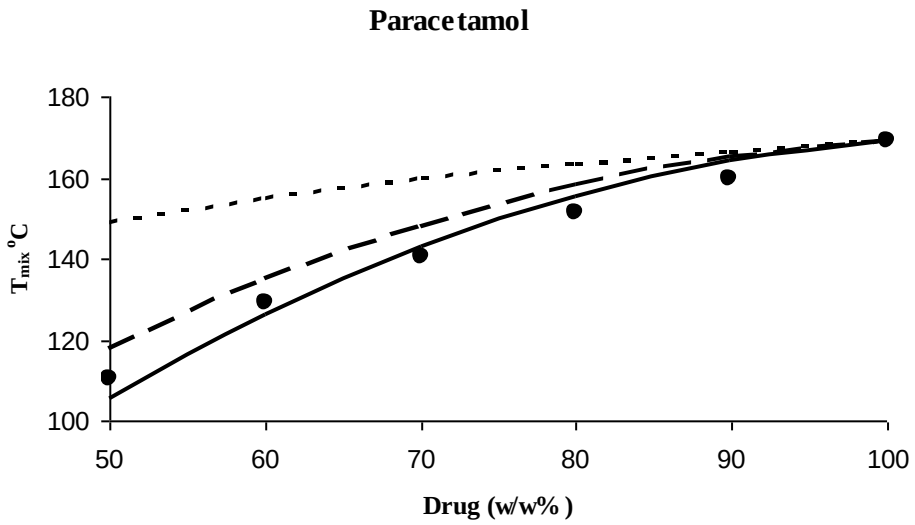

Figure 9. T_{mix} of Paracetamol and PEG 400

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

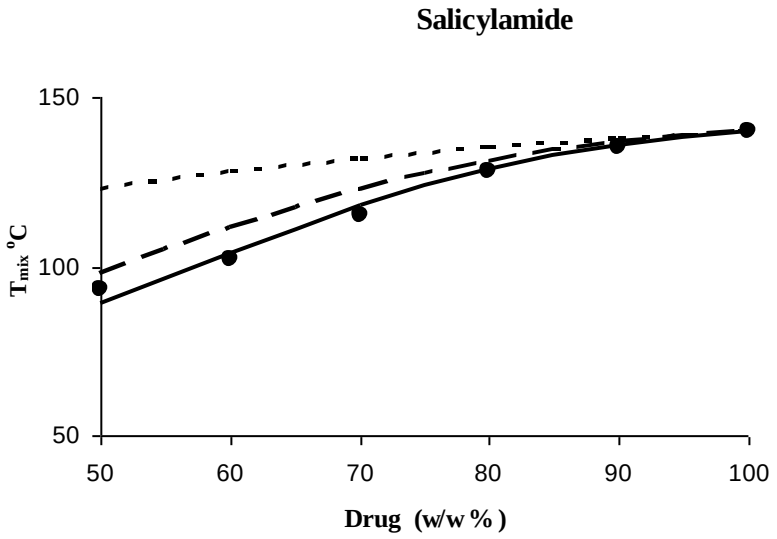

Figure 10. T_{mix} of Salicylamide and PEG 400

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

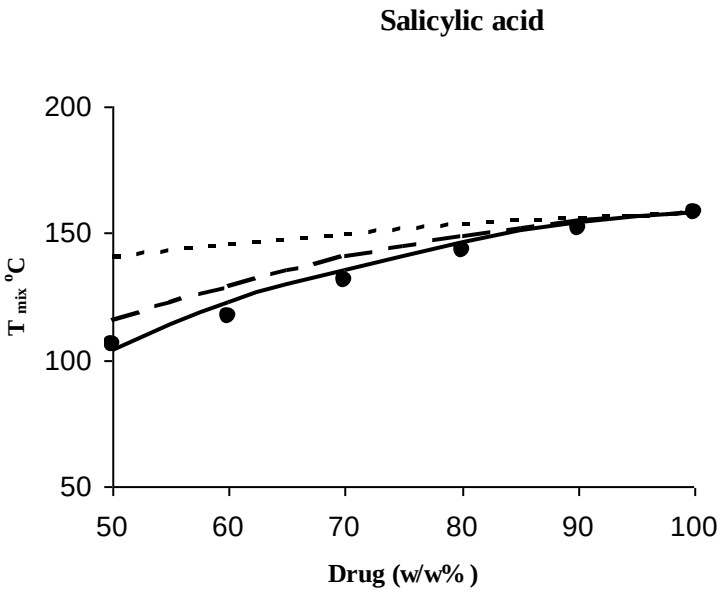

Figure 11. T_{mix} of Salicylic acid and PEG 400

Observed, •; ideal, (- - -) ; regular, (━ ━); quasi-regular, (──)

4.3. Ideal Solution Model:

The predictions of the ideal solution model are indicated by the dashed line in figures 3-11. It is clear that there is a rank order correlation between these values and the observed values indicated by the dark circle. However the predicted values are consistently higher than the observed values.

4.4. Regular Solution Model:

Attempts were made to find correlations between the errors in the ideal solution prediction and the differences in the solubility parameters, log K_{ow}, melting points and the number of hydrogen bonds between drug and PEG 400. No relationships were observed among any of these parameters.

However, as can be seen from Table 2, the regular solution model gives better predictions than the ideal solution model in all cases. This is expected since Scatchard-Hildebrand activity coefficients account for the non-ideal attractive interactions between the drugs and the polymer. Although the regular solution model improves the prediction over the ideal solution model, there is no solid agreement between the observed and the predicted values.

4.5. Quasi-Regular Solution Model:

In general, it is known that polymer solutions deviate from ideal behavior. The quasi-regular solution theory was developed to include the Flory-Huggins equation that

accounts for the non-ideal entropy of mixing. By doing so, we were able to obtain better predictions than both the ideal and regular solution models.

In the case of the polyethylene glycols the selection of the size of the repeating unit is somewhat arbitrary. Therefore, the number of repeating units in polyethylene glycol 400 for use in the Flory-Huggins equation was determined by comparing the experimental data for the nine drugs with calculations based upon integral numbers of N in Equation 28. The average absolute errors of the calculated melting points based upon different values of N are shown in Figure 2. As can be seen from the figure, the lowest error is obtained with an N of around 14, which corresponds to an ethylene or an oxymethylene unit. Since this value gives much better agreement with the experimental data than a value which is closer to the volume of the drug, it was used for all of the quasi regular solution calculations.

The melting points calculated by ideal, regular and quasi regular solution models are shown in Figure 3-11. Table 2, shows the observed and predicted melting temperatures for 50% (w/w) drug-PEG 400 mixtures. As indicated in the figures and Table 2, the average error associated with the quasi-regular solution model using an N of 14 gives the best predictions. This value corresponds to a repeating unit with a molecular weight of around 29 Daltons.

Table 2. Observed and Predicted Melting Temperatures T_{mix} for 50 (w/w)% Drug-PEG 400 Mixtures:

Drug Name	Observed T_{mix} (C°)	Ideal T_{mix}	Ideal Error	Regular T_{mix}	Regular Error	Quasi regular T_{mix}	Quasi regular Error
1-Naphthoic acid	110	137	27	118	8	115	5
Estrone	204	225	20	215	11	203	-1
Griseofulvin	176	191	15	182	6	172	-4
Indomethacin	108	135	27	121	13	109	1
Naproxen	107	120	21	120	21	116	9
Phenobarbital	120	147	27	131	11	119	-1
Paracetamol	110	149	39	118	8	106	-4
Salicylamide	93	123	30	98	5	89	-4
Salicylic acid	106	141	35	115	9	104	-2
Average error			**26.7**		**10.2**		**-0.2**
Average Absolute Error			**26.7**		**10.2**		**3.4**

CHAPTER V: INTRODUCTION OF PEG 4000 EUTECTIC MIXTURES

Since the introduction by Sekiguchi and Obi (1964)[6] of combining a drug and a biologically inactive water soluble substance to produce a eutectic mixture, there have been dozens of publications on improving the solubility and/or absorption of drugs by eutectic formation. Many of these utilize water-soluble polymers such as PEG and polyvinylpyrrolidone.

The drug dispersed in the polymer is ideally less crystalline (i.e., more amorphous), melt lower, and is more soluble than the pure crystalline drug (Hancock and Zografi (1997)[30]. This results in a more rapid dissolution rate and hopefully improved oral bioavailability.

Recent publications by Law (2002), Marsac et al. (2006, 2009) and Avula et al. (2010) have shown that the decrease in the melting point of a drug in the dispersion can be related to the solubility of the drug in the polymer via the van't Hoff equation[26, 31-33]. This study determined the solubility of nine drugs and drug-like compounds in PEG 4000 by the lowering of their melting point as a function of PEG concentration from zero to 50 percent. The melting point depressions were compared to the predictions of the ideal, regular, and quasi-regular solution models.

5.1. Background

Three solution models (ideal, regular, and quasi-regular) were used to characterize the entropy and enthalpy of melting for drug-PEG 4000 eutectic mixtures. Each of these were used to estimate the melting temperatures of several concentrations of the above drugs mixed with PEG.

5.2. Ideal Solution Model:

In the ideal solution model, it is assumed that the enthalpy of mixing ΔH_m is zero and the entropy of mixing ΔS_m is ideal. These assumptions lead to the following form or the van't Hoff equation

$$T_{mix} = \frac{T_m \cdot \Delta H_m}{\Delta H_m - R \cdot T_m \cdot \ln X_u} \qquad (25)$$

T_{mix} is its melting point of the mixture, T_m is the melting point of the pure drug, R is the universal gas constant, and X_u^{ideal} is the mole fraction of the solute.

5.3. Regular Solution Model:

The regular solution model is somewhat more realistic in that it accounts for drug-polymer interactions. Using the regular solution theory of Hildebrand which considers non-ideal enthalpy and ideal entropy of mixing gives the melting point of the mixture as

$$T_{mix} = \frac{T_m \cdot \Delta S_m - V_u \cdot (\delta_u - \delta_v)^2 \cdot \Phi_v^{\,2}}{\Delta S_m - R \cdot \ln X_u} \tag{26}$$

where δ_u and δ_v are the Hildebrand solubility parameters of the solute and solvent, respectively, Φ_v is the volume fraction of the solvent, and V_u is the molar volume of the solute.

5.4. Quasi-Regular Solution Model:

In polymeric solvent systems the entropy of mixing is generally not ideal. The entropy of the mixing of polymer solutions can be calculated using a statistical model created by Flory and Huggins (1944). This equation assumes that polymer segments and solute molecules of the mixture are divided into equal regions.

$$\Delta S_{mix} = -R \cdot (n_u \cdot \ln \Phi_u + n_v \cdot \ln \Phi_v) \tag{27}$$

where n_u is the number of moles of the solute, n_v is the number of moles of the solvent, Φ_u is the volume fraction of the solute, and Φ_v is the volume fraction of the polymeric solvent molecule.

Combining the non-ideal enthalpy of mixing (Eqn. 26) and the non-ideal entropy of mixing (Eqn. 27) in the overall free energy of mixing equation and differentiating with respect to n_u gives the new activity coefficient of the solute in the polymer:

$$\ln \gamma = \ln \Phi_u + \left(1 - \frac{1}{N}\right) \cdot \Phi_v + (\delta_u - \delta_v)^2 \frac{V_u \cdot \Phi_v^{\,2}}{RT_{mix}} \tag{28}$$

where *N* is the number of segments in each polymer molecule. Combining the ideal equation and Equation 29 gives:

$$\ln X_u = \left(\frac{\Delta S_u^m}{R}\right) \cdot \left(\frac{T_{mix} - T_m}{T_{mix}}\right) + \frac{V_u \cdot (\delta_u - \delta_v)^2 \cdot \Phi_v^{\,2}}{RT_{mix}} + \ln \Phi_u + \left(1 - \frac{1}{N}\right) \cdot \Phi_v \tag{30}$$

To solve for T_{mix}, Equation 30 is rearranged to:

$$T_{mix} = \frac{T_m \cdot \Delta S_m - V_u \cdot (\delta_u - \delta_v)^2 \cdot \Phi_v^{\,2}}{\Delta S_m - R \ln X_u + R\left(\ln \Phi_u + \left(1 - \frac{1}{N}\right) \cdot \Phi_v\right)} \tag{31}$$

Equation 31 represents the quasi-regular solution model which incorporates both the non-ideal enthalpy and the non ideal entropy of the mixing of the drug and polymer.

In Chapter 4 using PEG 400, it was determined that the best value of N is given by:

$$N = \frac{MW}{29} \tag{32}$$

where *MW* is the molecular weight of the PEG and 29 is the segment molecular weight. A molecular weight of 29 corresponds to an ethylene or an oxymethylene unit that is considerably smaller than the molecular weights of the drugs studied. The use of equation 35 gives PEG 4000 a value of 140 for N.

5.5. Experimental section:

5.5.1. Materials:

1-Naphthoic acid, Indomethacine, Estrone, Griseofulvin, Naproxen, Paracetamol, Salicylamide, Salicylic Acid, and PEG 4000 were obtained from Sigma Aldrich. Phenobarbital was purchased from Mallinckrodt.

5.5.2. DSC study:

Drug/PEG 4000 mixtures at different w/w % value were dissolved in methanol or chloroform. This was followed by spray drying or using a heated oven to remove the solvent. The dry mixture was ground using a mortar and pestle. A sample, weighing from 5-10 mg of each mixture, was put into an aluminum hermetic pan and covered with a vent hole. Samples were run on a DSC Q1000 from TA Instruments with a heating rate of 5ºC /min. During the heating, it was purged with dried nitrogen gas at a flow rate of 40ml/min. Duplicate samples were run up to 10-20º C above the melting point of the pure drug. Indium was used to calibrate the DSC. The enthalpy and temperature of the melting point of the mixtures were monitored by TA Instrument software.

5.5.3. TGA:

In order to distinguish between evaporation and melting, a TGA Q50 Thermogravimetric Analyzer from TA Instruments was used to measure the weight loss of some of the samples. The samples were purged with 60ml/min of nitrogen gas and were heated at a rate of 5ºC/min.

5.6. Drug Properties:

The acquisition of the melting points, solubility parameters, and heats of fusion of the nine drugs studied are described in Chapter 2 and their values are summarized in Table 1.

CHAPTER VI: RESULTS AND DISCUSSION

The observed melting points of each pure drug and mixtures containing 80, 70, 60, and 50 percent drug are shown Figures 12-20. The predicted melting temperatures according to the ideal, regular and quasi-regular solution models are indicated as dotted, dashed, and solid curves in the figures. (Note, that since the solubility parameter of naproxen is the same as that of PEG, the ideal and regular solution models are identical).

For some drugs a melting point was not observed when the polymer load is greater than 30%. This indicates that the drugs were completely dissolved in the polymer. The melting points of the nine drugs and their eutectic mixtures at 80, 70, 60 and 50 w/w% (drug-polymer) are summarized in the Table 3 along with the predicted melting points from the ideal, regular, and quasi-regular solution models

In all cases, the lowered melting point of the mixtures is a function of the quantity of the PEG-4000 present, i.e., the purity of the drug. This is because the presence of the polymer disrupts the crystal lattice, which in turn lowers the melting point. It is clear from the figures that the data for all nine compounds are best described by the quasi-regular solution model. This model, unlike the ideal and regular solution models, considers the effect of the non-ideal entropy of drug polymer mixing.

Table 3. Observed and Predicted Melting Temperatures T_{mix} for Drug-PEG 4000 Mixtures:

Percent	**80%**			**70%**			**60%**			**50%**		
Drug Name	**Obs**	**QR**	**Error**	**Obs**	**QR**	**Error**	**Obs**	**QR**	**Error**	**Obs**	**QR**	**Error**
Estrone	248	249	1	243	244	1	236	238	2	229	229	0
Griseofulvin	216	217	1	212	210	-2	206	203	-3	197	194	-3
Indomethacin	154	157	3	150	153	3	143	147	4	---	---	---
Naproxen	147	152	5	142	149	7	138	145	7	---	---	---
1-Naphthoic ac.	153	156	3	146	149	3	---	---	---	---	---	---
Phenobarbital	169	171	2	163	165	2	154	156	2	---	---	---
Paracetamol	163	162	-1	155	153	-2	143	140	-3	---	---	---
Salicylamide	134	134	0	128	126	-2	118	115	-3	---	---	---
Salicylic acid	149	152	3	142	144	2	---	---	---	---	---	---
Average error			1.89			1.33			0.86			-1.5
Average Absolute Error			**2.11**			**2.67**			**3.43**			**1.5**

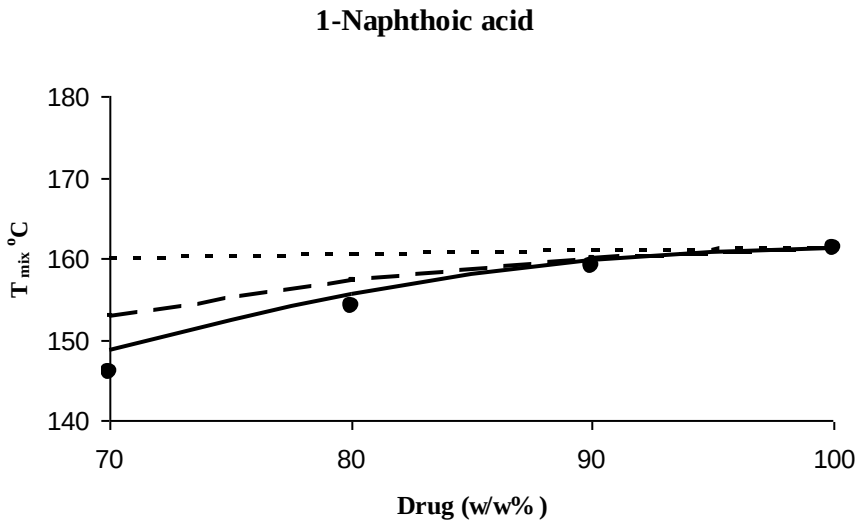

Figure 12. T_{mix} of 1-Naphthoic acid and PEG 4000

Observed, •; ideal, (- - -) ; regular, (━ ━); quasi-regular, (━━)

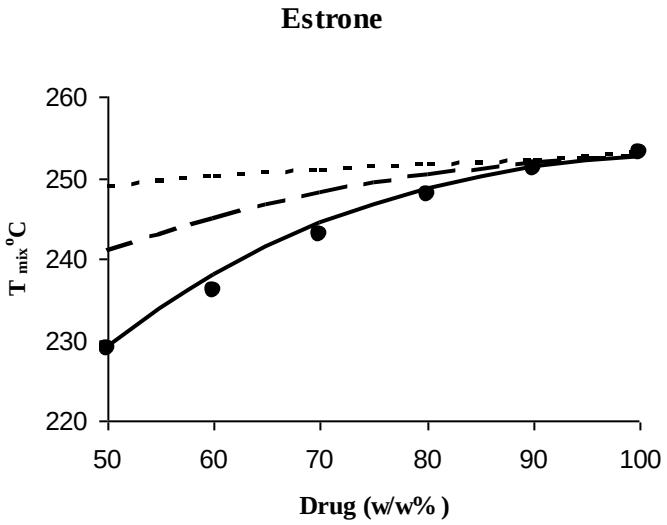

Figure 13. T_{mix} of Estrone and PEG 4000

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

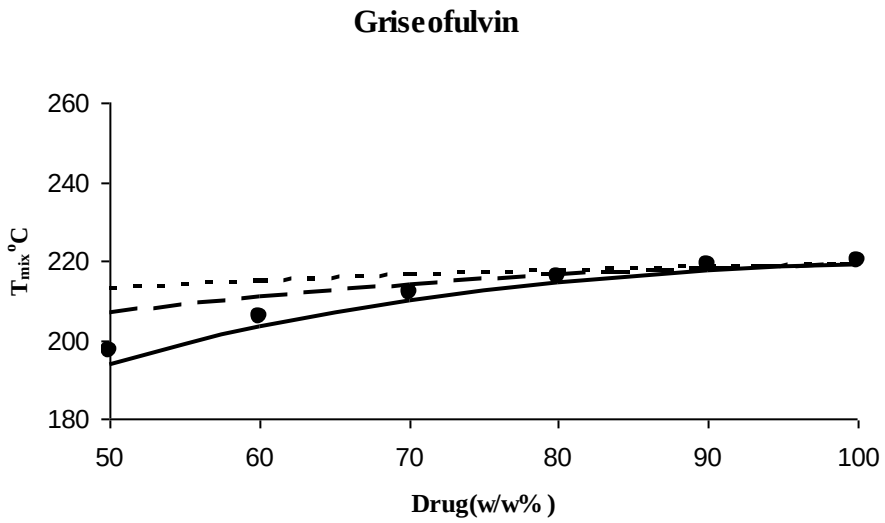

Figure 14. T_{mix} of Griseofulvin and PEG 4000

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (——)

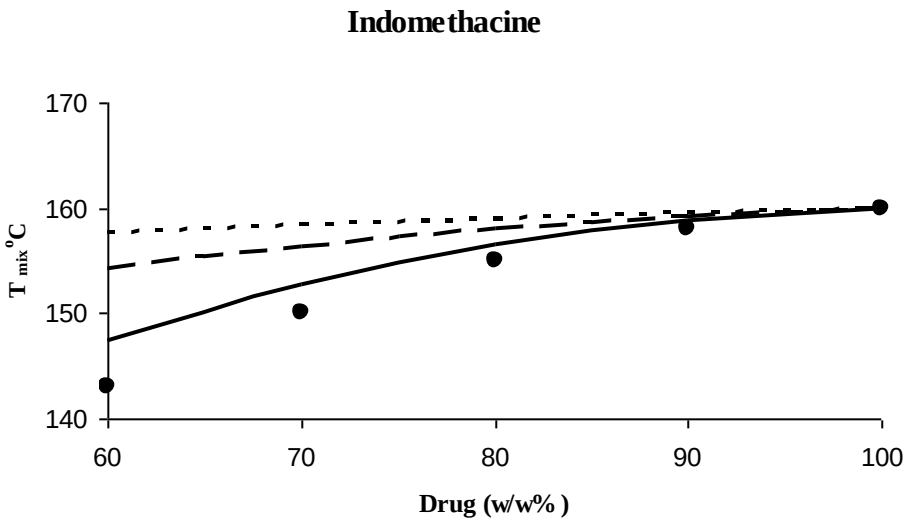

Figure 15. T_{mix} of Indomethacin and PEG 4000

Observed, •; ideal, (- - -) ; regular, (━ ━); quasi-regular, (═══)

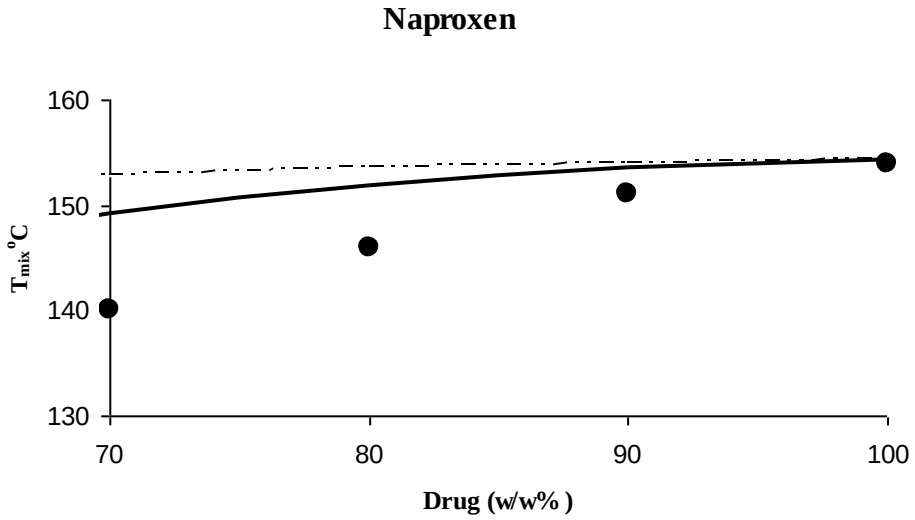

Figure 16. T_{mix} of Naproxen and PEG 4000

Observed, •; ideal, (- - -) ; regular, (━ ━); quasi-regular, (▬)

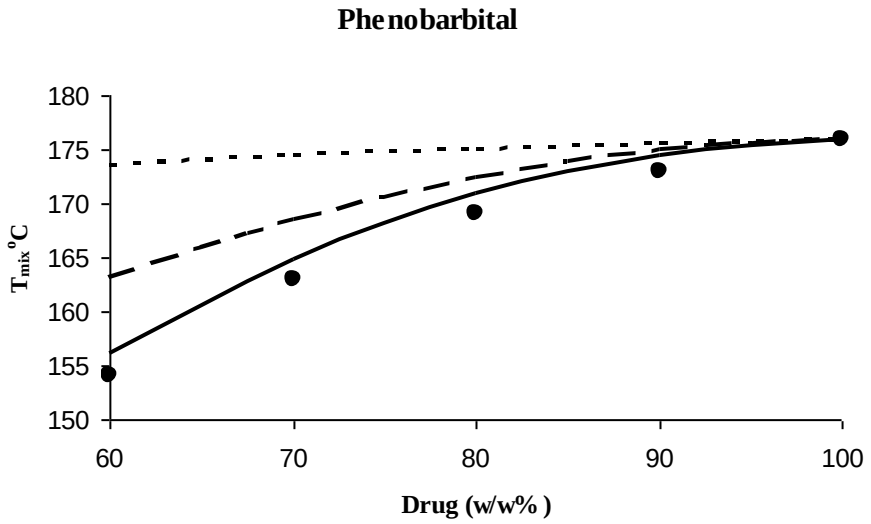

Figure 17. T_{mix} of Phenobarbital and PEG 4000

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (——)

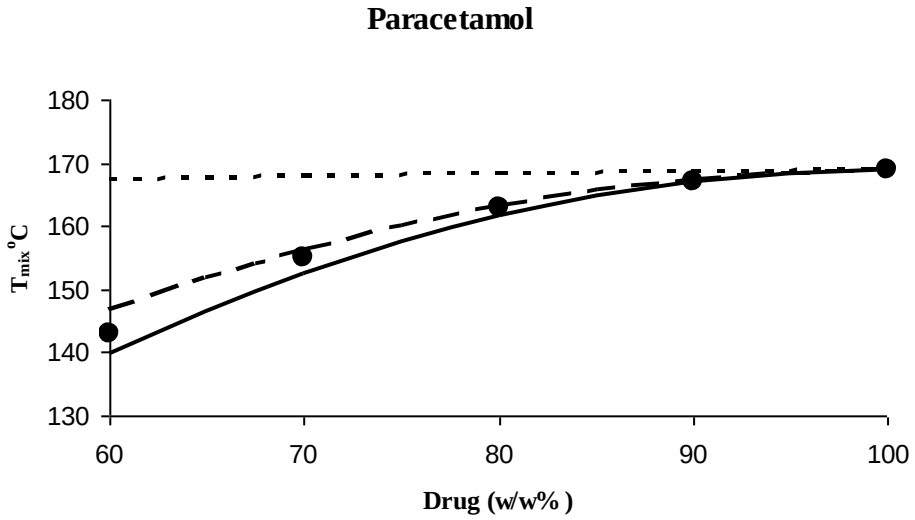

Figure 18. T_{mix} of Paracetamol and PEG 4000

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (——)

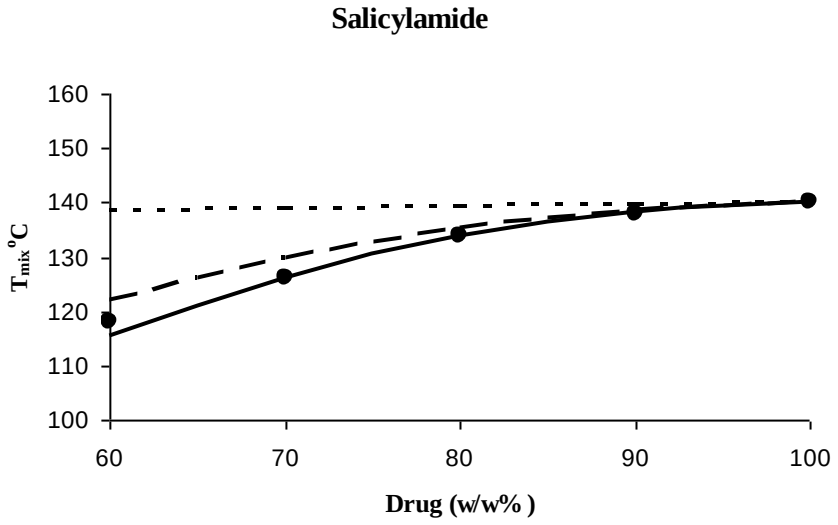

Figure 19. T_{mix} of Salicylamide and PEG 4000

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (——)

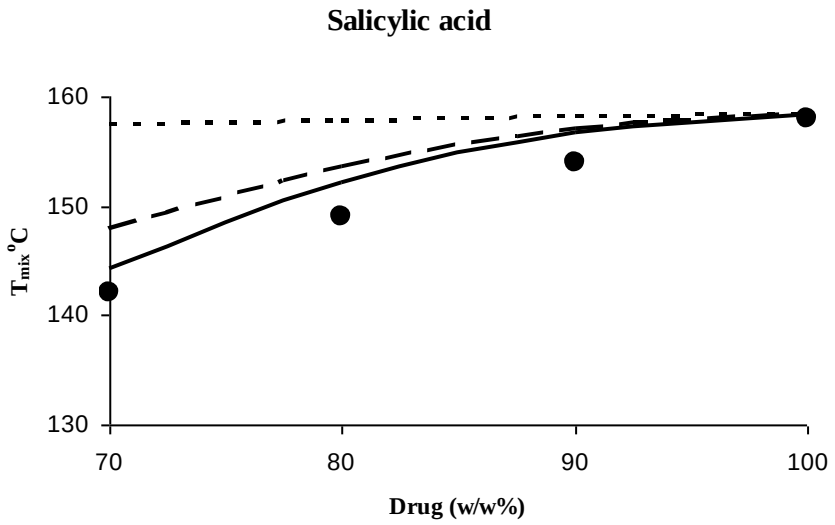

Figure 20. **T_{mix} of Salicylic acid and PEG 4000**

Observed, •; ideal, (- - -) ; regular, (— —); quasi-regular, (———)

SUMMARY

Chapter 1 discusses the background and the advantages of solid dispersion eutectic mixtures for poorly water-soluble drugs. Different techniques and polymers have been used for making these mixtures. In this chapter, the amorphous polymer, Polyethylene Glycol (PEG) 400, was examined as the selected polymer for the study. It was the carrier polymer used for the 9 tested drugs.

In Chapter 2, the discussion revolves around the three solution models that were used to predict the lowering of the melting point of the drug in the eutectic mixture. These three solution models were: ideal, regular, and quasi regular. The derivation and the assumptions for all three models were based on the Clausius-Clapeyron equation. Its form was modified to cater to each of the three different solution models.

Chapter 3 reviews the materials and methods used for preparing the eutectic mixtures. The mixtures were prepared using different w/w% value of drug varying from 50%-100%. Two samples of the eutectic mixtures were run on the DSC, TGA and hot stage. The melting point was determined using the TA Instrument software program. This chapter also describes the physical properties of each drug that is represented in Table 1.

Chapter 4 analyzes the results that were obtained from DSC. It also shows the comparison between the actual and predicted results using the three solution models. These are depicted in nine graphs. An explanation for the error between the actual and

the predicted results for each solution model is also provided. It was determined that the quasi regular solution model, which accounts for non-ideal entropy as well as non-ideal enthalpy of mixing, gave reasonably accurate predictions of the melting point lowering observed for PEG 400 and the nine studied drugs. During this chapter, it was determined that N, the number of repeating segment in the polymer, in the quasi-regular solution model with a value of 14 was the best number to represent the AAE. This was concluded (in Equation 28) by solving for integral numbers of methylene and ether groups. An average of 14 cm^3/group was used.

Chapter 5 introduces the study of PEG 4000 eutectic mixtures. The chapter commences with examples of similar solution models used by various scientists. This section describes the solid dispersion of the nine drugs, using PEG 4000, by the solvent evaporation method. The study in this chapter examined the effect of the polymer size in the lowering of the melting point of the drug. The three solution models were once again used to predict the eutectic mixture's temperature.

In Chapter 6, the study analyzed the error between the actual and predicted results. This chapter notes that the quasi-regular solution model is once again concluded to be the best to describe for the polymer/drug eutectic mixtures. This solution model, with a value of 140 for N (adding a zero from the PEG 400 N value of 14), gave the best prediction of the melting points of the polymer/water soluble drug mixtures.

REFERENCES

1. Chiou, W.L. and S. Riegelman, *Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin.* J Pharm Sci, 1969. **58**(12): p. 1505-10.

2. Chiou, W.L. and S. Riegelman, *Increased dissolution rates of water-insoluble cardiac glycosides and steroids via solid dispersions in polyethylene glycol 6000.* J Pharm Sci, 1971. **60**(10): p. 1569-71.

3. Mayersohn, M. and M. Gibaldi, *New method of solid-state dispersion for increasing dissolution rates.* J Pharm Sci, 1966. **55**(11): p. 1323-4.

4. Craig, D.Q., *The mechanisms of drug release from solid dispersions in water-soluble polymers.* Int J Pharm, 2002. **231**(2): p. 131-44.

5. Leuner, C. and J. Dressman, *Improving drug solubility for oral delivery using solid dispersions.* Eur J Pharm Biopharm, 2000. **50**(1): p. 47-60.

6. Sekiguchi, K., N. Obi, and Y. Ueda, *Studies on Absorption of Eutectic Mixture. Ii. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits.* Chem Pharm Bull (Tokyo), 1964. **12**: p. 134-44.

7. Vervaet, C. and J.P. Remon, *Bioavailability of hydrochlorothiazide from pellets, made by extrusion/spheronisation, containing polyethylene glycol 400 as a dissolution enhancer.* Pharm Res, 1997. **14**(11): p. 1644-6.

8. Tachibana, M., Y. Kawazoe, K. Aoki and W. Nakahara, *A New Method for the Preparation of 4-Hydroxyaminoquinoline 1-Oxide.* Gann, 1965. **56**: p. 85-6.

9. Khan, M.A., A. A. Karnachi, Agarwal V., S. R. Vaithiyalingam, S. Nazzal and I. K. Reddy, *Stability characterization of controlled release coprecipitates and solid dispersions.* J Control Release, 2000. **63**(1-2): p. 1-6.

10. Veiga, F., C. Fernandes, and P. Maincent, *Influence of the preparation method on the physicochemical properties of tolbutamide/cyclodextrin binary systems.* Drug Dev Ind Pharm, 2001. **27**(6): p. 523-32.

11. Nazzal, S., I. I. Smalyukh, O. D. Lavrentovich and M. A. Khan, *Preparation and in vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation*. Int J Pharm, 2002. **235**(1-2): p. 247-65.

12. Friedrich, H., B. Fussnegger, K. Kolter and R. Bodmeier, *Dissolution rate improvement of poorly water-soluble drugs obtained by adsorbing solutions of drugs in hydrophilic solvents onto high surface area carriers.* Eur J Pharm Biopharm, 2006. **62**(2): p. 171-7.

13. Vippagunta, S.R., Z. Wang , S. Hornung and S. L. Krill, *Factors affecting the formation of eutectic solid dispersions and their dissolution behavior.* J Pharm Sci, 2007. **96**(2): p. 294-304.

14. Zajc, N., A. Obreza, M. Bele and S. Srčič, *Physical properties and dissolution behaviour of nifedipine/mannitol solid dispersions prepared by hot melt method.* Int J Pharm, 2005. **291**(1-2): p. 51-8.

15. Law, D., S. L. Krill , E. A. Schmitt, J. J. Fort , Y. Qiu , W. Wang and W. R. Porter, *Physicochemical considerations in the preparation of amorphous ritonavir-poly(ethylene glycol) 8000 solid dispersions.* J Pharm Sci, 2001. **90**(8): p. 1015-25.

16. Patel, R.P. and M.M. Patel, *Physicochemical characterization and dissolution study of solid dispersions of Lovastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30.* Pharm Dev Technol, 2007. **12**(1): p. 21-33.

17. Newa, M., K. H. Bhandari, J. Kim, B. Yoo, H. Choi, C. Yong, J. Woo and W. Lyoo, *Preparation and evaluation of fast dissolving ibuprofen-polyethylene glycol 6000 solid dispersions.* Drug Deliv, 2008. **15**(6): p. 355-64.

18. Newa, M., K. H. Bhandari , J. O. Kim, J. S. Im, J. A. Kim, B. K.Yoo, J. S. Woo, H. G. Choi and C. S. Yong. *Enhancement of solubility, dissolution and bioavailability of ibuprofen in solid dispersion systems.* Chem Pharm Bull (Tokyo), 2008. **56**(4): p. 569-74.

19. Newa, M., K. H. Bhandari, D. X. Lee, J. H. Sung, J. A. Kim, B. K. Yoo, J. S. Woo, H. G. Choi and C. S. Yong. *Enhanced dissolution of ibuprofen using solid dispersion with polyethylene glycol 20000.* Drug Dev Ind Pharm, 2008. **34**(10): p. 1013-21.

20. Newa, M., K. H. Bhandari, D. X. Li, J. O. Kim, D. S. Yoo, J. A. Kim, B. K. Yoo, J. S. Woo, H. G. Choi and C. S. Yong. *Preparation and evaluation of immediate release ibuprofen solid dispersions using polyethylene glycol 4000.* Biol Pharm Bull, 2008. **31**(5): p. 939-45.

21. Ford, J.L., *The influence of polyethylene glycol molecular weight variation on the properties of glutethimide-polyethylene glycol solid dispersions.* Pharm Acta Helv, 1984. **59**(9-10): p. 280-8.

22. Martin, A., *Physical Pharmacy*. 1993, Baltimore: Lippincott Williams & Wilkins.

23. Yalkowsky, S.H., *SOLUBILITY and SOLUBILIZATION in Aqueous Media*. 1999, New York: Oxford University Press.

24. Yalkowsky, S.H. and M. Wu, *Estimation of the ideal solubility (crystal-liquid fugacity ratio) of organic compounds.* J Pharm Sci. **99**(3): p. 1100-6.

25. Neau, S.H., S.V. Bhandarkar, and E.W. Hellmuth, *Differential molar heat capacities to test ideal solubility estimations.* Pharm Res, 1997. **14**(5): p. 601-5.

26. Law, D., W. Wang, E. A. Schmitt and M. A. Long, *Prediction of poly(ethylene) glycol-drug eutectic compositions using an index based on the van't Hoff equation.* Pharm Res, 2002. **19**(3): p. 315-21.

27. Barton, F.M., Handbook of Solubility Parameters and Other Cohesion Parameters. 1991, Boca Raton: CRC Press.

28. Nair, R., N. Nyamweya, S. Gönen, L. J. Martínez-Miranda and S. W. Hoag, *Influence of various drugs on the glass transition temperature of poly(vinylpyrrolidone): a thermodynamic and spectroscopic investigation.* Int J Pharm, 2001. **225**(1-2): p. 83-96.

29. Pena, M.A., A. Reíllo, B. Escalera and P. Bustamante**,** *Solubility parameter of drugs for predicting the solubility profile type within a wide polarity range in solvent mixtures.* Int J Pharm, 2006. **321**(1-2): p. 155-61.

30. Hancock, B.C. and G. Zografi, *Characteristics and significance of the amorphous state in pharmaceutical systems.* J Pharm Sci, 1997. **86**(1): p. 1-12.

31. Avula, S.G., K. Alexander and A. Riga, Predicting eutectic behavior of drugs and excipients by unique calculations. J Therm Anal Calorim, 2010. **90**(1): p. 10-15.

32. Marsac, P. J., S. L. Shamblin, and L. S. Taylor, *Theoretical and practical approaches for prediction of drug-polymer miscibility and solubility.* Pharm Res, 2006. **23**(10): p. 2417-26.

33. Marsac, P.J., T. Li, and L.S. Taylor, *Estimation of drug-polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters.* Pharm Res, 2009. **26**(1): p. 139-51.