DRUG SOLUBILIZATION USING N-METHYL PYRROLIDONE: EFFICIENCY AND MECHANISM

By

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DEDICATION

TO MY PROFESSION

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ABSTRACT

The solubilization efficiency of N-methyl pyrrolidone (NMP) has been determined and compared to that of ethanol and propylene glycol for 13 poorly soluble drugs. NMP is a more efficient solubilizer for all these drugs. The solubility enhancement as high as about 800-fold is obtained in 20% v/v NMP solution as compared to water.

The mechanism of drug solubilization by NMP has also been investigated. It is proposed that NMP enhances drug solubility by simultaneously acting as a cosolvent and a complexing agent. A mathematical model to estimate drug solubility in NMP-water mixture is proposed, according to which the total solubility enhancement is a sum of these two effects. This model describes the experimental data well and is more accurate than the existing models. The cosolvent effect of NMP is demonstrated by a large and uniform reduction in the surface tension of water as a function of its concentration. Complexation is supported by the fact that it's strength is reduced upon increasing the temperature or lowering the polarity of the medium. Increasing the medium polarity on the other hand strengthens complexation. A strong correlation exists between log K_{ow} of the drugs and the respective cosolvency coefficients. The correlation between log K_{ow} and the respective complexation coefficients is weak suggesting that factors like molecular shape and aromaticity are significant in determining the complexation strength. This is confirmed by the absence of a significant complexation with linear molecules. It is also noticed that besides NMP, two other pyrrolidone derivatives enhance drug solubility following the same mechanism.

SPECIFIC AIMS

- The first aim of this study is to determine the solubilization efficiency of N-methyl pyrrolidone (NMP) for a wide variety of drugs. The solubilization efficiency of NMP will be compared to that of two traditional cosolvents: ethanol (EtOH) and propylene glycol (PG). EtOH and PG are chosen on the basis of their high popularity and safety. The ratio of the solubilities obtained in presence of 20% v/v solubilizer to the solubility in absence of solubilizer will used to compare their solubilization efficiencies.

- The second aim is to investigate into the mechanism of drug solubilization by NMP. We propose that NMP can act as a cosolvent as well as a complexing agent. Thus, NMP should be a stronger solubilizer than what would be predicted solely on the basis of its cosolvent properties. A mathematical model accounting for the simultaneous and additive cosolvency and complexation effects, will be proposed. The accuracy and the significance of this model will be compared to that of other existing theories. Additional experiments supporting the presence of the cosolvency and the complexation will be performed. In addition, the applicability of this model will be tested on drug solubilization by other pyrrolidone derivatives.

CHAPTER 1: INTRODUCTION

The aqueous solubility of a drug is one of its most important physicochemical properties. A low aqueous solubility and slow dissolution can potentially limit a drug's absorption from the gastrointestinal tract. The aqueous solubility of drug is of prime importance when a direct administration to the blood stream is required. From the drug development standpoint, often the drug solution is required to perform pharmacological, toxicological and pharmacokinetic studies. Thus, poor aqueous solubility not only limits a drug's biological application but also challenges its pharmaceutical development. As a result, investigation into new solubilizers and techniques for solubility enhancement is very important. In order to design strategies for enhancing drug solubility, it is essential to understand the factors governing it.

1.1 Factors Governing Solubility:

According to the General Solubility Equation[1], the aqueous solubility of an organic nonelectrolyte or a weak electrolyte is given by:

$$log\ S_w = 0.5 - log\ K_{ow} - 0.01(MP - 25) \qquad (1)$$

where S_w is the aqueous solubility of the solute; K_{ow} is its octanol-water partition coefficient and MP is its melting point in degree Celsius.

According to this equation the factors controlling the solubility of a solute are its activity and its crystallinity. The above equation has been found to be very useful in estimating the aqueous solubility of nonelectrolytes[2-6].

1.2 Approaches to Enhance Drug Solubility:

Several approaches have been used to increase the aqueous solubility of drugs. The choice of method depends upon the physicochemical and biopharmaceutical properties of the drug as well as the desired route of administration. These methods basically involve alteration of either the activity term or the crystal term. A flow chart comprising of the most common of these approaches is presented here[7]:

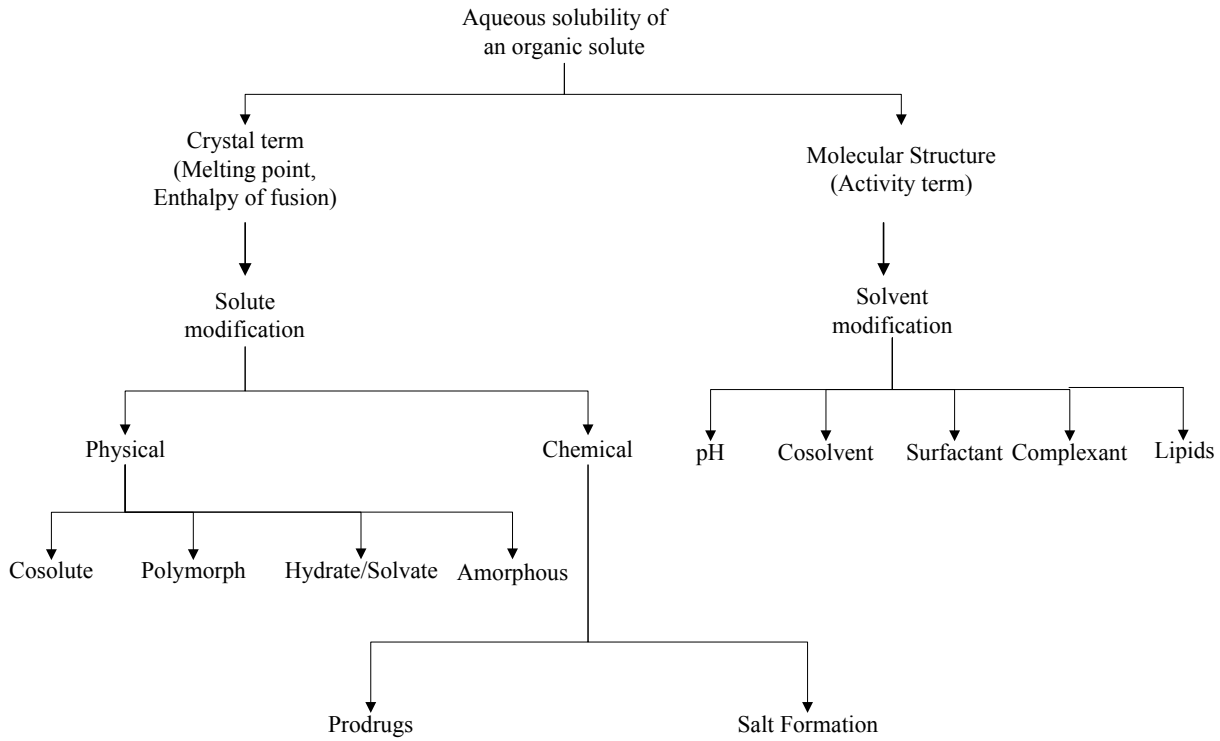


Figure 1: Flow chart of the general approaches to enhance the aqueous solubility of drugs

The use of cosolvents and complexing agents are important approaches and have been widely studied. Both these techniques will be discussed here in more details.

1.2.1 Cosolvency:

The use of cosolvents is one of the most potent approaches to solubilization, particularly for unionized drugs. About 13% of the FDA approved pharmaceutical products contain cosolvents. Ethanol, propylene glycol, polyethylene glycol and glycerin are examples of commonly used cosolvents in drug formulations.

1.2.1.1 Drug Solubilization using Cosolvents: The poor aqueous solubility of a non-polar drug is attributed to the strongly self-associated structure of water which effectively "squeezes-out" the drug. Addition of a cosolvent to water reduces this self-association, thereby increasing the drug solubility. Typically, a cosolvent molecule contains hydrogen bond donor and/or acceptor groups and a non-polar region. The former interacts with water to ensure mutual miscibility or at least a high solubility, while the later reduces the polarity of the medium by disrupting the intermolecular hydrogen-bonding network of water. The magnitude of structure related properties of water, such as surface tension and dielectric constant, reduce upon addition of cosolvent. The efficiency of a cosolvent as a solubility enhancer depends on the extent to which it weakness the self-association of water, which is a function of its relative non-polarity. A less polar cosolvent will generally have a higher solubilization efficiency[8].

Various theories and models have been proposed to estimate the drug solubility in cosolvent-water mixtures. These models are mostly empirical in nature. Some of the important models are discussed here.

1.2.1.2 Parabolic Models: A number of parabolic models have been proposed to estimate the solubility profile in cosolvent-water systems. These models are based on the regular solution theory[9] of Hilederbrand. According to this theory, the solubility of a liquid solute is given by:

$$\log X_u = \frac{-V_u(\delta_u - \delta_v)^2 \phi_v^2}{2.303RT} \qquad (2)$$

where X_u is the mole fraction solubility of solute u in solvent v; V_u is the molar volume of the solute; δ_u and δ_v are the solubility parameters of the solute and the solvent, respectively; ϕ_v is the volume fraction of the solvent; R is the gas constant and T is the temperature in Kelvin.

The solubility parameter is a measure of the strength of molecules association in a system. Mathematically, it is given by:

$$\delta = \sqrt{\frac{\Delta E_v}{V}} \qquad (3)$$

where ΔE_v is the energy of vaporization and V is the molar volume of the system.

This theory can be applied for the estimation of the drug solubility in a cosolvent-water mixture, which is a function of its solubility parameter (δ_u) and the solubility parameter of the solvent mixture (δ_{mix}).

The solubility parameter of the solvent mixture is approximated by the linear combination of the solubility parameters of water and the cosolvent:

$$\delta_{mix} = f_w\delta_w + f_c\delta_c = \delta_w - f_c\delta_w + f_c\delta_c \qquad (4)$$

where f_w and f_c are the volume fractions of water and cosolvent, respectively; while δ_w and δ_c are their solubility parameters.

Combining equations 2 and 4 gives:

$$log\ X_u = \frac{-V_u(\delta_u - \delta_w + f_c[\delta_w - \delta_c])^2 \phi_{mix}{}^2}{2.303RT} \qquad (5)$$

The general form of this equation is parabolic and is often written as:

$$\boxed{log\ S_{mix} = log\ S_w + af_c + bf_c{}^2} \qquad (6)$$

where a and b are empirical constants.

Yalkowsky and Roseman[10] used this parabolic relationship for the estimation of solubility in cosolvent-water systems. They demonstrated a good correlation between the log K_{ow} of the drug and both a and b terms. Paruta et al.[11] and Martin et al.[12,13] used the same form of the equation with dielectric constant and solubility parameter, respectively, in place of f_c. Since the regular solution theory is mostly applicable to non-hydrogen bonding systems, the use of a correction factor has been suggested when applied to aqueous systems.

1.2.1.3 Log-Linear Model: Yalkowsky and coworkers[14-17] proposed that the solubility of a nonelectrolyte in a cosolvent-water mixture is an exponential function of the volume fraction of the cosolvent:

$$\log S_{mix} = f_c \log S_c + (1 - f_c) \log S_w \qquad (7)$$

where S_c is the solubility of the drug in pure cosolvent.

Rearrangement of equation 7 results in:

$$\log S_{mix} = \log S_w + (\log S_c - \log S_w) f_c \qquad (8)$$

$$\boxed{\log S_{mix} = \log S_w + \sigma f_c} \qquad (9)$$

where σ is the end-to-end slope of the solubilization curve and is defined as:

$$\sigma = (\log S_c - \log S_w) = \log\left(\frac{S_c}{S_w}\right) \qquad (10)$$

According to the log-linear model, an exponential increase is observed when the solubilities are plotted against cosolvent fraction on a linear scale. On a semi-log scale this corresponds to a linear increase with a slope of σ. This is illustrated in figures 2 and 3. Figure 2 presents the profile on a linear scale while figure 2 presents that on a semi-log scale.

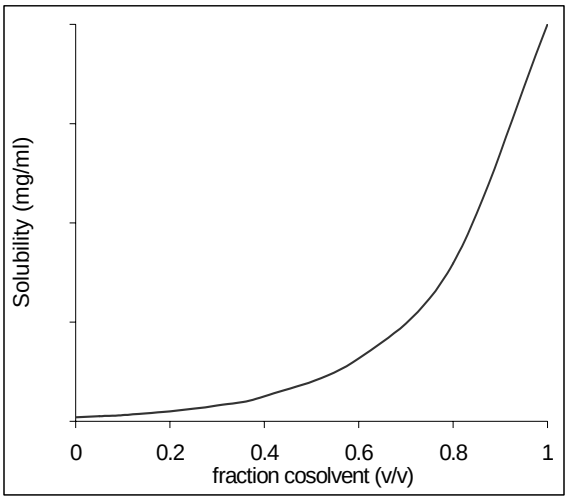


Figure 2: Solubility vs. f cosolvent (linear scale)

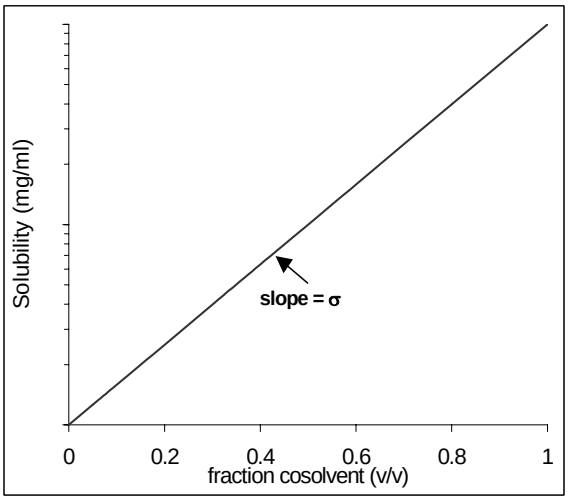


Figure 3: Solubility vs. f cosolvent (semi-log scale)

The solubility of a solute in pure cosolvent is given by the following equation that is analogous to the General Solubility Equation (equation 1):

$$log\ S_c = constant - log\, K_{oc} - 0.01(MP - 25) \qquad (11)$$

where K_{oc} is the octanol-cosolvent partition coefficient of the solute.

Hansch and Leo[18] have demonstrated a linear relationship between log K_{oc} and log K_{ow}:

$$log\, K_{oc} = s\, log\, K_{ow} + t \qquad (12)$$

Combining equations 1, 10, 11 and 12:

$$\sigma = \log K_{ow} - \left(s \log K_{ow} + t\right) + constant - 0.5 \qquad (13)$$

or:

$$\sigma = s^* \log K_{ow} + t^* \qquad (14)$$

where s^* and t^* are empirical constants for a particular cosolvent.

Millard et al.[19] validated equation 14 by demonstrating a good correlation between the log K_{ow} of the drug and σ. They also observed that the value for s^* is a function of the polarity of the cosolvent. Less polar cosolvents have higher s^* values and are stronger solubility enhancers.

Equation 9 can be extended if multiple non-interacting cosolvents are used:

$$\log S_{mix} = \log S_w + \sum \sigma_i f_i \qquad (15)$$

where i's signify the individual cosolvents.

According to equation 15, the solubilization effect of cosolvents is additive.

Modifications of the Log-Linear Model: The log-linear model works best for the estimation of the solubility of non-polar drugs i.e., drugs that are less polar than the cosolvent. A negative deviation from the log-linearity is observed at higher cosolvent concentrations for semi-polar drugs i.e., drugs that are less polar than water but more polar than the cosolvent. Several modified versions of the log-linear model have been proposed to account for this deviation. Li et al.[20] observed that the solubility curves are linear up to $f = 0.5$. They showed that the end-to-half slope ($\sigma_{0.5}$) is more appropriate than the end-to-end slope (σ) for the estimation of the solubilities of non-polar and semi-polar drugs. They proposed the following form of the log-linear model for the estimation of solubility up to $f = 0.5$:

$$\boxed{log\, S_{mix} = log\, S_w + \sigma_{0.5} f_c} \qquad (16)$$

Recently, Machatha and Yalkowsky[21] have proposed a bilinear model using solubility data for ethanol-water mixtures. This model uses more variables but is applicable to polar, semipolar and non-polar compounds. It was shown to be more accurate than the end-to-half slope model and the parabolic model. A simplified form of this model is:

$$\boxed{\log S_{mix} = \log S_w + \left(\sigma_A f_c + \frac{(\sigma_B - \sigma_A) f_c}{1 + 10^{-\alpha(f_c - 1)}} \right)} \qquad (17)$$

where σ_A and σ_B are the slopes of the initial and the final asymptotes, respectively; and α is a cosolvent specific empirical constant.

A good correlation between each of the two slopes and log K_{ow} of the drugs was observed.

Assumptions in the Log-Linear model: The log-linear model is based on the following assumptions:

1) The free energy of mixing of water and cosolvent is zero. Thus the properties of the mixture are a linear combination of the individual properties of water and the cosolvent (equations 4 and 7).
2) The crystal form, the conformation and the degree of hydration of the drug remain unaltered during solubilization.
3) The cosolvent interacts solely with water and not with the drug.

1.2.1.4 Excess Free Energy Model[22-24]: This model considers three component interactions in addition to the two component interactions on which the parabolic and the log-linear models are based. Although this model gives a more accurate description of the solubilization curves, it requires more input data and involves more parameters.

1.2.1.5: Phenomenological Model: This model is analogous to the regular solution theory based models with an extra term to account for the solvation of the solute by the solvent. Li et al.[25] found this model to be more accurate than the other models for the solubilization of certain polychlorinated biphenyls by alcoholic cosolvents. However, this model requires the use of 3 fitted parameters and may be more cumbersome to use.

1.2.1.6: UNIFAC Approach: This approach is the most sophisticated of all the above models. It considers all the possible interactions between the drug, water and cosolvent molecules. Due to a large number of such interactions, this approach requires a lot more input data and therefore, has a limited applicability.

1.2.2 Complexation:

1.2.2.1: Drug Solubilization using Complexation: Complexation is a popular approach for the solubility enhancement of drugs. Complexation of drug with a suitable ligand reduces the exposure of the formers hydrophobic region to water resulting in an increase in its aqueous solubility. The term complexation is used to describe drug-ligand association, both bonded and unbonded, resulting from a number of intermolecular interactions. For the purpose of this study, complexation will be considered as an unbonded association between the hydrophobic regions of the drug and ligand.

Complexation is an equilibrium process and the association constant, κ, for the formation of a 1:1 complex is given by:

$$\kappa = \frac{[S_{complex}]}{[S_w][L]} \qquad (18)$$

where $[S_w]$, $[L]$ and $[S_{complex}]$ are the equilibrium molar concentrations of the free drug, ligand and the complex, respectively.

The equilibrium concentration of the free ligand is related to the total ligand concentration, $[L_{total}]$ by:

$$[L_{total}] = [L] + [S_{complex}] \qquad (19)$$

The total aqueous solubility, $[S_{total}]$, of a drug undergoing 1:1 complexation is given by:

$$S_{total} = [S_w] + [S_{complex}] \qquad (20)$$

Combining equations 18,19 and 20 gives the general equation for drug solubilization by complexation:

$$[S_{total}] = [S_w] + \frac{\kappa[S_w]}{1+\kappa[S_w]}[L_{total}] \qquad (21)$$

$$[S_{total}] = [S_w] + \tau \cdot [L_{total}] \qquad (22)$$

where:

$$\tau = \frac{\kappa[S_w]}{1+\kappa[S_w]} \qquad (23)$$

According to equation 22, the total solubility of a drug undergoing complexation is a linear function of the total ligand concentration. The intercept of this line is equal to the solubility of the free drug and its slope is given by τ. On a semi-log plot this line will concave down. This is illustrated in figures 4 and 5. Figure 4 presents the profile on a linear scale while figure 5 presents the same data on a semi-log scale.

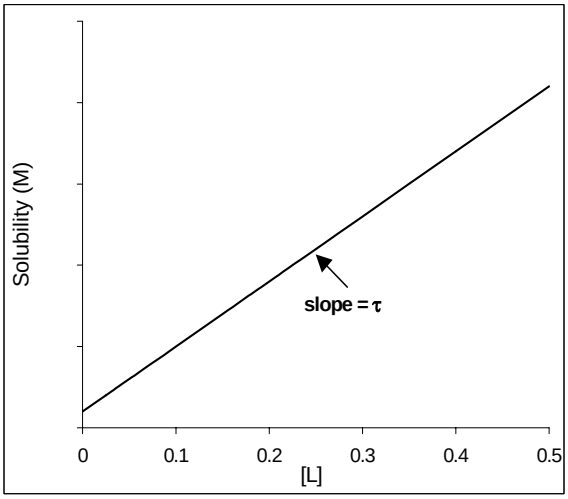


Figure 4: Solubility vs. [L] (linear scale)

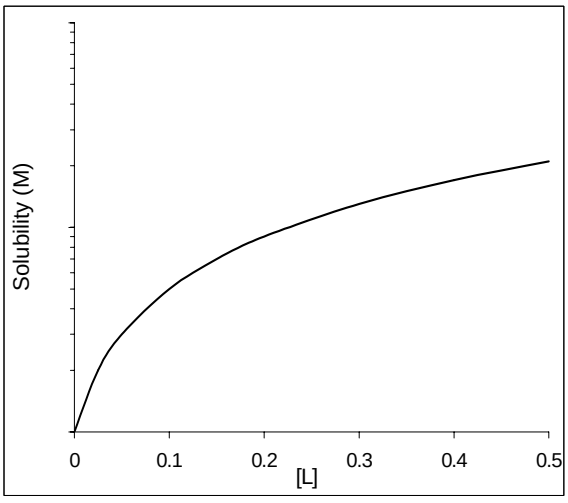


Figure 5: Solubility vs. [L] (semi-log scale)

The value of κ depends upon the strength of the drug-ligand interactions. It can be calculated from τ by rearranging equation 23:

$$\kappa = \frac{\tau}{[S_w](1-\tau)} \qquad (24)$$

If the drug undergoes strong complexation, the value of $\kappa[S_w]$ is >>1 and $\tau \approx 1$.

1.2.2.2: Factors Affecting the Strength of Complexation: The strength of complexation depends on the properties of the drug, the ligand and the solubilization medium. For a particular ligand, the size, shape, aromaticity and the non-polarity of the drug molecule will determine this strength. Various theories and models have been proposed to explain the dependence of complexation on the properties of the drug and the complexing agent. According to the maximum aromatic overlap model[26], the size of pi-electron system of the complexing agent is the single most important factor in determining the strength of complexation. In a different study it was shown that the electrostatic force of the donor-acceptor type plays an important role in complexation[27]. The role of hydrogen bonding in complexation has also been studied although a clear relationship could not be established[28,29].

The log P of drugs as a measure of their hydrophobicity has been correlated to the complexation constant with considerable success[28,29]. It has been postulated that a more non-polar drug molecule has a stronger driving force for undergoing complexation. This theory however, takes into account the overall non-polarity of the drug molecules.

Considering the total non-polarity may not be totally appropriate since only a part of the molecule may be undergoing complexation.

Higuchi and coworkers[30] proposed a model according to which the compounds capable of undergoing stacking can be classified into two classes (Class A and B) based on their structure. The compounds in class A have higher affinity for compounds in class B than for those in class A and vice versa. Although, many exceptions to this theory have been cited, it generally gives a good indication for the relative complexation strengths.

The drug interacts with the ligand to reduce its exposure to the solvent. The strength of this interaction is therefore, a direct function of the properties of the medium. Raising the temperature of the medium increases the disorder associated with the system, thereby reducing the likelihood of complexation[31,32]. Increasing the polarity of the medium is expected to increase the driving force behind complexation and will therefore, strengthen the interaction[33]. Reducing the polarity of the medium, on the other hand, diminishes this driving force and weakens the interaction[34,35].

1.2.2.3 Thermodynamics of Complexation: Thermodynamically, the standard free energy of complexation ($\Delta G°_{comp}$) is given by:

$$\Delta G°_{comp} = -2.303\, RT \cdot \log \kappa \qquad (25)$$

where R is the gas constant (8.314 $J \cdot mol^{-1}\ K^{-1}$) and T is the temperature in Kelvin.

The standard enthalpy of complexation ($\Delta H°_{comp}$) can be calculated from the κ values obtained at several different temperatures using the van't Hoff equation:

$$\log \kappa = -\frac{\Delta H°_{comp}}{2.303R} \cdot \frac{1}{T} + constant \qquad (26)$$

The standard entropy of complexation ($\Delta S°_{comp}$) is related to $\Delta G°_{comp}$ and $\Delta H°_{comp}$ by:

$$\Delta S°_{comp} = \frac{\Delta H°_{comp} - \Delta G°_{comp}}{T} \qquad (27)$$

The $\Delta H°_{comp}$ is a function of the difference between the affinities of drug for water and the ligand. Since a non-polar drug molecule will have a greater affinity for the ligand than for water, $\Delta H°_{comp}$ is negative. Complexation reduces the randomness associated with the solute molecules and therefore $\Delta S°_{comp}$ is also negative. For complexation to be thermodynamically feasible, $\Delta G°_{comp}$ must be negative. Thus, $\Delta H°_{comp}$ should be sufficiently large to overcome the effect of the entropy. In other words, the magnitude of $-\Delta H°_{comp}$ must be larger than that of $-T\Delta S°_{comp}$.

CHAPTER 2: N-METHYL PYRROLIDONE

2.1 Physicochemical Properties:

N-methyl pyrrolidone (NMP) is a water miscible, aprotic solvent with a log K_{ow} of –0.54. It contains a polar cyclic amide group and has a dipole moment of 4.09 D. Its dielectric constant is 32.2 and its solubility parameter is 22.9 MPa. It has a density of 1.03 gm/ml and a viscosity is 1.7 cP at 20˚C. It has a low vapor pressure of 0.3 millibars. It is thermally stable with a boiling point of 202˚C and therefore, can be used in formulations that require heat sterilization.

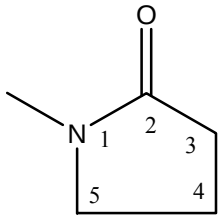
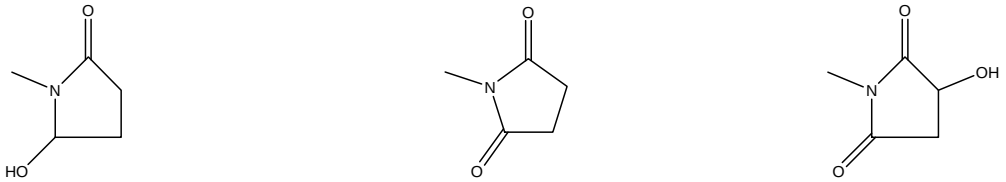


Figure 6: Structure of N-Methyl Pyrrolidone

NMP is generally considered to be chemically inert and has been used as a solvent in various organic reactions. However, the presence of strong conditions can affect the chemical stability of NMP. The carbonyl group (position 2) is affected by strong reducing agents and strong lewis acids. The adjacent carbon (position 3) can loose proton in the presence of a strong base. The presence of free radicals can remove the hydrogen radical from position 5. Ring-Opening Reactions break the bond between the 1- and 2- positions of the pyrrolidone ring. NMP can undergo hydrolysis if heated at a high temperature for a prolonged period (several hours) in presence of excess water.

2.2 Pharmacokinetic and Toxicity Profile:

N-methyl pyrrolidone is rapidly absorbed orally followed by a fast distribution to well perfused organs like liver, kidney and intestine[36]. The distribution half-life is about 30 minutes and the volume of distribution around 20 liters. It undergoes oxidation in liver and the metabolites are primarily excreted in urine. The elimination half-life is ~ 8 hours.



5-hydroxy-N-methyl pyrrolidone (75%) **N-methyl succinimide (15%)** **3-hydroxy-N-methyl succinimide (10%)**

Figure 7: Metabolites of N-Methyl Pyrrolidone

NMP has low toxicity both orally and parenterally[37,38]. Table 1 gives its toxicity profile.

Table 1: Acute toxicity profile of N-Methyl Pyrrolidone

ROUTE	SPECIES	LD_{50}
Oral	Rat	3500 mg/kg
Oral	Mouse	4100 mg/kg
Dermal	Rat	5000 mg/kg
Dermal	Rabbit	4000 mg/kg
Inh.	Rat	5.1 mg/kg
IV	Rat	2400 mg/kg
IV	Mouse	3500 mg/kg

The oral NOAEL (no observed adverse effect level) is 300 mg/kg/day while the IV NOAEL is 200 mg/kg/day. The toxicity symptoms include CNS depression, irritation in the respiratory tract and GIT disturbance.

2.3 Pharmaceutical Applications:

N-methyl pyrrolidone has been reported to increase the solubility and permeability of several drugs[39-45]. It is used in the formulations of several pharmaceutically active compounds. Some important marketed products containing NMP include:

1. Atridox® gel: Doxycycline formulation comprising of 57% w/v NMP; used for the treatment of chronic adult periodontis in humans.
2. Doxirobe® gel: Doxycycline formulation comprising of 57% w/v NMP; used for the treatment of periodontis in canine animals.
3. Nuflor® IV solution: Florfenicol formulation comprising of 25% v/v NMP; used as a broad-spectrum antibacterial for bovine animals.

2.3.1: Use of NMP as a permeability enhancer: NMP has been shown to enhance the transdermal permeability of several drugs. The addition of 2% NMP in an ointment formulation of mefanamic acid, increased the drug penetration by about 1.5 times[40]. In the same study it was shown that NMP significantly enhanced the topical bioavailability of betamethasone 17-benzoate. The anti-inflammatory activity of topically applied ibuprofen increased upon combining it with 5% NMP[41].

The permeability enhancing property of NMP is believed to be an outcome of two effects. NMP can dissolve in the lipid component of the stratum corneum and change its polarity. This will result in an increase of the drug solubility in the membrane thereby, enhancing its transcellular transport. In addition, NMP is a lipid disrupting agent (LDA) and its application on the skin increases the fluidity of the membrane. This increases the flux of transcellular movement of the drug.

2.3.2 Use of NMP as a solubility enhancer: As previously mentioned, NMP has been reported to enhance the aqueous solubility of poorly soluble drugs. Tarantino et al. reported significant solubility enhancements for several drugs[42] using NMP. A 30% NMP solution in water was used to enhance the solubility of propofol[43]. The solubility of tetracycline and oxytetracyclin improves substantially in the presence of NMP[44].

It is believed that NMP is a strong solubilizer. However, a direct comparison of the solubilization efficiencies of NMP with other solubilizing agents has not been widely studied. Furthermore, the mechanism by which NMP enhances drug solubility is not clearly understood. Some researchers believe that NMP acts as a cosolvent[43,44] while some others think of it as a complexing agent[44,45]. The polar disubstituted cyclic amide group of NMP molecule can interact with water to ensure its complete miscibility while the presence of the non-polar carbons disrupts the structure of water, thus enabling it to act as a cosolvent. In addition to the cosolvency effect, the presence of a substantially large and nearly planer non-polar region can result in direct hydrophobic interactions between the NMP and drug molecules to form a complex. The presence of such a complex will further increase the solubility of the drug in NMP-water mixtures.

CHAPTER 3: THE PROPOSED MODEL

Based on the structure of NMP it is proposed that NMP possess both, cosolvent and complexing properties. The total solubility of an unionized drug in presence of NMP can be calculated by simply adding these two effects. Mathematically, this can be stated as:

$$S_{total} = S_u + S_{cosolvency} + S_{complexation} \qquad (28)$$

where S_u is the solubility of the unionized drug in absence of any solubilizer; $S_{cosolvency}$ and $S_{complexation}$ are the solubilities obtained as an effect of the cosolvent and the complexing properties of NMP, respectively.

Equation 22 gives the solubility of the solute as a function of the molar concentration of the ligand. A similar equation can be written to calculate the solubility of a drug undergoing complexation with NMP as a function of the molar concentration of NMP:

$$[S_{total}] = [S_u] + \tau_{0.5} \cdot [NMP] \qquad (29)$$

where $\tau_{0.5}$ is the slope of the solubilization profile.

The molar concentration of NMP can be converted to its volume fraction f by dividing it by the molarity of pure NMP (10.4 M/L). Thus:

$$[S_{total}] = [S_u] + \tau_{0.5} \cdot f \cdot 10.4 \qquad (30)$$

It is proposed that NMP acts as a cosolvent also. Thus, the S_w in equation 30 is actually equal to the solubility of drug in NMP-water mixture. According to equation 16, the solubility of a drug in cosolvent-water mixture is an exponential function of the cosolvent concentration. Incorporating equation 16 in equation 30, we get:

$$S_{total} = (S_u \cdot 10^{\sigma_{0.5} f}) + \tau_{0.5} \cdot f \cdot 10.4 \qquad (31)$$

Equation 31 is graphically demonstrated in figures 8 and 9, which presents the solubility of a drug as a function of NMP concentration. The dashed line represents the solubility due to cosolvency (described by the first part of equation 31) and dotted line represents that due to complexation (described by the second part of equation 31). The total solubility is the sum of these two curves and is represented by the solid line.

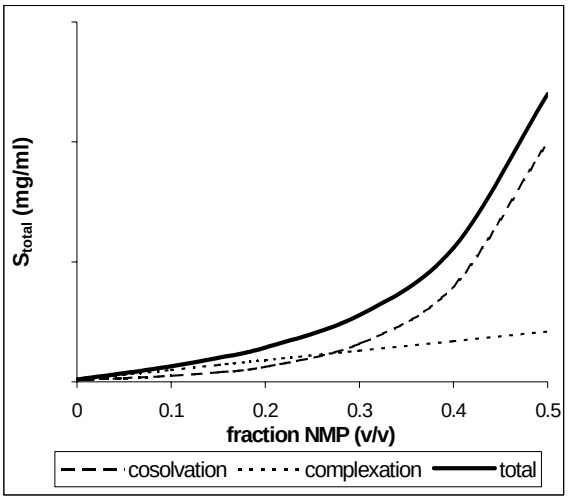


Figure 8: Solubility vs. f NMP (linear scale)

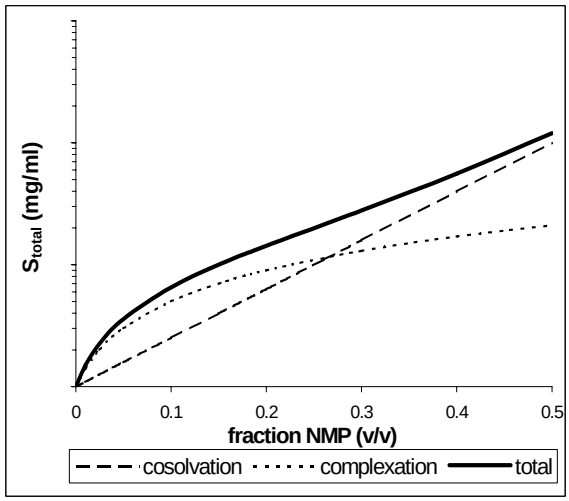


Figure 9: Solubility vs. f NMP (semi-log scale)

The shape of the solid line (total solubility) will depend upon the relative strengths of the two effects. It will be more linear (on a semi-log scale) if the cosolvent effect dominates the solubilization. On the other hand, a downward curvature will indicate a dominant complexation. The values of $\sigma_{0.5}$ and $\tau_{0.5}$ can be obtained by deconvolution of the total solubility using equation 31. The unit of $\tau_{0.5}$ in equation 31 is (mg/ml)/M. It can be converted to M/M by:

$$\tau_{0.5(M/M)} = \frac{\tau_{0.5(mg/ml\ M^{-1})}}{MW} \qquad (32)$$

where MW is the molecular weight of the drug.

The value of κ can be calculated from $\tau_{0.5}$ using equation 24.

ASSUMPTIONS : The proposed model is based on the following assumptions:

- Drug solubility due to cosolvency is exponentially related to the concentration of NMP.
- A 1:1 complex is formed between the drug and NMP and its concentration does not exceed its solubility up until f = 0.5.
- Cosolvency and complexation are mutually independent. In other words the drug-NMP interactions do not affect the cosolvent properties of NMP. On the other hand the complexation strength is not affected by concentration of NMP in the mixture.

CHAPTER 4: EXPERIMENTAL SECTION

4.1 Materials: A set of 13 structurally diverse drugs with poor aqueous solubility is used for the study (figure 10). These drugs vary widely in their aqueous solubility and the log K_{ow} (table 2). 7 of these drugs are weakly acidic, 4 weakly basic while 2 do not have any ionization site for practical purposes.

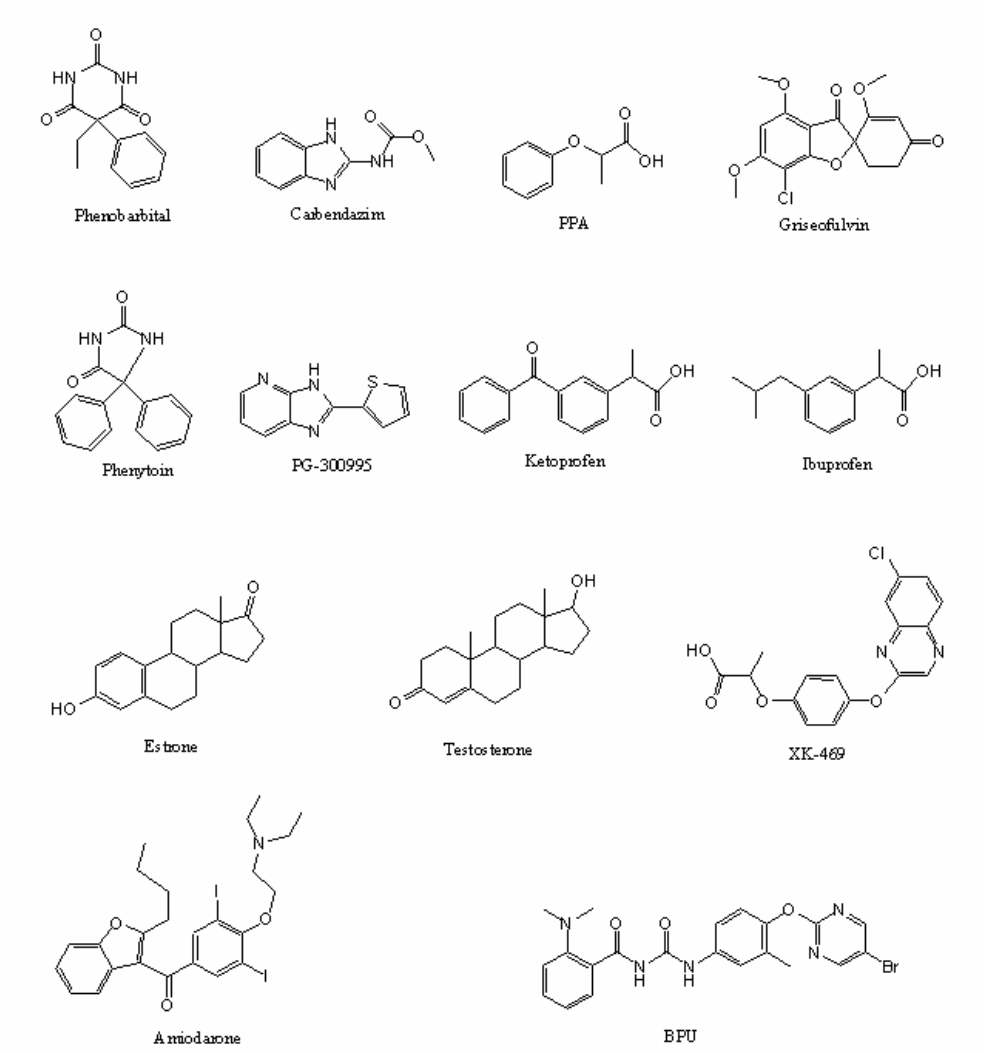


Figure 10: Structures of the drugs used for the study

Table 2: Properties of the drugs used for the study:

Drug	pK_a	Log K_{ow} (unionized form)	Log S_u (µg/ml)
Phenobarbital	7.4, 11.2[46] (acidic)	1.5	2.99
Carbendazim	4.5[47] (basic) 10.8[47] (acidic)	1.5	0.37
PPA	2.9[48] (acidic)	1.9	3.47
Griseofulvin	--	2.2	0.91
Phenytoin	8.3[46] (acidic)	2.5	1.03
PG-300995	3.7[49] (basic)	2.6	1.59
Ketoprofen	4.8[50] (acidic)	3.1	1.89
Estrone	10.8[51] (acidic)	3.1	-0.20
Testosterone	--	3.3	1.34
Ibuprofen	5.2[46] (acidic)	3.5	1.48
XK-469	2.7[48] (acidic)	3.9	-0.64
Amiodarone	6.0 (basic)	5.9	0.18
BPU	5.0[52] (basic)	6.2	-1.55

PPA: Phenoxypropionic acid; BPU: Benzoylphenyl urea derivative

Phenobarbital, griseofulvin, phenytoin, ketoprofen, estrone, testosterone, ibuprofen, amiodarone, N-methyl pyrrolidone and propylene glycol were purchased from Sigma, St Louis, MO. Carbendazim, 2-phenoxypropionic acid (PPA) were purchased from Aldrich, Milwaukee, WI. XK-469 and Benzoylphenyl urea derivative (BPU) were received from the National Cancer Institute, Bathesda, MD. PG-300995 was obtained from Proctor & Gamble, Cincinnati, OH. Ethanol was purchased from AAPER, Shelbyville, KY. All other chemicals were of reagent or HPLC grade and used without further purification.

4.2 Methods:

4.2.1 Solubility Determination: Aqueous solutions containing increasing volume fractions (0-0.5 v/v) of the three solubilizers (EtOH, PG and NMP) were prepared. For ionizable drugs, buffers were used instead of water to make the solutions. The pH of the buffers was maintained at least 2 units away from the pK_a of the respective drug. This was done to ensure that the drug predominantly exists in its unionized form. For example, pH was maintained at 7.0 in the case of carbendazim which has a basic pK_a of ~ 4.0. An excess amount of drug was added to the vials containing 1 ml of the aqueous solutions. The vials were placed in an end-over-end rotator at 20-rpm for sufficient length of time (> 5 days) under room conditions. The samples were then filtered through a 0.45-μm filter followed by the analysis of the drug content using HPLC analysis (Agilent 1100 HPLC with G1315B PDA detector, Agilent Technologies Palo Alto, CA with Chemstation software) HPLC methods for the drugs are presented in table 3. All experiments were performed in triplicate.

Table 3: HPLC methods for the drugs used for the study

Drug	**Column**	**Mobile Phase**	**Flow Rate (ml/min)**	**Injection Volume (µl)**	**Detection/ Reference (nm)**	**Retention Time (min)**
Phenobarbitone	Lichisorb RP-18	0.1% TFA : ACN (75 : 25)	2.0	20 µl	254/360	5.6
Carbendazim	Agilent C-18	DSPB pH 3 : ACN (20 : 80)	1.0	20 µl	280/360	4.0
PPA	Discovery C-18	0.1% TFA : ACN (65 : 35)	1.0	10 µl	220/380	6.0
Griseofulvin	Agilent Zorbax C-18	Water : MeOH (46 : 54)	1.0	20 µl	295/360	6.0
Phenytoin	Restek Pinnacle ODS	0.01% AA : MeOH (50 : 50)	1.0	50 µl	258/360	4.1
PG-300995	Agilent C-18	0.1% TFA : ACN (82 : 18)	1.0	20 µl	320/360	4.9
Ketoprofen	Agilent Zorbax C-8	PB pH 5.1 : ACN (60 : 40)	1.0	10 µl	260/360	5.0

Drug	Column	Mobile Phase	Flow Rate ml/min.	Injection Volume µl	Detection/ Reference nm	Retention Time min
Estrone	Agilent Zorbax C-8	Water : ACN (50 : 50)	0.9	100 µl	290/360	5.5
Testosterone	Agilent Zorbax C-8	Water : ACN (53:47)	1.0	5 µl	238/360	5.2
Ibuprofen	Agilent Zorbax C-8	PA pH 2.5 : ACN (35 : 65)	1.0	50 µl	254/360	4.0
XK-469	Discovery C-18	0.1% TFA : ACN (45:55)	1.0	10 µl	245/380	5.5
Amiodarone	Agilent Zorbax C-8	0.1% TFA : ACN (42 : 58)	1.0	20 µl	241/360	5.8
BPU	Lichisorb RP-18	Water : MeOH (20 : 80)	1.5	100 µl	286/390	7.7

AA: Acetic Acid; ACN: Acetonitrile; DSPB: Disodium Phosphate buffer; MeOH: Methanol; PA: Phosphoric Acid;

PB: Phosphate Buffer; TFA: Triflouroacetic Acid.

4.2.2 Solubilization Efficiency: The ratio of the solubility of the unionized form of the drug in the presence of 20% w/v solubilizer ($S_{0.2}$) to the solubility in absence of solubilizer (S_u) is used as the criteria for comparing the solubilization efficiencies of NMP to that of EtOH and PG.

4.2.3 Statistical Analysis: WinCurveFit version 1.1.8 for Windows (Kevin Raner Software, Victoria Australia) was used to deconvulute the experimental solubility based on equation 31. All the other analyses were performed using Microsoft Excel. The root mean square error (RMSE) was determined using the following relationship:

$$RMSE = \sqrt{\frac{\sum (experimental - calculated)^2}{n}} \qquad (33)$$

The level of significance was determined using a two-tailed t-test with $\alpha = 0.1$.

4.2.4 Surface Tension Measurement: The Drop-Number method was used to measure the relative surface tension of NMP-water mixtures. A constant flow syringe pump was used at a flow rate of 0.04 ml/minute to create the drops on the tip of a stainless steel value with a very fine and symmetric opening. The first 3 drops were sacrificed and the time required for the next 5 drops to form and fall was measured. The densities of the samples were measured using a pycnometer. Water and ethanol were used as the reference liquids.

The surface tension was calculated using the following equation:

$$\gamma_{sample} = \gamma_{water} \times \frac{T_{sample}}{T_{water}} \times \frac{\rho_{sample}}{\rho_{water}} \qquad (34)$$

where γ refers to the surface tension, T is the time required for 5 drops to form and fall and ρ is the density.

4.2.5 Thermal Analysis: Differential Scanning Calorimetry (DSC) (TA DSC Q-1000 series, New Castle, DE with Universal analysis software) was used to generate the thermograms for pure drugs, excess undissolved drug and the drug residue left after evaporation of a saturated solution of drugs in 50% NMP-Water mixture. The samples were dried, pulverized lightly and placed in tared aluminum pans. The sample weight was recorded and the pans were sealed. The samples were equilibrated at 30˚C for 5 minutes followed by heating at a rate of 10˚C/min to 300˚C.

CHAPTER 5: RESULTS AND DISCUSSION

5.1 Solubilization Efficiency of NMP:

The solubility enhancements ($S_{0.2}/S_u$) obtained for the drugs using the three solubilizers are presented in table 4 and figure 11. It can be seen that substantial solubility enhancements are obtained for all the 13 drugs using NMP. The solubility enhancement as high as about 800-fold is observed in 20% v/v NMP solution. NMP has higher solubilization efficiency than EtOH and PG for every drug studied. The use of NMP results in nearly 2-8 times higher solubilities than EtOH and nearly 2-20 times higher solubilities than PG. This result clearly demonstrates that at 20% v/v, NMP is a more powerful solubilizer than EtOH and PG, for the drugs studied. However, at 50% v/v, the solubilities obtained using NMP and EtOH are close. In other words, NMP is a stronger solubilizer than EtOH at low concentrations while at high concentrations their strengths are comparable. Based on their log K_{ow} values, NMP and EtOH are expected to have similar cosolvency strengths. Thus, the higher solubilization efficiency of NMP especially at low concentrations is interesting.

Table 4: Solubilization efficiencies of NMP, EtOH and PG:

Drug	Log K_{ow}	Log S_u (µg/ml)	$S_{0.2}/S_u$		
			NMP	EtOH	PG
Phenobarbital	1.5	2.99	6.2	2.1	1.5
Carbendazim	1.5	0.37	31.7	6.9	5.9
PPA	1.9	3.47	7.4	4.4	4.1
Griseofulvin	2.2	0.91	25.1	9.7	4.4
Phenytoin	2.5	1.03	29.1	6.5	4.5
PG-300995	2.6	1.59	15.3	7.3	3.3
Ketoprofen	3.1	1.89	47.4	6.1	3.2
Estrone	3.1	-0.20	47.0	13.7	6.8
Testosterone	3.3	1.34	14.9	8.6	4.2
Ibuprofen	3.5	1.48	20.6	10.8	6.4
XK-469	3.9	-0.64	50.2	9.1	4.5
Amiodarone	5.9	0.18	389.1	67.5	16.9
BPU	6.2	-1.55	795.8	102.5	145.0

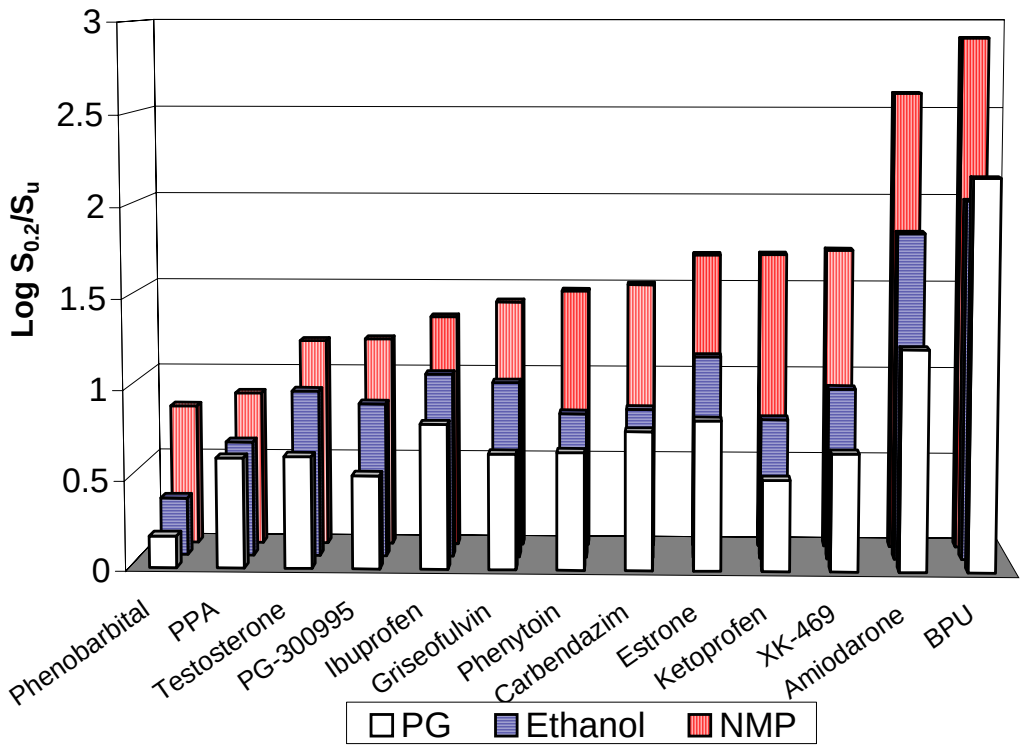


Figure 11: Solubilization efficiencies of NMP, EtOH and PG

5.2 Solubility Profiles of Drugs with NMP:

The ratio of the solubility observed in the presence of solubilizer to that in the absence of it (S_o/S_u) were plotted against the volume fraction of the three solubilizers on a semi-log scale. The solubility profiles of all the drugs with EtOH and PG are log-linear and follow equation 16. However, a distinct downward curvature in the solubility profiles for NMP was noticed for all the drugs, particularly at low concentrations. The solubility profiles of estrone and griseofulvin are presented as illustrations in figures 12 and 13, respectively. The darker line represents the solubility profile while the lighter line is the best-fit line forced through the origin. In both these examples, the profiles are curved at low NMP concentrations with a positive deviation from the log-linear model. At higher NMP concentrations the profiles start approaching linearity.

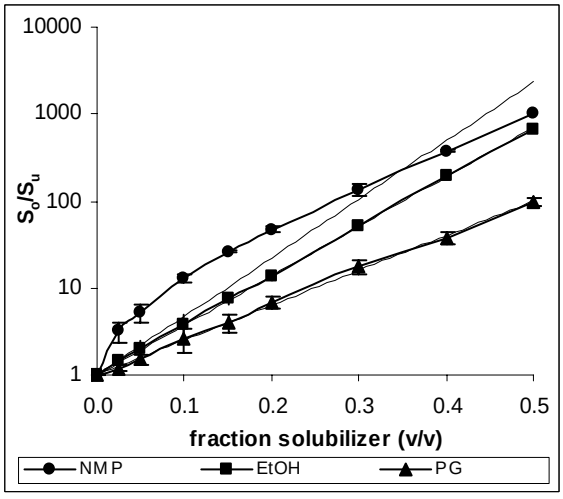


Figure 12: Solubility profile of estrone

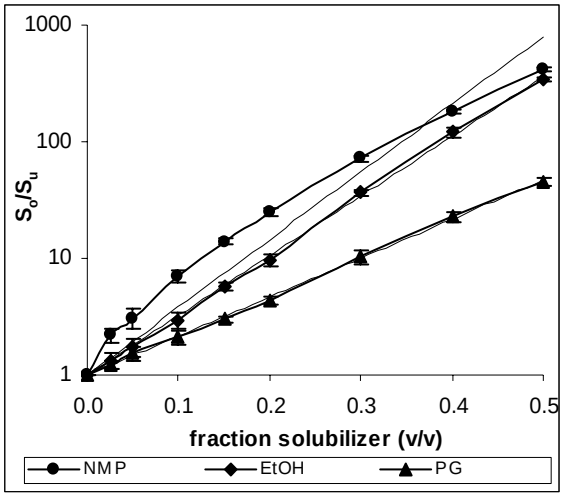


Figure 13: Solubility profile of griseofulvin

5.3: Mechanism of Drug Solubilization by NMP:

Based on the solubility profiles of the drugs in NMP-water mixtures, two interesting observations have been made. First, a higher solubilization efficiency of NMP than EtOH, particularly at low NMP concentrations. Second, the downward curvature in the solubility profiles along with a large positive deviation from log-linearity at low concentrations. In order to explain both these observations, it is proposed that NMP can simultaneously act as a cosolvent and a complexing agent and the overall solubility is a sum of the two effects. The cosolvent effect is an exponential function of NMP concentration while the complexation effect is a linear function of it. The total solubility therefore, is a sum on an exponential and a linear function of NMP concentration as described by the proposed model (equation 31). At low NMP concentrations, drug solubilization is primarily a result of its complexation effect. As the NMP concentration increases the cosolvent effect picks up and becomes the dominant factor at higher concentrations. This theory will explain both, a higher solubilization efficiency of NMP than noncomplexing cosolvents like ethanol as well as the curvature associated with the solubility profiles. The concentration at which the cosolvent effect becomes stronger than the complexation effect will depend on the strength of the two effects which is a function of the properties of the drug.

5.3.1 Application of the proposed model:

The proposed model was applied to the solubility profiles of the drugs. The solubility data were resolved into cosolvency and complexation components using equation 31. Figures 14 and 15 present the deconvoluted profile for estrone and griseofulvin. The cosolvency, complexation and the calculated total solubility are shown, as dashed, dotted and solid lines, respectively, along with the experimental values. At low concentrations of NMP the effect of complexation is dominant giving a downward curvature to the solubility profile on a semi-log scale. As the NMP concentration increases the cosolvency starts to dominate and the profile becomes linear. The calculated solubilities are in good agreement with the experimental data for both the drugs demonstrating the applicability of the proposed model.

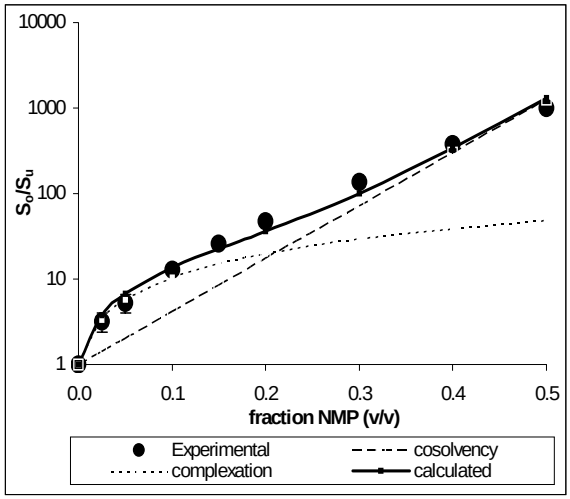


Figure 14: Deconvoluted profile of estrone

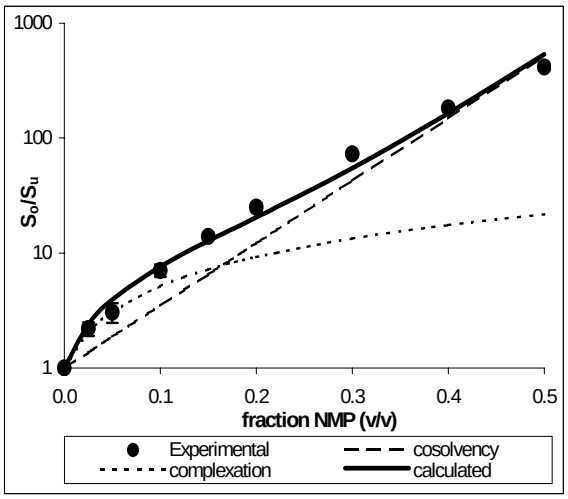


Figure 15: Deconvoluted profile of griseofulvin

The solubility data of all the other drugs were deconvoluted in a similar manner. The values of $\sigma_{0.5}$ and $\tau_{0.5}$ were calculated following the deconvolution. The value of κ was calculated from $\tau_{0.5}$ using equations 24 and 32. The values of $\sigma_{0.5}$ and κ are presented in table 5. High correlation coefficients (R^2) are obtained between the experimental and calculated solubilities for every drug demonstrating the accuracy of the proposed model.

Table 5: The cosolvency and complexation coefficients of the drugs used for the study:

Drug	Log K_{ow}	Log S_u (µg/ml)	$\sigma_{0.5}$	κ	R^2
Phenobarbital	1.5	2.99	3.9	1.4	1.00
Carbendazim	1.5	0.37	4.6	6.2	0.96
PPA	1.9	3.47	4.1	0.8	1.00
Griseofulvin	2.2	0.91	5.4	4.0	0.99
Phenytoin	2.5	1.03	6.1	4.0	1.00
PG-300995	2.6	1.59	4.8	2.1	1.00
Ketoprofen	3.1	1.89	6.5	2.4	1.00
Estrone	3.1	-0.20	6.2	9.4	0.99
Testosterone	3.3	1.34	5.0	2.1	1.00
Ibuprofen	3.5	1.48	5.8	2.9	0.99
XK-469	3.9	-0.64	6.6	7.6	1.00
Amiodarone	5.9	0.18	9.3	46.1	1.00
BPU	6.2	-1.52	10.0	26.8	1.00

5.3.2 Comparison of the Proposed Model with Existing Models:

The proposed model is compared to the Parabolic (equation 6), the Log-Linear (equation 16), the Bilinear (equation 17), and the Linear (equation 22) models. The calculated solubilities from each model were compared to the experimental values. The root mean square errors (RMSE) were calculated using equation 33. The significance of the calculation was tested using a paired two-tailed t-test with $\alpha = 0.1$. From the results presented in table 6, it can be seen that the proposed model is more accurate than the existing models and that its calculated values are not significantly different from the experimental values.

Table 6: Comparison of the proposed model with existing models:

Model	Equation	# of parameters	RMSE	p-value	Significance
Parabolic	6	2	0.13	0.09	No
Log- Linear	16	1	0.29	0.00	No
Bilinear	17	3	0.13	0.06	No
Linear	22	1	0.66	0.00	No
Proposed	**31**	**2**	**0.10**	**0.54**	**Yes**

5.3.3: Relation of Drug Polarity to the Cosolvency and Complexation Coefficients:

It has been discussed in chapter 1 that the cosolvency strength is a function of drug polarity (or non-polarity). A strong correlation between drug's log K_{ow} and the solubilization slope has been demonstrated[19]. On the other hand, the complexation strength is dependent on factors besides the non-polarity of the drug[22-26].

Figures 16 and 17 show the relationships of $\sigma_{0.5}$ and κ, respectively to the log K_{ow} of the 13 drugs studied.

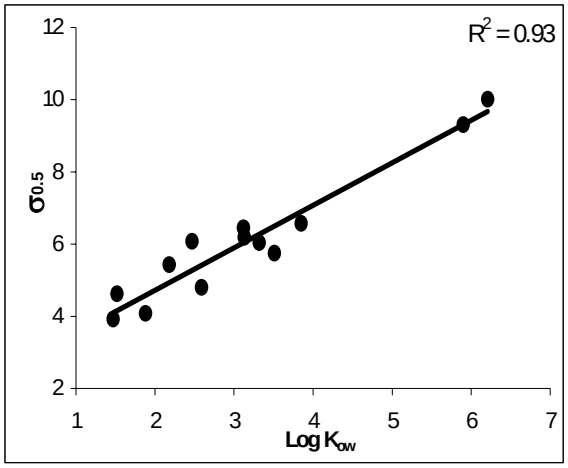


Figure 16: Correlation between log K_{ow} & $\sigma_{0.5}$

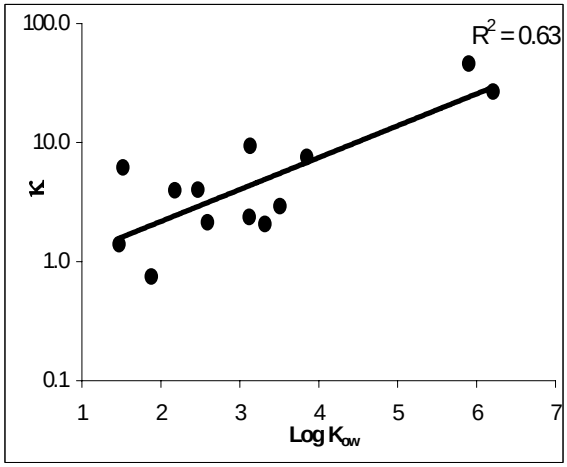
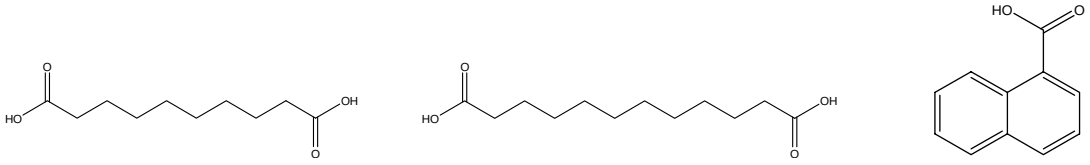


Figure 17: Correlation between log K_{ow} & κ

It can be seen that a strong correlation exists between the log K_{ow} of the drugs and the respective $\sigma_{0.5}$ values. This is in accordance to Millard et.al.[19]. The correlation between the log K_{ow} of the drugs and the respective κ values is weak, suggesting that other factors such as the solute's molecular shape and aromaticity are important in determining the complexation strength.

5.3.4 Effect of Molecular Shape & Aromaticity of the Solute on Complexation Strength:

In order to test this, solubility studies were performed on two linear aliphatic acids: sebacic acid (SA) and 1,12–dodecanedioic acid (DDA); and one aromatic acid: 1-naphthoic acid (NA). The structures of these compounds are given in figure 18.



Sebacic Acid (SA) **1,12-Dodecanedioic Acid (DDA)** **1-Naphthoic Acid (NA)**

Figure 18: Structures of the model solutes used for the study

Figure 19 presents the solubility profiles of the three compounds with NMP. The profiles of the aliphatic solutes follow log-linearity suggesting that their solubilization is a result of the cosolvent effect of NMP. The profile of NA resembles the typical profiles obtained for the 13 drugs, with a curvature and a large positive deviation from log-linearity. This suggests the presence of complexation between NA and NMP.

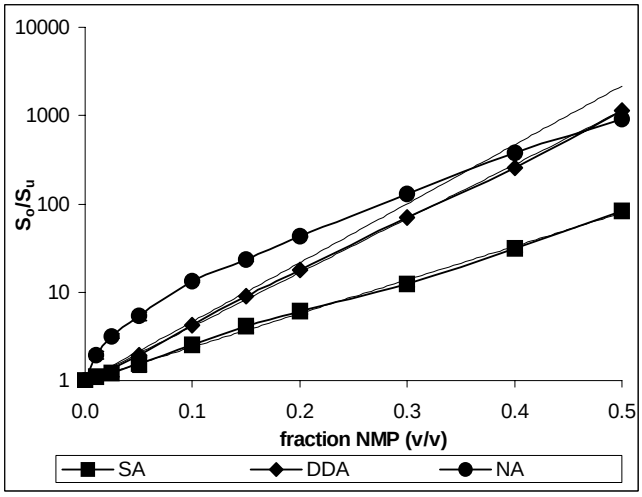


Figure 19: Solubility profiles of the model solutes

Table 7 presents the results from the deconvolution of the total solubility of the model solutes using equation 31. The complexation of NMP with DDA or SA is very weak and almost insignificant. Inspite the fact that NA and DDA have identical log K_{ow} values the κ value for NA is over 25 times higher than that for the later. This supports the idea that the presence of planer aromatic region on the solute molecule plays an important role in determining the complexation strength[21]. Stacking is a passive phenomenon and its strength is influenced by the presence of non-polar regions on the drug molecule. The log K_{ow} takes into account the overall non-polarity of the drug and using it alone to estimate the complexation strength will not be appropriate if only a small part of the drug molecule can interact with the ligand.

Table 7: The cosolvency and complexation coefficients of the model solutes:

Solute	Log K_{ow}	Log S_u (µg/ml)	$\sigma_{0.5}$	κ	R^2
Sebacic Acid	2.1	2.15	3.7	0.1	1.00
1,12-Decanedioic Acid	3.1	0.62	6.2	0.2	0.99
1-Naphthoic Acid	3.1	1.77	6.1	5.3	1.00

5.3.5 Additional Support for the Proposed Model:

The existence of simultaneous cosolvency and the complexation effects of NMP, is supported by the following experiments:

5.3.5.1 Effect of NMP on the surface tension of water:

A cosolvent weakens the self-associated structure of water. Thus, the magnitude of physical properties such as surface tension and dielectric constant that depends on the cohesion of water molecules reduces with the concentration of the cosolvent. Figure 20 presents the effect of NMP and EtOH on the surface tension water. It is evident that NMP reduces the surface tension of water at all volume fractions supporting its cosolvency behavior. The shape of the profile is similar to that of the EtOH-Water mixtures[53]. This observation is consistent with the reported lowering of the dielectric constant (reflecting reduction in the polarizability) of water with an increasing concentration of NMP[54].

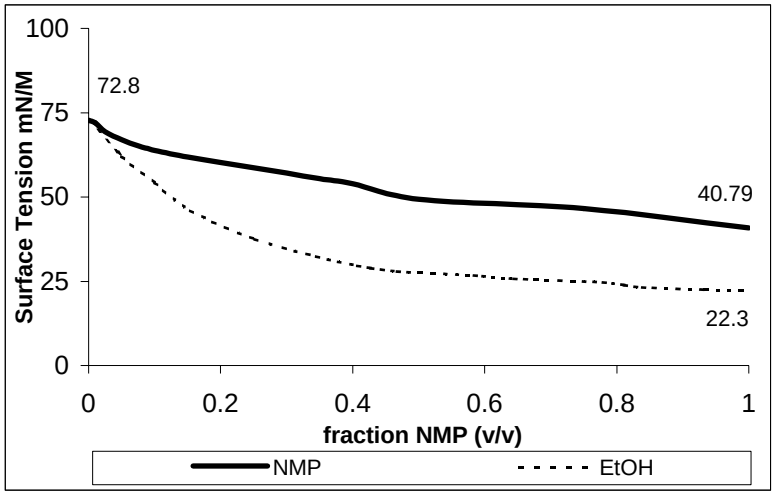


Figure 20: Surface Tension of cosolvent-water mixtures

5.3.5.2 Effect of Temperature:

Increasing the temperature of a system comprising of drug dissolved in NMP-water mixture affects the following interactions:

- Water-Water
- Drug-Drug
- Water-Drug
- Water-NMP
- Drug-NMP
- NMP-NMP

The relative strengths of the first three interactions determine the solubility of the drug in water. At higher temperatures, all these three interactions are weakened. The magnitude of the weakening of water-water interactions is generally greater than that of the drug-drug and water-drug interactions. Thus, the solubility of drugs in water increases with the temperature.

The Water-NMP interactions and the NMP-NMP interactions are weakened at higher temperature due to an increased entropic effect. As a result, the cosolvency effect of NMP may increase slightly with temperature. The Drug-NMP interactions are also weakened at higher temperatures. As the temperature increases, the magnitude $T\Delta S_{comp}$ increases making $\Delta G°_{comp}$ less negative and consequently making complexation less favorable and decreasing the κ.

In order to study the effect of temperature on the solubilization by NMP, studies using estrone and griseofulvin were preformed at 3 different temperatures. Figures 21 and 22 present the solubility profiles. The effect of temperature on the solubility of drug in water

is corrected by plotting the S_o/S_u. Therefore, a change in the profile will reflect the effect on temperature on the cosolvency and complexation effects of NMP.

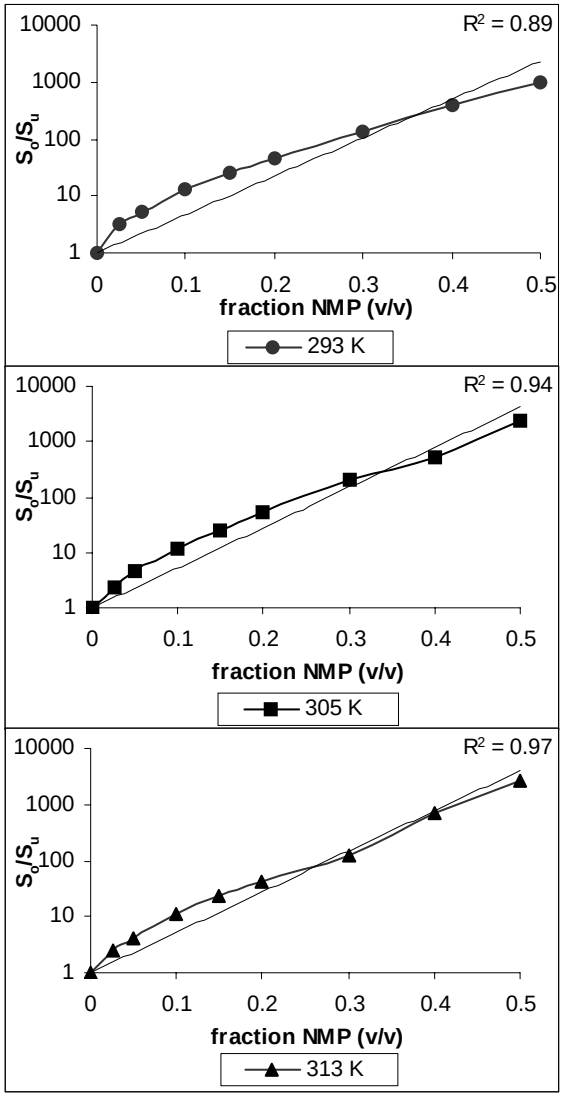


Figure 21: Solubility profile of estrone at different temperatures

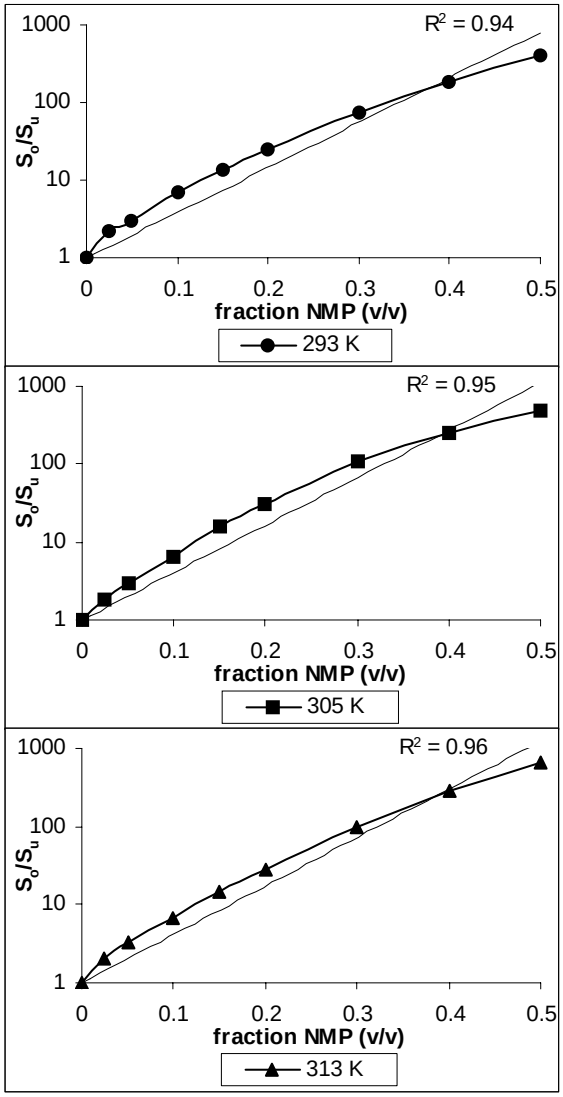


Figure 22: Solubility profile of griseofulvin at different temperatures

It can be seen from figures 21 and 22 that as the temperature is increased, both, the curvature of the solubility profile and the deviation from the log-linearity diminish for the two drugs. This indicates a lowering of the complexation effect at higher temperatures.

The solubilization coefficients were calculated at the three temperatures using equation 31 and are presented in table 8.

Table 8: Effect of temperature on the cosolvency & complexation coefficients:

Temperature	Estrone			Griseofulvin		
	Log S_u (μg/ml)	$\sigma_{0.5}$	κ	Log S_u (μg/ml)	$\sigma_{0.5}$	κ
293 K	-0.20	6.2	9.4	0.91	5.4	4.0
305 K	-0.07	6.7	6.8	1.03	5.6	3.7
313 K	0.15	6.9	5.5	1.19	5.7	3.6

It can be seen that σ increases with temperature. The effect of temperature is linear (figures 23 and 24) which indicates that the increase in σ is a result of an increased effect of the entropy.

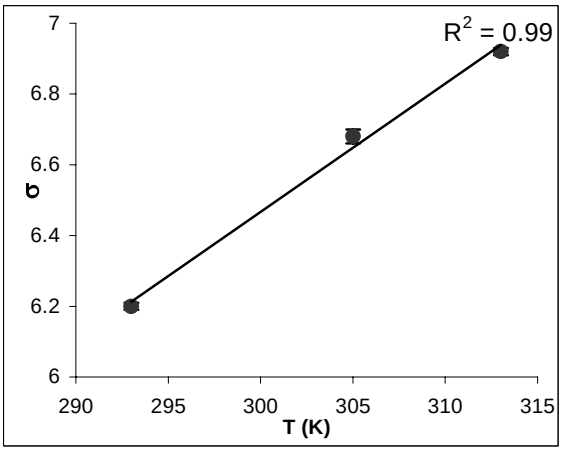


Figure 23: Effect of temp. on σ for estrone

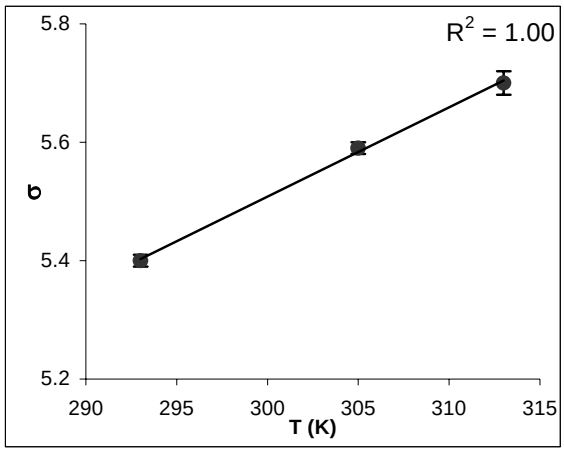


Figure 24: Effect of temp. on σ for griseofulvin

It can be seen from table 8 that κ decreases at higher temperatures. In order to calculate the thermodynamic parameters associated with Drug-NMP complexation, the log κ values were plotted against the inverse temperatures (van't Hoff plots). The $\Delta H°_{comp}$ were determined from the slope of these plots (Figures 25 and 26).

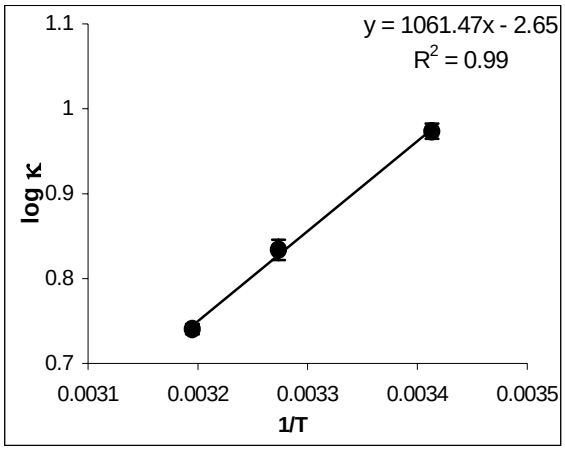


Figure 25: van't Hoff plot of κ for estrone

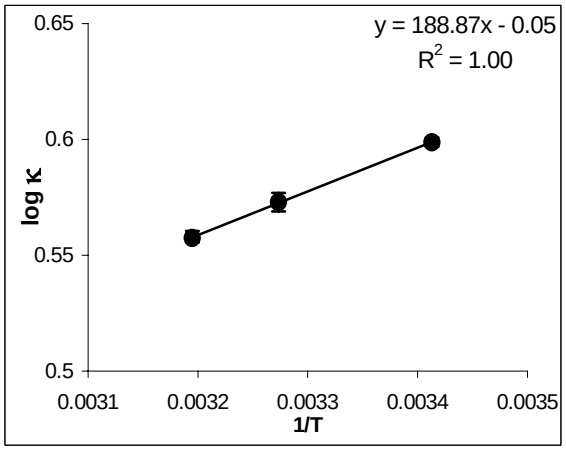


Figure 26: van't Hoff plot of κ for griseofulvin

Table 9 presents the values of $\Delta G°_{comp}$, $\Delta H°_{comp}$ and $T\Delta S°_{comp}$ for estrone and griseofulvin calculated using equations 25, 26 and 27. A negative $\Delta G°_{comp}$ supports the theory of complex formation. The magnitude and the sign of $\Delta H°_{comp}$ in both the examples suggest the presence of weak hydrophobic interactions between drug and NMP molecules.

Table 9: Effect of temperature on the thermodynamic parameters:

Temperature	Estrone			Griseofulvin		
	$\Delta H°_{comp}$ kJ/mole	$T\Delta S°_{comp}$ kJ/mole	$\Delta G°_{comp}$ kJ/mole	$\Delta H°_{comp}$ kJ/mole	$T\Delta S°_{comp}$ kJ/mole	$\Delta G°_{comp}$ kJ/mole
293 K	-20.33	-14.86	-5.46	-3.62	-0.25	-3.37
305 K	-20.33	-15.45	-4.88	-3.62	-0.26	-3.36
313 K	-20.33	-15.89	-4.44	-3.62	-0.27	-3.35

5.3.5.3 Effect of the self-association of the medium:

As discussed in chapter 1, stacking is a passive phenomenon and its strength is a function of the degree to which molecules comprising the medium are associated. In a highly polar or a self-associated medium like water, the driving force for a nonpolar drug molecule to undergo complexation is stronger. Thus, $\Delta H°_{comp}$ is more negative since a larger enthalpic gain is achieved upon complexation in such a system. This makes the $\Delta G°_{comp}$ more negative and the formation of complex more favorable.

The sensitivity of the Drug-NMP complexation coefficient κ to the self-association strength of the medium will support the theory of complex formation. In this study the strength of self-association of water was changed by the addition of EtOH or sodium chloride (NaCl). It is a well-known fact that addition of EtOH makes the hydrogen-bonding network of water weaker and thereby reduces its self-association. Addition of salt makes water more structured as the water molecules get positioned around the ions thereby making the entire system more associated. It should be noted that modifying the property of the medium also affects the intrinsic solubility of the drug.

Reducing the self-association of the medium: Table 10 presents the effect of EtOH concentration on the solubilization parameters of estrone and griseofulvin. The value of κ reduces with increasing EtOH concentration supporting the theory of complex formation.

Table 10: Effect of EtOH concentration on the cosolvency & complexation coefficients:

% EtOH (v/v)	Estrone			Griseofulvin		
	Log S_u (µg/ml)	$\sigma_{0.5}$	κ	Log S_u (µg/ml)	$\sigma_{0.5}$	κ
0	-0.20	6.2	9.4	0.91	5.4	4.0
10	0.53	6.3	4.6	1.41	5.8	3.0
20	0.94	6.1	2.5	1.90	5.3	2.1

The values of $\sigma_{0.5}$ remained almost unchanged indicating that EtOH does not affect the cosolvency strength of NMP. It must be mentioned that the total solubility obtained in the presence of EtOH and NMP is close to the sum of their individual cosolvent effects, following equation 15. Table 11 presents the solubility of estrone and griseofulvin in solutions containing NMP and EtOH. The solubilities obtained in presence of a combination of 10% NMP and 10% EtOH is close to that obtained in 20% NMP solution. Therefore, a combination of EtOH-NMP may be extremely useful for attaining desired solubility enhancement without using too much of any one of these solubilizers. Such a combination will have low toxicity while comparable solubility gains can be achieved.

Table 11: Solubility of drugs in aqueous mixtures containing NMP and EtOH:

Drug	Log S_u (µg/ml)		
	No solubilizer	20% NMP	10% EtOH + 10% NMP
Estrone	-0.20	1.47	1.45
Griseofulvin	0.91	2.31	2.21

Increasing the self-association of the medium: As discussed before, the addition of salt makes water more structured resulting in a decrease in the water solubility of a drug and an increase in the driving force behind complexation. Table 12 presents the effect of NaCl concentration on the solubilization parameters of estrone and griseofulvin. As expected, the value of κ increased with increasing NaCl concentration. The cosolvent effect of NMP also increases since a cosolvent is expected to have a greater influence on a more structured aqueous medium.

Table 12: Effect of NaCl concentration on the cosolvency & complexation coefficients:

NaCl (M)	Estrone			Griseofulvin		
	Log S_u (μg/ml)	$\sigma_{0.5}$	κ	Log S_u (μg/ml)	$\sigma_{0.5}$	κ
0.0	-0.20	6.2	9.4	0.91	5.4	4.0
0.5	-0.27	6.5	10.0	0.81	5.5	4.1
1.0	-0.49	7.0	12.6	0.67	5.8	4.2

5.3.6: Effect of NMP on the Crystal Form of the Drugs:

It has been discussed in chapter 1, one of the assumptions of the log-linear model is that the crystal form of the drug remain unaltered during solubilization. In order to check whether the deviation from the log-linearity noticed with NMP is due to the change in drug's crystal form, thermal analysis of estrone and griseofluvin was performed before and after solubilization. No change in terms of the melting point or the melting endotherm was noticed in the thermograms for both these drugs (figures 27 and 28).

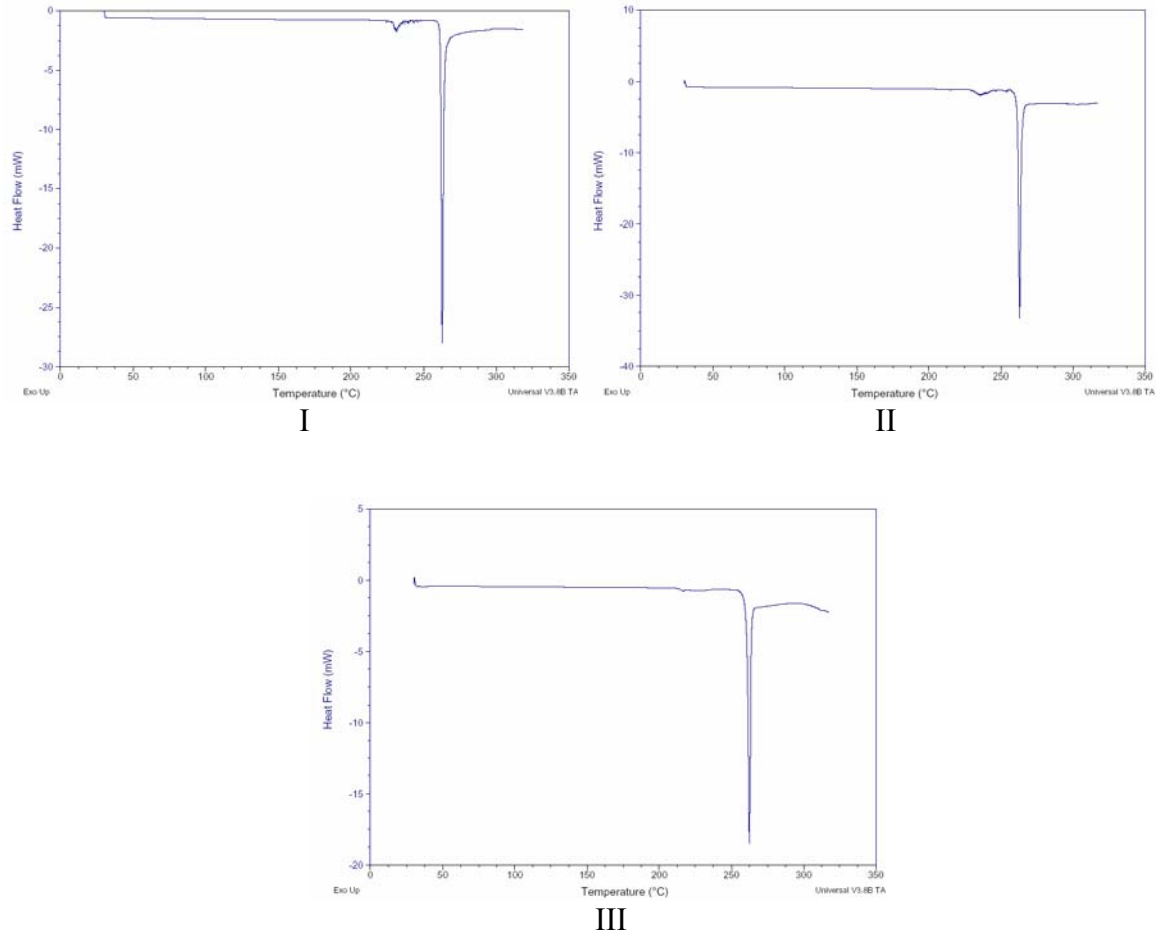


Figure 27: Thermograms for Estrone Samples
I: Pure drug; II: Excess undissolved drug; III: Drug residue after evaporation of saturated sol.

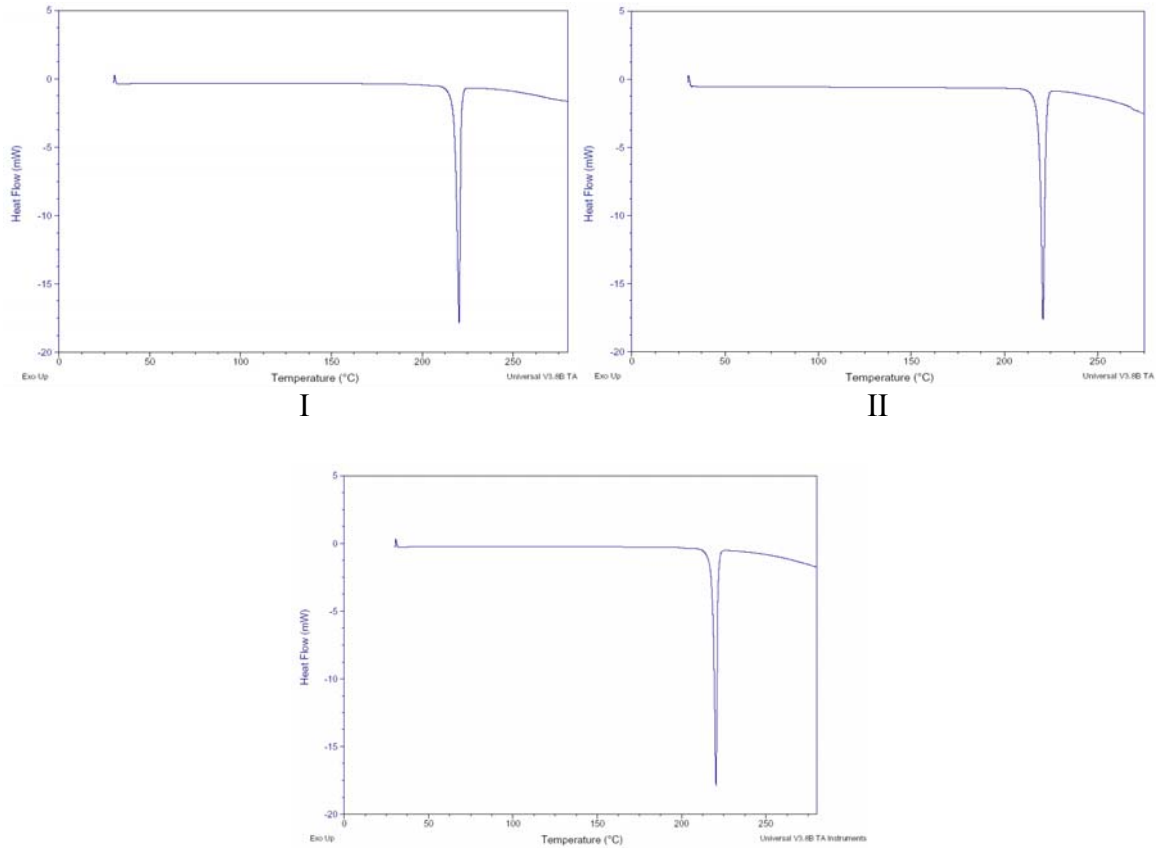
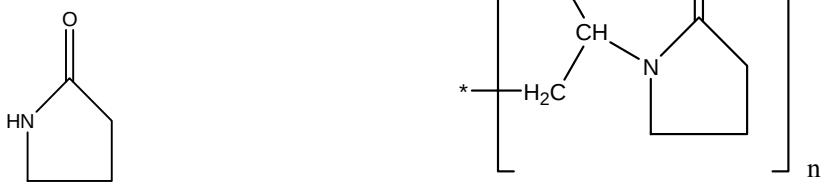


Figure 28: Thermograms for Griseofulvin Samples
I: Pure drug; II: Excess undissolved drug; III: Drug residue after evaporation of saturated sol.

CHAPTER 6: DRUG SOLUBILIZATION USING OTHER PYRROLIDONE DERIVATIVES

The dual mechanism of drug solubilization, i.e., cosolvency and complexation, by NMP is considered to be an outcome of its structure. NMP is completely miscible with water due to the presence of the polar cyclic amide group. NMP functions like a cosolvent by introducing four carbons per molecule that reduce the hydrogen-bonding network of water. NMP can also stack with the hydrophobic region of drug molecules by virtue of the presence of a nearly planer non-polar region. Therefore, it is expected that other pyrrolidone derivatives sharing these structural attributes will behave in the same manner. In order to test this, the solubilization of drugs using two other pyrrolidone derivatives, 2-pyrrolidone (2-P) and polyvinyl pyrrolidone (PVP grade 12), was studied. Their structures are presented in figure 29.



2-Pyrrolidone (2-P) **Polyvinyl Pyrrolidone (PVP)**

Figure 29: Structures of the other pyrrolidone derivatives used for the study

6.1 Solubility Profiles of Drugs with 2-P and PVP:

The solubility profiles of estrone and griseofulvin were obtained with 2-P and PVP as solubilizers. Figures 30-33 present these profiles. These profiles resemble those obtained with NMP, with a characteristic curvature and a positive deviation from log-linearity at low concentration of the solubilizer. This supports the idea that 2-P and PVP share the mechanism of drug solubilization with NMP.

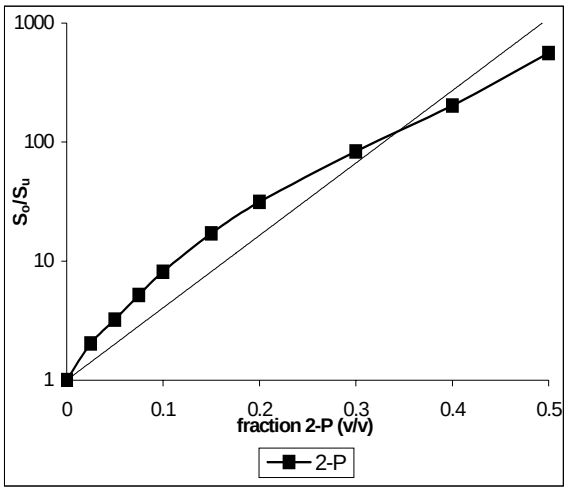


Figure 30: Solubility profile of estrone with 2-P

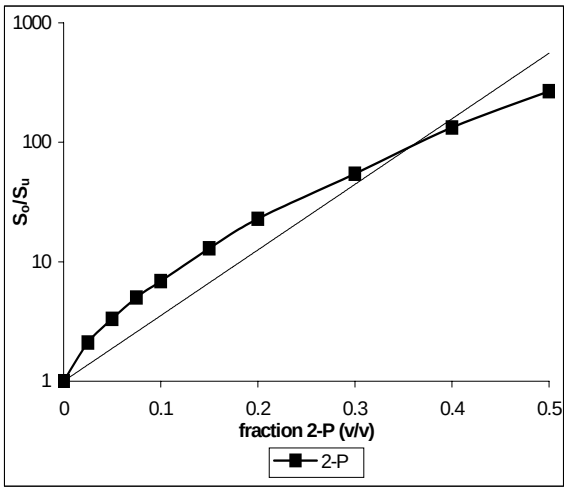


Figure 31: Solubility profile of griseofulvin with 2-P

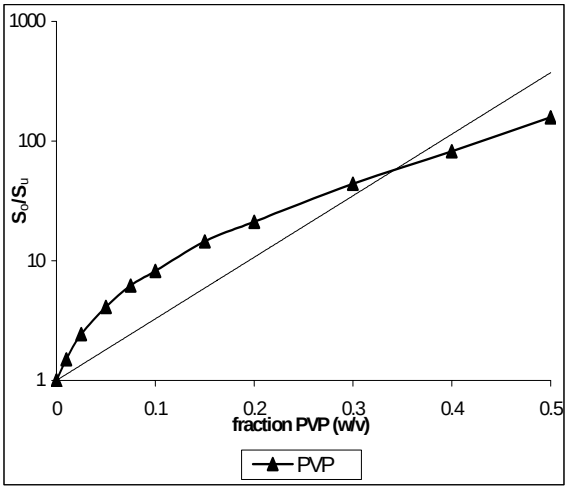


Figure 32: Solubility profile of estrone with PVP

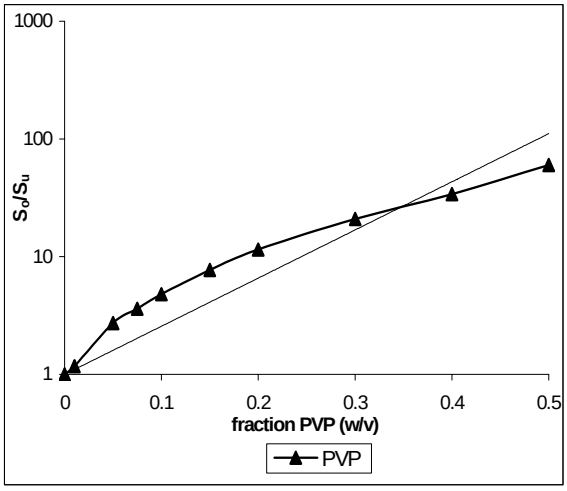


Figure 33: Solubility profile of griseofulvin with PVP

6.2 Relative Strengths of 2-P and PVP as Cosolvents and Complexing Agents:

The solubility data obtained for the two drugs with 2-P and PVP were deconvoluted. The values of $\sigma_{0.5}$ and κ were calculated following the deconvolution. Table 13 presents these along with the values obtained with NMP for reference:

Table 13: Cosolvency and complexation coefficients obtained with pyrrolidone derivatives:

Solubilizer	Estrone		Griseofulvin	
	$\sigma_{0.5}$	κ	$\sigma_{0.5}$	κ
NMP	6.2	9.4	5.4	4.0
2-P	5.7	3.2	5.0	3.0
PVP	4.3	143.8	3.4	66.2

It can be seem that 2-P is a weaker cosolvent and a weaker complexing agent than NMP. The strength of a cosolvent is a function of its non-polarity[19]. 2-P is more polar than NMP as it contains one less carbon atom. Thus, it will have a smaller effect on the structure of water, which explains its weaker cosolvent characteristics. The complexation strength is also dependent on the structure of the ligand. A slightly weaker complexation strength of 2-P can be explained on the basis that it has fewer carbons than NMP. The presence of the $-CH_3$ group on the NMP molecule may affect the complexation strength in two ways. The $-CH_3$ group increases the non-polarity of the molecule and will strength its interaction with the drug molecules. At the same time the $-CH_3$ group may strerically hinder the complexation. From the data, it seems that the influence of the first effect is larger than the second effect and as a consequence NMP is a stronger complexing agent.

According to table 13, PVP is a weaker cosolvent and a stronger complexing agent than NMP. PVP is a polymer (18-25 monomers) of N-vinylpyrrolidone. Due to its polymeric structure, PVP may not be able to interact with water as much as NMP. As a consequence, its influence on the hydrogen-bonding network of water is smaller than that of NMP which explains its weaker cosolvent strength. The complexation strength of PVP however, is much stronger due to the presence of 18-25 planer non-polar regions per molecule.

SUMMARY

N-methyl pyrrolidone is a potent solubility enhancer for drugs. It is a stronger solubilizer than both EtOH and PG for the 13 drugs studied. It simultaneously acts as a cosolvent and a complexing agent and the total solubility obtained is a sum of these two effects. A mathematical model for describing this mechanism of solubilization has been proposed. The model describes the experimental data well and is found to be both, more accurate and more significant than the existing models. Based on this study it can be said that NMP is a good choice as a solubilizer in the pharmaceutical industry.

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