ESTIMATION OF ETHANOL /WATER SOLUBILITY PROFILES

by

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DEDICATION

This is dedicated to my family, for their inspiration, guidance, love and support.

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ABSTRACT

The goal of this study was to develop a simple means of estimating the cosolvent/water solubility profile using just the available properties ($logK_{ow}$, dielectric constant etc.) of the solute, cosolvent and water. Ethanol was used as the model cosolvent.

One of the most commonly used polarity indicators is the octanol/water partition coefficient ($logK_{ow}$). Numerous programs are used to predict the $logK_{ow}$. The calculated values of $logK_{ow}$ from three of the most commonly used programs ClogP®, ACD/logPdb® and KowWin® were compared to experimental values. It was found that all three programs have a user friendly interface but ClogP appears to be more accurate.

While the ethanol/water solubility profiles of very polar and very non-polar drugs are monotonic, many semi-polar drugs show a maximum solubility at an ethanol volume fraction (f_{max}) between zero and one. A new empirical function that describes this deviation from linearity was applied to the experimental data for fifty-one compounds. The proposed model was a more accurate predictor of the co-solvent solubility profile than a general third order polynomial with the same number of parameters. The f_{max} value was also accurately predicted from the first derivative of the model.

A sigmoidal relationship was observed between the value of f_{max} and $logK_{ow}$ of the solute. Combining this sigmoidal relationship with the previously reported linear relationship between $logK_{ow}$ and the initial slope of the plot of log

solubility vs. ethanol composition enables the estimation of the total ethanol/water solubility profiles of semi-polar compounds from just $\log K_{ow}$.

A new bilinear function was also introduced to address the deviation from linearity. This model accounts for both the initial and terminal slopes in the ethanol/water solubility profiles of semi-polar solutes. The proposed model is dependent only on $\log K_{ow}$ and an empirical constant that is cosolvent specific. It is also more accurate than the log-linear model and a general parabolic model.

A solubility case study using Antalarmin, a novel stress inhibitor was performed. This study illustrates the use of cosolvents as solubility enhancers as well as pH, surfactants, complexants and lipid based systems.

CHAPTER 1
INTRODUCTION

Drug solubility is of vital importance in the pharmaceutical field. Drug solubility and dissolution rate are often the rate limiting factors to drug absorption from the gastrointestinal tract (Rubino 1984). The factors that govern solubility need to be understood before selecting a technique to improving the solubility. There are two major factors that determine the aqueuous solubility of a drug.

1) The activity of the drug in aqueous media.

2) The crystallinity of the compound

The activity/polarity of the drug may be defined using one of the following indices: dielectric constant, solubility parameter, surface tension, interfacial tension and the octanol/water partition coefficient. Rubino and Yalkowsky (1987) evaluated these polarity indexes for the estimatimation of aqueous solubility. For the purpose of this manuscript the octanol/water partition coefficient will be used as the polarity index of choice.

The melting point of a compound is a good indicator of crytsallinity. The more crystalline the compound the higher its melting point.

Numerous models have been proposed for the estimation of the aqueous solubility. Among these is that of Hansch (1968) who showed that for a large number of organic liquids;

$$log\ S_w = A - B\ log\ K_{ow} \qquad 1.1$$

This was later refined by Valvani and Yalkowsky (1981) and then by Jain and Yalkowsky (2001).

$$log\ S_w = 0.5 - log\ K_{ow} \qquad 1.2$$

This equation is applicable to compounds that are liquid at room temperature (~25^{o}C) and are completely miscible with octanol. As stated before, polarity is a key factor in the solubility of a compound. The value of logK_{ow} can be estimated from structure by a number of group contribution schemes. In Chapter 2 three of the most popular predictive programs for logK_{ow} will be analyzed. (Machatha and Yalkowsky 2005).

As stated above the crystallinity of a drug plays a role in determining its solubility. Mishra (1988) and Mishra and Yalkowsky (1990) defined the ideal molar solubility X_i as a function of the entropy of fusion ΔS_f, melting point $T_{m,}$ in Kelvins and absolute temperature of 298K.

$$log\ X_i = -\Delta S_m \left(\frac{T_m - 298K}{2.303RT} \right) \qquad 1.3$$

Expressing the melting point in ^{o}C equation 1.3 becomes;

$$log\ X_u^{ideal} = -\Delta S_m \left(\frac{T_m - 25^o C}{690R} \right) \qquad 1.4$$

Walden (1908) showed that the entropy of fusion of coal tar derivatives is approximately 6.79R. Walden's rule was extended to rigid organic

nonelectrolytes by Martin (1979) and Yalkowsky (1979). Applying this approximation to equation 1.4;

$$log\ X_u^{ideal} \approx -0.01\left(MP - 25^o C\right) \qquad 1.5$$

Combining equations 1.2 and 1.4 we get the General Solubility Equation (GSE);

$$log\ S_w = 0.5 - log\ K_{ow} - 0.01\left(MP - 25^o C\right) \qquad 1.6$$

Where S_w is the molar solubility, MP is the melting point, $logK_{ow}$ is the octanol/water partition coefficient. Note that this equation makes use of the two physicochemical properties, activity/polarity and melting point.

Yalkowsky and Valvani (1980a and b) and Jain and Yalkwosky (2001) showed the applicability of the general solubility equation by testing it on hundereds of organic non-electrolytes.

Several methods have been used to increase drug solubility. The choice of method is dependent upon the physicochemical characteristics of the drug as well as its biopharmaceutical and toxicological nature and the route of administration. These methods include pH adjustment, salt formation, micelle formation, complexation and cosolvency.

If the drug can be classified as a base or an acid, pH adjustment is one viable way of increasing solubility. The ionized form is significantly more soluble than the unionized form. Salt formation also relies on the ionization potential of the solute. These approaches may not be able to significantly increase the solubility to the desired level. Other limitations include the stability of the drug and other excipients at the different pH. The combination of pH with other vehicles like surfactants, complexants and cosolvents is also a viable option in improving solubility.

Surface active agents are amphiphiles and have defined non-polar and polar regions. Micelle formation reduces the interaction between the non-polar region of the surfactant and the aqueous media. Above the critical micelle concentration (CMC) the drug in the micelle is at equilibrium with drug in solution. Surfactants are safe in low concentrations hence their solubilization power is reduced. Also the solubility increase using surfactants is one to five fold and is not that effective. Ionic surfactants are extremely toxic and cannot be used intraveneously. Certain non-ionic surfactants are frequently used at low concentrations for example Cremaphor and polysorbate 80.

Complexation is defined as the noncovalent stoichiometric association of two or more molecules in a single structure. This is another technique that could be employed to increase solubility. The solubility enhancement obtained is typically 1-5~ fold. Also the concentration of complexants used is limited by toxicity issues. The structure of the

drug must have either the appropriate sites for complexation or it must be of the right molecular size and orientation.

Crystal packing manipulation is yet another way of increasing drug solubility. This is where a drug is recrystallized in a more unstable form and hence a lower melting point. This could be an amorphous form of the original compound and thus be higher in energy and more unstable. This mode of altering the solubility is laborious and requires time for the formation of the new crystal form. Also, the amorphous form must be able to revert to the more stable lower energy form.

Cosolvency is one of the most effective and readily available methods for improving solubility, which is the addition of a water miscible organic materiasl. The addition of cosolvent lowers the polarity of the aqueous system, resulting in an increase in solubility of non-polar solutes while reducing that of polar ones. Cosolvents, such as propylene glycol, ethanol, glycerin and polyethylene glycol are used in 13% of FDA approved parenteral products, in which ethanol is the most commonly used.

Many theories have been introduced to explain cosolvent solubilization at a molecular level. A simple and intuitive way is to realize that most cosolvents have hydrogen bonding groups as well as hydrocarbon regions. The hydrophilic portion associates with the water while the hydrophobic portion disrupts the hydrogen bonding network of the water molecules. This in turn reduces water's capability of "squeezing out" non-polar solutes from solution. Another simplistic viewpoint would be to recognize that the addition of cosolvent to water reduces its polarity, making it favorable for the semi-polar and non-polar solutes to dissolve.

Various models have been used to predict the cosolvent/water solubility profiles. These include parabolic and log-linear models. The log-linear model of Yalkowsky and Rosemann (1981) describes an exponential increase in non-polar drug solubility with a linear increase in cosolvent concentration. There are also numerous parabolic models that have been used to predict the cosolvent/water solubility profile for semi-polar solutes. Paruta et al. (1964) correlated the cosolvent solubility with a parabolic function of the dielectric constant of the solvent mixture. Martin et al. (1979, 1981) proposed a parabolic relationship between solute solubility and the solubility parameter of a solvent mixture. Recently, Ruckenstein et al. (2003) applied fluctuation theory to generate a new parabolic relationship. These parabolic relationships are based on regular solution theory. As was shown by Hilderbrand (1929) and Scatchard (1933) and later reiterated by Yalkowsky (1999), regular solution theory is not applicable to solutions where hydrogen bonding or ionic interactions are dominant.

Ethanol is the most commonly used cosolvent due to its low toxicity and low cost. Ethanol/water systems have the most data available and therefore, ethanol will be used as the model solvent for this study.

In Chapters 3, 4 and 5, various theories and models will be employed in estimating the ethanol/water solubility profiles. (Mathatha et al. 2004, 2005) A solubility case study of the novel stress inhibitor Anatalarmin using different solubility techniques is presented in Chapter 6. The estimation of cosolvent/water solubility profiles is of significance not only in pharmaceutical science but also in the chemical and environmental fields.

CHAPTER 2

ESTIMATION OF THE OCTANOL/WATER PARTITION COEFFICIENT

2.1 Introduction

The octanol/water partition coefficient (K_{ow}) is the ratio of a compound's concentration in octanol to its concentration in water when the phases are at equilibrium. Since partition coefficient values (K_{ow}) can range over many orders of magnitude they are normally expressed in logarithmic form (logK_{ow}). The partition coefficient has been widely used in calculating numerous physical properties such as membrane transport and water solubility.

Eros et al.(2002) and Mannhold and van de Waterbeemd (2001), have looked at various predictors of logK_{ow}. In this manuscript we will focus on three commonly used programs: ClogP® v4.0 (BioByte Corp. 1999) , ACD/logPdb® v7.0 (Advanced Chemistry Development, Inc., Toronto ON, Canada, 2003) , and KowWin® v1.67 (Syracuse Research Corporation (SRC) Syracuse NY 2000). Mannhold and van de Waterbeemd (2001) described these programs as substructure approaches where the final log K_{ow} is determined by summing the single-atom or fragment contributions.

Note that these programs are designed to determine the partition coefficient of the non-ionized form of a compound. Edward et al. (1997) conducted a study where they tested the accuracy of the three programs on 34 analogs of pyridoxal

isonicotinoyl hydrazone. They showed that the programs are not particularly good predictors of logK_{ow} for zwitterionic, tautomeric and charged compounds as well as for strongly hydrogen bonding compounds. In this report the accuracy and ease of use of ClogP, ACd/logP and KowWin will be evaluated using the data set of Rytting et al. (2004).

2.2 Method

2.2.1 Acquisition of Data

In order to avoid any bias, the compounds selected by Rytting et al. (2004) are used as the evaluation set. Fourteen of the 122 reported compounds were omitted due to lack of experimental values of logK_{ow}. The partition coefficients of the remaining 108 compounds were determined using ClogP®, ACD/logPdb®, and KowWin®. The experimental logK_{ow} values were acquired from references listed in the ACD/logP database. If more than one reference was listed the average logK_{ow} was taken as the experimental value

2.2.2 Statistical Analysis

The average absolute error (AAE) was determined using the relationship below.

$$AAE = \frac{\sum |observed - predicted|}{n} \quad (2.1)$$

Where n is the number of compounds studied.

T-tests were performed on the logarithmic data using Microsoft Excel 1997 (Los Angeles, CA). The P-value was determined using a paired t-test with a two tailed distribution. The significance level was set at 0.05 hence, if the P-value is <0.05 then the two data sets are considered to be significantly different.

2.3. Results and Discussion

The data were separated into three groups. The first group consists of all the compounds with reported experimental logK_{ow} values. The second group consists of all of the compounds which are not zwitterionic or tautomeric. The third group consisted of the zwitterionic and tautomeric compounds. The experimental and predicted logK_{ow} values from each of programs are listed in APPENDIX A.

The calculation of the partition coefficient of the drug sulindac, shown in Figure 2.1, by the three methods is illustrated in Table 2.1. Sulindac is in a class of medications known as non-steroidal anti-inflammatory drugs. It is used to treat rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, a rheumatic disorder involving the spine and large joints. It also treats both acute painful

shoulder and gouty arthritis. All three programs use somewhat similar molecular breakdown schemes. However, there are significant differences in the use of non-constitutive descriptors. ClogP and ACDlogP use different inter-fragmental interaction parameters, while KowWin simply adds a constant. These are discussed in more detail by Mannhold and van de Waterbeemd (2001).

Figure 2.1 Chemical Structure of Sulindac.

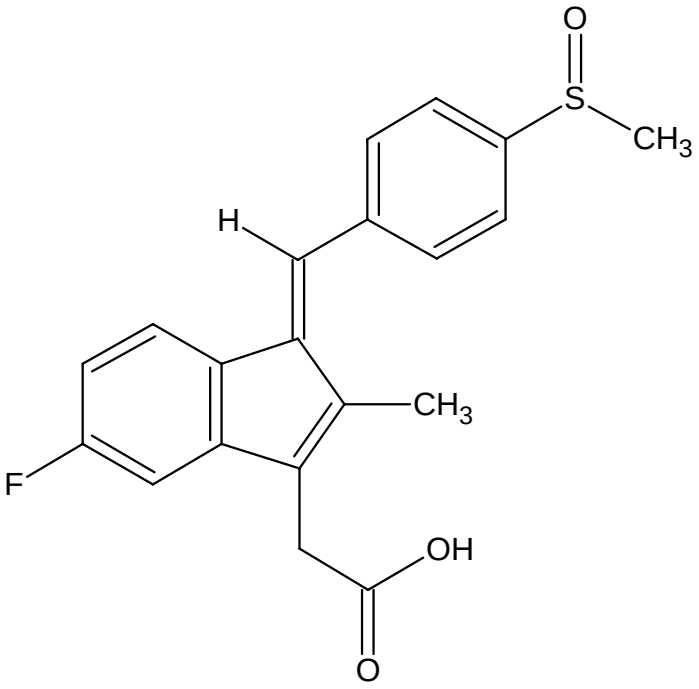


Table 2.1 Fragmentation and calculation of the logK_{ow} of sulindac using ClogP, ACD/logP and KowWin

	Type	**KowWin**	**ACd/log P**	**ClogP**
Flouride	Fragment	0.2004	0.5007	0.370
Sulfoxide	"	-2.1103	-2.1284	-2.12
-C aromatic	"	0.294		
-CH aromatic	"	-	0.3697	0.130
-CR aromatic	"	-	-0.0793	-
-COOH aliphatic	"	-0.6895	-1.1945	-1.070
-CH_2 aliphatic	"	0.4911	0.5314	-
-CH_3 aliphatic	"	0.5473	0.9091	-
aliphatic isolating C	"	-	-	0.195
Connecting aromatic C	"	-	0.0840	-
-H on isolating carbons	"	-	-	0.227
=CH- (olefinic carbon)	"	0.3836	0.2722	-
chain and cluster branches	Branch	-	-	-0.130
Chain and alicyclic (net)	Bonds	-	-	-0.540
Allylic structure	Proximity	-	-	0.200
Phenyl-fragment pair	"	-	-	0.150
Vinylic	Interaction		0.750	-
Aliphatic	"	-	0.0678 0.1509 0.2750	-
Aromatic	"		-0.0428 0.0722	-
Equation constant		0.2290	-	-
Log Kow		**4.28**	**3.59**	**3.16**

Table 2.2 Average absolute errors and P-values of compounds listed in APPENDIX A

		AAE (P-values)		
Group	**n[a]**	**KowWin**	**ACD/logPd b**	**ClogP**
All Compounds	108	0.358 (0.0032)	0.386 (0.0002)	0.329 (0.3035)
w/o tautomers and zwitterions	85	0.282 (0.0176)	0.281 (0.0086)	0.250 (0.6828)
tautomers and zwitterions	23	0.638 (0.0658)	0.774 (0.0049)	0.623 (0.1357)

[a]Where n is the number of compounds

A paired t-test was performed and the series of experimental values predicted by each program was compared to the series of experimental values to calculate a P-value for each program. The P-values as well as the average absolute errors (AAE) for each method are listed in Table 2.2.

It is clear from Table 2.2 that all three programs are associated with low absolute errors of prediction for uncharged, non-tautomeric compounds. However, ClogP clearly has the lowest error and the highest P-value for the compounds selected. Based on this data set ClogP is significantly better than ACDlogP and KowWin. This study confirms the conclusions of Edward et al. (1997), that the logK_{ow} values of zwitterionic and tautomeric compounds are poorly predicted by group contribution programs.

Graphs of the predicted against the experimental values from all three programs are shown in Figure 2.2.

It was observed that there were five compounds whose predicted values were one log unit or more off from the experimental value in at least two of the programs. These outliers are terfenadine, 5-aminosalicylic acid, bumetanide, diatrizoic and uric acid. This large error may be due to experimental or reporting error. The AAE was recalculated after excluding these compounds and the results are shown in Table 2.3.

Figure 2.2. Plots of experimental against predicted logK_{ow} values for the three programs (KowWin, ACD/logP, ClogP) □- non tautomers/zwitterions and Δ- zwitterions and tautomers.

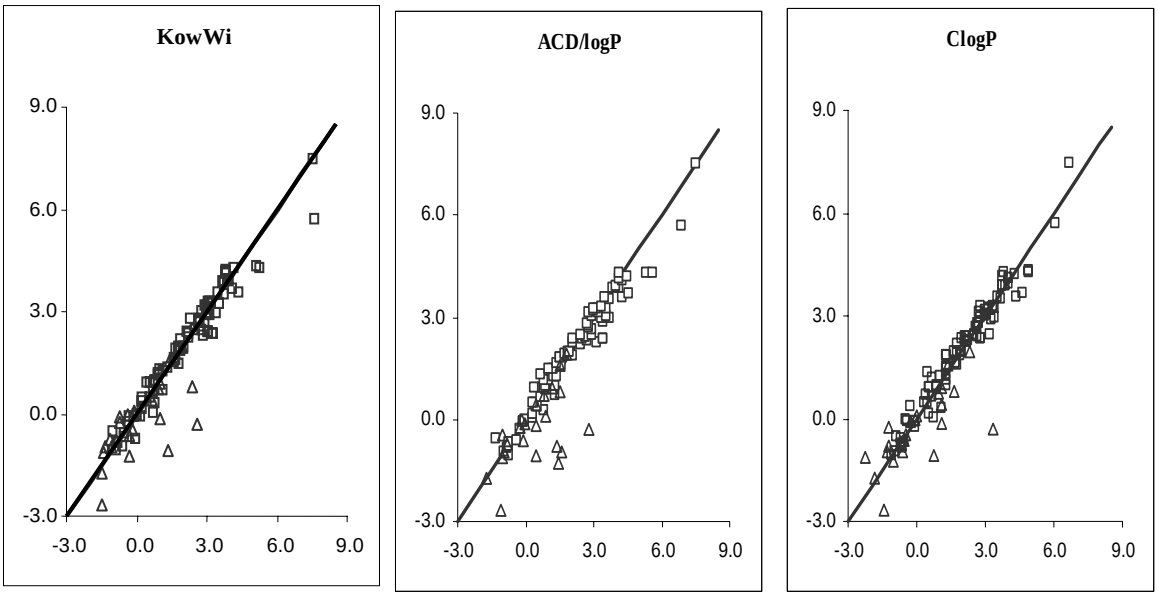


Table 2.3 Average absolute errors and P-values without the six outliers.

		AAE (P-values)		
Group	**n[a]**	**KowWin**	**ACD/logPdb**	**ClogP**
All Compounds	103	0.282 (0.0441)	0.327 (0.0019)	0.265 (0.5524)
w/o tautomers and zwitterions	84	0.262 (0.0313)	0.270 (0.0153)	0.248 (0.5906)
tautomers and zwitterions	19	0.371 (0.6921)	0.580 (0.0434)	0.341 (0.8004)

[a]Where n is the number of compounds

Table 2.4 Comparison between the three logK_{ow} prediction programs.

Item	KowWin	ACD/logP	ClogP
Input			
• SMILES	Yes	Yes	Yes
• CAS#	Yes	N/A	Yes
• Structure drawing	N/A [a]	Yes	N/A [a]
• Batch	Yes	Yes	Yes
• Online Availability	Yes	Yes	Yes
Calculations			
• In Database	13058	>12400	12800
• Distinguish Enantiomers	Yes	Yes	N/A
Output			
• Details of Calculation	Yes	Yes	Yes
• Accuracy	See table 3	See table 3	See table 3
• References Provided	1	Many	1
• Warnings	Yes	Yes	Yes
Determine other properties	Yes [b]	Yes [c]	Yes [d]
Cost ($)[e]	Free	2895 / 995	2500 /1500

[a] Convert structure to smiles name from MDL MOL file type.
[b] Comes as a Free suite program (EPI suite) down loaded from the EPA website.
[c] Dissociation constant (log D and pKa) and water solubility along with other physical property data are
available in ACD suite at a cost of $9895 for industry use and $2495 for academia.
[d] Biobyte corporation has suite program Bioloom that predicts logK_{ow}, logD and pKa at a cost of $3200 for industry
and $1600 for academia
[e] Cost ($) industry/ academia

While prediction accuracy is a major basis for the selection of a particular program there are a number of other factors that should be considered. Table 2.4 compares the three programs on the basis of several criteria.

As can be seen from Table 2.4, these programs considered are similar in many respects. For example, they each accept the common name and SMILES input which can be supplied in batch mode for large data sets. Each is available on-line or as a compact disc for use offline. They all utilize similar sized databases of about thirteen thousand experimental values to generate group values and correction factors. They each show the details of their calculations and provide warnings of potentially unreliable values.

In spite of their similarities there are significant differences, beside the greater accuracy of ClogP, among the programs. Some of the differences in utility and convenience are summarized below:

- ACD/logP contains a structure generating program. While this program is less user friendly than Chem Draw or other commercially available packages, it is convenient for single compound evaluation, especially for compounds with complex SMILES strings.
- Both ClogP and KowWin accept CAS numbers as input whereas ACD/logP does not.

- Unlike other programs, ClogP cannot account for stereochemistry. However this does not affect the results.
- The ACD/logP output includes many experimentally determined values along with complete citations, whereas both ClogP and KowWin include only one literature value for each compound.
- At present both ACD/logP and ClogP can be integrated with programs for other important molecular properties including water solubility. They both give the pH dependent distribution coefficient. The ACD suite program is the only one that can calculate pKa values. The KowWin suite has programs which can determine melting point, boiling point and vapor pressure.
- Interestingly ACD/logP costs nearly $400.00 more for industry and $500.00 less for academia than ClogP. On the other hand KowWin is available at no cost.

As it has been demonstrated using an independent data set, ClogP is a more accurate predictor of the octanol/water partition coefficient than ACD/logPdb and KowWin. All the three programs are similar in many respects and they all have user friendly interfaces. It is the prerogative of the individual as to which program they prefer to use.

CHAPTER 3

DEVIATION FROM LINEARITY

3.1 Introduction

Organic cosolvents especially ethanol are among the most powerful solubilizing agents. The prediction of solubility profiles in ethanol/water mixtures is of paramount interest and it facilitates understanding all cosolvent systems.

The cosolvent solubility profile of semi-polar compounds appear to have a maximum solubility when the polarity of the mixture is equal to that of the solute. Several parabolic models have been used to address this phenomenon most of which are based on regular solution theory. Regular solution theory is not applicable to aqueous based systems. Also the log-linear model was designed for determining the solubility for strongly non-polar compounds.

Parabolic models of cosolvent solubilization of the form in equation (3.1) have been used for predicting solubility in binary mixtures.

$$\log S_{mix} = \log S_w + af_c + bf_c^2 \qquad (3.1)$$

Where, S_{mix} and S_w are the total solubilities in the cosolvent mixture and water, respectively, *a* and *b* are constants and f_c is the volume fraction of cosolvent in the mixture.

Paruta et al.(1994) correlated solubility with a parabolic function of the dielectric constant of the solvent mixture. Martin et al. (1979, 1981) also proposed a parabolic relationship between solute solubility and the solubility parameter of a solvent mixture. Ruckenstein et al.(2003) applied fluctuation theory to generate a new parabolic model to predict solubility in aqueous mixed solvents.

Yalkowsky and Roseman (1981) proposed a log-linear model in the form of equation (3.2), which describes the exponential increase in aqueous solubility for non-polar organic compounds as the cosolvent concentration is increased.

$$\log S_{mix} = \log S_w + \sigma f_c \qquad (3.2)$$

The term σ defines the cosolvent solubilization power for a particular cosolvent-solute system whose value can be obtained experimentally from the slope of a plot of *log* S_{mix} vs f_c. Li et al. (1994) showed that for a given solvent there is a linear relationship between σ and the partition coefficient (log K_{ow}) of the solute. They also observed that in semi-polar solutes the solubilization curves are linear up to f_c = 0.5, after which they sometimes become parabolic. This parabolic behavior is dependent on how close the polarity of the solute is to that of the mixture. They also showed that the use of end to half slope ($\sigma_{0.5}$) instead of the end to end slope (σ) is more appropriate for such compounds, therefore the initial solubility by ethanol is described by;

$$\log S_{mix} = \log S_w + \sigma_{0.5} f_c \qquad (3.3)$$

In this chapter we will show that the following model is consistent with both the parabolic and the log-linear models and is also a better predictor of solubility in ethanol/water mixtures than previously published models.

$$\log S_{mix} = \frac{\log S_w + a f_c}{1 + b f_c + c f_c^{\,2}} \qquad (3.4)$$

Where *a, b* and c are constants. When the fraction of co-solvent (f_c) is small, equation (3.4) can be approximated to the log linear model described by equation (3.3). Note that the *a* term in equation 4 is the initial slope and is synonymous with $\sigma_{0.5}$ in equation 3.3. The empirical terms *b* and *c* characterize the change in solute/solvent interactions produced by increasing cosolvent concentration. The *b* term tends to affect the maximum solute solubility while *c* affects the terminal slope as f_c approaches unity.

This proposed model is compared to a general third order polynomial of the form:

$$\log S_{mix} = \log S_w + a' f_c + b' f_c^{\,2} + c' f_c^{\,3} \qquad (3.5)$$

Where a', b' and c' are constants.

3.2 Method

3.2.1 Acquisition of Data

The 51 compounds were arbitrarily selected and the published solubility data of Li et al. (1994) and Millard et al. (2003).

3.2.1 Statistical Analysis

Non-linear regression was performed on the logarithmic solubility data using WinCurve Fit Version 1.1.8, 2002, Kevin Rainer Software (Victoria, Australia). The root mean square errors (RMSE) were determined using the following relationship

$$RMSE = \sqrt{\frac{\sum (observed - predicted)^2}{n_{points}}} \qquad (3.6)$$

Where n_{points} is the number of experimental points in each data set. The average absolute error (AAE) was also determined using the relationship in equation 3.7.

$$AAE = \frac{\sum |observed - predicted|}{n_{points}} \qquad (3.7)$$

T-tests were performed using Microsoft Excel 1997 (Los Angeles, CA). The P-value was determined using a paired t-test with a two tailed distribution. The significance level was set at 0.05 hence, if the P-value is <0.05 then the two data

sets are considered to be significantly different. The partition coefficients were determined using ClogP® (BioByte Corp. 1999), and references herein.

3.3 Results and Discussion

Non-linear regression was applied to the data for fifty-one compounds with four hundred and sixty data points, using the models described by equation 3.4 and 3.5 and the absolute average errors (AAE) and the root mean square errors (RMSE) calculated for each of the models. From the individual AAE and RMSE for the proposed model (equation 3.4) and the third order polynomial (equation 3.5) that are listed in APPENDIX B, the average errors and the percent difference in the errors were determined and are shown in Table 3.1.

Table 3.1: Average of the Errors (AAE and RMSE) from compounds listed in APPENDIX B and the percent difference between the two models [equation (3.4) & equation (3.5)]

	AAE	**RMSE**
Equation (3.4)	0.029	0.035
Equation (3.5)	0.044	0.049
% Difference in error	34.2	28.9

The percent difference in the AAE (34.2%) and the RMSE (28.9%) was large enough (>20%) to postulate that the two data sets are significantly different. A paired *t*-test gives P-values of 0.00002 and 0.00036 respectively, confirming the hypothesis. It can, therefore, be concluded that the suggested model is a more accurate predictor of the ethanol/water solubility profile than a third order polynomial.

The model was also used to predict the fraction of ethanol that gives maximum solubility (f_{max}) and are tabulated in APPENIDX C. The average absolute difference in the predicted and experimental value of f_{max} for all the compounds is only 0.0376. A P-value of 0.4095 implies that the predicted f_{max} values are not significantly different from the experimental values. It should be noted that the fraction of ethanol producing maximum solubility tends to increase with increasing solute ClogP.

In Figures 3.1 and 3.2, the experimental ethanol/water solubility profile for oxolinic acid (Jouyban et al. 2002), was compared to predicted solubilities using the 3rd order polynomial and the suggested model. It was further compared to previously published data for the same solute performed by Ruckenstein et al. (2003), who used the following equation based on fluctuation theory.

$$\ln X_2^t = \frac{\left(\ln V - \ln V_3\right)\ln X_2^{b1} + \left(\ln V_1 - \ln V\right)\ln X_2^{b3}}{\ln V_1 - \ln V_3} \qquad 3.8$$

Where, V, V_3, V_1, are the molar volumes of the solute, water and cosolvent respectively.

The terms X_2^{b3} and X_2^{b1} are the solute solubility in pure water and cosolvent.

The solute molar volume is determined by;

$$V = X_1 V_1 + X_3 V_3 + eX_1 X_3 \qquad 3.9$$

and is not necessarily equal to the experimental molar volume of the solute.

Where e is an empirical parameter and X_3 and X_1 are the molar volumes of cosolvent and water.

Note that although equation 3.8 contains one less coefficient than equation 3.4, it requires an additional fitted value, i.e. the solubility in pure cosolvent.

It is apparent form Figure (3.1&3.2) and the average errors, in Table 3.2, that the suggested model is statistically a better predictor of the ethanol/water solubility profile and the f_{max} for oxolinic acid than the other models. The proposed model accounts for the initial log-linear relationship as well as the parabolic behavior of the solubility profile observed at higher fractions of ethanol. Furthermore this model has been proven to be statistically a better predictor of the ethanol solubility profile as well as the fraction of ethanol which gives the maximum solute solubility (f_{max}).

Figure 3.1: Comparison between experimental and the predicted solubilities (mg/ml) [(---) Ruckenstein, (▬) proposed model and (–) third order polynomial] of oxolinic acid plotted against mole fraction of ethanol.

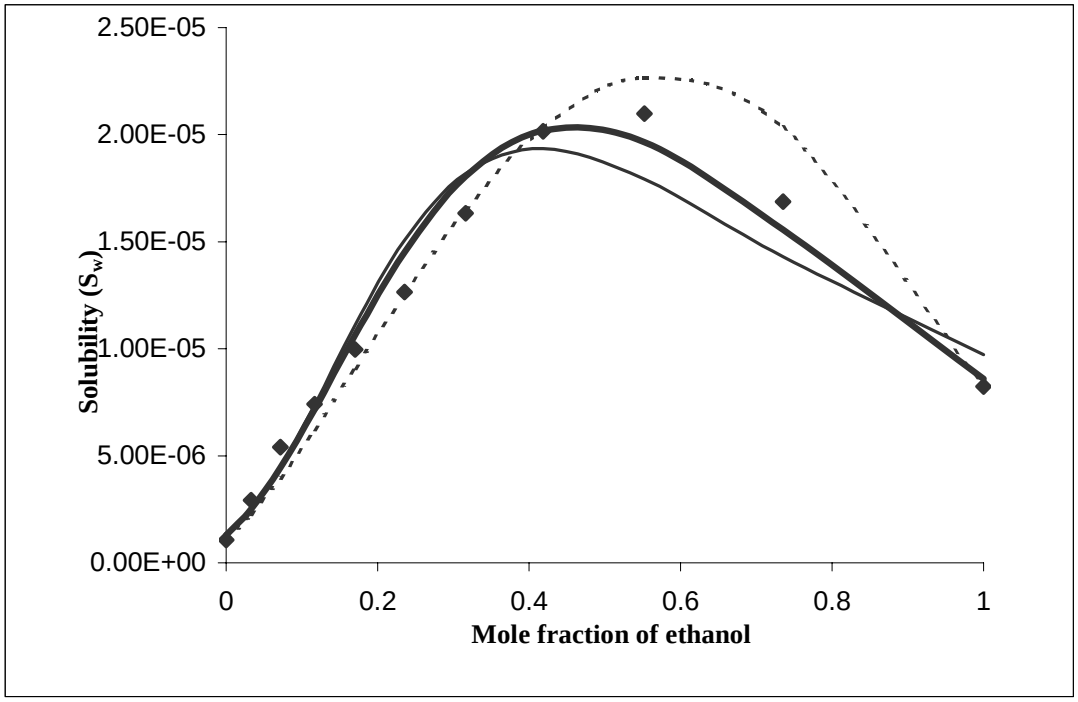


Figure 3.2 Comparison between experimental and the predicted solubilities(mg/ml) [(---) Ruckenstein, (▬) proposed model and (–) third order polynomial] of oxolinic acid plotted against volume fraction of ethanol.

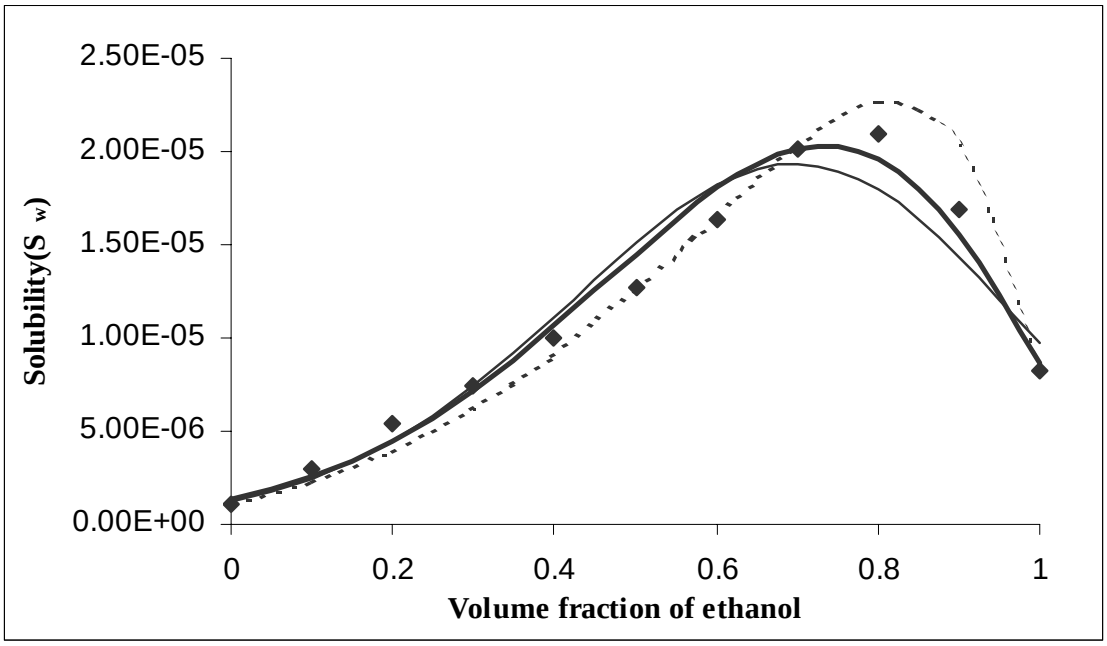


Table 3.2 AAE and RMSE calculated from the different models [equation (3.5), Ruckenstein & equation (3.4)] using oxolinic acid as the model compound

	AAE (log S)	**RMSE (log S)**
Ruckenstein's Model	0.044	0.064
Equation (3.4)	0.041	0.049
Equation (3.5)	0.057	0.063

CHAPTER 4

ESTIMATION OF THE ETHANOL/WATER SOLUBILITY PROFILE FROM THE OCTANOL/WATER PARTITION COEFFICIENT

4.1 Introduction:

Various theories and models of cosolvency including linear and parabolic models have been proposed to predict drug solubility profiles. Paruta et al. (1964) estimated solubility using a parabolic function of the dielectric constant of the solvent mixture, and Martin et al.(1979, 1981) proposed a parabolic relationship between solute solubility and the solubility parameter of a solvent mixture. Recently, Ruckenstein et al. (2003) applied fluctuation theory to generate a new parabolic model to predict solubility in aqueous mixed solvents.

Yalkowsky and Roseman (1981) and Rubino and Yalkowsky (1984) first demonstrated a log-linear relationship between the solubility of a non-polar solute and the fraction of cosolvent. This relation is described in equation 4.1.

$$\log S_{mix} = \log S_w + \sigma f_c \qquad (4.1)$$

Where S_{mix} and S_w are the solubilities in the cosolvent mixture and water, respectively, and f_c is the volume fraction of cosolvent. The term σ defines the cosolvent solubilization power for a particular cosolvent-solute system.

While the ethanol/water solubility profiles of very polar and very non-polar drugs are monotonic, many semi-polar drugs show a maximum solubility at an ethanol volume fraction (f_{max}) between zero and one. The polarity of semi-polar compounds lie between those of water and cosolvent. Li and Yalkowsky (1994) observed that in semi-polar solutes the solubilization curves are linear up to, f_c = 0.5, after which they sometimes become concave up. This non-linear behavior is dependent on how close the polarity of the solute is to that of the mixture. They showed that the use of end to half slope ($\sigma_{0.5}$) instead of the end to end slope (σ) is more appropriate for such compounds. The value of $\sigma_{0.5}$ is determined from experimental data using the relationship in equation 4.2.

$$\sigma_{0.5} = (\log S_{0.5} - \log S_w)/0.5 \qquad (4.2)$$

Where $S_{0.5}$ is the solubility at f_c = 0.5.

Thus:

$$\log S_{0.5} = \log S_w + \sigma_{0.5} f_c \qquad (4.3)$$

The addition of cosolvent lowers the polarity of the aqueous system, which in turn increases the solubility of non-polar solutes while reducing that of polar ones. Li and Yalkowsky (1994) showed that for ethanol, $\sigma_{0.5}$ is linearly related to the solute octanol/water partition coefficient (log K_{ow}) as described in equation 4.4.

$$\sigma_{0.5} = 1.274 + 0.791(\log K_{ow}) \quad (4.4)$$

More recently Machatha et al. (2004) showed that the apparent discrepancy between the parabolic and log-linear models can be resolved by using an equation of the form,

$$\log S_{mix} = \frac{\log S_w + af_c}{1 + bf_c + cf_c^2} \quad (4.5)$$

Where a, b and c are empirical parameters. This equation was found to fit the experimental data for 51 compounds better than a polynomial containing the same number of coefficients.

The relationship between the partition coefficient of the solute and the ethanol composition that produces maximum solubility was investigated. This combined with equation 3 will enable the crude estimation of the total solubility profile of a drug from its octanol/water partition coefficient.

4.2 Method

4.2.1 Acquisition of Data

Fifty-one compounds were arbitrarily selected from the published solubility data of Li and Yalkowsky (1994) and Millard et al.(2003).

4.2.2 Statistical Analysis

Non-linear regression was performed using WinCurve Fit Version 1.1.8, 2002, Kevin Rainer Software (Victoria, Australia).

The average absolute error (AAE) was determined using the relationship below.

$$AAE = \frac{\sum |observed - predicted|}{n} \qquad (4.6)$$

Where *n* is the number of compounds studied. T-tests were performed using Microsoft Excel 1997 (Los Angeles, CA). The P-value was determined using a paired t-test with a two tailed distribution. The partition coefficients were determined using ClogP® (BioByte Corp. 1999).

4.3. Results and Discussion

As expected, a linear relationship was found between log K_{ow} and $\sigma_{0.5}$ for the 51 compounds studied as shown in Figure 4.1. Most of the experimental $\sigma_{0.5}$ values were taken from Li et al.(1994) The data are described by equation 4.7 which is in agreement with equation 4.4.

$$\sigma_{0.5} = 1.143 + 0.939 \log K_{ow} \qquad (4.7)$$

(R^2 =0.905, SE=0.698)

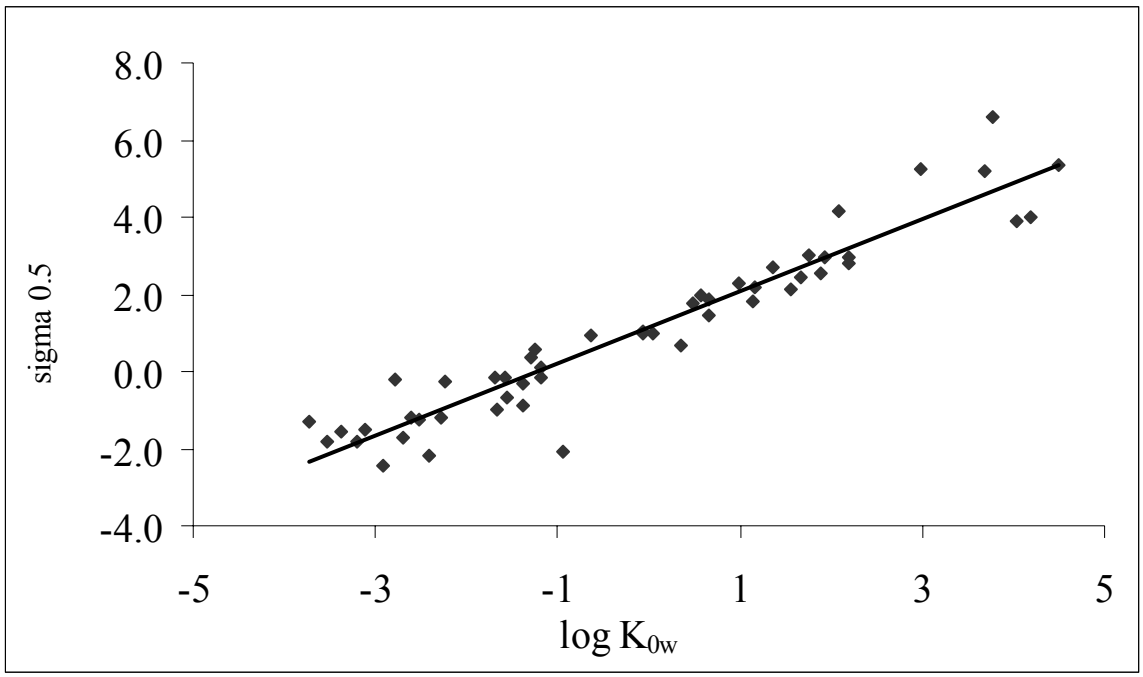
The slight difference between equation 4.7 and equation 4.4 is due to the fact that a different version of ClogP was used to determine the log K_{ow} values. The predicted $\sigma_{0.5}$ were compared to the experimental values and the absolute errors are listed in APPENDIX D. It is clear that the $\sigma_{0.5}$ values for this set of compounds are reasonably predicted from the logarithm of the partition coefficient. Combining equations 4.3 and 4.7 gives;

$$\log \frac{S_{mix}}{S_w} = (1.143 + 0.939 \log K_{ow}) f_c \qquad (4.8)$$

This equation enables the prediction of the dependence of solute solubility upon ethanol fractional concentration for any drug.

Of the 51 compounds studied 22 demonstrate distinct solubility maxima as the cosolvent composition increases, while 21 decrease monotonically and 8 increase monotonically. The latter have maxima at f_c = 0 and f_c =1 respectively.

Figure 4.1: Plot of Log K_{ow} v/s $\sigma_{0.5}$ with linear regression



From figure 4.2 it is apparent that there is a sigmoidal relationship between the experimental f_{max} and log K_{ow}. The localities of the maxima are reasonably determined by:

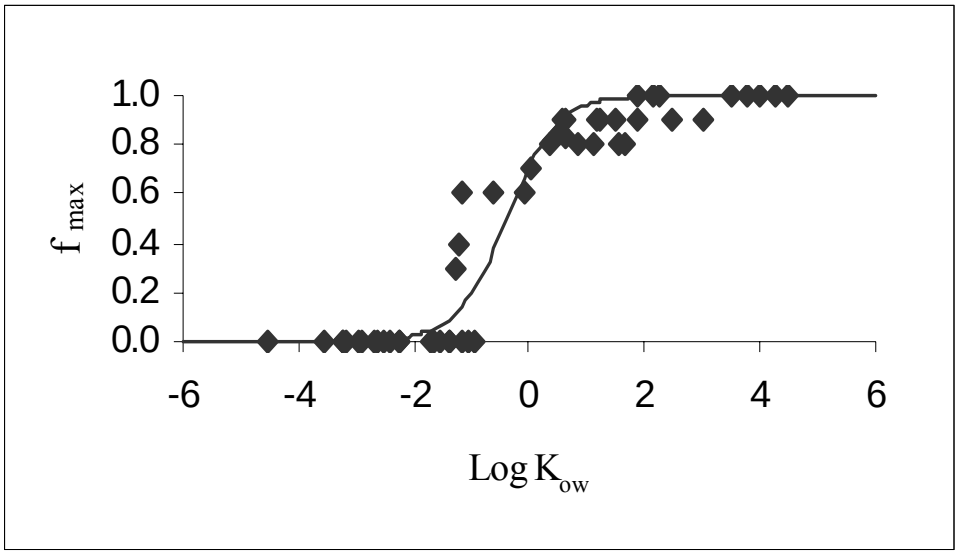
$$f_{\max} = \frac{1}{1+\left(\frac{K_{ow}^{\cos olvent} - 0.08}{K_{ow}^{solute}}\right)} \qquad (4.9)$$

($R^2 = 0.927$, SSE = 0.680)

The constant (0.08) represents the change in polarity of the binary mixture as the concentration of ethanol increases.

The absolute errors between the predicted f_{max} values from the experimental values for each compound were determined. These values are provided in APPENDIX E. The average absolute error (AAE) for all the compounds is only 0.00137 implying that the f_{max} values are reasonably predicted from just the partition coefficient.

Figure 4.2. Plot of Log K_{ow} v/s f_{max} where (♦) experimental f_{max} and (−) is the regression line using equation (4.8)

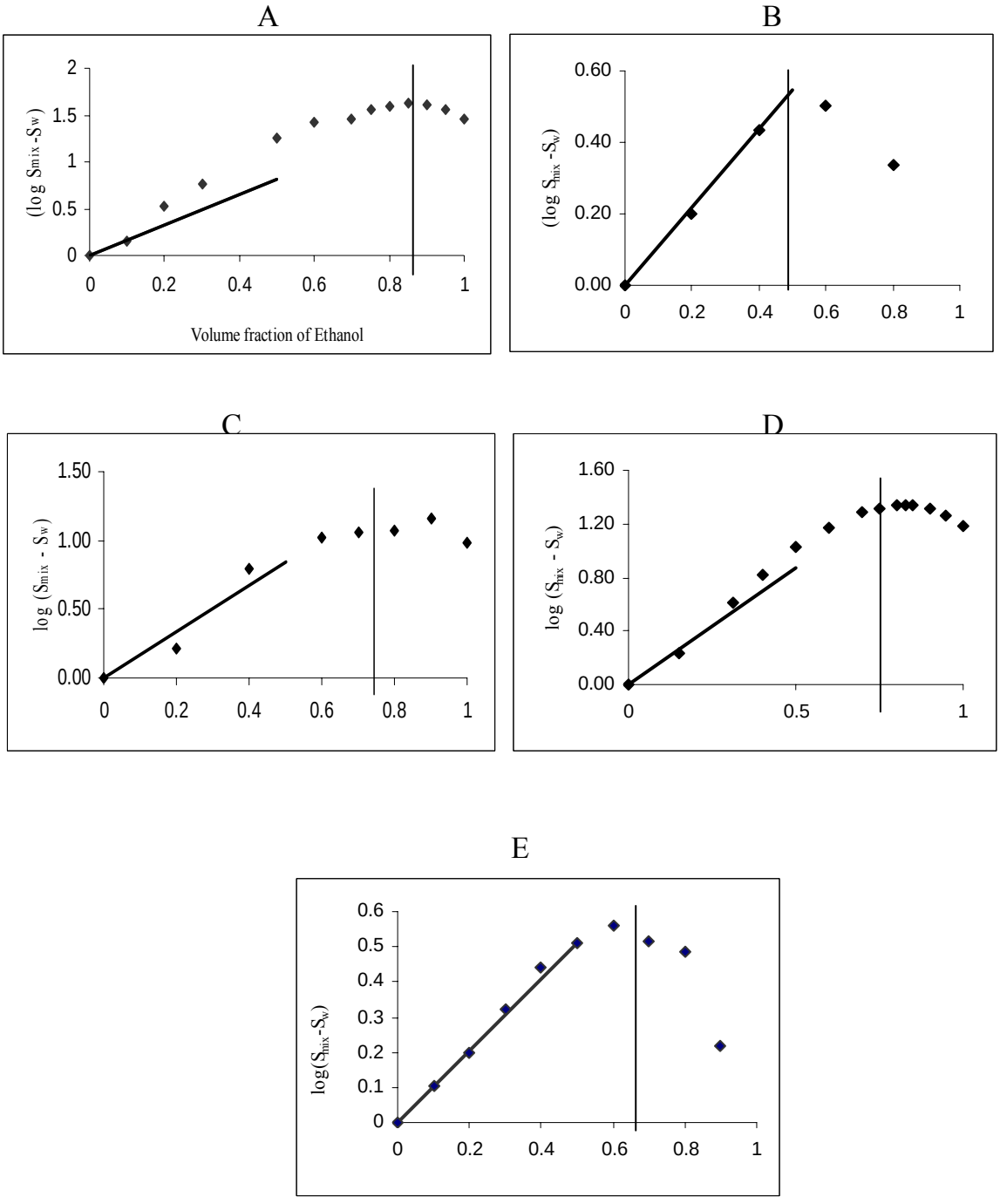


Since the initial slope ($\sigma_{0.5}$) and the fraction of ethanol that gives maximum solubility (f_{max}) can both be estimated from the K_{ow} of the solute it is possible to crudely predict the ethanol/water solubility profile of different compounds. The observed and predicted ethanol/water solubility profile for four model compounds (benzaimide, paracetamol, caffeine and formyl-leucine) are given in Figure 4.3.

The initial portion of the change in the solubility curve was determined using equation 4.8, where f_c is between 0 and 0.5, and the fraction of ethanol giving maximum solubility can be determined using equation 4.9.

The proposed sigmoidal and linear function of the octanol water coefficient (K_{ow}) reasonably predicts the fraction of ethanol that yields maximum solute solubility (f_{max}) and the intial slope ($\sigma_{0.5}$). From combining these two models provides a means of estimating the solubilization curve of a solute in an ethanol/water system from nothing more than just the octanol/water partition coefficient (K_{ow}).

Figure 4.3 Comparison between predicted and experimental ethanol/water solubility profiles for A: paracetamol, B: caffeine C: formyl-leucine, D: benzamide, E: Theophylline.



CHAPTER 5

BILINEAR MODEL

5.1 Introduction

Several parabolic models including those of Paruta et al.(1964), Martin et al.(1979, 1981) and Ruckenstein et al.(2003) have been used to predict the cosolvent/water solubility profiles. These models have the general form shown in equation 5.1.

$$log\, S_{mix} = a + bf + cf^2 \qquad (5.1)$$

Where a, b and c are constants that could represent different physicochemical properties of the solute and the cosolvent. *f* is the cosolvent composition.

Paruta et al. (1964) utilized the dielectric constant of the solution to generate a parabolic relationship. Martin et al. (1979, 1981) and Ruckentsein et al. (2003) derived their relationships from the solubility parameter of the solution components and fluctuation theory, respectively. These three relationships are derived from principles propagated by the regular solution theory; where the energy required to dissolve a solute in a mixed solvent is a function of the interactions between the solute and the mixed solvent. As was shown by Hildebrand (1929) and Scatchard (1933) and later reiterated by Yalkowsky

(1999), regular solution theory is not applicable to solutions where hydrogen bonding or ionic interactions are dominant.

It is interesting to note that a parabola described by equation 5.1 is symmetrical and asymptotes two vertical lines. There are other models that have been used in the prediction of cosolvent/water solubility profiles many of which have come from Jouyban and coworkers (2004). The most recent model incorporates the use of an artificial neural network.

Yalkowsky and Roseman(1981) observed that the logarithm of the solubility of a non-polar solute increases linearly with cosolvent composition. This log-linear relationship is described by;

$$log\, S_{mix} = log\, S_w + \sigma f \qquad (5.2)$$

Where S_w and S_{mix} are the solubility of the solute in water and the mixed solvent, respectively, f is the volume fraction of cosolvent and σ is a constant which describes the solubilizing power of the cosolvent for the solute. They also observed that the value of σ is positive for very nonpolar solutes and negative for very polar solutes.

Li et al.(1994) observed that the solubilization curves for semi-polar solutes are usually linear up to $f_c = 0.5$, after which they sometimes curve downwards.

This curvature is dependent on how close the polarity of the solute is to that of the mixture. They also showed that the use of end to half slope ($\sigma_{0.5}$) instead of the end to end slope (σ) is more appropriate for such compounds. Therefore the initial solubility by a cosolvent is described by;

$$log\, S_{mix} = log\, S_w + \sigma_{0.5} f_c \qquad (5.3)$$

Machatha and Yalkowsky (2004) noted that the solubility profile of semi-polar solutes appears to be somewhat parabolic in nature, but not fully, since the initial slope and the terminal slopes of the profile are not the same and are certainly not vertical. In order to resolve the apparent discrepancies between the log-linear model and the parabolic model and to explain the negative deviation from the log-linear model that is observed at high values of the volume fraction (*f*) of cosolvent, a bilinear model with a curved transition region was proposed. The bilinear model has an initial (normally ascending) asymptote with a slope of σ_A and a final descending asymptote with a slope of σ_B. (It is generally not symmetrical). The transition from the initial asymptote to the final asymptote is obtained by multiplying the initial asymptotic slope by the function [1-Q], and the final asymptotic slope by [Q] where:

$$log \frac{S_{mix}}{S_w} = \sigma_A f[1-Q] + \sigma_B f[Q] \qquad (5.4)$$

Where Q is defined by:

$$Q = \frac{1}{1+10^{-\alpha(f-1)}} \tag{5.5}$$

Note α is a constant which determines the maximum value of the function and the sharpness of the curvature. Also the value of Q is equal to zero at low volume fraction cosolvent and unity at high volume fraction cosolvent. Therefore the solubility in a mixed solvent can be rewritten as:

$$log\frac{S_{mix}}{S_w} = \sigma_A f\left(1-\frac{1}{1+10^{-\alpha(f-1)}}\right)+\frac{\sigma_B f}{1+10^{-\alpha(f-1)}} \tag{5.6}$$

This equation's accuracy in predicting the ethanol/water solubility profile was compared to the log-linear relationship and also a general parabolic model. It will be shown that the model described by equation 5.6 can describe the log-linear increase in solubility observed for highly non-polar solutes and the log-linear decrease in solubility observed for highly polar solutes, as well as the "parabolic" solubility profiles observed for semi-polar solutes. The regression based parameters σ_A and σ_B will be related to physicochemical properties of the solute.

5.2 Method

5.2.1 Acquisition of Data

The 52 solubility profiles were from the published solubility data of Machatha and Yalkowsky (2004).

5.2.2 Statistical Analysis

Non-linear regression was performed on the logarithmic solubility data using GraphPad Prism version 4.00 for Windows, GraphPad Software, San Diego California USA.

The root mean square errors (RMSE) were determined using the following relationship $RMSE = \sqrt{\frac{\sum (observed - predicted)^2}{n_{points}}}$ (5.7)

Where n_{points} is the number of experimental points in each data set.

T-tests were performed using Microsoft Excel 1997 (Los Angeles, CA). The P-value was determined using a paired t-test with a two tailed distribution. The significance level was set at 0.05 hence, if the P-value is <0.05, then the two data sets are considered to be significantly different.

5.3 Results and Discussion

It was empirically determined that α can be approximated to 3.6. Therefore equation 5.6 can be rewritten as:

$$log\frac{S_{mix}}{S_w} = \sigma_A f + \frac{(\sigma_B - \sigma_A)f}{1+10^{-3.6(f-1)}} \tag{5.8}$$

Note the constant 3.6 is only valid for ethanol/water mixtures.

The RMSE errors were calculated for all 52 compounds using the parabolic model, bilinear model and the log-linear model which are described by equations 5.1, 5.2 and 5.8 respectively. These errors are listed in APPENDIX F.

The average RMSE errors from the parabolic, bilinear and the log-linear models are 0.118, 0.067 and 0.417, respectively. Note that the average error for the parabolic model is twice that of the lowest; the bilinear model. A t-test was performed and all three errors are significantly different at a 95% confidence level.

The validity of the modified bilinear model described in equation 5.8 to predict the ethanol/water solubility profile for compounds with different shapes in their solubility profiles was tested on five different compounds, anthracene, barbital, caffeine and hydantoic acid. As seen in Figure 5.1 the model can indeed predict the profiles of different compounds.

Figure 5.1 Water/ethanol solubility profile estimation of anthracene, barbital, caffeine and hydantoic acid using equation 5.8 with optimized σ_A and σ_B values. Where (□) experimental values and the solid lines are the theoretical curves

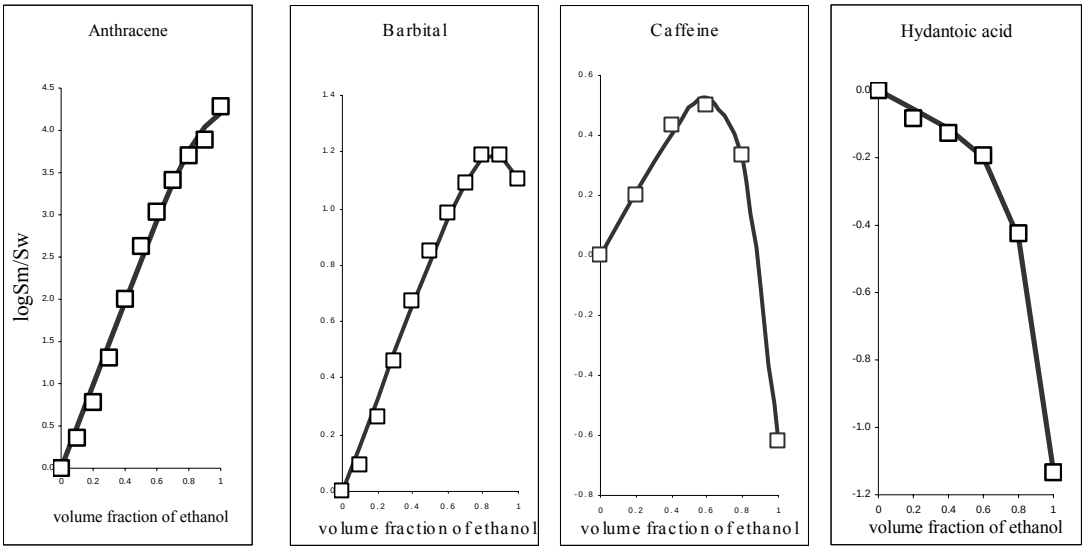
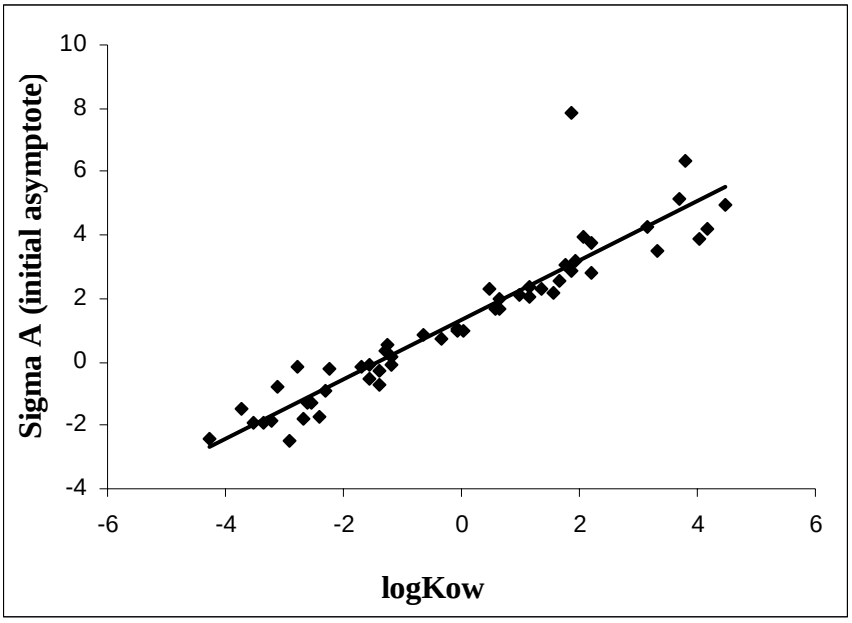
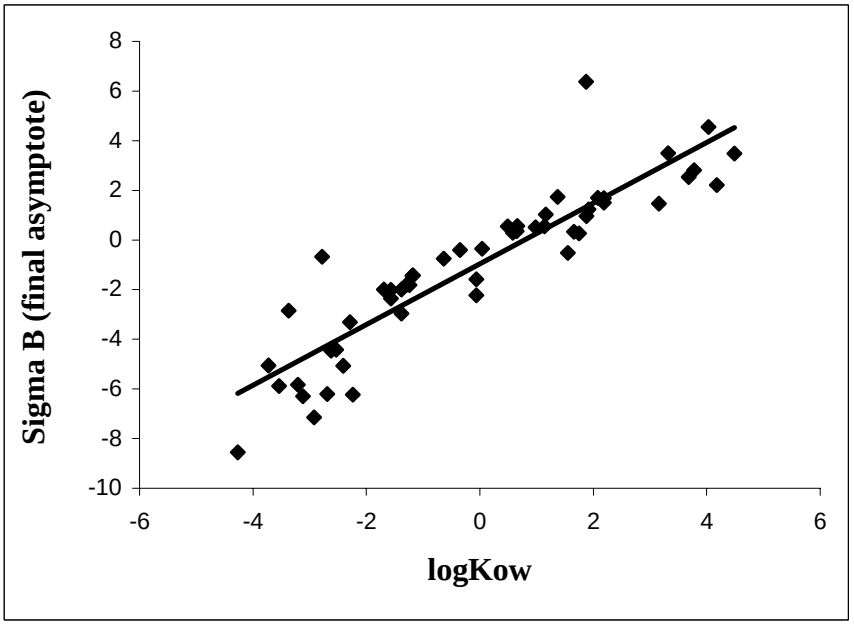


Figure 5.2 Plot of the predicted initial (σ_A) and terminal (σ_A) asymptotes from equation (5.8) against $\log K_{ow}$.





The values of the σ_A and σ_B described in equation 5.8 were determined by non-linear regression on the data for the fifty-two compounds. As shown in Figure 5.2, there is a linear relationship between the initial and terminal slopes and the $logK_{ow}$.

The linear relationships of both σ_A and σ_B to $logK_{ow}$ are described by the following equations:

$$\sigma_A = 1.32 + 0.933\, log\, K_{ow} \qquad (5.9)$$

($R^2 = 0.87$)

and,

$$\sigma_B = -0.960 + 1.22\, log\, K_{ow} \qquad (5.10)$$

($R^2 = 0.81$)

Incorporating these relationships into equation 5.8 gives:

$$log\frac{S_{mix}}{S_w} = (1.32 + 0.933\, log\, K_{ow})f + \left[\frac{(-2.28 + 0.287\, log\, K_{ow})f}{\left(1 + 10^{-3.6(f-1)}\right)}\right] \qquad (5.11)$$

The bilinear model is only dependent on the $logK_{ow}$ of the solute and the constant 3.6 which is specific for just ethanol/water mixtures.

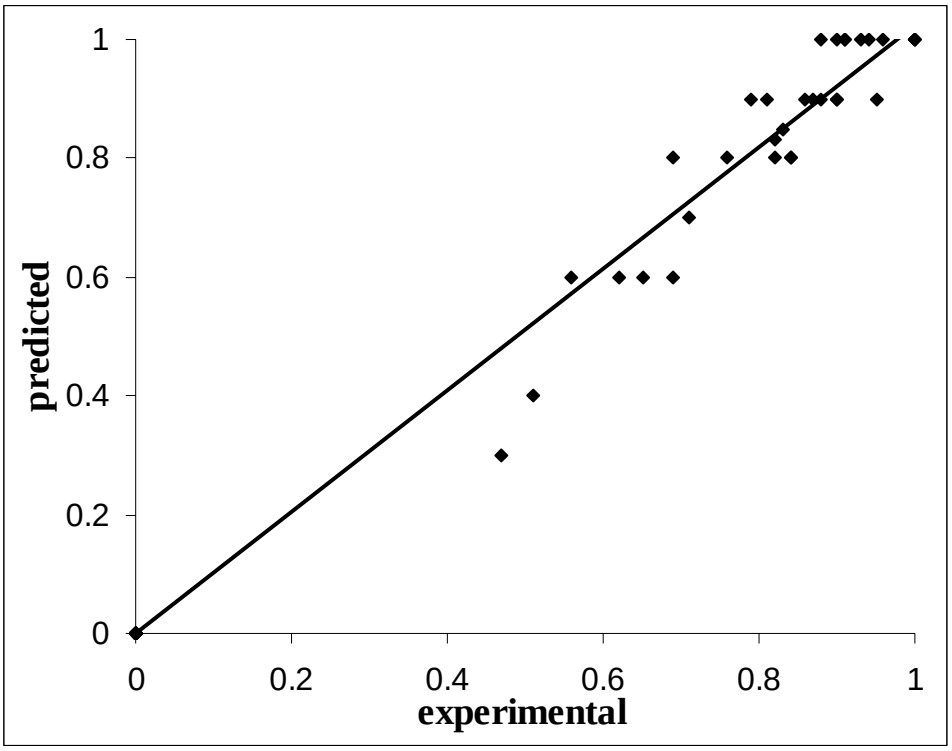
The initial asymptote (σ_A) correlates well with the experimental initial slope ($\sigma_{0.5}$) with an $R^2 = 0.98$.

The value of the volume fraction of ethanol that gives maximum solubility (f_{max}) can also be calculated. By equating the derivative of the proposed bilinear model

to zero we can solve for f_{max}. The predicted values of f_{max} using the bilinear model are compared to the experimental values listed in APPENDIX G and plotted in figure 5.3.

A t-test showed that the predicted values were not significantly different from the experimental f_{max} values.

Figure 5.3. Plot of the predicted vs experimental f_{max} values listed in APPENDIX G.



It is abundantly clear from the RMSE errors that the proposed bilinear model is a better predictor of the ethanol/water solubility profile than the log-linear model and a general parabolic model. This bilinear model has been shown to be versatile and can fit solubility profiles of different shapes and is not restricted to a parabolic curve. This model is simple and is dependent on only two parameters the slopes of initial asymptote (σ_A) and the final asymptote (σ_B) which have been further related to the logarithm of the octanol/water partition coefficient. The bilinear model is now just a function of the octanol/water partition coefficient of the solute and a single empirical constant which is cosolvent specific.

CHAPTER 6

CASE STUDY

SOLUBILITY STUDY SOLUBILIZATION AND PREFORMULATION STUDY OF ANTALARMIN: A NOVEL STRESS INHIBITOR

6.1. Introduction

The aqueous solubility of a pharmaceutically active compound is an important property that governs its oral bioavailability. Hence, it is necessary to evaluate drug solubility during preformulation and formulation studies. If the drug is poorly soluble various solubilization strategies like pH, cosolvency etc. can be used; either alone or in combination. The physicochemical factors that control the solubility of any compound are its crystallinity and its polarity (or its non-polarity). Thus, the approaches to increase the solubility center on reducing the crystallinity of the compound or modification of the media in which the compound is to be dissolved. The former can be accomplished by either micronization, spray drying or freeze drying among other methods. The modification of the properties of the dissolution media can be achieved by either adjusting the pH and/or the use of solubilizing agents like cosolvents, surfactants or complexating agents.

It has been demonstrated (Ran et al. 2005, Jain et al. 2001), both mathematically and practically, that a combination of pH control with any one of the other three

techniques is an especially effective way of increasing solubility. Using the combination approach reduces the quantities of excipients required thereby minimizing their undesired effects.

Recently, lipid-based drug delivery systems have been proposed as alternative approaches to increasing the bioavailability of poorly water-soluble drugs (Huberstone and Charman 1997). These systems are particularly useful for strongly non-polar drugs since they often have high solubility in oils, fats and long chain hydrocarbons (collectively referred to as lipids). The principle behind this approach is the use of a lipid to solubilize the drug, which is then dispersed/emulsified using a suitable amphiphilic agent. The emulsifiers are either biological, secreted in the gut or are surfactants that are added as part of the formulation. Self microemulsifying drug delivery system (SMEDDS), consist of a drug dissolved in an appropriate lipid with an emulsifying agent like a surfactant. The most important feature of these pre-concentrated mixtures is their ability to form isotropic nanoparticulate oil-in-water emulsions upon gentle agitation in aqueous media (Constantinides 1995). In addition to improving passive absorption, the presence of lipids can induce intestinal lymphatic uptake (Porter and Charman 2001).

This study will focus on various solubilization strategies for Antalarmin, an active corticotropin-releasing hormone-1 antagonist. This hormone is

associated with mental disorders such as anxiety, depression and substance abuse. Antalarmin has a melting point of 81-82ºC and molecular weight of 378.56. It has a calculated octanol/water partition coefficient (ClogP) value of 8.16 which is responsible for its poor intrinsic water solubility (<1μg/ml). Antalarmin is weakly basic with an aliphatic tertiary amine group as shown in figure 6.1. The compound has an estimated pKa of about 5.

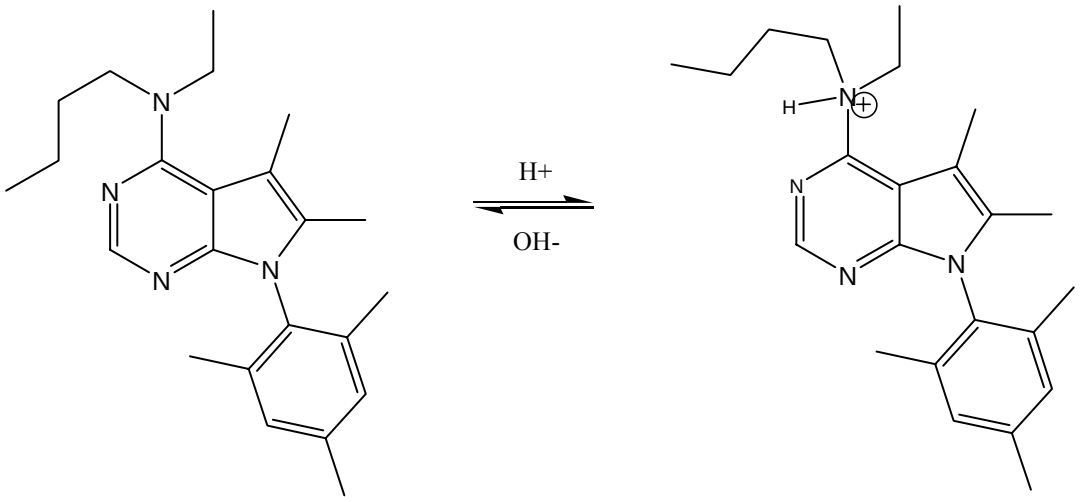


Figure 6.1 Structure of Antalarmin (unionized and ionized form)

At low pH the drug exists in its ionized form and will have a higher solubility. In this study the use of low pH either alone and in combination with; cosolvents (ethanol (EtOH), propylene glycol (PG) and polyethylene glycol 400 (PEG 400)), surfactants (cremaphor EL (Cre-EL), polyoxyethylene sorbitan mono-oleate (Tween 80), sodium lauryl sulfate (SLS) and cetyltrimethylammonium bromide (CTAB)) and complexating agents (hydroxypropyl β-cyclodextrin (HP- β -CD), sulfobutyl ether β -cyclodextrin (SBE- β -CD) and nicotinamide; will be explored in an attempt to enhance solubility. It is believed that due to its high Clog P value, Antalarmin might have good solubility in lipids or highly non-polar vehicles. Hence, lipid based formulations will also be assessed.

6.2 Materials and Methods

6.2.1 Materials

Antalarmin was provided by the National Cancer Institute and used as received. HP- β -CD with an average molecular weight of 1380-1500 and an average degree of substitution of 0.6-0.9 was obtained from Wacker Biochem Corporation (Adrian, MI). SBE- β -CD with an average molecular weight of 2160 and an average degree of substitution of 6-7.1 was a gift from Cydex, L. C. (Overland Park, KS). Vitamin E TPGS and Gelucire 44/14 were received as

gifts from Eastman, U.K. and Gattefosse, France respectively. All other chemicals were of reagent grade, purchased from Sigma (St. Louis, MO) or Aldrich (Milwaukee, WI) and used without further purification.

6.2.2 Buffer Preparation

The pH-solubility studies were performed over a pH range of 1-10 using a citric acid - disodium phosphate buffer system (0.1 M). The pH was adjusted using 1 M hydrochloric acid and 1 M sodium hydroxide solutions. The ionic strength of the buffer was maintained at 0.2 M using sodium chloride.

6.2.3 High performance liquid chromatography (HPLC) analysis

An Agilent 1100 HPLC system with a G1315B PDA detector (Agilent Technologies) was used. A Waters RP18 column (150*3.9mm) was used with a mobile phase composed of 87:13 methanol/water mixture.The flow rate was 1.0 ml/min and the effluent was detected at 310nm at a reference wavelength of 360nm. The injection volume was 100 µl. The compound had a retention time of about 5.5 minutes. The linear concentration range for the method was 0.1-200 µg/ml. All experimental data are the average of duplicate values with an average error of less than 5%.

6.2.4 Solubility Determination

An excess amount of Antalarmin was added to 4-ml screw capped glass vials containing 1 ml of an aqueous solution at pH 1.00 ± 0.15, pH 2.00 ± 0.15 and pH 7.00 ± 0.15 of various concentrations of cosolvents, surfactants and complexing agents. The highest concentrations of the solubilizing agents used in the study were lower than or equal to the concentrations that have been used in FDA approved marketed formulations (Wade and Weller 1994). The samples were placed in an end-over-end rotator for 7-10 days under ambient room temperature (~25^{o}C). The pH of the vials was maintained through out the period using hydrochloric acid and sodium hydroxide. Samples were then filtered through 0.45-μm PTFE filters and solubility determined by HPLC analysis.

6.3. Results and Discussion

6.3.1 Solubilization using pH control

Figure 6.2 shows the effect of pH on the solubility of Antalarmin. The experimental data (diamonds) fits well with the theoretical line and agrees with the estimated pKa close to 5. It is clear that the solubility increases exponentially with decreasing the pH below its pK_a. The solubility at pH 7.0 is 0.0009 mg/ml while that at pH 2.0 it is only 1.018 mg/ml.

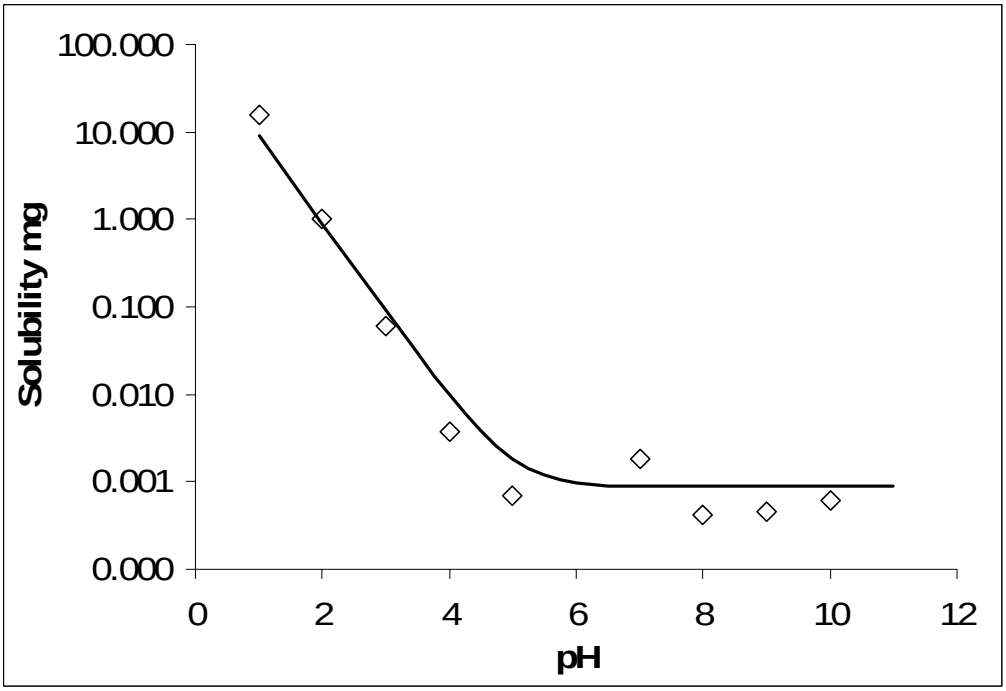


Figure 6.2: pH-solubility profile for Antalarmin

6.3.2 Solubilization using combination of pH and different solubilizing agents

Since there was a significant increase in solubility at pH 2, a preliminary study using cosolvents, surfactants and complexating agents at pH 2 and pH 7 was attempted.

6.3.2.1 Combination of pH Control and Cosolvents

Three commonly used cosolvents, EtOH, PG and PEG 400 were used in combination with buffers at pH 2 and 7. Table 6.1 presents the solubilization slopes (σ) obtained for different cosolvents at pH 2. The solubilities at pH 7 were below the detection limit and thus have not been reported.

As shown in Figure 6.3 the highest solubilization was observed with EtOH than the other two cosolvents. This can be explained on the basis of their relative polarities. Cosolvents increase the aqueous solubility of non-polar compounds by breaking the hydrogen bonding interactions of water. Thus, they make water less polar and reduce its “squeezing out” effect. Ethanol, being the least polar has a greater impact on the structure of water as compared to other cosolvents hence a higher solubility.

Table 6.1 Solubilization slopes for cosolvents

Cosolvent	pH 2 $\sigma_{ionized}$
EtOH	5.19
PG	2.74
PEG 400	2.36

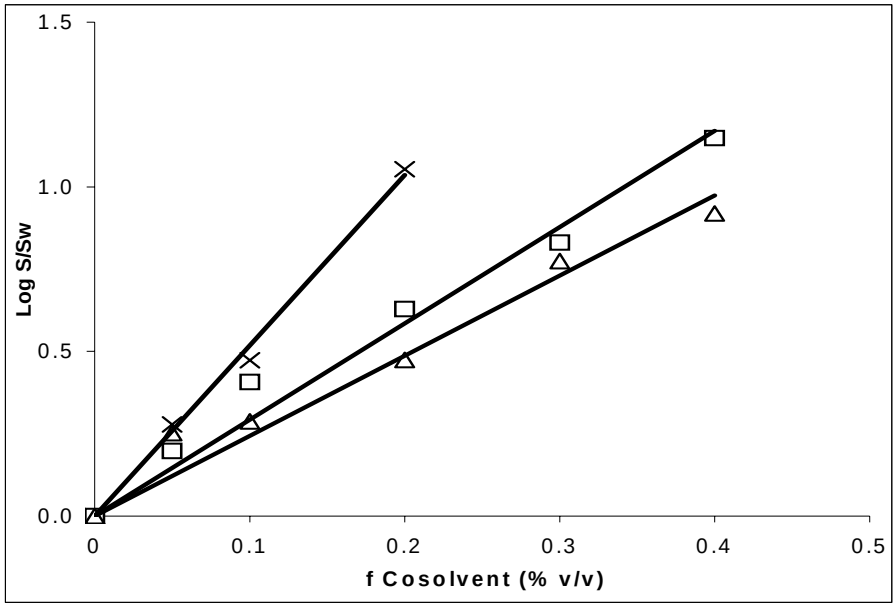
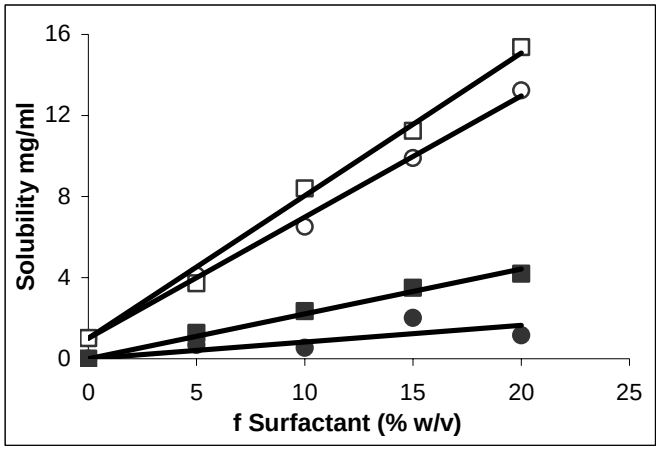


Figure 6.3 Solubilization using cosolvents at pH 2.0 (EtOH-X, PG-□ and PEG-Δ)

6.3.2.2 Combination of pH control and Surfactants

Two non-ionic (Tween 80 and Cre-EL), one anionic (SLS) and one cationic (CTAB) surfactants were used in combination with buffers at pH 2 and 7. Figure 6.4 shows that the solubility of Antalarmin increases in a linear fashion with increase in surfactant concentration. The overall increase in the solubility is higher at pH 2 due to the combined effect of low pH and the presence of surfactants. At pH 2, SLS is the most effective surfactant due to the electrostatic attraction between the positively charged drug and the negatively charged surfactant unlike CTAB which is least effective due to charge repulsion. Amongst the non-ionic surfactants Cre-EL has a greater effect than Tween-80.

A



B

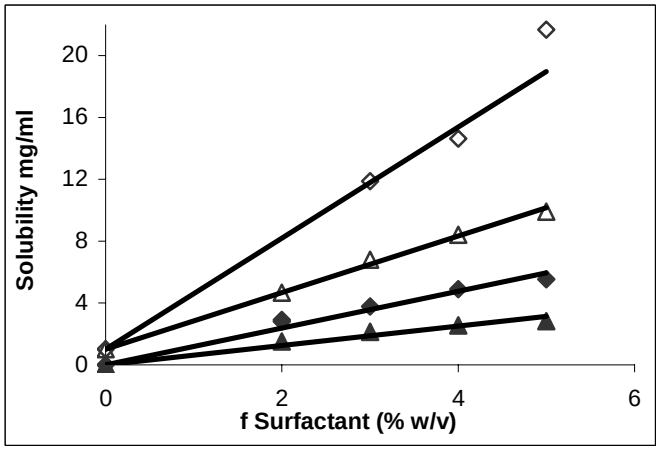


Figure 6.4 Solubilization using surfactants (Tween 80 pH 2-○, Tween 80 pH 7-●; Cre-El pH 2-□, Cre-EL pH 7- ■, SLS pH 2, SLS pH 7;CTAB pH 2- Δ, CTAB pH ▲ 7-

6.3.2.3 Combination of pH control and Complexants

The effect of complexant on the solubility of Antalarmin was determined using the two inclusion complexants (HP-β-CD and SBE-β-CD) and a stacking complexant (nicotinamide), at pH 2 and 7. Figure 6.5 shows a linear increase in the solubility with increasing concentrations of complexants indicating the formation of a 1:1 complex. The solubilities at pH 7 were negligible at low fractions of complexants and are not plotted.

SBE-β-CD displays higher solubilization efficiency due to a strong interaction between the cationic drug and the negatively charged complexant molecule. The stacking complex with nicotinamide is weak and hence a lower solubilzation slope is observed.

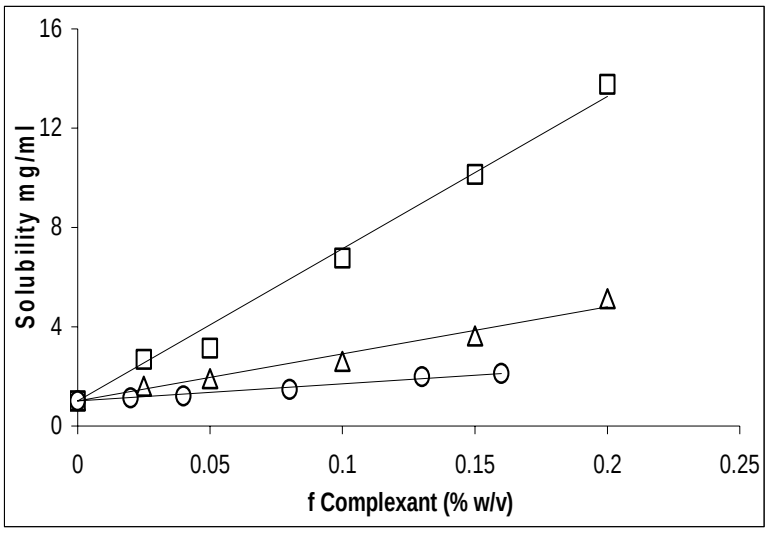


Figure 6.5 Solubilization using complexating agents at pH 2.0 (SBE-β-CD-□; HP-β-CD-Δ and nicotinamide-○)

6.3.3 Solublization using selected formulations at pH 1

While it is not practical to give oral preparations at very high pH, formulations at low pH are acceptable for oral administration. Emetrol (anti-nausea liquid) is available over the counter. It is a solution of phosphoric acid and sugars with a pH around 1.3. On the basis of the high solubility obtained at pH 2, the following formulations were tested at pH 1; 20% Cre-EL, 20% HP-β-CD, 20% SBE-β-CD and the 10% EtOH + 40% PG. The initial study was not performed at pH 1 due to the limited availability of the drug.

Table 6.2 presents the solubilities obtained in various formulations.

Table 6.2 Solubility of Antalarmin in various formulations:

	Solubility (mg/ml)		
	pH 7.0	**pH 2.0**	**pH 1.0**
Intrinsic (Buffer)	< 0.001	1.12	15.56
20% EtOH	0.001	11.52	--
40% PG	0.002	14.32	--
40% PEG	<0.001	8.46	--
10% EtOH + 40% PG	--	35.20	140.71
20% Tween 80	0.46	13.23	--
20% Cre-EL	0.84	15.37	122.52
5% SLS	1.11	21.69	--
5% CTAB	0.57	9.91	--
20% HP-β-CD	3.61	5.14	93.84
20% SBE-β-CD	0.61	13.76	141.80
16% Nicotinamide	0.09	2.12	--

6.3.4 Lipid based formulations

Antalarmin's strong non-polarity (ClogP~8.16) makes it a good candidate for formulation using a lipid-based system. The solubility of Antalarmin was determined in Gelucire 44/14, Vitamin E TPGS and Oleic Acid all in combination with other vehicles like ethanol, propylene glycol, cremaphor and labrasol. The choice of surfactant was limited to only non-ionic surfactants since they are likely to offer superior in vivo stability (Lawrence and Rees 2000).

Four formulations were selected on the basis of their dispersion characteristics upon dilution in water.

As it can be seen in Table 6.3, the use of lipids has a dramatic effect on the solubility of the drug. Formulations 1 and 2 have low solubilities compared to the other two formulations. The composition of formulation 4 is the same as Norvir® a marketed product of an anti-HIV drug ritonavir. Ethanol is a widely used cosolvent but may be toxic when used in large amounts. Formulation 3 is similar to Formulation 4, but labrasol is used in place of ethanol. Labrasol is obtained from coconut oil and shows high tolerance and low toxicity with an LD_{50} of 22 g/kg for rats. (Kreilgaard 2000). It was originally developed as a pharmaceutical additive for the solubilization of hydrophobic drugs. It was found to improve intestinal absorption of drugs after oral administration (Tran et al. 1999, Kommuru et al. 2001).

Table 6.3 Lipid based formulations:

Formulation #	Composition	Form	Solubility (mg/ml)
1	Gelucire 44/14 (60%); PG (40%)	Waxy Solid	70.9
2	Vitamin E TPGS (60%); PG (40%)	Waxy Solid	58.5
3	Oleic Acid (20%); Labrasol (40%); Cre-EL (40%)	Liquid Solution	119.4
4	Oleic Acid (20%); EtOH (40%); Cre-EL (40%)	Liquid Solution	265.4

The poor solubility of Antalarmin is a direct result of it strong non-polarity ($\log K_{ow} \approx 8.16$) and not due to its crystallinity. Therefore, different techniques have been employed to increase its solubility. The study shows the viability of using the combination of pH control and cosolvents, surfactants or complexants. The applicability of a lipid system on a strongly non-polar compound like Antalarmin, is also demonstrated.

Based on the data there are four promising formulations for Antalarmin, three of which are solutions; 20% Cre-EL, 10% EtOH + 40%PG and 20% SBE-β-CD all buffered at pH 1 and have solubilities >100mg/ml. The fourth is a SMEDDS formulation comprising of 20% Oleic Acid + 40% Cre-EL + 40% Labrasol. Each of the formulations have solubilities >100 mg/ml.

APPENDIX

APPENDIX A. COMPARISON BETWEEN THE THREE LOGK_{OW} PREDICTION PROGRAMS

Name	**MW**	**MP (°C)**	**KowWin**	**ACD**	**ClogP**	**Exp.**
1,2,3-Trichlorobenzene	181.45	52.6	3.81	4.27	4.04	4.09
2-Naphthol	144.17	122	2.69	2.70	2.65	2.78
5,5-Diphenylhydantoin	252.27	296.5	2.16	2.52	2.08	2.38
5-Aminosalicylic Acid *	153.14	280	0.98	0.46	1.06	-0.16
5-Fluorocytosine [#]	129.09	296	-0.72	-1.78	-1.65	
Acetazolamide *	222.25	258.5	-0.73	-0.26	-1.25	-0.26
Adenine *	135.13	110	-0.73	-0.03	-0.29	-0.11
Adenosine *	267.24	234.5	-1.38	-1.02	-2.27	-1.12
Allopurinol	136.11	350	-1.03	-1.33	-0.88	-0.55
Aminopyrine	231.3	108	0.60	0.76	0.57	0.90
Ampicillin *	349.4	200.5	-0.88	1.35	-1.20	-0.81
Aspirin	180.16	135	1.13	1.20	1.02	1.25
Atropine	289.37	115	1.91	1.50	1.32	1.82
Azathioprine *	277.26	243.5	-0.09	0.90	0.01	0.10
Baclofen *	213.66	207	-1.32	1.56	-0.62	-0.96
Benzamide	121.14	130	0.74	0.70	0.65	0.65
Benzocaine	165.19	89	1.80	1.95	1.92	1.97
Benzoic acid	122.12	122.4	1.87	1.90	1.88	1.87
Biphenyl	154.21	70	3.93	3.98	4.03	3.91
Bumetanide *	364.42	230.5	2.57	2.78	3.36	-0.30
Butamben	193.25	58	2.78	3.60	2.98	3.02
Butylparaben	194.23	68.5	3.47	3.50	3.57	3.57
Caffeine	194.19	238	0.16	-0.13	-0.06	-0.07
Camphor	152.24	179.8	3.04	2.10	2.18	2.38
Carbamazepine	236.27	191.5	2.25	2.70	1.98	2.32
Cephradine [#]	349.4		1.01	0.98	-1.53	
Chloramphenicol	323.13	151	0.92	1.00	1.28	1.14
Chlorthalidone [#]	338.76	225	1.59	-0.74	0.45	
Chlorzoxazone [#]	169.57	191.75	1.99	2.29	1.87	
Cimetidine	252.34	142	0.57	0.40	0.35	0.47
Clofazimine	473.4	211	7.55	7.50	6.69	7.48
Corticosterone *	346.47	145	1.99	1.80	2.32	1.94
Cortisone	360.45	222	1.81	1.20	1.30	1.47
Cytosine *	111.1		-1.47	-1.71	-1.85	-1.73
Dapsone	248.3	175.5	0.77	0.90	0.89	0.97

Deoxycorticosterone	330.47	141.5	3.12	3.40	3.25	2.88
Dexamethasone	392.47	263	1.72	2.10	1.75	1.89
Diatrizoic Acid *	613.92		1.37	0.45	0.73	-1.05
Diflunisal	250.2	210.5	4.41	4.30	4.39	3.56
Estriol	288.39	282	2.81	2.90	3.20	2.45
Estrone	270.37	255.3	3.43	3.70	3.38	2.95
Ethylparaben	166.18	116	2.49	2.40	2.51	2.47
Ethynylestradiol-17-alpha	296.41	143.5	4.12	4.52	4.61	3.67
Fenbufen	254.28	186	3.18	3.00	3.14	3.20
Flufenamic acid	281.23	125	5.15	5.60	4.88	4.32
Fluorouracil	130.08	282	-0.81	-0.78	-0.58	-0.85
Flurbiprofen	244.26	110	3.81	4.10	3.75	4.16
Folic Acid #	441.4		3.66	-2.32	-2.17	
Glafenine #	372.81	169.5	0.42	3.49	3.04	
Griseofulvin	352.77	220	1.92	2.40	1.75	2.18
Guaifenesin #	198.22	78.75	-1.05	0.57	0.10	
Guanine *	151.13		-1.05	-0.98	-1.28	-0.94
Haloperidol	375.87	148.7	4.20	4.10	3.85	4.29
Hydrochlorothiazide	297.74	274	-0.07	-0.07	-0.40	-0.07
Hydrocortisone	362.47	218.5	1.62	1.40	1.70	1.65
Hydroflumethiazide	331.28	272.5	0.22	0.50	-0.25	0.36
Hyoscyamine	289.37	108.5	1.91	1.50	1.32	1.83
Ibuprofen	206.28	76	3.79	3.70	3.68	3.50
Indapamide #	365.83	161	5.78	2.09	2.94	
Indoprofen	281.31	213.5	2.32	2.77	2.74	2.77
Iopanoic Acid #	570.93	156.1	3.00	4.19	4.89	
Ketoprofen	254.28	94	3.00	2.80	2.76	3.12
Khellin #	260.25	154.5	-0.26	1.66	2.57	
Linuron	249.1	93.5	2.91	3.20	3.00	3.16
Mefenamic acid	241.29	230.5	5.28	5.30	4.94	4.29
Methocarbamol #	241.24	93	0.00	0.55	0.15	
Methylparaben	152.15	131	2.00	1.86	1.99	1.96
Metronidazole	171.16	159	0.00	-0.01	-0.46	-0.02
Minoxidil	209.25	248	1.35	0.69	0.48	1.33
Nadolol	309.4	125	1.17	1.29	0.38	0.71
Nalidixic acid	232.24	229.5	1.64	1.00	1.32	1.50
Naphthalene	128.17	80.2	3.17	3.35	3.32	3.30
Naproxen	230.26	153	3.10	3.00	2.82	3.26
Nitrofurantoin *	238.16		-0.17	-0.99	-0.47	-0.47

Norethisterone	298.42	203.5	2.99	3.38	2.78	2.97
Norfloxacin *	319.33	220.5	-0.31	1.48	-0.99	-1.26
p-Aminobenzoic Acid *	137.14	187.75	0.96	0.83	0.98	0.73
p-Aminosalicylic acid *	153.14	150.5	0.98	1.14	1.06	0.91
Paracetamol	151.16	169.75	0.27	0.34	0.49	0.48
Perphenazine	403.97	97	3.82	4.50	4.32	4.20
Phenacetin	179.22	134.5	1.67	1.60	1.77	1.57
Phenolphthalein	318.33	260	3.06	2.63	2.63	2.41
Phenylbutazone	308.38	105	3.52	3.16	3.38	3.23
Praziquantel [#]	312.41	137	2.42	2.44	3.36	
Prednisolone *	360.45		1.40	1.49	1.38	1.59
Primidone	218.25	281.5	0.73	0.40	0.88	0.91
Progesterone	314.47	126	3.67	4.00	3.77	3.87
Propylparaben	180.2	96.5	2.98	2.90	3.04	3.04
Pyrazinamide	123.11	190	-0.53	-0.37	-0.71	-0.60
Quinidine	324.42	174.5	3.29	3.40	2.79	2.36
Quinine	324.42	177	3.29	3.44	2.79	2.36
Salicylamide	137.14	140	1.03	1.40	1.28	1.28
Salicylic Acid	138.12	158	2.24	2.06	2.19	2.24
Spironolactone	416.57	134	2.88	3.12	2.25	2.26
Strychnine	334.42	280	1.85	1.70	1.66	1.93
Sulfacetamide	214.24	183	-0.60	-0.96	-0.98	-0.96
Sulfadiazine	250.27	252.5	-0.34	-0.12	-0.09	-0.07
Sulfamerazine	264.3	236.5	0.21	0.30	0.57	0.14
Sulfamethazine	278.33	176	0.76	0.80	1.07	0.28
Sulfamethoxazole	253.28	171.5	0.48	0.90	0.55	0.89
Sulfanilamide	172.2	165.5	-0.55	-0.72	-0.57	-0.70
Sulfathiazole	255.31	202	0.72	0.30	0.72	0.05
Sulindac	356.41	183.5	4.28	3.59	3.16	3.24
Sulpiride *	341.42	179	0.65	0.45	1.11	0.42
Tenoxicam *	337.37	211	2.40	1.52	1.61	0.81
Terfenadine	471.68	147.5	7.62	6.90	6.09	5.69
Tetraethylthiuram Disulfide	296.52	70	3.76	3.88	3.88	3.88
Theobromine	180.17	357	-0.05	-0.72	-0.69	-0.77
Theophylline *	180.17	272.5	-0.39	-0.17	-0.06	-0.02
Thiamphenicol	356.22	165.3	-0.33	-0.27	-0.10	-0.27
Thymine *	126.11		-0.32	-0.12	-0.56	-0.62
Triamcinolone	394.44	270	0.96	0.83	0.67	1.16

Triamterene	253.27	201	0.80	1.34	1.31	0.98
Trimethoprim	290.32	201	0.73	0.80	0.88	0.91
Uracil	112.09	335	-0.87	-0.71	-1.06	-1.06
Uric Acid *	168.11		-1.46	-1.08	-1.46	-2.66
Xanthine *	152.11		-1.15	-0.81	-0.70	-0.73

Note:

* zwitterionic and tautomeric compounds

[#] compounds without reported logK_{ow} values.

APPENDIX B. ABSOLUTE AVERAGE ERRORS AND ROOT MEAN SQUARE ERRORS CALCULATED FROM THE TWO MODELS. [EQUATION (3.4) AND EQUATION (3.5)]

Compounds	**ClogP**	**[a]n**	**AAE**		**RMSE**	
			(3.4)	**(3.5)**	**(3.4)**	**(3.5)**
Histidine	-3.73	8	0.015	0.027	0.018	0.033
Asparagine	-3.54	5	0.007	0.016	0.010	0.019
Glutamine	-3.37	5	0.005	0.006	0.006	0.007
Glycine	-3.21	10	0.014	0.065	0.016	0.072
Alanine	-3.12	10	0.008	0.049	0.010	0.055
Glycyglycine	-2.92	7	0.013	0.066	0.016	0.074
Tartaric acid	-2.78	12	0.002	0.005	0.002	0.005
glutamic acid	-2.69	6	0.033	0.086	0.038	0.102
amino-isobutyric acid	-2.62	5	0.003	0.006	0.004	0.007
amino-n-butyric acid	-2.53	6	0.004	0.040	0.005	0.044
Aspartic Acid	-2.41	9	0.046	0.087	0.062	0.104
dl-Valine	-2.29	7	0.023	0.054	0.026	0.058
Aminocaproic acid	-2.24	10	0.025	0.094	0.029	0.105
Hydantoin	-1.69	7	0.018	0.022	0.020	0.027
Leucine	-1.67	5	0.017	0.012	0.022	0.014
Tryptophan	-1.57	8	0.038	0.016	0.042	0.019
Phenylalanine	-1.56	8	0.015	0.034	0.018	0.040
Hydantoic acid	-1.38	6	0.013	0.031	0.016	0.020
Norleucine	-1.38	10	0.030	0.049	0.035	0.055
Zalcitabine	-1.29	11	0.017	0.021	0.022	0.026
Didanosine	-1.24	11	0.042	0.095	0.050	0.062
Formylglycine	-1.19	9	0.006	0.024	0.008	0.027
Methylhydantoic acid	-1.18	6	0.015	0.018	0.020	0.020
Triglycine	-0.94	7	0.045	0.070	0.057	0.079
5-Ethylhydantoin	-0.64	7	0.061	0.075	0.071	0.019
Formyl-aminobutyric acid	-0.35	7	0.041	0.009	0.051	0.011
Caffeine	-0.06	6	0.021	0.025	0.026	0.032
Zidovudine	0.04	11	0.016	0.016	0.022	0.024
Paracetamol	0.49	13	0.059	0.028	0.083	0.034
Formylleucine	0.58	8	0.030	0.053	0.043	0.063
Benzamide	0.65	14	0.015	0.009	0.019	0.012
Barbital	0.66	11	0.017	0.012	0.018	0.014

P-aminobenzoic acid	0.98	6	0.019	0.031	0.023	0.036
Metharbital	1.14	11	0.015	0.026	0.018	0.028
Acetanilide	1.16	13	0.016	0.022	0.021	0.027
Phenobarbital	1.37	12	0.015	0.012	0.017	0.015
Oxolinic acid	1.55	11	0.041	0.057	0.049	0.063
Strychnine	1.66	7	0.035	0.019	0.038	0.054
Camphoric acid	1.75	12	0.036	0.035	0.047	0.052
Furosemide	1.87	13	0.130	0.108	0.148	0.133
Benzoic Acid	1.88	11	0.026	0.077	0.029	0.083
Benzocaine	1.92	11	0.030	0.045	0.038	0.048
Phenytoin	2.08	11	0.040	0.049	0.046	0.053
Alprazolam	2.19	9	0.019	0.027	0.022	0.035
salicylic acid	2.19	6	0.007	0.062	0.007	0.067
Diazepam	2.99	11	0.043	0.044	0.054	0.057
Ibuprofen	3.68	8	0.102	0.100	0.120	0.123
beta-estradiol	3.78	6	0.031	0.075	0.034	0.085
Biphenyl	4.03	11	0.067	0.086	0.069	0.092
Indomethacine	4.18	10	0.050	0.073	0.058	0.083
Anthracene	4.49	11	0.049	0.080	0.061	0.091

[a] n is the number of experimental points in each data set

[b] ClogP is the octanol/water partition coefficient.

APPENDIX C. COMPARISON BETWEEN PREDICTED AND EXPERIMENTAL F_{MAX} VALUES.

Compounds	**[a]n**	**Predicted**	**Experimental**	**Difference**
Paracetamol	13	1.00	0.85	0.15
Oxolinic acid	11	0.70	0.80	0.1
Methylhydantoic acid	6	0.50	0.60	0.1
Strychnine	7	0.80	0.80	0.0
Phenobarbital	12	1.00	0.90	0.1
Methobarbital	11	0.80	0.80	0.0
Indomethasine	10	1.00	1.00	0.0
Barbital	11	0.80	0.90	0.1
Benzoic Acid	11	1.00	1.00	0.0
Anthracene	11	1.00	1.00	0.0
Biphenyl	11	1.00	1.00	0.0
Hydantoic acid	6	0.00	0.00	0.0
5-Ethylhydantoin	7	0.60	0.60	0.0
Hydantoin	7	0.00	0.00	0.0
Alprazolam	9	1.00	1.00	0.0
Diazepam	11	1.00	0.90	0.1
Didanosine	11	0.50	0.40	0.1
Furosemide	13	1.00	1.00	0.0
Zidovudine	11	0.70	0.70	0.0
Zalcitabine	11	0.50	0.30	0.2
Aspartic Acid	9	0.00	0.00	0.0
Norleucine	10	0.00	0.00	0.0
dl-Valine	7	0.00	0.00	0.0
Glycyglycine	7	0.00	0.00	0.0
Histidne	8	0.00	0.00	0.0
Tryptophan	8	0.00	0.00	0.0
Alanine	10	0.00	0.00	0.0
Aminocaproic acid	10	0.10	0.00	0.1
Phenylalanine	8	0.00	0.00	0.0
Tartaric acid	12	0.00	0.00	0.0
Leucine	5	0.00	0.00	0.0
beta-estradiol	6	1.00	1.00	0.0
Caffeine	6	0.60	0.60	0.0
Phenytoin	11	0.90	0.90	0.0
Ibuprofen	8	0.80	1.00	0.2
Benzocaine	11	1.00	0.90	0.1
P-aminobenzoic acid	6	1.00	0.80	0.2
salicylic acid	6	1.00	1.00	0.0
camphoric acid	12	0.80	0.90	0.1

Glycine	10	0.00	0.00	0.0
Formylglycine	9	0.00	0.00	0.0
Formylleucine	8	0.80	0.90	0.1
amino-n-butyric acid	6	0.00	0.00	0.0
amino-isobutyric acid	5	0.00	0.00	0.0
glutamic acid	6	0.00	0.00	0.0
Asparagine	5	0.00	0.00	0.0
Glutamine	5	0.00	0.00	0.0
formyl-aminobutyric acid	7	0.90	0.80	0.1
Benzamide	14	0.80	0.83	0.03
Acetanilide	13	0.90	0.90	0.0
Triglycine	7	0.00	0.00	0.0

[a] n is the number of experimental points in each data set

APPENDIX D. COMPARISON BETWEEN PREDICTED AND EXPERIMENTAL SIGMA 0.5 ($\sigma_{0.5}$) VALUES.

Compounds	**log K_{ow}**	**experimental**	**predicted**	**Error**
Histidine	-3.73	-1.29	-2.36	1.07
Asparagine	-3.54	-1.81	-2.18	0.37
Glutamine	-3.37	-1.57	-2.02	0.45
Glycine	-3.21	-1.83	-1.87	0.05
Alanine	-3.12	-1.53	-1.79	0.26
Glycyglycine	-2.92	-2.43	-1.60	0.83
Tartaric acid	-2.78	-0.21	-1.47	1.26
Glutamic acid	-2.69	-1.72	-1.38	0.34
Amino-iso-butyric acid	-2.62	-1.18	-1.32	0.13
Amino-n-butyric acid	-2.53	-1.25	-1.23	0.02
Aspartic Acid	-2.41	-2.18	-1.12	1.06
dl-Valine	-2.29	-1.20	-1.01	0.19
Aminocaproic acid	-2.24	-0.26	-0.96	0.70
Hydantoin	-1.69	-0.17	-0.44	0.28
Leucine	-1.67	-1.00	-0.42	0.58
Tryptophan	-1.57	-0.15	-0.33	0.18
Phenylalanine	-1.56	-0.65	-0.32	0.33
Norleucine	-1.38	-0.88	-0.15	0.73
Hydantoic acid	-1.38	-0.32	-0.15	0.16
Zalcitabine(DDC) [1]	-1.29	0.38	-0.07	0.45
Didanosine(DDI) [1]	-1.24	0.58	-0.02	0.60
Formylglycine	-1.19	-0.15	0.03	0.17
Methylhydantoic acid	-1.18	0.10	0.03	0.07
Triglycine	-0.94	-2.10	0.26	2.36
5-Ethylhydantoin	-0.64	0.94	0.54	0.40
Formyl-aminobutyric acid	-0.35	0.67	1.47	0.80
Caffeine	-0.06	1.00	1.09	0.09
Theophylline	-0.06	1.03	1.09	0.06
Zidovudine(AZT) [1]	0.04	1.00	1.18	0.18
Paracetamol	0.49	1.76	1.60	0.16
Formylleucine	0.58	2.00	1.69	0.31
Benzamide	0.65	1.86	1.75	0.11
Barbital	0.66	1.44	1.76	0.32
P-aminobenzoic acid	0.98	2.27	2.06	0.20
Metharbital	1.14	1.81	2.21	0.40

Acetanilide	1.16	2.18	2.23	0.05
Phenobarbital	1.37	2.68	2.43	0.25
Oxolinic acid [1]	1.55	2.14	2.60	0.46
Strychrine [1]	1.66	2.46	2.70	0.25
Camphoric acid	1.75	3.03	2.79	0.24
Benzoic Acid	1.88	2.55	2.91	0.36
Benzocain	1.92	2.98	2.95	0.03
Phenytoin	2.08	4.17	3.10	1.07
Alprazolam [1]	2.19	2.81	3.20	0.39
Salicylic acid	2.19	2.98	3.20	0.22
Diazepam	2.99	5.24	3.95	1.29
Ibuprofen [1]	3.68	5.20	4.60	0.60
beta-estradiol [1]	3.78	6.60	4.69	1.91
Biphenyl	4.03	3.90	4.93	1.03
Indomethacine	4.18	4.01	5.07	1.06
Anthracene	4.49	5.34	5.36	0.02

[1.] $\sigma_{0.5}$ values calculated from experimental data and the rest from Li et al[1]

APPENDIX E. COMPARISON BETWEEN PREDICTED AND EXPERIMENTAL F_{MAX} VALUES.

Compounds	**log K_{ow}**	**experimental**	**predicted**	**Error**
Histidne	-3.73	0.00	0.00	0.00
asparagine	-3.54	0.00	0.00	0.00
glutamine	-3.37	0.00	0.00	0.00
glycine	-3.21	0.00	0.00	0.00
Alanine	-3.12	0.00	0.00	0.00
Glycyglycine	-2.92	0.00	0.00	0.00
Tartaric acid	-2.78	0.00	0.00	0.00
glutamic acid	-2.69	0.00	0.00	0.00
amino-iso-butyric acid	-2.62	0.00	0.01	0.01
amino-n-butyric acid	-2.53	0.00	0.01	0.01
Aspartic Acid	-2.41	0.00	0.01	0.01
dl-Valine	-2.29	0.00	0.01	0.01
Aminocaproic acid	-2.24	0.00	0.01	0.01
Hydantoin	-1.69	0.00	0.05	0.05
Leucine	-1.67	0.00	0.05	0.05
Tryptophan	-1.57	0.00	0.06	0.06
Phenylalanine	-1.56	0.00	0.06	0.06
Norleucine	-1.38	0.00	0.09	0.09
Hydantoic acid	-1.38	0.00	0.09	0.09
Zalcitabine(DDC)	-1.29	0.30	0.11	0.19
Didanosine(DDI)	-1.24	0.40	0.12	0.28
Formylglycine	-1.19	0.00	0.14	0.14
Methylhydantoic acid	-1.18	0.60	0.14	0.46
Triglycine	-0.94	0.00	0.22	0.22
5-Ethylhydantoin	-0.64	0.60	0.36	0.24
formyl-aminobutyric acid	-0.35	0.80	0.85	0.05
Caffeine	-0.06	0.60	0.68	0.08
Theophylline	-0.06	0.60	0.68	0.08
Zidovudine(AZT)	0.04	0.70	0.73	0.03
Paracetamol	0.49	0.85	0.88	0.03
Formylleucine	0.58	0.90	0.90	0.00
benzamide	0.65	0.83	0.92	0.09
Barbital	0.66	0.90	0.92	0.02
P-aminobenzoic acid	0.98	0.80	0.96	0.16
metharbital	1.14	0.80	0.97	0.17
acetanilide	1.16	0.90	0.97	0.07
Phenobarbital	1.37	0.90	0.98	0.08
Oxolinic acid	1.55	0.80	0.99	0.19

Strychrine	1.66	0.80	0.99	0.19
camphoric acid	1.75	0.90	0.99	0.09
Benzoic Acid	1.88	1.00	0.99	0.01
Benzocain	1.92	0.90	1.00	0.10
Phenytoin	2.08	0.90	1.00	0.10
Alprazolam	2.19	1.00	1.00	0.00
salicylic acid	2.19	1.00	1.00	0.00
Diazepam	2.99	0.90	1.00	0.10
Ibuprofen	3.68	1.00	1.00	0.00
beta-estradiol	3.78	1.00	1.00	0.00
Biphenyl	4.03	1.00	1.00	0.00
Indomethacine	4.18	1.00	1.00	0.00
Anthracene	4.49	1.00	1.00	0.00

APPENDIX F. ROOT MEAN SQUARE ERRORS CALCULATED FROM THE PARABOLIC, BILINEAR AND LOG-LINEAR MODELS IN EQUATIONS 6.1, 6.8 AND 6.2 RESPECTIVELY.

		RMSE		
Compounds	**n**	**parabolic**	**bilinear**	**log-linear**
Triglycine	7	0.277	0.025	1.010
Histidine	8	0.087	0.005	0.275
Asparagine	5	0.128	0.003	0.627
Glutamine	5	0.007	0.034	0.623
Glycine	10	0.158	0.035	0.148
Alanine	10	0.195	0.050	0.982
Glycyglycine	7	0.213	0.025	0.854
Tartaric acid	12	0.017	0.005	0.092
glutamic acid	6	0.217	0.076	0.790
amino-isobutyric acid	5	0.025	0.017	0.179
amino-n-butyric acid	6	0.140	0.017	0.574
Aspartic Acid	9	0.220	0.092	0.759
dl-Valine	7	0.146	0.043	0.461
Aminocaproic acid	10	0.271	0.047	0.988
Hydantoin	7	0.093	0.018	0.356
Tryptophan	8	0.097	0.050	0.372
Phenylalanine	8	0.097	0.052	0.457
Hydantoic acid	6	0.094	0.014	0.380
Norleucine	10	0.137	0.057	0.316
Zalcitabine	11	0.052	0.056	0.396
Didanosine	11	0.081	0.075	0.456
Formylglycine	9	0.074	0.020	0.288
Methylhydantoic acid	6	0.095	0.023	0.294
5-Ethylhydantoin	7	0.071	0.023	0.296
Formyl-aminobutyric acid	7	0.069	0.024	0.211
Caffeine	6	0.135	0.000	0.582
Theophylline	10	0.080	0.027	0.364
Zidovudine	11	0.148	0.032	0.257
Paracetamol	13	0.057	0.053	0.349
Formylleucine	8	0.083	0.076	0.282
Benzamide	14	0.061	0.031	0.324
Barbital	11	0.061	0.035	0.214
P-aminobenzoic acid	6	0.044	0.056	0.256
Metharbital	11	0.078	0.053	0.279
Acetanilide	13	0.070	0.041	0.248
Phenobarbital	12	0.092	0.087	0.488
Oxolinic acid	11	0.065	0.132	0.147
Strychnine	7	0.119	0.055	0.508

Camphoric acid	12	0.069	0.201	0.414
Furosemide	13	0.361	0.420	0.364
Benzoic Acid	11	0.103	0.112	0.543
Benzocaine	11	0.110	0.083	0.345
Phenytoin	11	0.122	0.090	0.419
Alprazolam	9	0.103	0.063	0.365
salicylic acid	6	0.129	0.106	0.258
Diazepam	11	0.122	0.086	0.513
Naphthalene	6	0.000	0.000	0.000
Ibuprofen	8	0.249	0.197	0.462
Beta-estradiol	6	0.155	0.134	0.645
Biphenyl	11	0.152	0.204	0.200
Indomethacine	10	0.172	0.147	0.419
Anthracene	11	0.129	0.123	0.267

APPENDIX G. EXPERIMENTAL AND PREDICTED F_{MAX} VALUES AND THE ABSOLUTE ERRORS.

Compounds	N	log K_{ow}	experimental	predicted	Error
Triglycine (glyglygly)	7	-4.27	0	0	0
Histidne	8	-3.73	0	0	0
asparagine	5	-3.54	0	0	0
glutamine	5	-3.37	0	0	0
glycine	10	-3.21	0	0	0
Alanine	10	-3.12	0	0	0
Glycyglycine	7	-2.92	0	0	0
Tartaric acid	12	-2.78	0	0	0
glutamic acid	6	-2.69	0	0	0
calcium oxalate	11	-2.63	0	0	0
amino-isobutyric acid	5	-2.62	0	0	0
amino-n-butyric acid	6	-2.53	0	0	0
Aspartic Acid	9	-2.41	0	0	0
dl-Valine	7	-2.29	0	0	0
Aminocaproic acid	10	-2.24	0	0	0
Hydantoin	7	-1.69	0	0	0
Tryptophan	8	-1.57	0	0	0
Phenylalanine	8	-1.57	0	0	0
Hydantoic acid	6	-1.38	0	0	0
Norleucine	10	-1.38	0	0	0
Zalcitabine(DDC)	11	-1.29	0.3	0.47	0.17
Didanosine(DDI)	11	-1.24	0.4	0.51	0.11
Formylglycine	9	-1.19	0	0	0
Methylhydantoic acid	6	-1.18	0.6	0.56	0.04
5-Ethylhydantoin	7	-0.64	0.6	0.69	0.09
formyl-aminobutyric acid	7	-0.35	0.8	0.76	0.04
Caffeine	6	-0.06	0.6	0.62	0.02
Theophylline		-0.06	0.6	0.65	0.05
Zidovudine(AZT)	11	0.04	0.7	0.71	0.01
Paracetamol	13	0.49	0.85	0.83	0.02
Formylleucine	8	0.58	0.9	0.81	0.09
benzaimide	14	0.65	0.83	0.82	0.01
Barbital	11	0.66	0.9	0.86	0.04
P-aminobenzoic acid	6	0.98	0.8	0.84	0.04
Methobarbital	11	1.14	0.8	0.84	0.04
acetanilide	13	1.16	0.9	0.9	0
Phenobarbital	12	1.37	0.9	0.95	0.05
Oxolinic acid	11	1.55	0.8	0.69	0.11

Strychrine	7	1.66	0.8	0.82	0.02
camphoric acid	12	1.75	0.9	0.79	0.11
furosemide	13	1.87	1	0.96	0.04
Benzoic Acid	11	1.88	1	0.88	0.12
Benzocain	11	1.92	0.9	0.88	0.02
Phenytoin	11	2.08	0.9	0.9	0
Alprazolam	9	2.19	1	0.91	0.09
salicylic acid	6	2.19	1	0.93	0.07
Diazepam	11	3.16	0.9	0.87	0.03
naphthalene	6	3.32	1	1	0
Ibuprofen	8	3.68	1	0.9	0.1
beta-estradiol	6	3.78	1	0.94	0.06
Biphenyl	11	4.03	1	1	0
Indomethasine	10	4.18	1	0.91	0.09
Anthracene	11	4.49	1	1	0

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