School of Pharmacy[1], Tabriz University of Medical Sciences, Tabriz, Iran, and Bradford School of Pharmacy[2], University of Bradford, Bradford, UK

Describing solubility of polymorphs in mixed solvents by CNIBS/R-K equation

A. JOUYBAN[1] and B. J. CLARK[2]

Different polymorphs of a drug often possess various solubility, melting point, stability, density and x-ray diffraction. Polymorphs of slightly soluble drugs may affect the dissolution rate of the drug and one polymorph can act as a more active therapeutic agent than other polymorphic forms of the same drug [1]. It has been established that polymorphs usually show different bioavailability [2]. As an example, aspirin is at least a dimorphic drug and it has been presented that form II produced higher serum total salisylate concentration than form I [3]. It also should be noted that the solubility of enantiomers of chiral solutes is different from each other in the pure or mixed solvents [4, 5].

Mixing a miscible cosolvent with water is a common and easy to use technique for affecting the aqueous solubility of poorly water-soluble drugs. In a paper [6] solubility behaviour and dissolution rates of two polymorphs of mefenamic acid in mixed solvents have been studied. Polymorph II showed higher solubilities in comparison with polymorph I in different solvent media possessing the polarity ranging from 47.8 to 18.5 $MPa^{1/2}$. The authors applied a power series of solvent's Hildebrand solubility parameter to correlate the solubility of polymorphs with respect to the solvent polarity. The faster dissolution rate of polymorph II has been reported in different dissolution media. A concentration peak of polymorph II is obtained quickly (within 15 min) in pure ethyl acetate and ethanol-ethyl acetate mixture (50 : 50), whereas a maximum concentration plateau is attained more slowly in more polar dissolution media, i.e. water, ethanol and water-ethanol mixture (50 : 50). DSC thermograms of the solid phase taken from this stage (maximum solubility) show no difference with that of polymorph II. A decrease of concentration of polymorph II is observed to reach the final solubility values of polymorph I within 48 to 112 h, dependent on the polarity of the dissolution media. DSC thermograms from this stage show a total conversion of polymorph II to form I. The dissolution rate of polymorph I shows a different pattern from polymorph II. It increases with time to reach a plateau corresponding to the equilibrium solubility [6].

Mathematical representation of solubility data in mixed solvents enables researchers to predict the solubility of drugs. There are a number of models presented for describing the solubility of drugs in mixed solvents. Most of these models were briefly reviewed in a previous paper [7]. These models will need a minimum number of experimental solubility data for computing the model constants. The number of required solubility data is an important parameter, especially in the preformulation stage of a new drug when only a small amount of the drug is available. Therefore, any general model to calculate the solubility in mixed solvents could be beneficial.

The combined nearly ideal binary solvent/Redlich-Kister model (CNIBS/R-K) promises good fit ability with solubility of a solute in a binary solvent system [7]. The applicabilities of the model for correlating solubility data in aqueous-cosolvent mixtures [8], describing the multiple solubility maxima in the mixed solvents, correlating solubility data at different temperatures [9], predicting the solubility of structurally related drugs in binary solvent mixtures [10] and representation of the electrophoretic mobility of analytes in capillary zone electrophoresis [11] have been reported. This model is also able to predict the solute solubility in ternary mixtures based on model constants calculated from experimental solubility data in subbinary mixtures [12] and the theoretical basis of CNIBS/R-K model has been provided [13]. However, this model has not been tested for correlating/predicting the solubility of polymorphs in solvent mixtures. In this communication, the applicability of CNIBS/R-K model to calculate the solubility of two polymorphs of mefenamic acid in two binary solvents with a common solvent is presented. The model is:

$$\ln X_m = f_1 \ln X_1 + f_2 \ln X_2 + f_3 \ln X_3 + f_1 f_2 \sum_{i=0}^{p} A_i (f_1 - f_2)^i + f_2 f_3 \sum_{i=0}^{p} B_i (f_2 - f_3)^i . \quad (1)$$

Where X_m, X_1, X_2 and X_3 are the mole fraction solubility of each polymorph in mixture and pure solvents 1–3, respectively, f_1–f_3 denote volume fraction of solvents 1–3 in the absence of the solute and A_i and B_i represent solute-solvent interaction parameters which calculated by least squares analysis. The basic model contains another interaction terms for expressing interaction between solvents 1 and 3. The first three terms in equation 1, i.e. $f_1 \ln X_1 + f_2 \ln X_2 + f_3 \ln X_3$, represent the ideal mixing solubility behaviour of the solute and the variations of physicochemical properties of crystalline form of the drugs are included in X_1–X_3 terms. Numerical values of the interaction parameters (terms A and B in equation 1) are expected to be nearly constant for polymorphs in a given solvent mixture. We examined this assumption by employing experimental data of the solubility of two polymorphs of mefenamic acid in water-ethanol and ethanol-ethyl acetate binary mixtures [6].

The equation developed for describing the solubility behaviour of polymorph I of mefenamic acid in water-ethanol and ethanol-ethyl acetate mixtures is:

$$\ln X_m = -12.631 f_1 - 6.310 f_2 - 5.563 f_3 - 3.308 f_1 f_2 - 2.319 f_1 f_2 (f_1 - f_2) + 3.165 f_1 f_2 (f_1 - f_2)^2 + 3.870 f_2 f_3 - 1.859 f_2 f_3 (f_2 - f_3) + 3.264 f_2 f_3 (f_2 - f_3)^2 \quad (2)$$

Where f is the volume fraction of the solvent, and 1, 2 and 3 refer to water, ethanol and ethyl acetate, respectively. The equation for polymorph II is:

$$\ln X_m = -12.321 f_1 - 5.977 f_2 - 5.313 f_3 - 3.305 f_1 f_2 - 4.838 f_1 f_2 (f_1 - f_2) - 3.804 f_1 f_2 (f_1 - f_2)^2 + 3.332 f_2 f_3 - 1.521 f_2 f_3 (f_2 - f_3) + 2.692 f_2 f_3 (f_2 - f_3)^2 \quad (3)$$

The validity of the model constants has been checked using t-test and the constants are statistically significant at the 0.05 level.

To assess the accuracy of the models for reproducing experimental data, the mean percentage deviations, *MPD*, is

calculated by:

$$\mathrm{MPD} = \frac{100}{N} \sum \left(\frac{|(X_m)_{Calc.} - (X_m)_{Exp.}|}{(X_m)_{Exp.}} \right) \quad (4)$$

Where N is the number of data points in each set, $(X_m)_{Calc.}$ denotes calculated data and $(X_m)_{Exp.}$ represents experimental solubilities which are taken from the reference [6].

Romero et al. [6] employed a power series of solvent's Hildebrand solubility parameter for correlating solubility data of the polymorphs. The model for polymorph I is:

$$\ln X_m = -56.4928 + 6.611\delta_m - 0.2937\delta_m^2 + 0.005283\delta_m^3 - 0.0000341\delta_m^4 \quad (5)$$

And for polymorph II:

$$\ln X_m = -27.8450 + 2.6043\delta_m - 0.0906\delta_m^2 + 0.0008974\delta_m^3 \quad (6)$$

In which δ_m is the Hildebrand solubility parameter of mixed solvent calculated based on the solubility parameter of pure solvents:

$$\delta_m = f_1\delta_1 + f_2\delta_2 + f_3\delta_3 \quad (7)$$

The fit ability of the equations is evaluated by fitting the experimental data of polymorphs I and II as separate sets. MPD values for correlative eqs. (2) and (3) are 7.7 and 2.5% for polymorphs I and II, respectively, where the MPD values for back-calculated solubility of polymorphs I and II are based on equations 5 and 6 are 13.2 and 13.2%, respectively. These calculations could be employed to screen the experimental data to detect the possible outliers. Also, the equations are capable of predicting the unmeasured solubilities after training by a minimum number of experimental data. The average MPD values for the proposed and for previously published models are 5.1 and 13.2%, respectively. The proposed equation improves the fit ability of the solubility profile by a factor of 2.6 in comparison with eqs. (5) and (6) [6].

To check the prediction capability of CNIBS/R-K model, the solubility of polymorph I and II are predicted by eqs. (2) and (3). The resultant MPD values are 13.4 and 12.8%. It should be noted that the solubility data of polymorph I (or II) are not included in computing the model constants of eqs. (3) (or 2). This means that one can predict the solubility of other polymorphs in mixed solvents using the solubility data of the polymorph in pure solvents and their interaction parameters, which are calculated on the basis of the solubility of one polymorph in a given solvent mixture. The corresponding MPD values for predicted solubilities of polymorph I by eq. (6) and of polymorph II by eq. (5) are 26.5 and 20.7%, respectively. The overall mean percentage derivation (MPD) for the proposed and previously published models are 13.1 and 23.6% and these represent an improvement factor in the prediction capability of the proposed model of 1.8. The criterion in choosing a model is its accuracy and therefore the MPD values should be as low as possible.

One can reproduce solubility data for both polymorphs with a single equation and the value of MPD obtained for 33 data points fitted into equation 1 is 8.5%. As a comparison Romero et al. [6] employed a modified version of their model to reproduce the solubility curves of both polymorphs as:

$$\ln X_m = -18.2826 + 0.5452\ln X_1 + 2.3687\delta_m - 0.0836\delta_m^2 + 0.0008337\delta_m^3 \quad (8)$$

Table: Mean percentage deviations (MPD) for the equations studied using different numerical methods

	Polymorph	N[a]	Eq. (1)	Eqs. (5), (6)
Correlative equations	I	20	7.7	13.2
	II	13	2.5	13.2
	both I and II	33	8.5	17.5 (for Eq. 8)
Predictive equations	I using data of II	20	13.4	26.5
	II using data of I	13	12.8	20.7

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

where X_1 denotes the mole fraction solubility of each polymorph in pure solvent 1 (water) and from this equation the MPD is 17.5%. With the equation proposed here there is an improvement by a factor of 2.1.

The summary of the accuracy of the discussed models for correlation and prediction purposes is presented in the Table. Careful examination of the Table reveals that the proposed equation is superior to the previously published equations both from correlation and prediction points of view. Although it should be noted that both models produced very small MPD's when compared with values of 117 to 2500% [14]. However, the overall advantage of the proposed model is that it produced correlative errors less than experimental uncertainty (usually ~10%) and therefore, it is suggested to use the proposed model to calculate the solubility of different polymorphs in mixed solvent system.

References

1 Martin, A.; Bustamante, P. Chun; A. H. C.: Physical Pharmacy, 4th ed., pp. 266–272, Lea and Febiger, Philadelphia, 1993
2 Haleblian, J. K.: J. Pharm. Sci. **64**, 1269 (1975)
3 Tawashi, R.: J. Pharm. Pharmacol. **21**, 701 (1969)
4 Dwivedi, S. K.; Sattari, S.; Jamali, F.; Mitchell, A. G.: Int. J. Pharm. **87**, 95 (1992)
5 Greenstein, J. P.; Winitz, M.: Chemistry of Amino Acids, Vol. 1, pp. 523–568, John Wiely & Sons, New York, 1961
6 Romero, S., Escalera, B., Bustamante, P.: Int. J. Pharm. **178**, 193 (1999)
7 Jouyban-Gh., A.; Valaee, L.; Barzegar-Jalali, M.; Clark B. J.; Acree, W. E. Jr.: Int. J. Pharm. **177**, 93 (1999)
8 Barzegar-Jalali, M.; Jouyban-Gh., A. : Int. J. Pharm. **140**, 237 (1996)
9 Jouyban-Gh., A.; Acree, W. E. Jr.: Int. J. Pharm. **167**, 177 (1998)
10 Jouyban-Gh., A.; Barzegar-Jalali, M.; Acree, W. E. Jr.: Int. J. Pharm. **166**, 205 (1998)
11 Jouyban-Gh., A.; Khaledi, M. G.; Clark, B. J.: J. Chromatogr. A **868**, 277 (2000)
12 Jouyban-Gh., A.; Clark, B. J.; Acree, W. E. Jr.: Chem. Pharm. Bull. **48**, 1866 (2000)
13 Acree, W. E. Jr.: Thermochim. Acta **198**, 71 (1992)
14 Huuskonen, J.; Rantanen, J.; Livingstone, D.: Eur. J. Med. Chem. **35**, 1081 (2000).

Received May 13, 2002
Accepted July 24, 2002

A. Jouyban
School of Pharmacy
Tabriz University
of Medical Sciences
Tabriz 51664
Iran
jouyban@tbzmed.ac.ir