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RESEARCH PAPER

Solubility Prediction for Furosemide in Water-Cosolvent Mixtures Using the Minimum Number of Experiments

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ABSTRACT

The mole fraction solubility of a poorly water soluble loop diuretic, furosemide, was determined in aqueous binary mixtures of ethanol, propylene glycol, and glycerol from 0% to 100% cosolvent concentrations at 25°C. Solubility predictions based on the minimum number of experimental data points were performed using the commonly used accurate cosolvency models: the three-suffix excess free energy (3xEFE), the mixture response surface (MRS), the combined nearly ideal binary solvent/Redlich-Kister (CNIBS/R-K), and the general single model (GSM). This prediction method was tested using three sets of solubility data for furosemide generated in this study and 11 data sets collected from the literature. The average percentage deviations (APDs) were 8.4 ± 3.8, 13.6 ± 7.3, 7.4 ± 2.8, and 7.6 ± 2.9, respectively, for 3xEFE, MRS, CNIBS/R-K, and GSM models. Using 3xEFE, CNIBS/R-K, and GSM models, which are theoretically related, a mean predicted solubility (MPS) approach was also proposed. The APD for this method was 7.3 ± 2. 3. The mean differences between MRS and the others were statistically significant ($p < .001$*). The results showed that one can employ solubility prediction based on a minimum of five experimental data points, and the expected APD is less than 10%.*

Key Words: *Cosolvency models; Furosemide; Solubility prediction; Water-cosolvent mixture.*

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INTRODUCTION

Furosemide, 5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino] benzoic acid, is an effective and widely used loop diuretic agent. It is used orally and is mainly absorbed from the stomach. Since furosemide is practically insoluble in the acidic medium of the stomach, its solubility is the rate-determining step in the oral absorption and bioavailability of the drug (1). One of the methods of increasing the solubility of the drug substances in water-based liquid formulations is the use of cosolvents. This work presents such data for three water-cosolvent mixtures.

The main aim of mathematical modeling of cosolvency is to enable researchers to predict the solubility of a drug in a given mixed solvent system. A number of equations has been proposed so far (2–10), and the correlation ability of most of them have been compared in a recent paper (11). The prediction of solubility using available cosolvency models suffers from the fact that it relies on curve-fitting parameters, which are usually computed using experimental data points. To improve the ability of predicting the solubility of a solute in a mixture of solvents, it is possible to determine the solubility in a limited number of concentrations of the cosolvent f_c and then predict the solubility at any other f_c values. This approach has not been considered extensively in the pharmaceutical literature. To test this method and also to compare the prediction capability of the cosolvency models, the solubility of furosemide was determined in binary aqueous mixtures of three pharmaceutical cosolvents: ethanol, propylene glycol, and glycerol.

It is important to determine the solubility of sparingly soluble drugs in the minimum number of mixtures with different concentrations of cosolvent and be able to apply the results to calculate the solubility at any other concentrations of the cosolvent. In high-throughput screening of drug candidates generated from combinatorial libraries, it is important to predict the solubility in a mixed solvent system using a minimum number of experimental data points.

THEORETICAL TREATMENT

The first equation that was considered for correlating the solubility data in binary solvent systems is derived from an excess free energy approach (3). The original model was proposed in two-, three-, and four-suffix forms. The three-suffix equation was used in this study because it contains five constant terms and/or curve-fitting parameters. The three-suffix excess free energy model is

$$\ln X_m = f_c \ln X_c + f_w \ln X_w - A_{c-w} f_c f_w (2f_c - 1)(V_2/V_c) + 2A_{w-c} f_c^2 f_w (V_2/V_w) + C_2 f_c f_w \quad (1)$$

where X is the mole fraction solubility of the solute; f denotes the solute-free volume fraction of the solvent; subscripts m, c, and w are mixed solvent, pure cosolvent, and water, respectively; A stands for a solvent-solvent interaction term, which is estimated from vapor pressure equilibria; V is the molar volume, with subscript 2 used for the solute; and C_2 is the solute–mixed solvent interaction term (3). Although the authors proposed that the C_2 term can be calculated from a single data point (12), employing experimental solubility data instead of vapor pressure data to calculate the model constants leads to more accurate results (unpublished results). Therefore, the modified form of the model that was used in this study is presented by Eq. 2:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + A_1 f_c^2 f_w + A_2 f_c f_w \quad (2)$$

where $A_1$and A_2 are the model constants calculated using the least-squares method. From the theoretical point of view, A_1 and A_2 are equal to $[-2A_{c-w}(V_2/V_c) + 2A_{w-c}(V_2/V_w)]$ and $[A_{c-w}(V_2/V) + C_w]$, respectively.

The mixture response surface model that has a statistical basis is expressed in different forms with different numbers of variables, ranging from three to five. The form of the model with five constants is

$$\ln X_m = \beta_1 f_c' + \beta_2 f_w' + \beta_3 (1/f_c') + \beta_4 (1/f_w') + \beta_5 f_c' f_w' \quad (3)$$

in which β_1–β_5 are the model parameters. The variables f_c' and f_w' are calculated by $f_c' = 0.96 f_c + 0.02$ and $f_w' = 0.96 f_w + 0.02$ (4). By converting f values to f', the model can cover the whole range of volume fractions of the cosolvent (f_c: 0–1).

The combined nearly ideal binary solvent/Redlich-Kister equation (CNIBS/R-K) is derived from a thermodynamic mixing model that includes contributions from both two-body and three-body interactions (5). This model is expressed by the following equation:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w \sum_{i=0}^{n} M_i (f_c - f_w)^i \quad (4)$$

where M_i stands for the model constants, which are calculated via regressing $[\ln X_m - f_c \ln X_c - f_w \ln X_w]$ versus

$f_c f_w(f_c - f_w)^i$ using a no intercept least squares analysis (13). The CNIBS/R-K model is adequately able to represent the spectrum of solution behavior from ideal to highly nonideal systems (8,14). The CNIBS/R-K model contains as many curve-fit parameters as required to describe the actual measured data accurately, and the results of our recent paper indicated that it is the most accurate model among the cosolvency models (11). In this study, the following form of the CNIBS/R-K model was employed:

$$\ln X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w[M_1 + M_2(f_c - f_w) + M_3(f_c - f_w)^2] \quad (5)$$

The general single model was derived from Eqs. 2 and 5 by substitution of f_w with $1 - f_c$ and appropriate rearrangements (9). The general single model is expressed as a power series of f_c:

$$\ln X_m = K_0 + K_1 f_c + K_2 f_c^2 + K_3 f_c^3 + K_4 f_c^4 + \cdots \quad (6)$$

where K_0–K_4 are the model constants.

Equations 2, 5, and 6 have a similar theoretical basis (9). However, they show over-or underestimation for the solute solubilities at individual f_c values. A possible reason for this is that the models have different independent variable arrangements that can affect the numerical values of the constants and therefore the prediction capability of the models. To provide more accurate solubility predictions, the mean predicted solubility (MPS) approach is proposed. The MPS is calculated by

$$MPS = \frac{(X_m)_{\text{Eq. 2}} + (X_m)_{\text{Eq. 5}} + (X_m)_{\text{Eq. 6}}}{3} \quad (7)$$

where $(X_m)_{\text{Eq. 2}}$, $(X_m)_{\text{Eq. 5}}$, and $(X_m)_{\text{Eq. 6}}$ are the predicted solubilities based on five data points as the training set using Eqs. 2, 5, and 6, respectively.

EXPERIMENTAL

Material

Furosemide was purchased from Chinoa (Hungary); ethanol, propylene glycol, glycerol, and methanol were analytical grade (Merck, Germany). Double-distilled water was used in this work.

Measurement of Solubility

An excess amount of furosemide was added to the solvent mixture in a sealed flask and incubated at 25°C using a thermostated water bath while shaking. The solvent mixtures were prepared using appropriate volume fractions of the cosolvents and water. The dissolution curves of furosemide dissolved versus time were studied. When the saturation concentration was attained (after 24 h), the solid phase was removed by filtration. The clear solution was diluted by a water-methanol mixture (50:50) and assayed using an ultraviolet-visible (UV-Vis) spectrophotometer (Shimadzu, Japan) at 275.4 nm. The density of the filtered solution was measured using a 10-ml pycnometer. Each experiment was repeated at least twice.

Computational Method

We evaluated the studied models two different ways. First, to assess the prediction ability of different models, the experimentally determined solubilities of furosemide at f_c 0, 0.2, 0.5, 0.8, and 1 were employed to calculate the constants of the models. Then, the trained models were used to predict the solubility of furosemide at other f_c values. The predicted solubilities were compared with real experimental data and the mean of the average percentage deviation (APD) was calculated as an accuracy criterion. In the second approach, the correlation ability of the models was assessed by fitting all data points to the models to obtain the constants. The back-calculated solubilities obtained in this way were compared with the experimental data. The APD was calculated using

$$APD = \frac{100}{N} \Sigma \frac{|X_m^{\text{Calculated}} - X_m^{\text{Observed}}|}{X_m^{\text{Observed}}}$$

where N is the number of data points in each set. All calculations were carried out using SPSS software.

RESULTS AND DISCUSSION

The experimental and predicted solubilities of furosemide at different concentrations of the cosolvents are shown in Table 1. In all of the studied cosolvents, the solubility of furosemide increased with an increase in the concentration of the cosolvent. However, the relationship between $-\ln X_m$ and f_c is not quite linear (Fig. 1). It can be seen that the solubilization power of the cosolvent (σ = slope of $-\ln X_m$ vs. f_c) is inversely related to the number of hydroxyl groups in the molecule. This observation can be quantitatively expressed by correlating σ and polarity of the cosolvents. The σ values for cosolvent systems prepared from ethanol, propylene glycol, and glycerol are 8.044, 7.916, and 4.071, respectively. The solubility parameter δ can be used as a measure of the

Table 1

The Experimental and Predicted Log Solubilities of Furosemide Using Different Equations

			Predicted Solubilities by Equation				
	f_c	Experimental	2	3	5	6	7
Cosolvent							
	0.00	−12.98	—	—	—	—	—
	0.05	−12.94	−12.87	−13.95	−13.06	−12.88	−12.93
	0.10	−12.74	−12.68	−13.49	−12.93	−12.63	−12.74
	0.20	−12.24	—	—	—	—	—
Ethanol	0.25	−11.73	−11.64	−11.61	−11.74	−11.59	−11.66
	0.30	−11.22	−11.19	−11.01	−11.19	−11.15	−11.18
	0.40	−9.86	−10.18	−9.88	−10.01	−10.20	−10.12
	0.50	−8.87	—	—	—	—	—
	0.60	−8.09	−8.08	−8.00	−7.91	−8.14	−8.04
	0.70	−7.18	−7.17	−7.26	−7.17	−7.20	−7.18
	0.80	−6.65	—	—	—	—	—
	0.90	−6.21	−6.05	−6.20	−6.31	−6.04	−6.13
	1.00	−6.03	—	—	—	—	—
Propylene glycol	0.00	−12.98	—	—	—	—	—
	0.05	−12.88	−12.90	−12.96	−12.81	−12.85	−12.85
	0.10	−12.57	−12.74	−12.73	−12.63	−12.69	−12.69
	0.20	−12.17	—	—	—	—	—
	0.25	−11.96	−11.93	−11.85	−11.89	−11.92	−11.91
	0.30	−11.71	−11.56	−11.50	−11.56	−11.57	−11.57
	0.40	−10.79	−10.72	−10.74	−10.80	−10.76	−10.76
	0.50	−9.90	—	—	—	—	—
	0.60	−8.85	−8.82	−8.97	−8.90	−8.85	−8.85
	0.70	−8.00	−7.86	−7.96	−7.86	−7.85	−7.86
	0.80	−6.88	—	—	—	—	—
	0.90	−6.23	−6.19	−5.77	−6.07	−6.13	−6.13
	1.00	−5.59	—	—	—	—	—
Glycerol	0.00	−12.98	—	—	—	—	—
	0.05	−13.01	−12.92	−13.00	−12.96	−12.94	−12.94
	0.10	−12.92	−12.86	−12.93	−12.92	−12.87	−12.88
	0.20	−12.74	—	—	—	—	—
	0.30	−12.48	−12.48	−12.48	−12.48	−12.47	−12.48
	0.40	−12.21	−12.20	−12.16	−12.16	−12.18	−12.18
	0.50	−11.79	—	—	—	—	—
	0.60	−11.49	−11.41	−11.36	−11.37	−11.41	−11.40
	0.70	−10.95	−10.89	−10.87	−10.89	−10.90	−10.89
	0.80	−10.32	—	—	—	—	—
	0.90	−9.50	−9.56	−9.69	−9.62	−9.58	−9.59
	1.00	−8.73	—	—	—	—	—

polarity of drug and cosolvents. The δ values for ethanol, propylene glycol, and glycerol are 13.0, 14.8, and 17.7 $(cal/cm^3)^{1/2}$, respectively (20). The solubility parameter of furosemide was calculated using Fedor's group contribution method (21). The value obtained is 13.5 $(cal/cm^3)^{1/2}$. The lower the solubility parameter of the cosolvent, the higher the σ value will be.

Based on the Hildebrand solubility approach, maximum solubility occurs when the solubility parameter of the solute is equal to that of the solvent. A suitable mathematical relationship between the physicochemical properties (like the solubility parameter) of the cosolvent and its solubilization power (σ) may be used to choose the best cosolvent at a minimum concentration.

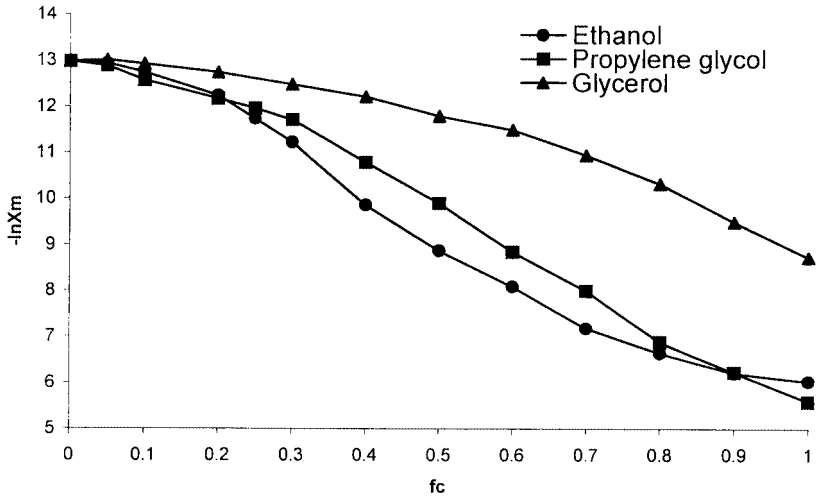

Figure 1. Logarithm of the mole fraction solubility of furosemide at different concentrations of the cosolvents f_c.

Because of possible toxicity of the cosolvent and also the cost of the final product, finding the optimum cosolvent and its concentration are of value in the pharmaceutical industry. Usually the optimum system is chosen by trial and error. It is, however, possible to employ mathematical relationships to reduce the number of required experiments.

Whole data points were fitted to the models, and the back-calculated solubility values were used to compute APD. This analysis shows the fitness of the models. The results are shown in Table 2. Investigation of the mean APD of correlated data points reveals that the order of accuracy of the models is as follows:

Eq. 5 > Eq. 7 > Eq. 2 > Eq. 6 > Eq. 3

In real conditions, one wishes to use the models for prediction purposes. To evaluate the predictive ability of the models, the five data points (experimental data at $f_c = 0$, 0.2, 0.5, 0.8, and 1) were employed to calculate the constants of the models, and then the solubilities at other f_c values were predicted. The predicted solubilities were used to calculate APD values. The following is the order of accuracy of different models in predicting solubility, as judged from the mean APD calculated for predicted data points in Table 2:

Eq. 7 > Eq. 2 > Eq. 5 > Eq. 6 > Eq. 3

As mentioned in the Introduction, the main aim of cosolvency modeling is to provide accurate predictions to

Table 2

*Average Percentage Deviation (*APD*) Values for Different Correlative and Predictive Equations Using Furosemide Solubility Data*

			Equation				
Numerical Method	Cosolvent	N[a]	2	3	5	6	7
Correlated data points	Ethanol	13	11.2	18.9	6.2	13.7	9.2
	Propylene glycol	13	5.7	10.8	5.3	5.6	5.2
	Glycerol	12	3.8	4.4	3.3	3.4	3.4
		Mean	6.9	11.4	4.9	7.5	5.9
Predicted data points	Ethanol	8	9.1	21.8	9.8	11.7	6.5
	Propylene glycol	8	7.3	15.1	8.1	7.0	7.0
	Glycerol	7	5.4	6.9	5.9	5.4	5.6
		Mean	7.3	14.6	7.9	8.0	6.4

[a] N is the number of correlated/predicted data points of each data set.

Table 3

Prediction Error Average Percentage Deviation (APD) for the Collected Solubility Data in Water-Ethanol and Water-Propylene Glycol Mixtures

Solute	Reference	N[a]	Equation				
			2	3	5	6	7
Oxolinic acid[b]	16	6	14.6	11.0	1.8	11.8	8.9
Paracetamol[b]	17	8	10.4	6.6	10.5	10.5	10.4
Sulfanilamide[b]	18	7	4.4	5.9	3.9	3.9	4.0
Butyl *p*-aminobenzoate[c]	19	6	8.5	9.4	8.7	6.7	8.0
Butyl *p*-hydroxybenzoate[c]	19	6	16.7	33.6	7.1	10.1	10.1
Ethyl *p*-aminobenzoate[c]	19	6	5.4	11.6	7.0	4.8	5.8
Ethyl *p*-hydroxybenzoate[c]	19	6	10.2	16.0	10.2	10.7	10.3
Methyl *p*-aminobenzoate[c]	19	6	3.3	8.0	4.8	3.0	3.5
Methyl *p*-hydroxybenzoate[c]	19	6	5.6	15.1	5.6	5.7	5.6
Propyl *p*-aminobenzoate[c]	19	6	6.9	12.5	7.9	6.7	7.0
Propyl *p*-hydroxybenzoate[c]	19	6	9.9	16.2	12.0	7.9	9.9
		Mean	8.7	13.3	7.2	7.4	7.6

[a] N is the number of predicted data points of each data set.
[b] The cosolvent was ethanol.
[c] The cosolvent was propylene glycol.

optimize the concentration of the cosolvent in liquid pharmaceutical formulations. To investigate the prediction capability of the models further, 11 previously published data sets in water-ethanol and water–propylene glycol mixtures were employed. The details of the data and resulting APD values are presented in Table 3. The accuracy order is

Eq. 5 > Eq. 6 > Eq. 7 > Eq. 2 > Eq. 3

Taking into account all 14 data sets studied in this work, the overall mean APD values were calculated (Fig. 2).

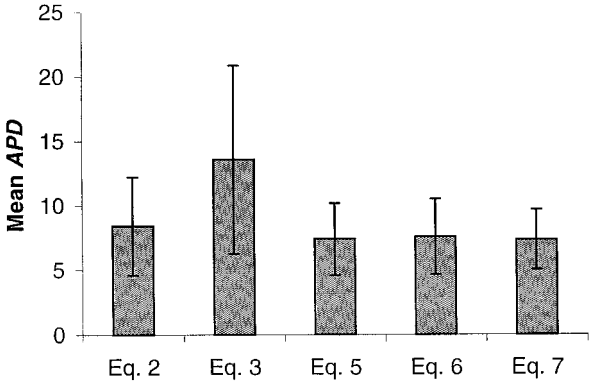

Figure 2. The mean APD values and their standard deviations for predicted solubilities using different equations.

Based on the results illustrated in Fig. 2, the overall order of accuracy is

Eq. 7 > Eq. 5 > Eq. 6 > Eq. 2 > Eq. 3

To test the statistical significance of the mean differences, one-way analysis of variance was used, and the results indicate that the mean differences are significant ($p < .001$). To determine if any equation behaved differently from the others, Duncan's multiple range test was employed. The results showed that there are no significant differences among Eqs. 2, 5, 6, and 7, however, Eq. 3 is different from the other models.

In conclusion, we showed that solubility prediction based on the minimum number of experiments gives reasonably accurate results, and one can use this method to save time and speed the process of optimization of the cosolvent concentration. A minimum number of experiments at f_c with equal intervals (e.g., 0, 0.25, 0.50, 0.75, and 1) may provide more accurate predictions with a percentage error of less than 10%.

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