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Il Farmaco 57 (2002) 555–557

IL FARMACO

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# Prediction of benzodiazepines solubility using different cosolvency models

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Received 3 December 2001; accepted 15 March 2002

**Abstract**

The solubility of four benzodiazepines (BZPs) including diazepam (DIZ), lorazepam (LRZ) clonazepam (CLZ), and chlordiazepoxide (CHZ) in water-cosolvent (ethanol propylene glycol and polyethylene glycol 200) binary systems were studied. In general, increasing the volume fraction of cosolvents resulted in an increase in the solubility of benzodiazepines. The mole fraction solubilities were fitted to the various cosolvency models, namely extended Hildebrand approach (EHA), excess free energy (EFE), combined nearly ideal binary solvent/Redlich-Kister (CNIBS/R-K), general single model (GSM), mixture response surface (MR-S), double log-log (DL-L), and linear double log-log (LDL-L). The results showed that DL-L model was the best model in predicting the solubility of all drugs in all the water–cosolvent mixtures (OAE% = 4.71). The minimum and maximum errors were observed for benzodiazepine's solubility in water–propylene glycol and water–ethanol mixtures which were 2.67 and 11.78%, respectively. Three models (EFE, CNIBS/R-K and LDL-L) were chosen as general models for solubility descriptions of these structurally similar drugs in each of the solvent systems. Among these models, the EFE model was the best in predicting the solubility of benzodiazepines in binary solvent mixtures (OAE% = 11.19). 

*Keywords:* Cosolvency models; Benzodiazepines; Binary solvent mixtures; Prediction of solubility

## 1. Introduction

Benzodiazepines (BZPs) are practically water insoluble drugs that are widely used as sedatives and hypnotics. Solubility characteristic of poorly soluble drugs like BZPs in water–cosolvent mixtures is important in the pharmaceutical industry, especially in the formulation of liquid dosage forms. Different methods were used for solubilization of benzodiazepines [1–5]. Most of the solubilization studies were focused on diazepam [1–4], and other BZPs received little attention, especially from cosolvency point of view.

A number of methods have been presented in order to estimate the solubility of drugs in solvent mixtures. These can be classified into three groups of theoretical, semiempericals based on the Hildebrand solubility approach and empirical methods [6–9]. The aim of the present study was to investigate the effect of different cosolvents on the solubility of BZPs and to compare the accuracy and predictability of different cosolvency models in fitting the BZPs solubility.

## 2. Materials and methods

BZPs including diazepam (DIZ), lorazepam (LRZ), clonazepam (CLZ) and chlordiazepoxide (CHZ) were prepared from Loghman Phamaceutical (Tehran, Iran). Cosolvents including ethanol (EtOH), propylene glycol (PG) and polyethylene glycol (PEG200) (Merck, Germany) were used.

Saturated solubilities of BZPs in water–cosolvent mixtures of various ratios were evaluated. Saturated solutions were prepared by adding excess drug to the vehicles and shaking for 24 h at 30 °C. The solutions were then filtered, diluted and analysed by UV spectrophotometer (Perkin–Elmer 402). The density of the saturated solutions was measured by pycnometer.

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0014-827X/02/$ - see front matter 
PII: S0014-827X(02)01247-8

### 2.1. Data fitting equations

In order to estimate solubility in binary solvent mixtures, various cosolvency models were used. These models enable us to predict and calculate the suitable solvent composition needed to make an acceptable formulation of poorly soluble drugs, especially in formulation of liquid dosage forms. Some of these models are theoretical, EFE (Eq. (1)) [7], CNIBS/R-K (Eq. (2)) [10], GSM (Eq. (3)) [11]; while others are semiempirical based on Hildebrand solubility approach, EHA (Eq. (4)) [12], or empirical, MR-S (Eq. (5)) [13], LDL-L (Eq. (6)) [12], DL-L (Eq. (7)) [14].

$$\log X_m = f_a \log X_a + f_b \log X_b + A_{1-3} f_a f_b (q_2/q_1) \quad (1)$$

where $X_m$ is the solute solubility in the solvent mixture, $f_a$ and $f_b$ are the volume fractions of the solvents a and b in the mixture, $X_a$ and $X_b$ denote the solubility in the neat solvents a and b, $A_{1-3}$ and $A_{3-1}$ represent the vapor pressure of the mixed solvent, and $q_1$ and $q_2$ are the molar volume of solvents a and b, respectively.

$$\log X_m = f_a \log X_a + f_b \log X_b + f_a f_b \Sigma S_i (f_a - f_b)^i \quad (2)$$

in which $S_i$ is the model constant and $i$ is equal to 0–3.

$$\log X_m = \Sigma B_j (f_a)^j \quad (3)$$

in which $B_j$ is the model constant and $j = 1$–5.

$$-\log X_m = -\log X_2^i + V_2 \phi_1^2 / 2.303RT(\delta_1^2 + \delta_2^2 - 2W) \quad (4)$$

where $X_2^i$ represents the ideal solubility, $V_2$ molar volume of solute, $\phi_1$ denotes the volume fraction of solvent, $R$ is the molar gas constant, $T$ is the absolute temperature, $\delta_1$ and $\delta_2$ are the solubility parameters of solvent and solute, respectively, $W$ represents the solute–solvent interaction and is calculated by the ($W = C_{0+} C_1\delta_1 + C_2\delta_1^2 + C_3\delta_1^3 + C_4\delta_1^4 + C_5\delta_1^5$) empirical power series expressed by this equation in which $C_0$–$C_5$ are the curve fitting parameters.

$$\log X_m = W_1 f'_a + W_2 f'_b + W_3 f'_a f'_b \quad (5)$$

Table 1
The percent average errors (AE%) of the different cosolvency models for each solvent system and the overall average errors (OAE%) and the best adherence percent (BA%)

| Equations | Water–PG | Water–PEG | Water–EtOH | OAE (%) |
|---|---|---|---|---|
| EHA | 6.86 | 4.63 | 11.76 | 7.75 |
| EFE | 4.21 | 8.81 | 8.90 | 7.31 |
| CNIBS/R-K | 3.99 | 7.80 | 8.10 | 6.63 |
| GSM | 6.91 | 10.51 | 9.93 | 9.12 |
| MR-S | 6.44 | 9.12 | 11.21 | 8.92 |
| LDL-L | 6.24 | 6.43 | | 6.33 |
| DL-L | 2.67 | 5.26 | 6.19 | 4.71 |

in which $W_1$–$W_3$ are the coefficients of the regression models and $f'_a$ and $f'_b$ are given by $f'_a = 0.96 f_a + 0.02$ and $f'_b = 0.96\ f_b + 0.02$.

$$\log[\log(X_m/X_b)] = \log\{\log[(X_m)_{0.5}/X_b]\} + \text{slope} \log(f_a/f_b) \text{ when } 0 < f_a \leq 0.5 \quad (6a)$$

$$\log[\log(X_a/X_m)] = \log\{\log[X_a/(X_m)_{0.5}]\} + \text{slope} \log(f_b/0.5) \text{ when } 0 < f_b \leq 0.5 \quad (6b)$$

$$\log(-\log X_m) = \Sigma B_k (\log f_a)^k \quad (k = -3, -2, -1, 0, 1, 2, 3) \quad (7)$$

$B_k$ is constant of the model. The percent average error was calculated for each drug in binary mixtures of a given water–cosolvent mixture using Eq. (8).

$$AE\% = 1/N\ \Sigma \left| 100[(X_m)_p - (X_m)_e]/(X_m)_p \right| \quad (8)$$

where $N$ is the number of data points, $(X_m)_p$ and $(X_m)_e$ denote the predicted and experimental mole fraction solubility at a given volume fraction of water–cosolvent. The percentage overall average error (OAE%) was calculated using Eq. (9).

$$OAE\% = (\Sigma\ AE\%)/Z \quad (9)$$

in which $Z$ is the number of cosolvents binary mixtures.

## 3. Results and discussion

In general, increasing the volume fraction of the cosolvents resulted in an increase in the solubility of drugs. The mole fraction solubilities were fitted into the cosolvency models. The average of AE% for DIZ, LRZ, CHZ and CLZ, and the percent overall average errors (OAE%) for the water–cosolvent systems for each model are shown in Table 1. The DL-L model is the best model in predicting the solubility of the benzodiazepines in all the water–cosolvent mixtures. OAE% for DL-L and LDL-L are 4.71 and 6.33, respectively, which are significantly lower than those for the other equations. Based on the results presented in Table 1, it can be concluded that the DL-L is the most accurate model for estimation of BZPs solubility in the experimented solvent mixtures. The ranking of models based on OAE% is represented as follows.

DL-L > LDL-L > CNIBS/R-K > EFE > EHA > MR-S > GSM.

Table 1 also shows that the drug solubility in water–EtOH mixture fits most poorly to all the models (the greatest AE%). This is probably due to the presence of

Table 2
The AE% of the different models for each of the drugs in water–EtOH solvent mixture

| Equations | DIZ | LRZ | CLZ | CHZ |
|---|---|---|---|---|
| EHA | 12.54 | 12.89 | 8.46 | 12.84 |
| EFE | 10.93 | 12.09 | 3.53 | 9.08 |
| CNIBS/R-K | 9.71 | 11.05 | 2.97 | 8.68 |
| GSM | 12.89 | 13.13 | 4.01 | 9.71 |
| DL-L | 9.57 | 9.41 | 0.96 | 4.82 |
| MR-S | 8.86 | 12.11 | 9.31 | 14.59 |

Table 3
The percent average errors of general equations for all solvent systems and data series

| | EFE | CNIBS/R-K | LDL-L | EHA |
|---|---|---|---|---|
| **Water–PG** | **11.26** | **10.99** [b] | **11.92** | **15.77** |
| DIZ | 6.00 | 5.32 [a] | 5.70 | 19.74 |
| LRZ | 10.25 [a] | 10.91 | 19.18 | 12.25 |
| CHZ | 12.96 | 12.52 | 9.84 [a] | 18.85 |
| CLZ | 15.83 | 15.22 | 12.96 [a] | 12.23 |
| **Water–EtOH** | **9.57** [b] | **9.88** | | **27.28** |
| DIZ | 4.87 [a] | 5.00 | | 20.32 |
| LRZ | 10.39 | 10.10 [a] | | 28.73 |
| CHZ | 10.58 [a] | 11.58 | | 25.73 |
| CLZ | 12.44 [a] | 12.82 | | 34.35 |
| **Water–PEG** | **14.25** | **14.04** | **11.48** [b] | |
| DIZ | 5.14 | 4.70 [a] | 10.03 | |
| LRZ | 10.43 [a] | 10.84 | 11.15 | |
| CHZ | 19.29 | 25.29 | 10.57 [a] | |
| CLZ | 16.13 | 15.34 | 14.19 [a] | |
| **OAE (%)** | 11.19 | 11.64 | 11.70 | 21.52 |
| **MD (%)** | 3.88 | 5.01 | 5.37 | 4.51 |

[a] The minimum of percent average errors calculated for each drug in a certain binary solvent system among the models.
[b] The minimum of percent average errors among the different models for all the drugs in a particular binary solvent mixture.

a peak in the graphs of solubility versus volume fraction of ethanol. The peak was observed for all the drugs except CLZ. Table 2 shows the AE% of the models for individual drugs in water–ethanol solvent mixtures. The minimum average error is observed for clonazepam (CLZ) due to the absence of a peak in the graphs of solubility.

Due to the structural similarity of BZPs, we sought for general equations capable of predicting the solubilities of all the drugs in each of the binary solvent mixtures. The models investigated in this way were LDL-L, EFE and CNIBS/R-K. The AE% of each drug in particular solvent system from the general equations, the AE% of all drugs in a certain solvent system, OAE%, and mean percent deviations of average errors (MD%), to the general equations are presented in Table 3. The table shows that the EFE model is the best model in terms of the lowest OAE% and MD%. The EFE model for the solubility of all the drugs in water–PG mixture is presented as an example:

Drugs in water–PG:

$$\log X_m = f_c \log X_c + f_w \log X_w + 1.00219 f_c^2 f_w - 0.79989 f_c f_w^2 + 1.705814 f_c^2 f_w^2$$

Drugs in water–EtOH:

$$\log X_m = f_c \log X_c + f_w \log X_w + 3.952059 f_c^2 f_w - 1.064829 f_c f_w^2 + 5.839277 f_c^2 f_w^2$$

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