Solubility of Lamotrigine and Diazepam in Propylene Glycol + Water + Carboxymethyl Cellulose at a Temperature of 298.2 K

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The simultaneous effects of propylene glycol and carboxymethyl cellulose (CMC) on the solubility of two antiepileptic drugs, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine (commonly known as lamotrigine) and 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-one (commonly known as diazepam), at $T = 298.2$ K were investigated. The aqueous solubility of drugs in the presence of propylene glycol and different concentrations of CMC [(0.02, 0.2, 1, and 2) $g \cdot L^{-1}$] increased. The data were fit to a modified version of the Jouyban−Acree model for modeling the simultaneous effects of the cosolvent and polymer on the solubility of drugs. The overall mean relative deviation (MRD) was 15.8 %, and the solubilities of drugs could be predicted at different propylene glycol and CMC concentrations using an interpolation technique.

Introduction

The solubility of drugs is an important and still challenging subject in the pharmaceutical industries because its knowledge makes it possible to choose the best solvent for dissolving a drug and solves various problems like medical solutions, injectable formulations, and low bioavailability of drugs.[1] In drug formulation investigations, there are different methods for modifying drug solubility such as crystallization, oil formulations, complexation, salt formation, using pro-drugs, and cosolvency.[2−6] The cosolvency or addition of a cosolvent (permissible organic solvent) to the aqueous solution to alter the solubility of drugs is the most commonly used method. It must be noticed that, in the pharmaceutical industry, the toxicity of the cosolvents is another important issue and the cosolvent concentration should be kept as low as possible. The often-used method to optimize the solvent composition of solvent mixtures for dissolving a desired amount of a drug in a given volume of the solution is the trial-and-error approach, which is time-consuming and expensive.

Using the polymers as an adjutant ingredient for various purposes such as loading a drug is very common. The addition of polymers causes alterations in the solubility of drugs,[7,8] decreasing the gastrointestinal side effects and toxicity of drugs,[9,10] decreasing the dermal irritation of some skin products,[11] changing target therapy in cancers,[12] masking the unfavorable taste of some drugs, avoiding the fast elimination of drugs, and producing the pH-resistant formulations.[13−15]

To continue our systematic investigations on the solubility of drugs in water + cosolvent mixtures, the available cosolvency models and their advantages and limitations were recently reviewed.[16] Of the numerous models developed in recent years, the Jouyban−Acree model is perhaps one of the more versatile models. The model provides very accurate mathematical descriptions for how the solute solubility varies with both temperature and solvent composition. The model for representing the solubility of a solute in a binary mixture at various temperatures is

$$\log w_{2,m}^{Sat} = w_3 \log w_{2,3}^{Sat} + w_4 \log w_{2,4}^{Sat} + \left[\frac{w_3 w_4}{T/K}\sum_{i=0}^{2} J_i (w_3 - w_4)^i\right] \quad (1)$$

where $w_{2,m}^{Sat}$ is the solute mass fraction solubility in the mixtures at temperature T, w_3 and w_4 denote propylene glycol and water mass fractions in the absence of the solute and polymer, $w_{2,3}^{Sat}$ and $w_{2,4}^{Sat}$ denote the mass fraction solubility of the solute in the propylene glycol and water in the presence of polymer, respectively, and J_i are the constants of the model computed by a regression analysis.[16] To represent the simultaneous effects of cosolvent and polymer on the solubility of drugs, eq 1 was modified as[17]

$$\log w_{2,m}^{Sat} = (w_3 - w_1)\log w_{2,3}^{Sat,w_1=0} + (w_4 - w_1)\log w_{2,4}^{Sat,w_1=0} + \left[\frac{(w_3 - w_1)(w_4 - w_1)}{T/K}\sum_{i=0}^{2} A_i\{(w_3 - w_1) - (w_4 - w_1)\}^i\right] \quad (2)$$

where $w_{2,3}^{Sat,w_1=0}$ and $w_{2,4}^{Sat,w_1=0}$ are the mass fraction solubility of the solute in the neat propylene glycol and water in the absence of polymer ($w_1 = 0$), taken from a previous work,[18] so we do not need to measure the drug's solubility in pure solvents in the presence of carboxymethyl cellulose (CMC), and A_i is the model constant.

Experimental solubilities of several antiepileptic drugs in propylene glycol + water mixtures (in the absence of polymers) were reported in a previous work.[18] In this work, the experimental solubilities of lamotrigine and diazepam in propylene glycol + water mixtures in the presence of four different concentrations of CMC at $T = 298.2$ K are reported. There were no published data on the solubility of these drugs in CMC + propylene glycol + water mixtures in the literature. In addition, the applicability of a modified version of the Jouyban−Acree model to the measured drug solubility is illustrated.

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Table 1. Details of Calibration Curves of Drugs

drug	ε / L·mol^{-1}·cm^{-1}	C / mol·L^{-1}	correlation coefficient (standard error)	calibration curve (A: absorbance)
lamotrigine	8283 to 8597	$2.2\cdot10^{-5}$ to $6.6\cdot10^{-5}$	0.999 (0.001)	$A = 8136.9C + 0.0102$
diazepam	10835 to 11454	$2.2\cdot10^{-5}$ to $6.7\cdot10^{-5}$	0.998 (0.018)	$A = 11637.0C - 0.0201$

Experimental Method

Materials. 6-(2,3-Dichlorophenyl)-1,2,4-triazine-3,5-diamine (commonly known as lamotrigine) with a mass fraction purity of 0.996 and CAS No. 84057-84-1 was purchased from Arastoo Pharmaceutical Company (Iran), and 7-chloro-1-methyl-5-phenyl-3*H*-1,4-benzodiazepin-2-one (commonly known as diazepam) with a mass fraction purity of 0.997 and CAS No. 439-14-5 was purchased from Sobhan Pharmaceutical Company (Iran). The purity of these chemicals was checked by the determination of their melting temperatures of 489.2 K for lamotrigine that compares favorably with the literature values of (489.2 to 491.2) K[19] and a temperature of 405.2 K for diazepam which lies within the temperature range of (404.2 to 408.2) K reported in ref 19. In addition, a comparison of the measured solubilities in monosolvents with the corresponding data from the literature was also favorable.[20−23] Drug powders were used as received from the pharmaceutical company, and no further purification was done on the powders. Propylene glycol (with a mass fraction purity of 0.995) was purchased from Merck (Germany), and CMC (as sodium salt with the mass fraction purity of 0.995) was purchased from Dow wolff Cellulosics GmbH (Germany). Double-distilled water was used for preparation of the solutions.

Apparatus and Procedures. The binary solvent mixtures were prepared by mixing the appropriate volumes of the solvents with the uncertainty of 0.1 mL. The volume fractions were converted to mass fractions by employing the density of the solvents. The solubility of lamotrigine and diazepam in the presence of four different concentrations of CMC in propylene glycol + water mixtures was determined by equilibrating an excess amount of the solid at a temperature of 298.2 K using a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system maintained constant to within ± 0.2 K (Nabziran, Tabriz, Iran). After a sufficient length of time (> 72 h), the saturated solutions of the drugs were centrifuged at 12 000 rpm for a time of 420 s, diluted with water, and then assayed at (306 and 250) nm, respectively, for lamotrigine and diazepam, using a UV−vis spectrophotometer (Beckman DU-650, Fullerton, USA). Concentrations of the diluted solutions were determined from the calibration curves. Details of calibration curves were shown in Table 1. Each experimental data point represents the average of at least three repetitive experiments with the measured mol·L^{-1} solubilities being reproducible to within ± 3.5 %. Calculated standard deviations of solubilities (mol·L^{-1}) ranged from $\sigma_{n-1} = 0.0000024$ to $\sigma_{n-1} = 0.0150311$.

Computational Methods. The mass fraction solubility is calculated using

$$w_2 = \frac{\text{grams of solute}}{\text{grams of CMC} + \text{grams of solute} + \text{grams of propylene glycol} + \text{grams of water}} \quad (3)$$

The experimental solubility data of each drug in the binary solvents and different concentrations of CMC [(0, 0.02, 0.2, 1, and 2) g·L^{-1}] were regressed using eq 2 by employing the experimental solubilities of drugs in neat propylene glycol and water taken from a previous work.[18] The mean relative deviation (MRD) was used to check the accuracy of the prediction methods and is calculated using

$$\text{MRD} = \frac{\sum\left\{\dfrac{|(w_{2,\text{m}}^{\text{Sat}})_{\text{calculated}} - (w_{2,\text{m}}^{\text{Sat}})|}{(w_{2,\text{m}}^{\text{Sat}})}\right\}}{N} \quad (4)$$

where N is the number of data points in each set. All computations were carried out using the statistical package for the social sciences (SPSS).

Table 2. Experimental Molarity $C_{\text{m}}^{\text{Sat}}$ and Mass Fraction $w_{2,\text{m}}^{\text{Sat}}$ Solubilities of Diazepam (2), in Propylene Glycol (3) + Water (4) Mixtures in the Presence of Various Concentrations of CMC (1) Expressed as a Mass Fraction of CMC (w_1) at a Temperature of 298.2 K

w_3	w_1	$C_{\text{m}}^{\text{Sat}}$/mol·L^{-1}	$w_{2,\text{m}}^{\text{Sat}}$
	CMC 0.02 g·L^{-1}		
0.09683	0.00002	0.00023	0.00007
0.19433	0.00002	0.00045	0.00013
0.29250	0.00002	0.00084	0.00024
0.39129	0.00002	0.00162	0.00047
0.49058	0.00002	0.00357	0.00103
0.59012	0.00002	0.00751	0.00218
0.68896	0.00002	0.01734	0.00504
0.78776	0.00002	0.02802	0.00814
0.88632	0.00002	0.03994	0.01161
	CMC 0.2 g·L^{-1}		
0.09681	0.00020	0.00025	0.00007
0.19430	0.00020	0.00043	0.00012
0.29245	0.00020	0.00080	0.00023
0.39120	0.00020	0.00175	0.00050
0.49052	0.00020	0.00332	0.00096
0.58996	0.00020	0.00779	0.00226
0.68908	0.00020	0.01613	0.00468
0.78780	0.00020	0.02721	0.00790
0.88694	0.00020	0.03691	0.01073
	CMC 1 g·L^{-1}		
0.09674	0.00100	0.00024	0.00007
0.19414	0.00101	0.00042	0.00012
0.29221	0.00101	0.00074	0.00021
0.39088	0.00101	0.00177	0.00051
0.49014	0.00102	0.00317	0.00092
0.58964	0.00102	0.00686	0.00199
0.68870	0.00102	0.01522	0.00442
0.78772	0.00102	0.02473	0.00718
0.88642	0.00102	0.03610	0.01049
	CMC 2 g·L^{-1}		
0.09664	0.00200	0.00023	0.00006
0.19395	0.00201	0.00044	0.00013
0.29192	0.00202	0.00069	0.00020
0.39049	0.00202	0.00173	0.00050
0.48968	0.00203	0.00296	0.00086
0.58908	0.00203	0.00665	0.00193
0.68860	0.00204	0.01219	0.00354
0.78769	0.00204	0.02135	0.00620
0.88750	0.00204	0.02842	0.00827

Results and Discussion

Tables 2 and 3 list the experimental solubilities of lamotrigine and diazepam in propylene glycol + water mixtures in the presence of different concentrations of CMC at a temperature of 298.2 K. The solubility of drugs increased with the addition

Table 3. Experimental Molarity C_m^{Sat} and Mass Fraction $w_{2,m}^{Sat}$ Solubilities of Lamotrigine (2), in Propylene Glycol (3) + Water (4) Mixtures in the Presence of Various Concentrations of CMC (1) Expressed as a Mass Fraction of CMC (w_1) at a Temperature of 298.2 K

w_3	w_1	C_m^{Sat}/mol·L^{-1}	$w_{2,m}^{Sat}$
	CMC 0.02 g·L^{-1}		
0.09682	0.00002	0.00049	0.00013
0.19432	0.00002	0.00078	0.00020
0.29243	0.00002	0.00179	0.00046
0.39103	0.00002	0.00433	0.00112
0.48990	0.00002	0.00931	0.00242
0.58757	0.00002	0.02497	0.00649
0.68040	0.00002	0.06748	0.01741
0.76768	0.00002	0.13125	0.03342
0.82646	0.00002	0.32156	0.07836
	CMC 0.2 g·L^{-1}		
0.09681	0.00020	0.00050	0.00013
0.19428	0.00020	0.00073	0.00019
0.29240	0.00020	0.00145	0.00037
0.39105	0.00020	0.00341	0.00089
0.48986	0.00020	0.00891	0.00232
0.58763	0.00020	0.02385	0.00620
0.68191	0.00020	0.05821	0.01505
0.77160	0.00020	0.11058	0.02830
0.83823	0.00019	0.26325	0.06507
	CMC 1 g·L^{-1}		
0.09673	0.00100	0.00046	0.00012
0.19412	0.00101	0.00080	0.00021
0.29217	0.00101	0.00147	0.00038
0.39067	0.00101	0.00405	0.00105
0.48954	0.00101	0.00827	0.00215
0.58746	0.00101	0.02185	0.00568
0.68168	0.00101	0.05635	0.01456
0.77134	0.00100	0.10878	0.02783
0.84683	0.00098	0.21904	0.05469
	CMC 2 g·L^{-1}		
0.09663	0.00200	0.00059	0.00015
0.19393	0.00201	0.00082	0.00021
0.29187	0.00202	0.00143	0.00037
0.39029	0.00202	0.00393	0.00102
0.48923	0.00203	0.00683	0.00177
0.58897	0.00203	0.00811	0.00211
0.68512	0.00203	0.03303	0.00858
0.77583	0.00201	0.08227	0.02117
0.85141	0.00196	0.19359	0.04860

of propylene glycol at a given concentration of CMC. In the presence of different concentrations of CMC in the water-rich regions there is no significant change in solubility data, but in propylene glycol-rich regions, there is a significant decrease in solubility.

The generated data was fitted to eq 2, and the back-calculated solubilities were compared with the corresponding experimental data. The model constant and MRD values for lamotrigine and diazepam were computed and listed in Table 4. The lowest MRD (6.0 %) belongs to diazepam in the presence of 1 g·L^{-1} of CMC, and the highest one (43.5 %) belongs to lamotrigine in the presence of 2 g·L^{-1} of CMC. The overall MRD values were 8.9 % ($N = 36$) and 22.6 % ($N = 36$), respectively, for diazepam and lamotrigine, and the overall MRD was 15.8 %.

Fitting the experimental data of a drug in a given concentration of a polymer to eq 1 provides better results as it has been shown in an earlier paper;[17] however, to provide predictive models to be used in the pharmaceutical industry, we prefer to use eq 2, since it does not require any more data in monosolvent or mixed solvents after training by a minimum number of experimental data in solvent mixtures in the presence of a polymer.

Generally the overall MRD observed in these calculations shows that the Jouyban−Acree model is robust and could be used for prediction purposes with the error of 15.8 % using an interpolation technique. The produced error is in good agreement with that of a previous solubility data set of diazepam and lamotrigine in poly(vinyl pyrrolidone) + ethanol + water mixtures.[17]

Table 4. Model Constants and the MRDs of Equation 2

	N	A_0	A_1	A_2	100 MRD
diazepam[a]		187.605	397.361	257.422	
CMC 0.02 g·L^{-1}	9				9.2
CMC 0.2 g·L^{-1}	9				8.1
CMC 1 g·L^{-1}	9				6.0
CMC 2 g·L^{-1}C	9				12.4
					overall
					MRD: 8.9
lamotrigine[a]		−99.392	993.265	*b*	
CMC 0.02 g·L^{-1}	9				19.1
CMC 0.2 g·L^{-1}	9				14.1
CMC 1 g·L^{-1}	9				14.0
CMC 2 g·L^{-1}	9				43.5
					overall
					MRD: 22.6

[a] Solubility data of diazepam and lamotrigine in propylene glycol + water mixtures in the absence of CMC[18] was also included in the calculation of model constants. [b] Not significant.

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