Solubility of three basic drugs in propylene glycol + water mixtures in the presence of β-cyclodextrin

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Cosolvency and complex formation are the important methods to increase the solubility of drugs. These methods can be used to change solubility simultaneously. In this study, solubilities of three basic drugs, i.e. atenolol, diazepam and lamotrigine, were studied in binary mixtures of propylene glycol + water in the presence of cyclodextrin (CD) and atenolol in this solvent mixture in the absence of CD using saturating shake flask method. The generated solubility data was fitted to the Jouyban-Acree model and the solubility profile of each drug was compared with solubility data in the absence of CD that the solubility data of diazepam and lamotrigine taken from the literature.

Key words: Solubility – Cosolvency – Complexing agent – Jouyban-Acree model.

One of the crucial physicochemical properties in different stage of drug discovery and development is solubility [1]. Solubilization of drugs is very important to improve bioavailability and preparation of liquid dosage forms [2]. The more common methods to increase the aqueous solubility of sparingly soluble drugs are addition of 1) a cosolvent, 2) a surface active agent, 3) a hydrotropic agent, 4) a complexing agent and 5) other methods including the combined methods. Their effectiveness was compared by Rubino [3]. The graphical presentation of the solubility of pharmaceuticals against the added concentration of the above discussed solubilizing agents show linear, log-linear and a curve with a maximum patterns depend on the nature of the solute and solubilizing agent. There are similarities within solubilization mechanisms on the other hand, some agents possess dual actions (as examples; hydrotropic and complexing actions for sodium salicylate and nicotinamide [4] or cosolvent and surface active agent actions for polypropylene glycol ethers [5]). Some authors have stated that there is no need to distinguish between different types of solubilizing agents [6]. One of the simple and common method to improve solubility of a drug is cosolveny. Cosolvency or solvent mixing was used to prepare topical, oral and parental dosage forms of poorly soluble drugs [7]. One of the common cosolvents in pharmaceutical sciences is propylene glycol (PG). It is stable and low toxic cosolvent that was used in preparation of many commercially available oral pharmaceutical products to solubilization of poorly soluble drugs. It can be used in high concentrations in the parenteral formulations such as oxytetracycline (67 to 75%), lorazepam (80%) and phenobarbital (68%) [2]. So solubility data of drugs in PG + water mixtures can be used in designing of required formulations and also it can help to understand the mechanism of solubility of drugs in these mixtures. Solubility of three antiepileptic drugs in PG + water mixtures in the absence of cyclodextrin (CD) was reported earlier [8]. Another useful method for solubilization of drugs is the addition of the complexing agents. They were used to improve the solubility of drugs as well as their stability and bioavailability. The main complexing agents in the pharmaceutical industries are cyclodextrins (CDs). They were applied in parenteral and intravenous solutions, tablet, ointment, suppository, eye drop and nasal spray formulations. CDs are used in preparation of nanparticles [9], polymer nanoparticles in drug delivery [10] e.g. for oral delivery of proteins [11]. They also can form stabilized dispersed systems [12]. In addition, CDs were used in drug delivery of lipophilic drugs [13-14]. The CDs have a central cavity that lipophilic moieties of drugs import in this cavity and drug-CD complex can be formed using non-covalent bonds. Kurkov and Loftsson reviewed the pharmaceutical applications of CDs [15] and Gref and Duchene [10] reviewed the applications of CDs in new drug delivery systems.

In some applications, a combination of the cosolvents and CDs was used to improve the solubility of drugs. The effect of ethanol on the complex formation of hydroxypropyl-β-cyclodextrin (HP-β-CD) with oleanolic acid and ursolic acid was studied by Li and coworkers [16]. Yalkowsky and coworker studied the effect of HP-β-CD on solubility of fluasterone in solvent mixtures. They concluded that cosolvent size and polarity, destabilization of drug-ligand complex and the formation of a ternary drug-ligand-cosolvent complex affect the fluasterone solubility [17].

Determination of solubility is a time consuming process and mathematical models could be used to predict drugs solubility as an alternative method. The Jouyban-Acree model was used to predict the solubility of drugs in solvent mixtures at a given temperature [7]:

$$\log C_m = f_1 \log C_1 + f_2 \log C_2 + \sum_{i=0}^{2} J_i \left[f_1 f_2 (f_1 - f_2)^2 \right] \qquad \textbf{Eq. 1}$$

C_m is the solubility in solvent mixture in mol.L^{-1} unit, C_1 and C_2 the solubility in neat solvents and f_1 and f_2 are volume fractions of solvents 1 and 2, respectively, and J_i terms are the model constants. This model requires two solubility data in the mono-solvents.

The solubility of diazepam and lamotrigine was reported in a previous work [8]. In this study, solubility data of atenolol in PG + water and with previous two studied drugs in this system at 25 °C in presence of 10 mM of CD were determined. The effects of different concentrations of PG + water on the solubility of drugs in the presence of CD were studied. In addition, solubility values were fitted to the Jouyban-Acree model and fitting accuracy of solubility data to this model was evaluated.

I. METHODS AND MATERIALS

1. Materials

Atenolol was purchased from Darou Pakhsh (Tehran, Iran), diazepam was gifted by Sobhan pharmaceutical company (Rasht, Iran),

lamotrigine and naproxen were purchased from Arastoo company (Tehran, Iran) and Mehban Shimi (Tehran, Iran), respectively. PG (> 0.99 mass fraction) was purchased from Scharlau (Spain), β-CD (0.99 mass fraction) from Merck (Germany) and distillated water used for preparation of the solutions and ethanol (0.935 mass fraction) from Jahan Alcohol Teb (Arak, Iran) was used for dilution of the saturated solutions for spectroscopic analyses.

2. Experimental methods

The binary solvent mixtures of PG + water were prepared by volume with the uncertainty of 0.01 mL and the 10 mM CD was added to each mixture. Different methods were presented for determining the solubility of drugs [18]. The solubility of studied drugs was determined using classical saturating shake-flask method. The excess drug was added to the prepared solutions and then they were inserted in a shaker (Behdad, Tehran, Iran) placed in an incubator equipped with a temperature-controlling system having uncertainty of 0.2 °C (Nabziran, Tabriz, Iran). After equilibrium (> 3 days), the saturated solution were centrifuged in 10000 rpm for 10 min (MSEMicro Center MSB010.CX2.5, Sanyo, Muriguchi City, Japan) and diluted by ethanol. The absorption of diluted solution were determined by ultraviolet-visible spectrophotometer (BeckmanDU-650, Fullerton, California, United States), according to their calibration curves. Solubility data of diazepam and lamotrigine was collected from a previous report [8] and the solubility of atenolol in PG + water mixtures in the absence of β-CD was determined in this work.

3. Computational methods

The experimental solubility data of drugs in PG + water + 10 mM CD was fitted to *Equation 1*. The required data points to predict the solubility data to this model are the solubility data in the mono-solvents. The fitted data of each drug in the studied systems and the back calculated solubilities were used to calculate the accuracy of fitness using mean deviation (MD) calculated using following equation:

$$MD = \frac{100}{N}\sum \left| \frac{C_{m,cal} - C_{m,\exp}}{C_{m,\exp}} \right| \qquad \textbf{Eq. 2}$$

II. RESULTS AND DISCUSSION

The experimental solubilities of the studied drugs in PG + water + 10 mM CD solution at 25 °C are listed in *Table I*. Each experimental data point is the average of at least three repeated measurements with the measured mole per liter solubilities being reproducible to within relative standard deviations (RSD) ranged from 0.3 to 4.9 %.

Figure 1 shows the solubility profile of atenolol in PG + water and PG + water + 10 mM CD mixtures. Aqueous solubility of atenolol obtained in this work is 0.06968 M and no significant increase is observed after addition of 10 mM CD. These findings are in agreement with the results of Ficarra *et al*. [19] where the solubilities in water and in water + 10 mM CD were reported as 0.071 M and 0.077 M, respectively. Mole fraction solubility of atenolol in aqueous buffer (pH 7.4) at 15, 20, 25, 30, 37 and 42 °C was reported as 0.00127, 0.00137, 0.00149, 0.00175 and 0.00193 [20]. The solubility of atenolol in PG + water mixtures was increased with the addition of PG, and then reached to the maximum value at 0.80 of PG and decreased with further addition of PG. This is not a common solubility pattern for PG + water mixtures where the maximum solubility is observed in neat PG, however, it is observed for atenolol and some other drugs, as an example for amlodipine besylate [21]. Addition of 10 mM CD changes the solubility of atenolol slightly as it is evident from *Figure 1*. There are some evidence from the literature on the formation of an inclusion complex between atenolol and CD [19, 22]. A possible reason for similar solubility pattern for atenolol in PG + water and PG + water + CD could be equal solubility of atenolol and its complexed form in the solutions.

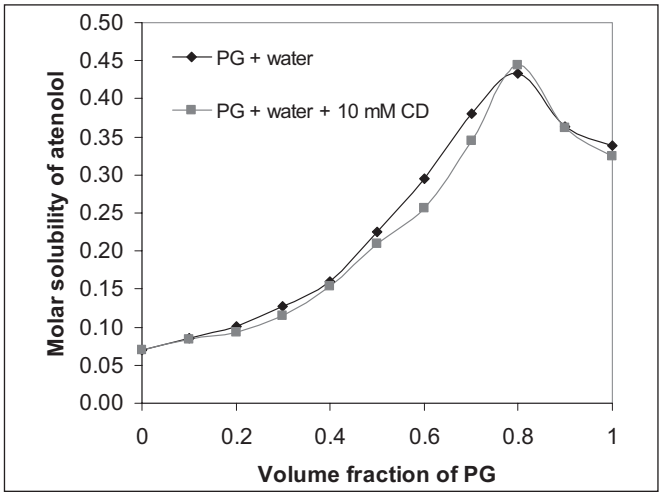

Figure 1 - Solubility profile of atenolol.

A generally trained version of the Jouyban-Acree model was proposed for predicting the solubility of drugs in PG + water mixtures at various temperatures (T) as [23]:

$$\log C_m = f_1 \log C_1 + f_2 \log C_2 + \left[\frac{37.03 f_1 f_2}{T} + \frac{319.490 f_1 f_2 (f_1 - f_2)}{T} \right] \qquad \textbf{Eq. 3}$$

The solubility of atenolol in PG + water mixtures is predicted using *Equation 3* and the obtained MD values is 17.5 %. The main advantage of *Equation 3* is that it requires the minimum experimental efforts, i.e. the solubility of a drug in the neat PG and water.

Figure 2 illustrates the solubility of diazepam in PG + water in the absence of CD [8] and in the presence of 10 mM CD. The aqueous solubility of diazepam is increased from 0.00015 M [8] (or 0.0001756 M [24], 0.0000232 M [25], 0.0001089 M [26], 0.0001510 M [27]) to 0.00558 M (solubility enhancement factor of 558) revealing the formation of a complex between diazepam and CD. Comparisons of the solubility of diazepam in water + CD and PG + CD mixtures with their corresponding values in the absence of CD reveal that the solubility of diazepam-CD complex is more than that of diazepam. The increased pattern of the solubility of diazepam is observed in PG + water + 10 mM CD mixtures revealing the possible formation of a ternary complex of diazepam-PG-CD and better solibilization of diazepam-CD complex in the presence of PG.

Figure 3 shows the solubility of lamotrigine in PG + water taken from a previous work [8] and in PG + water + 10 mM CD. The aqueous solubility of lamotrigine is increased from 0.00073 M [8] (or

Table I - Molar solubilities of atenolol, diazepam and lamotrigine in the investigated systems at 25 ºC.

Volume fraction of PG	Solvent system			
	Atenolol PG + water	Atenolol PG + water + CD	Diazepam PG + water + CD	Lamotrigine PG + water + CD
0.00	0.06968	0.06987	0.00558	0.00238
0.10	0.08509	0.08364	0.00556	0.00206
0.20	0.10075	0.09354	0.00717	0.00238
0.30	0.12733	0.11480	0.01263	0.00401
0.40	0.15917	0.15391	0.01758	0.00746
0.50	0.22438	0.20962	0.03951	0.01564
0.60	0.29559	0.25642	0.07752	0.03048
0.70	0.38104	0.34483	0.12921	0.08300
0.80	0.43267	0.44424	0.11319	0.15490
0.90	0.36331	0.36112	0.09004	0.08292
1.00	0.33924	0.32505	0.05641	0.04757

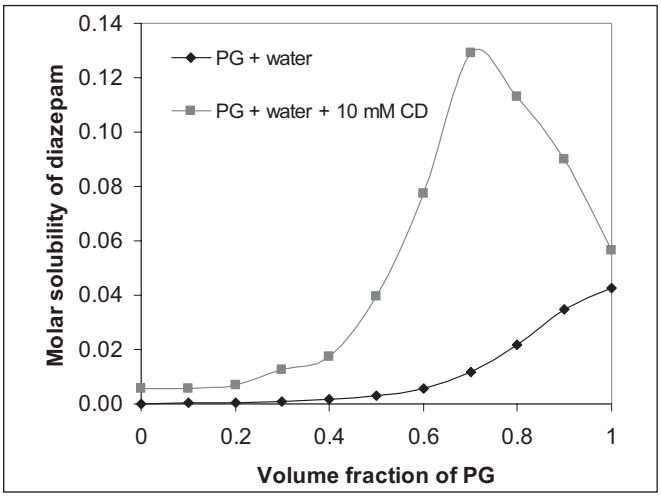

Figure 2 - Solubility profile of diazepam.

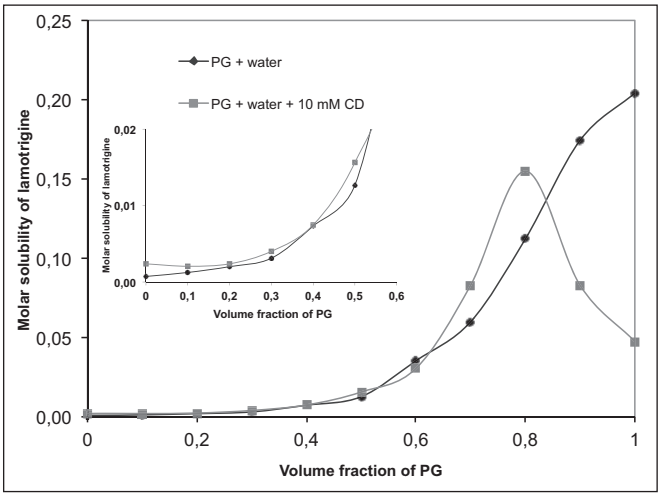

Figure 3 - Solubility profile of lamotrigine.

0.000664 M [28], 0.000898 M [29]) to 0.00238 M (solubility enhancement factor of 3.3). Formation of a complex between lamotrigine and CD is confirmed by earlier observations [30]. An increased solubility of lamotrigine in water at 25 °C by 1:1 inclusion complex of β-CD was reported by enhancement factor of 2.05 [28]. The increased pattern of the solubility of lamotrigine is observed in PG + water + 10 mM CD up to the 0.80 volume fraction of PG and further addition of PG was increased the solubility of lamotrigine even to less than its solubility in the absence of CD. A similar observation has been reported by Müller and Albers [31] where the solubility of methyltestosterone in the presence of a given concentration of 2-HP-β-CD was reduced by addition of increased concentrations of PG. The solubility reduction could be due to the complex dissociation in higher concentrations of the cosolvent [31]. Lamotrigine is a weak basic compound with the acid dissociation constant of 5.7 and it is expected to show more solubility in acidic solutions as evident from the literature data, i.e 0.00865 M in 0.1 M HCl [28]. Rahman *et al*. reported the solubility of lamotrigine in different pH values as 0.003553 M, 0.021477 M, 0.012378 M, 0.006873 M, 0.003475 M, 0.001445 M and 0.000625 M for pH values of 1.2, 2, 3, 4, 5, 6, 7 and 8, respectively [29].

Table II lists the model constants of fitting data to the *Equation 1* and MD values of each studied system. These findings show that the solubility data in PG + water and in PG + water + 10 mM CD could be fitted to the *Equation 1* with good accuracy.

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In conclusion, the generated data in this work extends the available solubility database of pharmaceuticals [32] and could be used in the pharmaceutical industries. There are good agreements between generated data in this work and the previously reported data in the literature. The Jouyban-Acree model fits very well to the data and could be used to predict the solubility data at other PG + water solvent compositions.

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Table II - Numerical values of the adjusted parameters of *Equation 1* and the mean deviation (MD) for the fitting solubilities of atenolol, diazepam and lamotrigine in PG + water mixtures and in presence of 10 mM CD.

Drug	Solvent system	J_0	J_1	J_2	MD
Atenolol	PG + water	195.715	299.513	0**	4.2
	PG + water + 10 mM CD	176.422	349.473	0**	3.6
Diazepam*	PG + water	61.681	133.889	684.395	5.7
	PG + water + 10 mM CD	433.870	995.795	-70.400	8.1
Lamotrigine*	PG + water	76.860	471.556	252.450	5.9
	PG + water + 10 mM CD	210.971	1402.150	471.292	9.4

*Data taken from a previous study [8]. **The value is not statistically significant ($p > 0.1$).

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ACKNOWLEDGMENT

The partial financial support of this work is provided by Islamic Azad University, Tabriz Branch is gratefully acknowledged.

MANUSCRIPT

Received 8 October 2012, accepted for publication 13 November 2012.