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Research Article

Solubility of Sodium Phenytoin in Propylene Glycol + Water Mixtures in the Presence of β-Cyclodextrin

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ABSTRACT

Background: Poor aqueous solubility of drugs is still a challenging aspect in drug discovery and development. Solubilization techniques such as cosolvency and complexation are used to solubilize poorly soluble drugs. A number of mathematical models presented for predicting the solubility of drugs in water+cosolvent mixtures and the Jouyban-Acree model promises more accuracy when compared with other algorithms. ***Methods:*** Solubility of sodium phenytoin in binary mixtures of propylene glycol + water in the presence of beta-cyclodextrin (β-CD) along with the solubility of sodium phenytoin in this solvent mixture in the absence of β-CD using saturating shake flask method were studied. The generated solubility data was fitted to the Jouyban-Acree model and the solubility profile of drug in the presence of β-CD was compared with solubility data in the absence of β-CD. ***Results:*** The solubility was increased by addition of propylene glycol and was decreased by addition of beta-cyclodextrin. The measured solubility data were used to evaluate the correlation ability of the Jouyban-Acree model employing the solubility data in monosolvent. These findings are supported by acceptable mean relative deviations values obtained when comparing the estimated and experimental solubilities. ***Conclusion:*** The addition of β-CD was decreased the solubilization power of propylene glycol.

Introduction

Solubility of drugs is an essential information in drug discovery and development investigations.[1] Solubilization of low-soluble drugs are required to improve their bioavailability and preparation of liquid dosage forms.[2] Cosolvency or solvent mixing is a commonly used solubilization method to prepare topical, oral and parenteral dosage forms of low-soluble drugs.[3] Propylene glycol (PG) is an odorless, colourless, viscous liquid that contains two hydroxyl groups. PG or 1,2-propanediol is considered as a relatively safe cosolvent which is used in oral, intravenous and topical pharmaceutical formulations.[4]
Complex formation of drugs with cyclodextrins (CDs) is another method for solubilization which are used alone or in combination with other solubilization agents such as surfactants or cosolvents. CDs mainly beta-cyclodextrin (β-CD) are used in the solubilization and/or stabilization of drugs in parenteral solutions, tablet, ointment, suppository, eye drop and nasal spray formulations.
Combination of the cosolvents and CDs are used to improve the aqueous solubility of drugs and was concluded that cosolvent size and polarity, destabilization of drug–ligand complex and the formation of a ternary drug–ligand–cosolvent complex affect the solubility of drugs.[5,6]
Solubilities of lamotrigine, diazepam and clonazepam in PG + water mixtures in the absence[7] and presence of β-CD[8] were reported. In this study, solubility of sodium phenytoin (for chemical structure see Figure 1) in PG + water mixtures in the presence of 5 or 10 mM of β-CD at 25 ºC are determined and mathematically represented using a common cosolvency model.

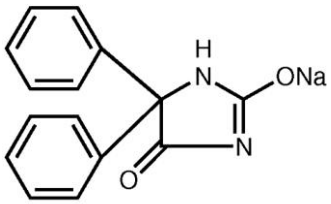

Figure 1. Chemical structure of sodium phenytoin.

Methods and Materials

Materials

Sodium phenytoin (with mass fraction purity (m/m) of 0.993) was purchased from Alhavi pharmaceutical

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company (Tehran, Iran) and was in pharmaceutical grade according to United States Pharmacopeia. PG (>0.99) was purchased from Scharlau (Spain), β-CD (0.99) 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.

Experimental methods

The binary solvent mixtures of PG + water were prepared by mass with the uncertainty of 0.01 g. To prepare the solvent mixtures +5 or 10 mM β-CD, aqueous and PG solutions of + 5 or 10 mM β-CD were prepared, then appropriate masses of the solutions were mixed up. Different methods were presented for determining the solubility of drugs.[9] The solubility of sodium phenytoin was determined using saturating shake-flask method. Briefly, the excess drug was added to the prepared solutions and then they were placed on a shaker (Behdad, Tehran, Iran) in an incubator equipped with a temperature-controlling system (uncertainty of 0.2 ºC, Kimia Idea Pardaz Azarbayjan (KIPA) Co., Tabriz, Iran). After equilibrium (24 hrs), the saturated solutions were centrifuged in 10000 rpm for 10 min (MSEMicro Center MSB010.CX2.5, SANYO, Muriguchi City, Japan) and diluted by water + ethanol (96 % or 0.935 in mass fraction) 50:50 mixture. The absorbance was recorded at 258 nm using a UV-Vis spectrophotometer (Biotech-Ultraspec 2000, England). Concentrations of the diluted solutions were determined from the calibration curves. Each reported solubility value is an average of at three independent measurements. The mean relative standard deviation (RSD) of three repetitive experiments was 1.8 %.

Computational methods

In addition to the experimental determination of solubility, mathematical models are used to estimate drugs solubility as an alternative method. The Jouyban-Acree model is used to calculate the solubility of drugs in solvent mixtures at various temperatures[3] and presented as:

$$\log C_{m,T} = m_1 \log C_{1,T} + m_2 \log C_{2,T} + \sum_{i=0}^{2} J_i \left[\frac{m_1 m_2 (m_1 - m_2)^i}{T} \right] \quad \text{Eq.(1)}$$

where $C_{m,T}$ is the molar solubility of the solute in solvent mixture, $C_{1,T}$ and $C_{2,T}$ denote the solubility in the mono-solvents at temperature T (K), m_1 and m_2 are mass fractions of solvents 1 and 2 in the absence of the solute, respectively, and J_i terms are the model constants. This model requires two solubility data in the mono-solvents and at least three data points in mixed solvents as input values.

The solubilization power (ω) of a cosolvent could be calculated according to:[10]

$$\omega = \frac{\log\left(\frac{C_{m,\max}}{C_{\min}}\right)}{m_{1,\max}} \quad \text{Eq.(2)}$$

In which $C_{m,max}$ is the maximum observed solubility and $m_{1,max}$ is the fraction of the cosolvent providing $C_{m,max}$.[10] C_{min} is the minimum solubility, i.e. aqueous solubility of sodium phenytoin in the absence of β-CD in this study.

The experimental solubility data of sodium phenytoin in PG + water mixtures in the absence and presence of 5 or 10 mM β-CD was fitted to Eq. 1. The fitted data of each drug in the studied systems were used to compute the accuracy of fitness using mean relative deviation (MRD) by:

$$MRD = \frac{100}{N} \sum \left| \frac{C_{m,cal} - C_{m,\exp}}{C_{m,\exp}} \right| \quad \text{Eq.(3)}$$

in which N is the number of data points in each set.

Results and Discussion

The measured solubilities of sodium phenytoin in PG + water in the absence and presence of 5 and 10 mM β-CD solutions at 25 ºC are listed in Table 1. Each experimental data point is the average of at least three repeated measurements with the measured molar solubilities being reproducible to within relative standard deviations (RSD) ranged from 0.4 to 6.1 %. An intrinsic (solubility of non-ionized form of the solute) aqueous solubility of 7.53×10^{-5} M[11] and apparent or total (sum of ionized and non-ionized forms of the solute) aqueous solubility of 8.04×10^{-5} M[12] was reported for phenytoin and its sodium salt form increased the solubility to 0.27 M.[13] The generated solubility of sodium phenytoin in this work (0.2520 M) is in a good agreement with the reported value.

Figure 2 shows the solubility profile of sodium phenytoin in PG + water, PG + water + 5 mM β-CD and PG + water + 10 mM β-CD mixtures. Aqueous solubility of sodium phenytoin obtained in this work is 0.2520 M and is decreased after addition of 5 mM β-CD (0.2285 M) or 10 mM β-CD (0.1881 M). This could be due to lower solubility of the formed complex in comparison with the solubility of sodium phenytoin.

Figure 3 illustrates the solubility ratio of sodium phenytoin (from this work) to phenytoin (data taken from the literature[12]) in various mass fractions of PG at 25 °C. As expected, the solubility of the ionized drug and consequently total solubility is decreased with decreasing the polarity of the solvent system (usually represented by the dielectric constant of the solvent mixture). These sort of data could be used in re-crystalization studies where addition of an anti-solvent facilitates the crystallization process.

Table 1. Molar solubility of sodium phenytoin in the investigated systems at 25 ºC.

Mass fraction of PG	PG + water	PG + water + 5 mM β-CD	PG + water + 10 mM β-CD
0.00	0.2520	0.2284	0.1881
0.10	0.3561	0.2780	0.2405
0.20	0.3738	0.2955	0.2595
0.30	0.3953	0.3213	0.2751
0.40	0.4180	0.3449	0.3063
0.50	0.4406	0.3896	0.3338
0.60	0.4651	0.4147	0.3498
0.70	0.4840	0.4338	0.3687
0.80	0.5236	0.4539	0.3930
0.90	0.5786	0.5049	0.4236
1.00	0.6552	0.5761	0.4620

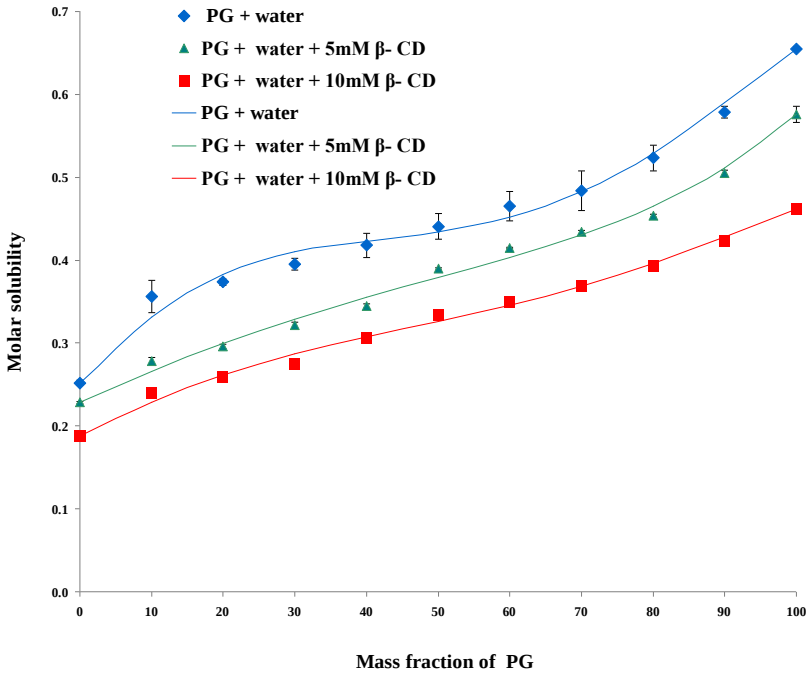

Figure 2. Molar experimental solubility of sodium phenytoin, and the back-calculated data with the lines.

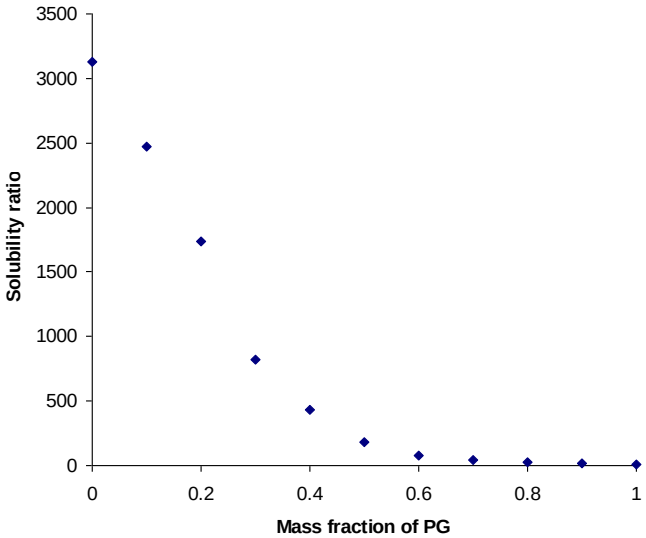

Figure 3. The solubility ratio of sodium phenytoin to phenytoin in various mass fractions of propylene glycol at 25 °C.

Table 2. Numerical values of the constants of Equation 1 and the mean relative deviation (MRD) for the fitting molar solubility of sodium phenytoin in PG + water mixtures and in presence of 5 or 10 mM β-CD.

Solvent system	J_0	J_1	J_2	MRD
PG + water	33.857	-168.756	0[a]	2.0
PG + water + 5 mM β-CD	22.860	-77.218	0[a]	1.9
PG + water + 10 mM β-CD	52.084	-83.708	52.815	1.4
				1.8

[a]The value is not statistically significant (p>0.1).

Table 2 lists the model constants of fitting data to the Eq. 1 and MRD values of each studied system. These findings show that the solubility data in PG + water, PG + water + 5 mM β-CD and PG + water + 10 mM β-CD could be fitted to the Eq. 1 with good accuracy. The MRD values vary between 1.4 to 2.0 % with the overall value of 1.8 %. Concerning the computed model constants, it is possible to predict the solubility of the investigated drug in all possible compositions of the mixtures. One could simplify the Jouyban-Acree model at isothermal condition as:

$$\log C_m = m_1 \log C_1 + m_2 \log C_2 + \sum_{i=0}^{2} J_i \left[m_1 m_2 (m_1 - m_2)^i \right] \quad \text{Eq.(4)}$$

however, we recommend the model as it appears in Eq. 1. Using this version, it is possible to train the model at 25 °C and then predict the solubility in PG + water mixtures at other temperatures of interest employing the solubility data in the mono-solvents. This has been shown in earlier works[14-16] and such a capability could be extended for cosolubilization/desolubilization using cosolvents and complexing agents too.

Table 3 reports the calculated ω values for aqueous mixtures of PG, PG + 5 mM β-CD and PG + 10 mM β-CD. Addition of β-CD was slightly decreased the solubilization power of PG from 0.42 to 0.26. It should be noted that ω values are in logarithmic scale and one unit decrease in ω means solubility change by a factor of 10.

In conclusion, the generated data in this work extends the available solubility database of pharmaceuticals[17] and could be used in the pharmaceutical industries. Decreased solubility by addition of a complexing agent could provide diverse solubility data for proposing global cosolvency models. 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 solvent compositions.

Table 3. Numerical values of the solubilization powers PG , PG + 5 mM β-CD and PG + 10 mM β-CD02.

Solvent system	ω
PG + water	0.42
PG + water + 5 mM β-CD	0.36
PG + water + 10 mM β-CD	0.26

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Conflict of Interest

The authors report no conflicts of interest.

References

1. Di L, Fish PV, Mano T. Bridging solubility between drug discovery and development. *Drug Discov Today* 2012;17:486-495. doi:10.1016/j.drudis.2011.11.007
2. Strickley RG. Solubilizing excipients in oral and injectable formulations. *Pharm Res* 2004;21:201-230. doi:10.1023/b:pham.0000016235.32639.23
3. Jouyban A., Review of the cosolvency models for predicting solubility of drugs in water-cosolvent mixtures. *J Pharm Pharm Sci* 2008;11:32-58.
4. Zar T, Graeber C, Perazella M.A. Reviews: recognition, treatment, and prevention of propylene glycol toxicity. *Semin Dial* 2007;20:217-219. doi:10.1111/j.1525-139x.2007.00280.x
5. Li R, Quan P, Liu DF, Wei FD, Zhang Q, Xu QW. The influence of cosolvent on the complexation of HP-β-cyclodextrins with oleanolic acid and ursolic acid. *AAPS PharmSciTech* 2009;10:1137-1144. doi:10.1208/s12249-009-9317-z
6. He Y, Li P, Yalkowsky SH. Solubilization of fluasterone in cosolvent/cyclodextrin combinations. *Int J Pharm* 2009;264:25-34. doi:10.1016/s0378-5173(03)00389-2
7. Shayanfar A, Acree Jr WE, Jouyban A. Solubility of lamotrigine, diazepam, clonazepam, and phenobarbital in propylene glycol+ water mixtures at 298.15 K. *J Chem Eng Data*. 2009;54:1153-1157. doi:10.1021/je800931z
8. Soltani N, Shayanfar A, Djozan D, Jouyban A. Solubility of three basic drugs in propylene glycol + water mixtures in the presence of β-cyclodextrin. *J Drug Deliv Sci Tech* 2013;23:187-190. doi:10.1016/s1773-2247(13)50028-1
9. Jouyban A, Fakhree MAA. Experimental and Computational Methods Pertaining to Drug Solubility. In: *Acree Jr WE (Ed) Toxicity and Drug Testing, InTech Publisher*: New York, 2012. doi:10.5772/19206

10. Jouyban A, Fakhree MAA. A new definition of solubilization power of a cosolvent. *Pharmazie* 2007;63:317-319.
11. Yalkowsky SH; He Y, Jain P. *Handbook of Aqueous Solubility Data*. 2nd ed. CRC Press:Boca Raton,FL,2010. doi:10.1201/ebk1439802458
12. Yalkowsky SH, Rubino JT. Solubilization by cosolvents I: organic solutes in propylene glycol–water mixtures. *J Pharm Sci* 1985;74:416-421. doi:10.1002/jps.2600740410
13. Chiang PC, Wong H. Incorporation of physiologically based pharmacokinetic modeling in the evaluation of solubility requirements for the salt selection process: A case study using phenytoin. *AAPS J* 2013;15:1109-1118. doi:10.1208/s12248-013-9519-x
14. Jouyban A, Shokri J, Barzegar-Jalali M, Hassanzadeh D, Acree Jr WE, Ghafourian T, Nokhodchi A., Solubility of chlordiazepoxide, diazepam, and lorazepam in ethanol + water mixtures at 303.2 K. *J Chem Eng Data* 2009;54:2142-2145. doi:10.1021/je900200k
15. Jouyban A, Acree Jr WE. Comments on "Solubility of ethyl maltol in aqueous ethanol mixtures". *J Chem Eng Data* 2009;54:1168-1170.
16. Ahmadian S, Soleymani J, Panahi-Azar V, Fakhree MAA, Acree Jr WE, Jouyban A. Solubility of phenothiazine in water, ethanol, and propylene glycol at 298.2 to 338.2 K and their binary and ternary mixtures at 298.2 K. *J Chem Eng Data* 2011;56:4352-4355.
17. Jouyban A. - Handbook of Solubility Data for Pharmaceuticals. CRC Press, Boca Raton, FL;2009.