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Solubilization of celecoxib, lamotrigine and phenytoin using ethanol and a nonionic surfactant

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ABSTRACT

Using micellar medium as a solubilization technique is an influential approach for solubilization of drugs with high hydrophobicity. It may be combined with cosolvency to provide more solubility. This work reports the effects of Tween 80 as a nonionic surfactant and ethanol as a commonly used cosolvent on the solubilities of celecoxib, phenytoin and lamotrigine at 298.2 K. As experimental results approved the effect of Tween 80 on the solubility of celecoxib is more than the others. The experimental data points were fitted to the Jouyban-Acree, general single and modified Wilson models and then back-calculated solubilities were calculated where the mean percentage deviations were 9.7%, 13.3% and 14.0%, respectively.

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1. Introduction

Aqueous solubility of drugs/drug candidates is a limiting factor in developing new synthetic drugs and it is one of the important physicochemical properties which is usually measured experimentally and no accurate and reliable model is available to predict the aqueous solubility [1]. Concerning the high rate of solubility problem for new drugs (40%) [2], various methodologies are utilized to increase the solubility of pharmaceuticals. The cosolvency, using various mixtures of solvents, is the simple and most commonly used method to increase the solubility of drugs. The other solubilization methods such as solid dispersion, micronization, chemical modification, pH adjustment, emulsions, liposomes, pharmaceutical salts, complexation, micellar solubilization, percolation, hydrotropy etc., were comprehensively discussed in the literature [2,3] where the advantages and disadvantages of the methods disclosed, also others references are available to understand the various solubilization processes [4–6]. Factors such as particle size of a drug, temperature of the saturated solution, local pressure (mainly for gaseous solutes), nature of the solute and solvent, molecular size, polarity and various polymorphs of a drug affect the solubility value of drugs [7].

Celecoxib, *p*-[5-*p*-methylphenyl–3-(trifluoromethyl)-1H-pyrazol–1–yl] benzenesulfonamide, is a member of nonsteroidal anti-inflammatory drug with the pK_a of 11.1 and the log P of 3.5 [8]. Celecoxib possesses low aqueous solubility and high permeability therefore belongs to class II of biopharmaceutical classification system (BCS). Chakma et al. [9] utilized various types of the solidified Tween 80 to increase the solubility of celecoxib where the solubility increased from 0.00204 mg/mL to the 0.1009, 0.1157, 0.1518 and 0.1449 mg/mL using Aerosil, Neusilin, Fujicalin and Pineflow ST, respectively. Wafaa et al. [10] used the cosolvency (ethanol) and surfactants (Tween 80 and Solutol HS 15) effects on the solubility of celecoxib by measuring in a very limited compositions of the solubilizing agents. Other solubilization methods were also applied to increase the solubility of celecoxib including solid dispersion [11] and complexing agents [12]. Lamotrigine is the second studied drug from class II of BCS. Available solubility data of lamotrigine was listed in a recent paper [13].

Phenytoin, 5,5-diphenyl–2,4–imidazolidinedione belongs to anticonvulsant drugs which acts by lowering the brain abnormal electrical activity. From solubility point of view, phenytoin is practically insoluble

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in water. However its solubility in ethanol is higher than chloroform or ether; and is lower than acetone [8]. Solubility of phenytoin in aqueous binary solvent mixtures of 1,4-butanediol, ethanol, methanol, glycerine, polyethylene glycol 200, polyethylene glycol 400, propylene glycol and sorbitol at 298 K was reported by Rubino et al. [14]. Solubility of sodium phenytoin in aqueous mixtures of ethanol [15] and propylene glycol [16] at various temperatures were reported from our research group along with the combined effects of salt form + propylene glycol + β-cyclodextrin on the solubilization of phenytoin [17]. Solubility data of phenytoin in ethanol + water + sodium dodecyl sulfate (SDS) was also reported in an earlier work [18]. Kawakami et al. [19] investigated the solubility of phenytoin using various surfactants (*i.e.* SDS and Tween 80) and cosolvents such as dimethyl acetamide, ethanol, polyethylene glycol 400 and glycerol where the effect of both micellar and cosolvency were studied in cosolvent fractions up to 0.20 (w/v) and 2 or 4% (w/v) of SDS and Tween 80. Based on the reported results, Tween 80 enhances the solubility of phenytoin as well as SDS. However in the aqueous system, the solubilization capacity of the SDS is higher than Tween 80 (*e.g.* about 1.5 magnitude of orders). This phenomenon can be explained as results of the ionic nature of the SDS which solubilize the drug more effectively.

Hall [20] applied Tween 80 to study its effect on the aqueous solubility and the critical miscibility ratio of salicylic acid to Tween 80 solution. Also, Razvi et al. [21] investigated the effect of Tween 80 on the solubility of ibuprofen. As a new approach, Chakma et al. [9] applied solidified Tween 80 in order to increase the solubility of celecoxib. Li et al. [22] utilized SDS and Tween 80 to study their effects on the dissolution trends and solubility of carbamazepine–nicotinamide cocrystal.

To continue our systematic investigations on the solubilization of poorly soluble drugs, in this work, combined effects of Tween 80 (a non-ionic surfactant) and ethanol as a pharmaceutical cosolvent on the solubility of celecoxib, lamotrigine and phenytoin are investigated in solvent compositions ranging from 0.00 to 1.00 fractions of ethanol. As another purpose of this work is to model the measured solubility data to provide trained equations for predictive purposes.

2. Materials and methods

2.1. Materials

Celecoxib (0.995 in mass fraction) and lamotrigine (0.98 in mass fraction) were purchased from Arastoo Pharmaceutical Company (Tehran, Iran), and phenytoin (0.998 in mass fraction) was purchased from Alhavi Pharmaceutical Company (Tehran, Iran). Ethanol (0.995 in mass fraction) was purchased from Scharlau (Spain). Tween 80 (0.999 in mass fraction) was purchased from Merck (Darmstadt, Germany). Double distilled water was used in this study (Shahid Ghazi pharmaceutical company, Tabriz, Iran). All solutions were directly prepared from received analytical reagent grade substances without further purifications. Table 1 listed further details of the used substances.

2.2. Apparatus and procedures

A solubility setup based on laser monitoring technique was used to measure the solubility of the drugs. The full details of the setup are presented in an earlier publication of our group [23]. The setup was validated according to the re-measured solubility data and was used in a number of earlier works [13,24–26]. All weight measurements were done with an electronic balance (Sartorius, Germany) with an uncertainty of 0.01 g and also in some cases 0.0001 g balance were applied (Mettler Toledo, Switzerland).

2.3. Computational methods

2.3.1. The Jouyban-Acree model

The solubility of a drug in a mixed solvent system at various temperatures (T) with respect to solvent composition and T is described by:

$$\ln\ x_{m,T} = m_1^0\ \ln\ x_{1,T} + m_2^0\ \ln\ x_{2,T} + \left[m_1^0 m_2^0 \sum_{i=0}^{2} A_i \frac{\left(m_1^0 - m_2^0\right)^i}{T}\right] \quad (1)$$

where $x_{m,T}$ represents the mole fraction solubility of solute in the solvent mixtures at a given temperature T, m_1^0 and m_2^0 are the mole fractions of the solvents 1 and 2 in the solute free solvent mixtures, $x_{1,T}$ and $x_{2,T}$ are the mole fraction solubility of the solutes in mono-solvents 1 and 2 [27,28]. The A_i terms (the model constants) could be computed by a no-intercept least square analysis by regressing $(\ln x_{m,T} - m_1^0 \ln x_{1,T} - m_2^0 \ln x_{2,T})$ against $\frac{m_1^0 m_2^0}{T}$, $\frac{m_1^0 m_2^0 (m_1^0 - m_2^0)}{T}$ and $\frac{m_1^0 m_2^0 (m_1^0 - m_2^0)^2}{T}$ [29]. The A_i terms represent the non-ideal mixing behavior of the saturated solutions of a solute in neat cosolvent and water, $x_{1,T}$ and $x_{2,T}$, in the absence or presence of Tween 80. Eq. (1) provided the most accurate results when compared with similar models [30,31].

When the solubility of a drug in mixed solvent at isothermal condition is considered, Eq. (1) reduces to the classical version of the combined nearly ideal binary solvent/Redlich-Kister equation [32] as:

$$\ln\ x_m = m_1^0\ \ln\ x_1 + m_2^0\ \ln\ x_2 + \left[m_1^0 m_2^0 \sum_{i=0}^{2} W_i \left(m_1^0 - m_2^0\right)^i\right] \quad (2)$$

in which W_i terms are the model constants. Our previous investigations showed that when Eq. (1) is trained at one temperature, the solubility of the drug in the solvent mixtures could be predicted at other temperatures of interest if the solubility in the mono-solvents are known [33–36]. Therefore we prefer to use Eq. (1) rather than Eq. (2) in the modeling projects.

2.3.2. The general single model

A polynomial model was commonly used in the literature [37,38] for representing the solubility of drugs in a given binary solvent at isothermal condition. The model which is called general single model [39] is:

$$\ln\ x_m = B_0 + B_1\left(m_1^0\right) + B_2\left(m_1^0\right)^2 + B_3\left(m_1^0\right)^3 + B_4\left(m_1^0\right)^4 \quad (3)$$

in which B terms are the model constants. The model could be derived from Eq. (2) and a number of cosolvency models by replacing m_2^0 with $(1 - m_1^0)$ and some algebraic manipulations as described in a previous work [39].

Table 1
List of the used materials in this research article.

Material	Purity[a]	CAS number	Formula	Molar mass	Source	
Celecoxib	0.995	169590–42–5	$C_{17}H_{14}F_3N_3O_2S$	381.4	Arastoo	Iran
Lamotrigine	0.98	84057–84–1	$C_9H_7Cl_2N_5$	256.1	Arastoo	Iran
Phenytoin	0.998	57–41–0	$C_{15}H_{12}N_2O_2$	252.3	Alhavi	Iran
EtOH	0.995	64-17-5	C_2H_5OH	46.1	Scharlau	Spain
Tween 80	0.999	9005-65-6	$C_{64}H_{124}O_{26}$	1310.0	Merck	Germany
Water	$<1.5\ \mu S \cdot cm^{-1}$	7732-18-5	H_2O	18.0	Shahid Ghazi	Iran

[a] Mass fraction.

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