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Solubility modelling and solvent effect for domperidone in twelve green solvents

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ABSTRACT

Solid solubility is a significant physical property for a drug development and design. In the present work, the domperidone solubility, which has less study in the near-term, was reported, which was determined by the shake-flask method in twelve green solvents e.g. methanol, ethanol, isopropanol, *n*-propanol, *n*-butanol, isobutanol, acetonitrile, *N*,*N*-dimethylformamide (DMF), water, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylacetamide (DMA), ethylene glycol (EG) at the temperatures from 278.15 to 318.15 K under atmospheric pressure ($p = 101.2$ kPa). The domperidone solubility in the twelve solvents increased with the increasing temperature. At a desired temperature, they obeyed the following order from high to low in these solvents: DMA > DMSO > DMF > butanol > *n*-propanol > (isobutanol, EG) > ethanol > isopropanol > methanol > acetonitrile > water. The experimental solubility was described mathematically with the Buchowski–Książczak λh equation, Apelblat equation Wilson model and NRTL model. The largest percentage of relative average deviation was 3.28×10^{-2}, and the maximum value of root-mean-square deviation was 3.16×10^{-5}. On the basis of the Wilson model, the mixing properties, e.g. mixing Gibbs energy, mixing enthalpy, mixing entropy, activity coefficient at infinitesimal concentration and reduced excess enthalpy were computed. Moreover, the solvent effect was studied by using the concept of Kamlet-Taft Linear Solvation Energy Relationship. The type and extent and direction of solvent-solvent and solute-solvent interactions were identified.

1. Introduction

The drugs' solubility in neat and solvent mixtures is a significant physico-chemical parameter for the design of liquid dosage forms, purification of raw material, and understanding of the mechanisms of the chemical and physical stability of pharmaceutical dissolution [1,2]. It affects the therapeutic efficacy, absorption, pharmacokinetic and biopharmaceutical properties of drugs [1–4]. At early stages, solubility evaluation is essential during the drug developing procedure. The low solubility in water of drugs frequently brings about low bioavailability and insufficient absorption. Therefore, improvement of solubility of drugs has a critical importance during the formulation development processes [5].

Domperidone (CAS Reg. No. 57808-66-9) is chemically described as 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)-propyl] 4-piperidinyl]-1,3-dihydro-2H-benzimidazol-2-one. Its structure is given in Fig. 1. Domperidone is a dopamine (D2) receptor antagonist. It is used for the treatment and prevention of acute nausea and vomiting of any cause, especially cytotoxic therapy and radiotherapy [6]. According to Biopharmaceutical Classification System (BCS), domperidone is categorized under class II drugs due to poorly water-soluble and highly permeable [7–12]. Because of its nearly insoluble in water, it decreases its bioavailability to 13–17% after oral administration [7,8]. Additionally, the poor solubility limits the capability for its delivery via buccal or rectal ways and requires the use of powerful solubilization technique [13,14].

In order to overcome the disadvantage of poor aqueous solubility, which results in a large variation in bioavailability and makes the difficulty in design of pharmaceutical formulation, several approaches have been developed [12,15–20]. Among them, the solid dispersion technology offers the possibility to reduce the particle size of drug to a molecular level. This technique necessitates lots of accurate solubility data of the drug in different solvents. So it is essential to determine systematically the domperidone solubility for liquid pharmaceutical systems. It may provide a demonstrative description of its physicochemical properties, thermodynamic functions and the mechanisms regarding the physical and chemical stability of pharmaceutical dissolution. However, despite the usefulness of domperidone, the physicochemical properties of this drug in different solvents have not been

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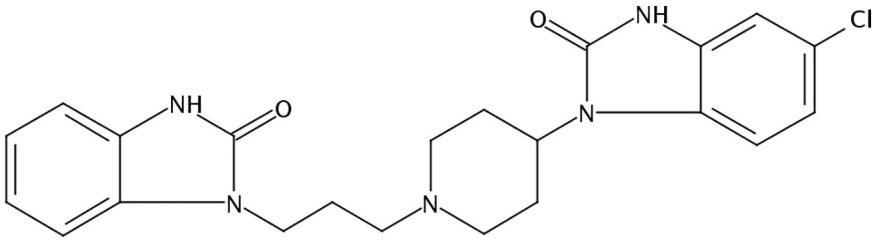

Fig. 1. The chemical structure of domperidone.

studied systematically up to yet. A thorough literature search shows that only the solubilities of domperidone in water and in different pH solutions at 298.2 K or 295 K are available [9–12].

According to the considerations mentioned above, the main objective of the present work is to report the equilibrium solubility of domperidone in green neat solvents of methanol, ethanol, isopropanol, *n*-propanol, butanol, isobutanol, acetonitrile, DMF, water, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylacetamide (DMA), ethylene glycol (EG) at different temperatures. This investigation extends the solubility data about drug in neat solvents [1] and also allows estimating the respective thermodynamic properties of the solution as well as solvent effect on the solubility.

2. Solubility modelling

In this paper, five models are employed to describe the experimental solubility, which are Apelblat equation [21–23], Buchowski–Książczak λ*h* equation [24], Wilson model [25], NRTL model [26] and Kamlet-Taft linear solvation energy relationship model [27].

2.1. Apelblat equation

The Apelblat equation, which is firstly used by Apelblat and Manzurola [21–23], may provide a relatively more accurate description of solid solubility in neat solvent. This equation is expressed as

$$\ln x = A + \frac{B}{T/\mathrm{K}} + C\ \ln(T/\mathrm{K}) \tag{1}$$

here x is the mole fraction solubility of solute in neat solvents at absolute temperature T/K; A, B and C are the empirical parameters.

2.2. Buchowski–Książczak λh equation

The Buchowski–Książczak λ*h* equation having two parameters λ and h is suggested by Buchowski and co-workers [24]. It may correlate the solubility data well for lots of systems.

$$\ln\left[1+\frac{\lambda(1-x)}{x}\right] = \lambda h\left(\frac{1}{T/\mathrm{K}} - \frac{1}{T_{\mathrm{m}}/\mathrm{K}}\right) \tag{2}$$

where λ and h are equation parameters in Buchowski–Ksiazaczak λ*h* equation; T_m is the melting temperature of domperidone in Kelvin. The parameter λ is in relation to the non-ideality of solution, which is considered as the association number of solute molecules in associating system, and h is in relation to the excess enthalpy of solution.

$$hR = \Delta_{\mathrm{fus}}H + H^{\mathrm{E}}/x \tag{3}$$

here R is the universal gas constant ($8.314\ \mathrm{J\cdot K^{-1}\cdot mol^{-1}}$).

2.3. Wilson equation

Based on the thermodynamic principles, the liquid−solid equilibrium may be expressed by a universal equation as Eq. (4) [28].

$$\ln(x\cdot\gamma) = \frac{\Delta_{\mathrm{fus}}H}{R}\left(\frac{1}{T_m}-\frac{1}{T}\right) - \frac{1}{RT}\int_{T_{\mathrm{m}}}^{T}\Delta C_{\mathrm{p}}dT + \frac{1}{R}\int_{T_{\mathrm{m}}}^{T}\frac{\Delta C_{\mathrm{p}}}{T}dT \tag{4}$$

here γ_1, T_{m}, $\Delta_{\mathrm{fus}}H$, ΔC_{p} and R are the activity coefficient, melting point of solute, enthalpy of fusion of solute at its melting point, difference of heat capacities between subcooled liquid and solid, and the gas constant, respectively. And since ΔC_{p} is usually small, this equation is simplified as:

$$\ln(x_{\mathrm{i}}\cdot\gamma_{\mathrm{i}}) = \frac{\Delta_{\mathrm{fus}}H}{R}\left(\frac{1}{T_{\mathrm{m}}/\mathrm{K}} - \frac{1}{T/\mathrm{K}}\right) \tag{5}$$

In neat solvents, the activity coefficient of solute expressed by the Wilson equation is described as Eq. (6) [25].

$$\ln\gamma_1 = -\ \ln(x_1+\Lambda_{12}x_2) + x_2\left[\frac{\Lambda_{12}}{x_1+\Lambda_{12}x_2} - \frac{\Lambda_{21}}{x_2+\Lambda_{21}x_1}\right] \tag{6}$$

$$\Lambda_{\mathrm{ij}} = \frac{V_{\mathrm{j}}}{V_{\mathrm{i}}}\ \exp\left(-\frac{\lambda_{\mathrm{ij}}-\lambda_{\mathrm{jj}}}{R(T/\mathrm{K})}\right) = \frac{V_{\mathrm{j}}}{V_{\mathrm{i}}}\ \exp\left(-\frac{\Delta\lambda_{\mathrm{ij}}}{R(T/\mathrm{K})}\right) \tag{7}$$

here V_{i} is the molar volume attained via molar mass divided by density of component i. $\Delta\lambda_{\mathrm{ij}}$ denote the interaction energy parameter ($\mathrm{J\cdot mol^{-1}}$) between the components i and j.

2.4. NRTL model

The NRTL model [26] is proposed on the basis of the local composition concept. It is expressed as Eqs. (8)–(11).

$$\ln\gamma_1 = x_2^2\left[\frac{\tau_{21}G_{21}^2}{(x_1+G_{21}x_2)^2} + \frac{\tau_{12}G_{12}^2}{(x_2+G_{12}x_1)^2}\right] \tag{8}$$

$$G_{\mathrm{ji}} = \exp(-\alpha_{\mathrm{ji}}\tau_{\mathrm{ji}}) \tag{9}$$

$$\alpha_{\mathrm{ij}} = \alpha_{\mathrm{ji}} \tag{10}$$

$$\tau_{\mathrm{ij}} = \frac{g_{\mathrm{ij}}-g_{\mathrm{jj}}}{RT} = \frac{\Delta g_{\mathrm{ij}}}{RT} \tag{11}$$

Δg_{ij} are equation parameters regarding the interaction energy. α denotes the adjustable parameter in NRTL model.

Assuming that the interaction parameters in Wilson and NRTL models have a linear relationship with temperature [29,30], Λ_{ij} in Wilson equation and τ_{ij} in NRTL equation may be described as Eqs. (12) and (13).

$$\tau_{\mathrm{ij}} = a_{\mathrm{ij}} + \frac{b_{\mathrm{ij}}}{T/\mathrm{K}} \tag{12}$$