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Preferential solvation of diazepam in some aqueous co-solvent mixtures

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ABSTRACT

The preferential solvation parameters ($\delta x_{1,3}$) of diazepam in binary solvent mixtures of {ethanol (1) + water (2)}, {propylene glycol (1) + water (2)}, {NMP (1) + water (2)} and {1,4-dioxane (1) + water (2)} at 298.2 K and {*tert*-butanol (1) + water (2)} at (299.2–313.2) K were derived from their available solubility values by using the inverse Kirkwood–Buff integrals method. The values of $\delta x_{1,3}$ vary non-linearly with the co-solvent (1) proportion in all the aqueous mixtures. For the former four co-solvent mixtures, the preferential solvation magnitude of diazepam by the co-solvent is highest in {1,4-dioxane (1) + water (2)} mixtures and lowest in {ethanol (1) + water (2)} mixtures. For the former four systems, the values of $\delta x_{1,3}$ are negative in water-rich mixtures, which indicates that diazepam could act as a Lewis base to establish hydrogen bonds with the proton-donor functional groups of the co-solvents (1) (with the exception of 1,4-dioxane). The same behaviour was also observed for ethanol (1) + water (2) mixtures with co-solvent-rich composition. In the {ethanol (1) + water (2)} mixtures with composition $0.241 < x_1 < 0.688$, {NMP (1) + water (2)} mixtures with composition $0.164 < x_1 < 1.0$, {propylene glycol (1) + water (2)} mixtures with composition $0.20 < x_1 < 1.0$ and {1,4-dioxane (1) + water (2)} mixtures with composition $0.175 < x_1 < 1.0$, diazepam is preferentially solvated by co-solvent. Some differences between the behaviours of diazepam in {*tert*-butanol (1) + water (2)} mixtures and the other four co-solvent mixtures were found.

1. Introduction

Solvation of solute molecules in co-solvent mixtures is of great importance in pharmaceutical sciences to acquire comprehensive information on their physicochemical properties. Solute solvation in co-solvent mixtures is a function of both solute–solvent and solvent–solvent interactions [1–3]. Specifically, the solute can interact differently with the solvent components. In this case, the composition of the solute solvation shell is different from the bulk, which leads to preferential solvation. It is mainly due to specific solute–solvent interactions (such as hydrogen bonding) or dielectric enrichment or both. For example, once a polar solute is solvated in a mixture of polar and nonpolar solvents, preferential solvation by polar solvents arises due to stronger dipole–dipole interaction between the solute and polar solvent.

Drug behaviour in co-solvent mixtures is very important for pharmaceutical scientists involved in several development stages including drug purification, pre-formulation studies, and pharmaceutical dosage form design [2,4,5]. Co-solvency has been widely employed in pharmacy, however, just at present the mechanisms relating to the decreasing or increasing drug solubility from a further physicochemical point of view start to be approached by the analysis of the preferential solvation of the solutes by the solvent components [6–11]. The preferential solvation of non-dissociate electrolyte drugs in co-solvent mixtures can be evaluated by the inverse Kirkwood–Buff integrals (IKBI). It describes the local compositions around the solute with respect to the different components present in the solvent mixtures. This treatment depends upon the values of the standard molar Gibbs energies of transfer of the solute (compound 3) from neat water (compound 2) to the solvent mixtures of {co-solvent (compound 1) + water (compound 2)} and the excess molar Gibbs energy of mixing for the binary mixtures free of solute. Therefore, this treatment is very important in pharmaceutical sciences to understand the molecular interactions of solute–solvent, because many solubility studies developed have been focused toward correlating or modelling the solubility and the possible prediction in solvent mixtures from the solubility in the neat solvents. Nevertheless, just a few of them have been intended to analyse the local environment around the drug molecules describing the local fraction of the solvent components (1 or 2) in the surrounding of solute [1–3,6–11]. Preferential solvation of many pharmaceutical compounds so far has not been studied.

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Diazepam (7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one; structure shown in Fig. 1) is used as hydrophobic model drug. Its physico-chemical properties, pharmacology and pharmacokinetic characteristics, synthesis routes as well as clinical uses were reviewed recently [12]. Solubility enhancement of diazepam by using common organic solvents, either neat or mixed with water, was reported by many authors. Common organic solvents investigated comprise ethanol [13–16], propane-1,2-diol [16–19], 1-methyl-2-pyrrolidinone [16,20,21], 1,4-dioxane [22] and *tert*-butyl alcohol [23]. On the other hand, the use of alternative solvents such as supercritical fluids [24] and ionic liquids [25], which are of increasing interest in the pharmaceutical industry [26–28], is more limited. Up to date, only solubility values for diazepam in supercritical carbon dioxide have been reported [29]. Nevertheless, no attempts have been made to evaluate the preferential solvation of this drug in the binary systems up to yet. In order to understand deeply the mechanisms relating to the increasing or decreasing drug solubility, therefore, the main purpose of this research was to evaluate the preferential solvation of diazepam in several aqueous co-solvent mixtures from available solubility data and other thermodynamic properties by using the IKBI method, which has been done previously in different co-solvent mixtures [1–3,6–11]. The five co-solvents studied in the present work are as follows: ethanol, propylene glycol, *tert*-butanol, 1-methyl-2-pyrrolidinone (NMP) and 1,4-dioxane. The results of our calculations are expressed in terms of the variation of the preferential solvation parameter $\delta x_{1,3}$ of this drug by the respective co-solvent.

2. Theoretical aspects

The IKBI method is useful for estimating the preferential solvation of non-electrolyte drugs in binary aqueous co-solvent mixtures, which describes the local solvent composition around the solute in comparison with the global mixtures composition [1–3,6–11]. The inverse Kirkwood-Buff integral equation is described as Eq. (1).

$$G_{i,3} = \int_0^{r_{cor}} (g_{i,3} - 1) 4\pi r^2 dr \tag{1}$$

here, $g_{i,3}$ is the pair correlation function for molecules of solvent i in the co-solvent (1) + water (2) mixtures around the solute diazepam (3); r is the distance between the centres of molecules of diazepam (3) and those of co-solvent (1) or water (2); and r_{cor} is a correlation distance for which $g_{i,3}$ $(r > r_{cor}) \approx 1$. Thus, for all distances $r > r_{cor}$ up to infinite, the value of the integral is essentially zero.

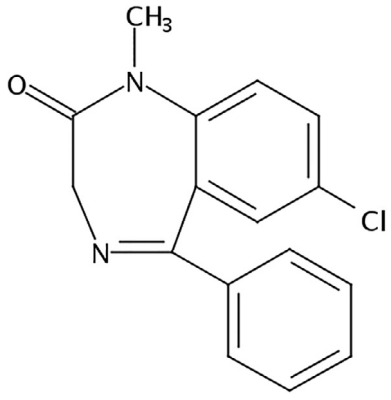

Fig. 1. Molecular structure of diazepam.

The preferential solvation parameter of diazepam (compound 3) by the co-solvent (compound 1) in {co-solvent (1) + water (2)} mixtures is expressed as [6–11]:

$$\delta x_{1,3} = x^L_{1,3} - x_1 = -\delta x_{2,3} \tag{2}$$

where $x^L_{1,3}$ is the local mole fraction of co-solvent (1) in the environment near to diazepam (3) and x_1 is the bulk mole fraction composition of co-solvent (1) in the initial binary solvent. Diazepam (3) is preferentially solvated by co-solvent (1) whenever $\delta x_{1,3} > 0$. Conversely, if $\delta x_{1,3}$ takes on a negative numerical value then diazepam (3) is preferentially solvated by water (2). Numerical values of $\delta x_{1,3}$ can be obtained from the inverse Kirkwood-Buff integrals for the individual solvent components analysed based on some thermodynamic quantities as shown in the following equations:

$$G_{1,3} = RT\kappa_T - \overline{V_3} + \frac{x_2 \overline{V_2} D}{Q} \tag{3}$$

$$G_{2,3} = RT\kappa_T - \overline{V_3} + \frac{x_1 \overline{V_1} D}{Q} \tag{4}$$

Here, κ_T is the isothermal compressibility of the co-solvent mixtures; $\overline{V_1}$ and $\overline{V_2}$ are the respective partial molar volumes of the solvents in the mixtures, and $\overline{V_3}$ is the partial molar volume of diazepam. The functions D and Q are defined as follows:

$$D = \left(\frac{\partial \Delta_{tr} G^o_{(3,2\rightarrow 1+2)}}{\partial x_1} \right)_{T,P} \tag{5}$$

$$Q = RT + x_1 x_2 \left[\frac{\partial^2 G^{Exc}_{1+2}}{\partial x_2^2} \right]_{T,p} \tag{6}$$

In Eqs. (5) and (6), $\Delta_{tr} G^0_{3,2\rightarrow 1+2}$ is the standard molar Gibbs energy of transfer of diazepam from neat water to {co-solvent (1) + water (2)}, and G^{Exc}_{1+2} is the excess molar Gibbs energy of mixing of the binary aqueous-organic solvent mixture free of diazepam. The preferential solvation parameter, expressed in terms of the above quantities, can be calculated from the inverse Kirkwood-Buff integrals by using Eq. (7).

$$\delta x_{1,3} = \frac{x_1 x_2 (G_{1,3} - G_{2,3})}{x_1 G_{1,3} + x_2 G_{2,3} + V_{cor}} \tag{7}$$

The correlation volume (V_{cor}) needed in the $\delta x_{1,3}$ calculation is obtained based on the following expression:

$$V_{cor} = 2522.5[r_3 + 0.1363(x^L_{1,3}\overline{V_1} + x^L_{2,3}\overline{V_2})^{1/3} - 0.085]^3 \tag{8}$$

where r_3 is the molecular radius of diazepam (expressed in nm) calculated as

$$r_3 = \sqrt[3]{\frac{3 \times 10^{21} \overline{V_3}}{4\pi N_{AV}}} \tag{9}$$

and N_{Av} is the Avogadro number. The correlation volume must be calculated by an iterative method because it depends on the local mole fractions. This iteration is accomplished by replacing $\delta x_{1,3}$ and V_{cor} in the Eq. (2) to calculate $x^L_{1,3}$ until a non-variant value of V_{cor} is acquired [1,2].

3. Results and discussion

The solubility of diazepam (3) in {ethanol (1) + water (2)} is taken from Ref. [14]; in {propylene glycol (1) + water (2)}, Ref. [17]; in {*tert*-butanol (1) + water (2)}, Ref. [23]; in {1-methyl-2-pyrrolidinone (1) + water (2)}, Ref. [20]; and in {1,4-dioxane (1)