J. Chem. Thermodynamics 142 (2020) 106010

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Equilibrium solubility determination, solvent effect and preferential solvation of amoxicillin in aqueous co-solvent mixtures of *N*,*N*-dimethylformamide, isopropanol, *N*-methyl pyrrolidone and ethylene glycol

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ARTICLE INFO

Article history:
Received 17 October 2019
Received in revised form 12 November 2019
Accepted 13 November 2019
Available online 15 November 2019

Keywords:
Amoxicillin
Solubility
Jouyban-Acree
Solvent effect
Preferential solvation

ABSTRACT

The mole fraction solubility of amoxicillin in four co-solvent mixtures of *N*,*N*-dimethylformamide (DMF) + water (2), isopropanol (1) + water (2), *N*-methyl pyrrolidone (NMP) (1) + water (2) and ethylene glycol (EG, 1) + water (2) at temperatures from 278.15 K to 328.15 K was determined by means of the shake-flask technique. At the same temperature and composition of DMF, isopropanol, NMP or EG, the solubility magnitude of amoxicillin was highest in the DMF (1) + water (2) mixture, and lowest in the isopropanol (1) + water (2) mixture. Through the Jouyban-Acree model, amoxicillin solubility was well correlated obtaining *RAD* lower than 4.55% and *RMSD* lower than 1.96×10^{-4}. Quantitative values for the local mole fraction of DMF (isopropanol, NMP or EG) and water nearby the amoxicillin were computed by means of the Inverse Kirkwood–Buff integrals method. In the DMF (1) + water (2) mixture with compositions $0.20 < x_1 < 1.00$, NMP (1) + water (2) mixture with compositions $0.165 < x_1 < 1.00$ and EG/isopropanol (1) + water (2) mixtures with compositions $0.25 < x_1 < 1.00$, amoxicillin was solvated preferentially by the co-solvent. In addition, solvent effect was modeled by linear solvation energy relationships in terms of KAT solvent polarity descriptors to detect the main intermolecular interactions controlling the solubility variation in solvent mixtures. Results showed that the work for cavity formation in solvent for solute's accommodation had the most significant effect on solubility variance over the entire composition range in all the mixed solvents.

1. Introduction

In recent times, research upon solubility of the pharmaceutical intermediates and drugs has become a growing focus in the pharmaceutical fields. The solubility of pharmaceutical intermediates and drugs in co-solvent solutions is an essential physicochemical property, which plays a major role in numerous physical and biological processes [1–4]. In addition, the solubility in aqueous co-solvent mixtures as a function of temperature and composition is important for purification of raw material and understanding the mechanisms concerning physical and chemical stability of the solid dissolutions [3,5,6]. It is usually regarded as a crucial factor in designing a crystallization process, wherein the knowledge of solubility is needed to control the desired polymorphic form, supersaturation, yield and particle size. Co-solvency is an effective and optional solubilization method which is considered to change the solid solubility, as aqueous co-solvent mixtures can be employed as reaction medium of many substances [1,6]. Low solubility in water is likely to result in formulation difficulty or low bioavailability during the clinical development [1,5,7]. Furthermore, drugs solubility in co-solvent mixtures allows us to carry out a thermodynamic analysis to deeply understand the molecular mechanisms relating to the drug dissolution process and evaluate the preferential solvation of a solute by the co-solvent components in solutions [8–11].

Amoxicillin (CAS Reg. No. 26787-78-0, structure shown in Fig. 1) is a commonly used penicillin antibiotic [12–15]. It is used to treat many different types of infection caused by bacteria, such as tonsillitis, bronchitis, pneumonia, gonorrhea, and infections of the ear, nose, throat, skin, or urinary tract. Amoxicillin is also sometimes used together with clarithromycin (Biaxin) to treat

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https://doi.org/10.1016/j.jct.2019.106010
0021-9614/

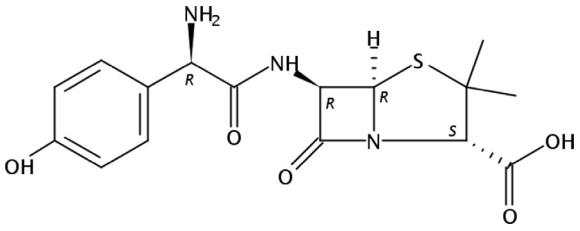

Fig. 1. The chemical structure of amoxicillin.

stomach ulcers caused by Helicobacter pylori infection. However, the amoxicillin solubility in water is low [16–21]. In the previous works, many methods, such as surfactant addition, cosolvency, complexation, and *p*H adjustment and so on, are used to solubilize drug candidates with low aqueous solubility [1,5]. The most powerful and effective tool is mixing a miscible and safe co-solvent with water [1–3,5,16–20]. Nevertheless, regardless of the usefulness of amoxicillin, the information on physicochemical properties, e.g. solubility, in mono-solvents and solvent mixtures are very scarce. A thorough literature search indicates that only the amoxicillin solubility in ethanol + water and sodium chloride + water mixtures and supercritical carbon dioxide at several temperatures is available [21–27]. However, the physicochemical property of amoxicillin in solvent mixtures has not yet been investigated systematically. This case stimuluses us to make in-depth research on the solubility and the solute–solvent and solvent–solvent interactions of amoxicillin in aqueous co-solvent mixtures.

For the co-solvency method, solvent selection is a vital process. The practicable solvents should be environmentally safe, commercially available, non-corrosive and thermally stable. In the pharmaceutical fields, the commonly employed co-solvents are *N,N*-dimethylformamide (DMF), ethanol, isopropanol, ethylene glycol (EG), dimethyl sulfoxide (DMSO) and so forth [1,3,5,6]. Isopropanol is a flammable compound with a strong odor. It dissolves a wide range of non-polar compounds. Compared to other alternative solvents, isopropanol is relatively non-toxic. It is often employed solely or in mixtures with other solvents for diverse aims containing in penetration-enhancing pharmaceutical compositions for the topical percutaneous and transepidermal uses [28,29]. DMF is a commonly used co-solvent in investigating the interrelation between solubility of drugs and medium polarity [30]. The solutions of DMF-water present very strong non-ideal, so it may serve in the solute solvation procedure through hydrophobic interactions and preferential solvation [31]. NMP is also a common co-solvent in pharmaceutical industry. It has strong solubilization capacity and is an important solvent in the extraction, crystallization and purification processes of many drugs [32]. EG is a safe and pharmaceutically acceptable solvent for industrial applications [33].

Based on these points-of-view, the main objectives of the present work are to report the solubility of amoxicillin in aqueous co-solvent mixtures of DMF, isopropanol, NMP and EG at temperature range from 278.15 to 328.15 K under atmospheric conditions and estimate some thermodynamic quantities of the mixtures.

2. Theoretical aspects

In the present paper, the Jouyban-Acree model [34,35] is employed to mathematically describe the amoxicillin solubility in aqueous co-solvent solutions of DMF, isopropanol, NMP and EG. Moreover, the KAT-LSER model is used to examine the solvent effect on the amoxicillin solubility [36–39].

2.1. Jouyban-Acree model

The Jouyban-Acree model, described as Eq. (1), may provide precise mathematical description for the dependence of solute solubility on both solvent composition and temperature for co-solvent solutions [34,35].

$$\ln x_{w,T} = w_1 \ln x_{1,T} + w_2 \ln x_{2,T} + \frac{w_1 w_2}{T/K} \sum_{i=0}^{2} J_i (w_1 - w_2)^i \quad (1)$$

herein $x_{w,T}$ is the mole fraction solubility of amoxicillin in mixtures at temperature T/K; w_1 and w_2 refer to, respectively, the mass fraction of co-solvents 1 (DMF, isopropanol, NMP or EG) and 2 (water) in the co-solvent solutions free of amoxicillin; $x_{1,T}$ and $x_{2,T}$ stand for the mole fraction solubility of amoxicillin in neat solvents at T; and J_i are the model parameters.

2.2. Solvent effect

In developing models based on quantitative structure–property relationships for solvent effect, considerable efforts have been devoted to quantitative description of the solvent polarity [39]. In this regard, Kamelt and Taft et al. introduce their well-known empirical model based on the linear solvation energy relationships concept [36–38]. This model, abbreviated KAT-LSER hereafter, divides the total change in free energy induced by the solvent into some separated intermolecular interaction energy terms. These terms account for both specific (e.g. hydrogen bonding) and non-specific electrostatic interactions (such as Keesom dipole–dipole, Debye dipole-induced dipole and London instantaneous induced dipole–dipole dispersion) that might occur between solute and solvent molecules. Three empirical solvent parameters named π^*, β and α have been introduced to describe the feature of the solvent at the molecular level. According to Kamlet et al., π^* represents dipolarity/polarizability as a scale to characterize the solvent's ability for non-specific interactions; β and α symbolize the capacity of solvent to act as a hydrogen-bond acceptor and hydrogen-bond donor in specific interactions, respectively [40–42]. KAT parameters are derived by the solvatochromic comparison method from a direct measurement of a change in the solute's electronic transition energy due to corresponding solvent effect. Hence, a linear correlation is expected between interaction energy terms defined by KAT parameters with the change induced by the solvent in Gibbs energy of a property (e.g. solubility). Therefore, the examination of KAT-LSER model gives opportunity to extract detailed information about the nature and significance of different solvation components playing in the solvent effect. In this way, another objective of this paper is to analyze the solvent effect upon the solubility variation of amoxicillin in aqueous co-solvent mixtures of DMF, EG, NMP and isopropanol through the KAT-LSER model in order to explain the relative importance and the nature of intermolecular interactions that bring about the solvent effect.

The general form of KAT-LSER model relates the Gibbs energy of solvation of a given solute (presented proportionally by the natural logarithmic form of the mole fraction solubility, ln$x$) in a linear correlation to different solute–solvent and solvent–solvent interaction energy terms as Eq. (2) [36–38].

$$\ln x_w = c_0 + c_1 \pi^* + c_2 \beta + c_3 \alpha + c_4 \left(\frac{V_s \delta_H^2}{100RT} \right) \quad (2)$$

here, the terms c_1 π^*, c_2 β and c_3 α relate to the energy for non-specific and specific solvent–solute interactions; The coefficients $c_{i=1\text{-}3}$ demonstrate sensitivity of the solute solubility to respective energy term. The last term $\frac{V_s \delta_H^2}{100RT}$ in the Eq. (2) refers to the cavity term that defines the energy term for solvent–solvent interactions.