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Solid-liquid equilibrium of erythromycin thiocyanate dihydrate in four mono-solvents and three binary solvent mixtures

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ABSTRACT

Solid-liquid equilibrium data of erythromycin thiocyanate dihydrate in four mono-solvents (methanol, ethanol, propan-1-ol and propan-2-ol) and three organic + water solvent mixtures (acetonitrile + water, acetone + water and ethanol + water) were determined by a gravimetric method under atmospheric pressure. The effects of content of organic solvents and temperature on the solubility were investigated and discussed. It was found that the content of organic solvents can significantly affect the solubility of erythromycin thiocyanate dihydrate. The modified Apelblat equation and NRTL model were applied to correlate the solubility data in mono-solvents. The GSM, two modified Jouyban-Acree models (the Van't-JA equation and the Apel-JA equation) and NRTL model were used to correlate the experimental data in three binary solvents systems. Computational results indicated that the *AIC* (Akaike's Information Criterion) values of two Jouyban-Acree models and NRTL model were lower than that of GSM in binary solvents mixtures, which means that the former three models are better for correlating the experimental solubility data. In addition, the mixing thermodynamic properties of erythromycin thiocyanate dihydrate in different solvents were also calculated based on the experimental solubility data and the NRTL model.

1. Introduction

Solid-liquid equilibrium data is one of the important thermodynamic properties since it can provide essential information for the design, analysis and optimization of the separation and purification processes in various fields e.g. pharmaceutical, chemical, food, petrochemical and material [1–3]. Erythromycin thiocyanate ($C_{38}H_{68}N_2SO_{13}$, CAS Registry No: 7704-67-8), is an antibiotic drug which is highly effective against gram-positive bacteria and mycoplasma infection [4–5]. Erythromycin thiocyanate is reported to have three hydrate forms, and dihydrate form is the most widely used form in industry [6–7]. As shown in Fig. 1, erythromycin thiocyanate dihydrate (abbreviated as ETD hereafter in this work) possesses a 14-membered lactone ring, a cladinose moiety and a desosamine moiety which is widely used as veterinary medicine or important intermediate for the preparation of other macrolide antibiotics [8]. During the manufacturing of ETD, the crystallization process directly affects the final quality of the ETD product [9]. Although it has been a long time since the launch of ETD, no experimental or theoretical study about the thermodynamics of ETD has been found from bibliographic retrieval.

In this work, the solubility data of ETD in four alcohol organic solvents (methanol, ethanol, propan-1-ol and propan-2-ol) and three different kinds of solvent mixtures (acetonitrile + water, acetone + water, ethanol + water) were experimentally measured under atmospheric pressure for the first time. The modified Apelblat equation and NRTL model were applied to correlate the solubility data in mono-solvents. The effects of cosolvent (organic solvents) and temperature on the solubility of ETD in binary solvent mixtures were also investigated and discussed. To extend the applicability of the solubility data, the GSM, two modified Jouyban-Acree models and NRTL model were used to correlate the experimental solubility data in three binary solvent mixtures. The mixing thermodynamic properties were also determined by the NRTL model and experimentally measured solubility data.

2. Experimental section

2.1. Materials

Erythromycin thiocyanate dihydrate was supplied by Shanghai Tonglian Pharm. Co. Ltd. (China). The water content of the provided ETD was determined to be 4.51 ± 0.2 mass% with a V20 Volumetric

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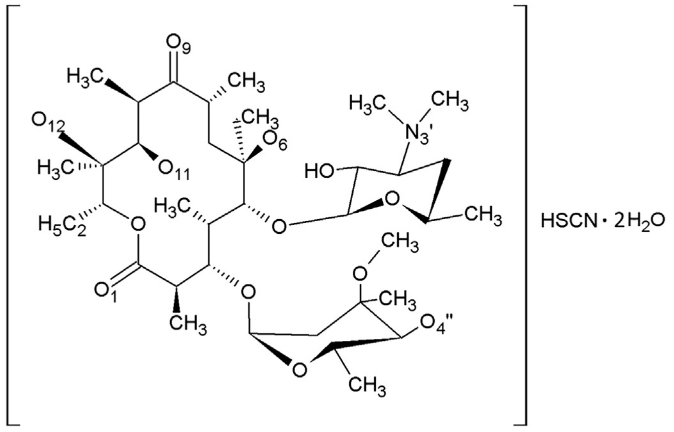

Fig. 1. Molecular structure of erythromycin thiocyanate dihydrate.

Karl Fischer Titrator (Mettler Toledo, Switzerland), which is close to the theoretical value 4.35%. The distilled deionized water was used throughout. Detailed information about methanol, ethanol, propan-1-ol, propan-2-ol, acetonitrile and acetone is given in Table 1.

2.2. Characterization by X-ray diffraction and DSC/TG

The X-ray diffraction patterns of the samples were measured to identify the crystallinity and identity of the experimental samples. Data collection was performed on Rigaku D/max-2500 (Rigaku, Japan) by using Gu Kα radiation (0.71073 Å). The data was collected in 2θ range from 2° to 50° by using the scanning rate of 1 step·s^{-1}.

Differential scanning calorimetry (DSC 1/500, Mettler Toledo, Switzerland) was used to obtain the melting properties of ETD under the protection of nitrogen (70 mL·min^{-1}). The mass of samples was 5–10 mg. The heating rate of samples was set at 10 K·min^{-1} and the temperature range of the experiment was from 308.15 to 458.15 K. Thermogravimetric was conducted on a Rigaku PTC-10A instrument. The sample (5–10 mg) was heated up at a rate of 10 K·min^{-1} and the TG curve was recorded from 293.15 K to 463.15 K under dry nitrogen protection (90 mL·min^{-1}).

2.3. Measurements of ETD solubility

The gravimetric method described in literature [10] was applied to determine the solubility data of ETD. For each measurement, mono-solvents or binary solvent mixtures with suitable content were prepared. The temperature was maintained at presetted value by electrical heating. Excess amount of solute was added into small glass reactors (provided by EasyMax™, Mettler Toledo, Switzerland, $V = 20$ mL) with pre-weighted solvents. Equilibrium was achieved by continuous magnetic mixing (400 rpm) for 8 h and the solution was kept static for another 2 h before 5 mL upper solution was withdrawn and filtered by using a preheated syringe with a membrane (0.45 μm) filter. The withdrawn clear solution was moved into another previously weighted petri dish (m_0). The petri dish was quickly and tightly closed and weighted (m_1') to determine the mass of the solution ($m_1' - m_0$). After the solvent was completely evaporated in an oven at 313.15 K, the petri dish was reweighed (m_1'') to determine the mass of the obtained solid ($m_1 = m_1'' - m_0$). All the samples were weighted using an analytical balance (Model AB204, Mettler-Toledo, Switzerland) with an accuracy of ±0.0001 g. Each experimental data point was an average of at least three experimental measurements to ensure the reliability of the solubility data. After solubility experiments, the identity of the solid phase samples was confirmed by PXRD and DSC.

Based on experimental data, the mole fraction solubility (x_1) can be calculated according to Eq. (1):

$$x_1 = \frac{m_1/M_1}{\sum_{i=1}^{n} m_i/M_i} \tag{1}$$

where m_i represents the mass of solute and solvents, and M_i stands for the molar mass (g·mol^{-1}) of solute and solvents. In this work, $n = 2$ represents mono-solvent, while $n = 3$ represents binary solvent mixtures. Among them, m_1 and M_1 represent the mass and molar mass of the solute, while m_2 and M_2 represent the mass and molar mass of the organic solvent (methanol, ethanol, propan-1-ol and propan-2-ol, acetonitrile and acetone), respectively. When the solvents were binary solvent mixtures (acetonitrile + water, acetone + water and ethanol + water), m_3 and M_3 represent the mass and molar mass of the water. The value of m_3 includes initial water mass and additional water mass from dihydrate.

3. Models for solid-liquid equilibrium data

3.1. The Apelblat equation

The Apelblat equation has been generally deemed that it could be well used in correlating the solubility in various solvents [11]. The equation is shown as Eq. (2).

$$\ln x_1 = A + B/T + C\ \ln T \tag{2}$$

where A, B and C were defined as parameters of the equation.

3.2. The GSM equation

The general single model (GSM), as a polynomial equation, was widely used to correlate the experimental solubility data of compounds in the pharmaceutical literature [12–14]. The model was derived from theoretically based cosolvency models, i.e. the excess free energy (EFE) and the combined nearly ideal binary solvent/Redlich-Kister (CNIBS/R-K) through some appropriate substitutions and rearrangements [15]. As shown in Eq. (3) GSM was a power series equation with respect to the concentration of one of the solvents in binary solvent systems.

$$\ln x_1 = B_0 + B_1 x_2^0 + B_2 \left(x_2^0\right)^2 + B_3 \left(x_2^0\right)^3 + B_4 \left(x_2^0\right)^4 \tag{3}$$

Table 1
Sources and mass fraction purity of chemicals.

Chemicals	Mass purity	Molar mass/g·mol^{-1}	Source
ETD	≥0.984(HPLC[a])	829.05	Shanghai Tonglian Pharm. Co., Ltd
Methanol	≥0.995(GC[b])	32.04	Tianjin Jiangtian Chemical Co., Ltd.
Ethanol	≥0.997(GC[b])	46.07	Tianjin Jiangtian Chemical Co., Ltd.
Propan-1-ol	≥0.995(GC[b])	60.10	Tianjin Jiangtian Chemical Co., Ltd.
Propan-2-ol	≥0.995(GC[b])	60.10	Tianjin Jiangtian Chemical Co., Ltd.
Acetonitrile	≥0.9999(GC[b])	41.05	Tianjin Jiangtian Chemical Co., Ltd.
Acetone	≥0.995(GC[b])	58.08	Tianjin Jiangtian Chemical Co., Ltd.

[a] High-performance liquid chromatography.
[b] Gas-liquid chromatography.