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Measurement of solubility of erythromycin acetone solvate in aqueous acetone solution between 298 K and 323 K

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ABSTRACT

Using a laser monitoring observation technique, the solubility of erythromycin acetone solvate in binary acetone + water solvent mixtures was measured by a synthetic method at temperatures ranging from 298.00 K to 323.00 K and at atmosphere pressure. The results of these measurements were correlated by the combined nearly ideal binary solvent CNIBS/Redlich–Kister equation and the modified Apelblat equation, respectively. For the solubility data studied, the CNIBS/Redlich–Kister equation was found to provide a more accurate mathematical representation of the experimental data.

1. Introduction

Erythromycin is a mixture of macrolide antibiotics produced by fermentation of strains of saccharopolysporaerythrea. Treatment with this antibiotic drug in human and veterinary practice is still very common, because of the high activity against gram-positive and a few gram-negative strains [1]. In addition, erythromycin is useful as an intermediate for the preparation of roxithromycin, azithromycin and clarithromycin. Erythromycin A (Fig. 1) is active component in erythromycin mixtures.

Crystallization processes are the critical steps that determine the quality of final product of erythromycin. Therefore, knowing the solubility of the product is a necessary condition in order to design the crystallization process properly. Erythromycin is purified in industry by anti-solvent crystallization from acetone + water mixtures. However, crystallization behavior is not understood satisfactorily. Therefore, some problems such as yield loss, improper addition rate of anti-solvent and so on, sometimes occur in an actual crystallization process. As a first step toward a fundamental understanding of erythromycin crystallization, solubility measurements should be performed in acetone + water mixed solvents. There are two types of erythromycin crystals (shown in Fig. 2). One is needle-like, which was acetone solvate, that is, a pseudopolymorphic crystal of erythromycin, and the other is plate-like, which is a dihydrate and used in industries. The plate-like crystal was different from the obtained needle one not only in shape but also in crystal structure. The XRD patterns of the two crystal forms are shown in Fig. 3, which is consistent with the literature [2]. In a previous paper, we have reported the solubility of dihydrate in acetone + water mixed solvents [3]. In this work, solubility measurement of acetone solvate in acetone + water mixtures from 298.00 K to 323.00 K were performed, which can be used to make a further analysis of theoretical yield, anti-solvent addition rate and so on in real industrial crystallization.

Modelling of experimental solubility data enables researchers to represent mathematical aspects of solubility. A number of methods have been presented in order to estimate the solubility of solute in solvent mixtures. According to these methods, the solubility of a solute could be predicted in different systems. In the present study, the solubility of erythromycin acetone solvate in binary acetone aqueous solution was measured in the temperature range from 298.00 K to 323.00 K at atmosphere pressure by a laser monitoring observation technique, and the CNIBS/Redlich–Kister equation and semiempirical Apelblat equation were used to correlate and predict the solubility of erythromycin acetone solvate in acetone + water binary mixtures.

2. Experimental

2.1. Experimental materials

White and needle crystals of erythromycin acetone solvate (molecule weight 791.94) were used. The erythromycin acetone

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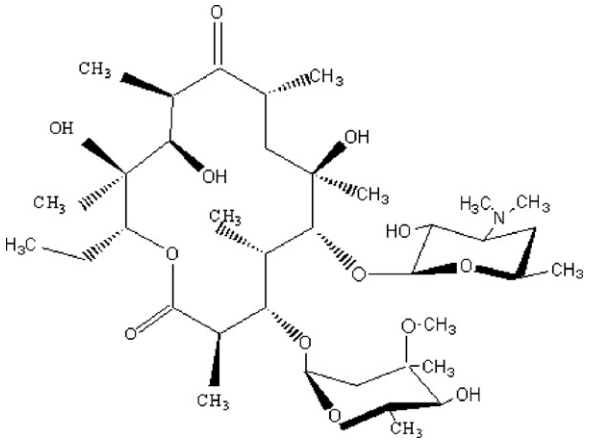

Fig. 1. Structure of erythromycin A.

solvate used for the solubility measurement had a purity of 99.0% (mass fraction), and it was obtained by purifying commercial erythromycin dihydrate which was obtained from Xi'an Rejoy Pharmaceutical Co. Ltd., China, First, 20.0 g of erythromycin dihydrate was dissolved in 80 mL of acetone at the temperature of 45 °C Then 160 mL of water was added and the mixture was stirred at 45 °C for 2 h. The wet crystals obtained by filtration were dried at 40 °C to obtain erythromycin acetone solvate. The acetone used (purchased from Tianjin Kewei Co. of China) for the experiments was of analytical reagent grade its purity is more than 99.5%. Distilled deionized water of HPLC grade was used.

2.2. Experimental method and apparatus

Solubility was measured by the synthetic method [4–6], which is described in the literature [3]. All the experiments were conducted three times, and the mean values were used to calculate the mole fraction solubility. The uncertainty of the experimental solubility values is not more than 0.5%.

The saturated mole fraction solubility of the solute (x_A) in solution is obtained as follows:

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B + m_C/M_C} \quad (1)$$

In which m_A, m_B and m_C represented the masses of solute, acetone, and water. M_A, M_B, and M_C are the molecule weight of solute, acetone, and water, respectively.

The differences in crystal morphology and XRD patterns between dihydrate and acetone solvate could be used to identify the specific solvate that coexisted with an equilibrated liquid solution. In this study, suspension samples withdrawn from the crystallizer were analyzed for the solid phase to verify the solid form present at equilibrium by microscope and XRD.

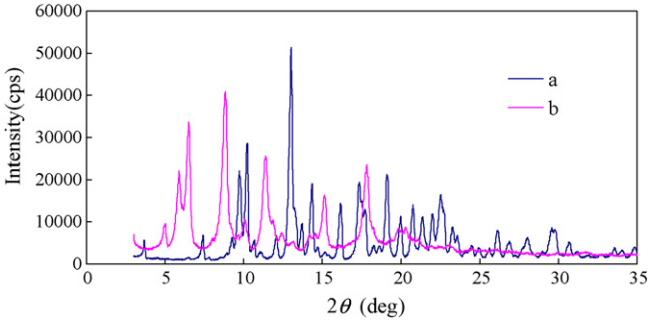

Fig. 3. XRD patterns of (a) granular and (b) needle crystals.

3. Results and discussion

3.1. Solubility data

The solubility data of erythromycin acetone solvate in acetone + water binary mixtures at the temperature range from 298.00 K to 323.00 K are listed in Table 1. X denotes water mole fraction of the binary solvent where solute was not present. From Table 1, it can be seen that solubility of erythromycin acetone solvate increases with increase of temperature within solvent composition studied. At a certain constant temperature, the solubility data of erythromycin acetone solvate in acetone + water mixed solvents decreases with increasing water content.

3.2. Data correlation

The solubility data in Table 1 are described by the combined nearly ideal binary solvent (CNIBS)/Redlich–Kister models suggested by Acree et al. [7–9]:

$$\ln x_A = x_B^0 \ln(x_A)_B + x_C^0 \ln(x_A)_C + x_B^0 x_C^0 \sum_{i=1}^{N} S_i (x_B^0 - x_C^0)^i \quad (2)$$

S_i is a model constant and N can be equal to 0, 1, 2, and 3, respectively. Depending on the values of N, four equations can be obtained from Eq. 2. x_B^0, x_C^0 refer to the initial mole fraction composition of the binary solvent calculated as if solute A was not present.

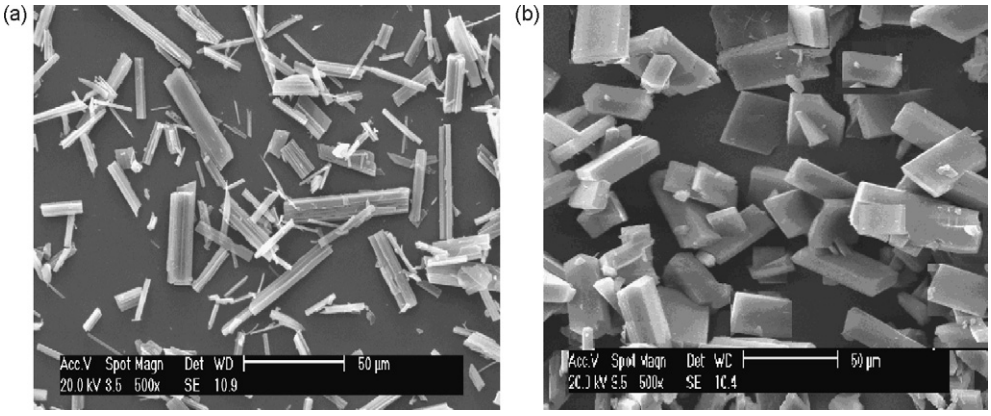

Fig. 2. SEM images of erythromycin solvates. (a) Acetone solvate and (b)dihydrate.