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Thermodynamic equilibrium and cosolvency of florfenicol in binary solvent system

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ABSTRACT

The solubility of florfenicol in binary solvent mixtures of acetone + (methanol or ethanol or isopropanol) was experimentally measured at temperature ranging from 278.15 K to 318.15 K under atmospheric pressure ($p = 0.1$ MPa) by using the gravimetric method. In all the tested solvent systems, the solubility of florfenicol increases monotonically with increasing temperature at fixed solvent composition. While, as regards solvent composition, it shows a cosolvency phenomenon where the solubility has a maximum at a certain solvent compostion. The cosolvency was interpreted via mathematical model correlation using modified Apelblat equation, NRTL model, combined nearly ideal binary solvent/ Redlich–Kister (CNIBS/R-K) model, and Jouban-Acree model. Moreover, thermodynamic properties of the investigated systems including entropy, enthalpy and Gibbs free energy of the solubility data were calculated using NRTL model. The solubility results may be helpful to developing a proper crystallization process of yielding florfenicol nanoparticles.

1. Introduction

Florfenicol ($C_{12}H_{14}Cl_2FNO_4S$, CAS No.: 73231-34-2, Fig. 1) is a new broad-spectrum antimicrobial drug which belongs to chloramphenicol and is known as the "anti-microbial star". It is widely used in veterinary clinical prevention and treatment of swine, cattle and other bacterial infectious diseases [1].

Although florfenicol has excellent antibacterial properties, it has a poor solubility in water, which reduce both the oral absorption and the bioavailability of florfenicol [2]. Various strategies such as the nanonization, complexation with cyclodextrin, and solid dispersions have been tested to solve this problem [3]. Nanonization is by far the best method for florfenicol because the added substance is the least and the purity of the medicine is the highest. Antisolvent precipitation is a commonly used method to nanosized drugs [4], in which solvent with high solubility and anti-solvent with very slight solubility are needed. The solubility of florfenicol in some pure solvents has been reported, including water, methanol, ethanol, acetone, tetrahydrofuran, 1-propanol, isopropanol, ethyl acetate, acetonitrile, 1,2-propanediol/water, and acetone/water [5,6]. Among these reported solvent systems, acetone is the preferred solvent prior to tetrahydrofuran with consideration of both solubility and toxicity. Although florfenicol has poor aqueous solubility, water is not a good anti-solvent because it cannot dissolve the necessary hydrophilic surfactant in nanonization of florfenicol [7]. Thus, organic solvents provide slight solubility, such as methanol, ethanol, and isopropanol are the practical anti-solvents. Unfortunately, there is a lack of solubility data on those solvent mixture systems which is necessary to develop an anti-solvent crystallization process.

In this work, the solubility of florfenicol in acetone mixtures with a series of commonly used alcohols was determined using the gravimetric method [8] at temperatures ranging from 278.15 K to 318.15 K under 0.1 MPa. Specific cosolvency phenomenon was found in the tested solvent systems and was interpreted using different models. Moreover, NRTL model was used to calculate the mixing thermodynamic properties such as enthalpy, entropy and, free Gibbs energy. The results could be helpful to develop a crystallization process for florfenicol.

2. Experimental section

2.1. Materials

Florfenicol (≥0.990 mass fraction) was offered by Ringpu Bio-Pharmacy Co. Ltd., China and was used without further treatment. It was verified to be form I [5] using powder X-ray diffraction (PXRD). All the solvents used in this work were purchased from Tianjin Kewei Chemical Co., China and used directly. The mass fraction purities of all selected solvents are higher than 0.995 (Table 1).

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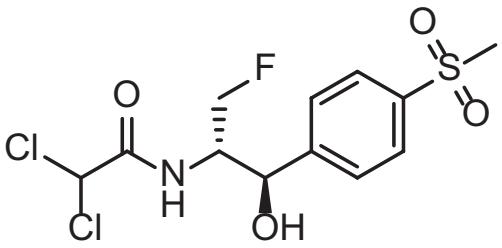

Fig. 1. The chemical structure of florfenicol.

2.2. Apparatus and methods

The gravimetric method used in this work is based on the literature [8]. Excess florfenicol were mixed with binary solvent mixture with known composition in a 70 mL jacketed glass vessel. The mixture was continuous stirred at a preset temperature under 1 atm. The temperature was controlled by a thermostat (Xianou Laboratory Instrument Works Co., Ltd., Nanjing) with an accuracy of ±0.1 K. The system was kept stirring for 10 h to make the two phases in equilibrium. After that, the magnetic stirrer was stopped to let the undissolved solute settle down for 30 min. The supernatant was then taken using a syringe fitted with a Millipore filter (0.45 μm) which was precooled/preheated to the measurement temperature. The filtrate was poured into a preweighed Petri dish and weighed quickly using an electric balance with accuracy of ±0.0001 g (ML204/02, Metter Toledo, Switzerland). The filtrate was then dried in a vacuum oven (DZ-2BC, Tianjin Taisite Instrument Co. Ltd., China) at $T = 313.15$ K and weighed periodically until fully dried (weight change < 0.05%). All the experiments were repeated at least three times and the average was used to calculate the mole fraction solubility at the corresponding condition according to Eq. (1).

$$x_F = \frac{m_F/M_F}{m_F/M_F + m_a/M_a + m_i/M_i} \tag{1}$$

where, x, m, and M represent the mole fraction solubility, the mass, and the molar mass, respectively. The subscript F, a, and i represent florfenicol, acetone, and the other alcohols respectively.

2.3. Characterization of florfenicol

The crystal form of florfenicol before and after solubility measurement was determined using Rigaku D/max-2500 (Rigaku, Japan) [9]. The melting properties of florfenicol were measured using DSC 1/500 (Mettler Toledo, Switzerland) under protection of nitrogen at a heating rate of 2 K/min. The DSC instrument was calibrated by indium and zinc before determination. The standard uncertainty for melting point measurement was 0.5 K and the standard uncertainty for enthalpy of fusion was 2%.

Table 1
Sources and mass fraction purity of chemicals.

Chemical name	Source	Mass fraction purity	Analysis method
Florfenicol	Ringpu Bio-Pharmacy Co. Ltd	≥0.99	HPLC[a]
Acetone	Tianjin Jiangtian Chemical	≥0.995	GC[b]
Methanol	Tianjin Jiangtian Chemical	≥0.995	GC[b]
Ethanol	Tianjin Jiangtian Chemical	≥0.995	GC[b]
Isopropanol	Tianjin Jiangtian Chemical	≥0.995	GC[b]

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

3. Thermodynamic models

3.1. The modified Apelblat equation

Apelblat et al. proposed a semi-empirical model shown as Eq. (2) in 1999 [10–12], ignoring the activity coefficient of the solute and assuming that the molar enthalpy of solution varies linearly with temperature. It is derived from Clausius-Clapeyron Equation, and commonly used to correlate the mole fraction solubility against the temperature.

$$\ln x_F = A + \frac{B}{T/K} + C\ \ln(T/K) \tag{2}$$

where x_F is the mole fraction solubility of solute. A, B, and C are model constants. T is the absolute temperature. The values of A and B differ because of different solution activity coefficient, while the value of C indicates the effect of T on $\Delta_{fus}H$.

3.2. The NRTL model

Based on the solid-liquid phase equilibrium theory, the fugacities of the solute in two phases at equilibrium should be equal. Hence Eq. (3) is given to show the relationship between the temperature and the equilibrium solubility [13].

$$\ln x_F = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \ln\gamma_i - \frac{1}{RT}\int_{T_m}^{T}\Delta C_p dT + \frac{1}{R}\int_{T_m}^{T}\frac{\Delta C_p}{T}dT \tag{3}$$

where $\Delta_{fus}H$, T_m, and R refer to the enthalpy of fusion, the melting point of solute, and gas constant, respectively. γ_i refers to the activity coefficient of solute in a saturated solution. x_F is the mole fraction solubility of solute, and T is the absolute temperature.

Considering the last two parts of the Eq. (3) are less important than the first two parts due to the negligible value of ΔC_p, Eq. (3) can be simplified to Eq. (4) [14].

$$\ln x_F = \frac{\Delta_{fus}H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) - \ln\gamma_i \tag{4}$$

γ_i should be calculated prior to calculate x_F from Eq. (4) [15,16].

The activity coefficient for binary solvent mixture systems can be simplified to Eq. (5)

$$\ln\gamma_i = \frac{(G_{ji}x_j + G_{kj}x_k)(\tau_{ji}G_{ji}x_j + \tau_{ki}G_{ki}x_k)}{(x_i + G_{ji}x_j + G_{ki}x_k)^2} + \frac{\tau_{ij}G_{ij}x_j^2 + G_{ij}G_{kj}x_jx_k(\tau_{ij}-\tau_{kj})}{(x_j + G_{ij}x_i + G_{kj}x_k)^2} + \frac{\tau_{ik}G_{ik}x_k^2 + G_{ik}G_{jk}x_jx_k(\tau_{ik}-\tau_{jk})}{(x_k + G_{ik}x_F + G_{jk}x_k)^2} \tag{5}$$

where, i, j and k are the component of the solution system and, G_{ij}, G_{ji}, G_{ik}, G_{jk}, G_{kj}, G_{ki}, τ_{ij}, τ_{ji}, τ_{ik}, τ_{jk}, τ_{kj}, τ_{ki}, are parameters of this model, which could be expressed as follows.

$$G_{ij} = e^{-\alpha_{ij}\tau_{ij}} \tag{6}$$

$$\tau_{ij} = \frac{\Delta g_{ij}}{RT} \tag{7}$$

$$\alpha_{ij} = \alpha_{ji} \tag{8}$$

where Δg_{ij} is the parameter of this model and α is an adjustable constant between 0 and 1.

3.3. The CNIBS/R-K model

The combined nearly ideal binary solvent/Redlich–Kister (CNIBS/R–K) model [17–22] is suitable for binary solvent systems.