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Solubility and solution thermodynamics of flofenicol in binary PEG 400 + water systems

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ABSTRACT

The solubility of florfenicol in PEG 400 + water solvent mixture was measured at seven temperatures from 293.15 K to 316.25 K. The modified Apelblat equation the General Single model and the Hybrid model were used to fit the experimental solubility data. The thermodynamic functions were obtained from the combination of the modified van't Hoff equation with the modified Apelblat model, including standard enthalpy, entropy and Gibbs energy change of solution. Results showed that: the mole solubility of florfenicol in binary PEG 400 + water solvent mixture increased with the increasing temperature and the mole fraction of PEG 400; the overall mean percentage deviation (*OMPD*) obtained from the modified Apelblat equation, the General Single model and the Hybrid model were 3.22, 3.73, 6.52, respectively. Thus, the modified Apelblat equation can give further accuracy and reliability of the solubility of florfenicol in the selected solvent systems than the other two fitted models. The solution process for florfenicol was always endothermic and the driving mechanism was mainly classified as the following three kinds in the temperature range from 293.15 K to 316.25 K: entropy-driving (from 0.0000 to 0.0064 in mole fraction of PEG 400), enthalpy and entropy driving (from 0.0064 to 0.0138 in mole fraction of PEG 400), enthalpy driving (from 0.0138 to 0.0458 in mole fraction of PEG 400).

1. Introduction

Florfenicol (2,2-dichloro-*N*-[(1*R*,2*S*)-3-fluoro-1-hydroxy-1-(4-methylsulfonylphenyl)-propan-2-yl] acetamide; $C_{12}H_{14}Cl_2FNO_4S$; CAS No: 73231-34-2; Fig. 1) is a fluorinated synthetic analog of thiamphenicol and broad spectrum antibiotic, which belongs to a group of agents used in veterinary medicine named amphenicols [1,2]. In many countries, it can be used as the replacement of chloramphenicol (CAP) in the prevention and treatment of animal diseases, such as bovine and porcine respiratory tract infections [3,4], actinobacillus pleuropneumonia [5] and respiratory disease [6] in pigs, and infectious bovine keratoconjunctivitis [7]. It is commercial available as premix [8] and injection [9]. Due to its very low water solubility (approximately 1 mg/ml), organic solvent must be added to achieve the desired drug concentration in a commercial liquid formulation[10]. However, the utilization of pharmaceuticals involved liquid solvent selection desires the unique solubility data, such as chemical reaction, pre-formulation, purification and liquid pharmaceutical production[11]. Therefore, a rapid and reliable model to predict drug solubility is necessary for the design of pharmaceutical manufacture.

It is well known that PEG 400, a low-toxic pharmaceutical cosolvent and miscible with water in all compositions, has been widely used in medicine design, especially those intended for peroral and parenteral administration [12]. In addition to be an ideal solubilizer for water insoluble drugs, it can be used as a cosolvent to direct the tradeoff between permeability decrease and solubility increase for oral administration of poor aqueous solubility drugs [13]. Moreover, it was also used as a environmentally friendly solvent for the preparation of biologically active compounds [14]. The solubility of florfenicol in methanol, ethanol, acetone and so on has been reported in the literature [15]. However, some hazardous industrial solvents, such as methanol, acetone, etc., possess so acute toxicity that limit their application in the field of pharmaceutical preparation. Thus, it is critically necessary to extend the solubility database for florfenicol to PEG 400 + water binary systems for the development of a certain pharmaceutical application.

In the present work, a static method [16] was employed to measure the solubility of florfenicol in binary PEG 400 + water solvent mixture at seven temperatures from 293.15 K to 316.25 K.

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Nomenclature

List of symbols

x_1	mole solubility of florfenicol
x_0	mole fraction of PEG 400 in binary solvent mixture
x_1^{cal}	the calculated mole solubility of florfenicol
MPD	the mean percentage deviation
OMPD	the overall mean percentage deviation
T	absolute temperature
R	gas constant
ΔH_s	enthalpy change of solution
ΔG_s	Gibbs energy change of solution
ΔS_s	entropy change of solution
$\Delta_{A\to B}H_S$	the transfer change of standard enthalpy from solvent composition *A* to *B*
$\Delta_{A\to B}S_S$	the transfer change of standard entropy from solvent composition *A* to *B*
$\Delta_{A\to B}G_S$	the transfer change of standard entropy from solvent composition *A* to *B*

The experimental solubility data was fitted by the modified Apelblat equation, the General Single model and the Hybrid model. In addition, the thermodynamic properties of the solution process, including the standard enthalpy, entropy and Gibbs free energy change obtained from the combination of the modified van't Hoff equation with the Apelblat model. At last, the thermodynamic functions of transfer were discussed as well.

2. Experimental

2.1. Materials and reagents

The materials were illustrated in Table 1.

2.2. Apparatus and procedure

The procedure used in this work was similar to our previous research [16]. Briefly, about 45 g PEG 400 + water solvent mixture, which was prepared at vary mass fraction of PEG 400. Then excess amount of florfenicol was added into a 150 ml volumetric Erlenmeyer flask with a rubber plug. The Erlenmeyer was placed in a thermostaticmechanical shaker (HZS-H water bath oscillator, China) for 48 h to reach solid–liquid equilibrium. After this process, another 1 h would be taken in order to settle down the suspended solute. A certain volumetric mixture was drawn by a preheated pipette after the equilibrium reached. The sample was filtered through a organic micro-porous membrane (0.22 μm) before analysis. A certain filtered mixture (5 ml) was removed to weigh the mass immediately, and another 2 ml mixture was analyzed by UV spectrophotometer (WFZ UV-2000, Unico, China) at 266 nm wavelength where there is a ultraviolet absorption peak for florfenicol after diluted by suitable methanol. The composition of the solvent

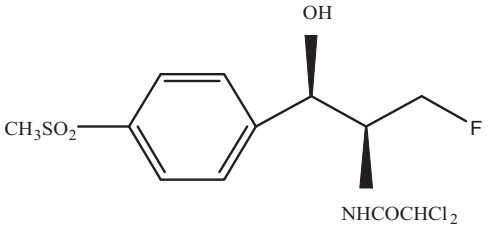

Fig. 1. Chemical structure formula of florfenicol.

mixture (x_0) was defined as Eq. (1). Each solubility data was determined in triplicate, and the mean value was used to calculate the mole solubility (x_1) based on Eq. (2).

$$x_0 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (1)$$

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (2)$$

where m_1, m_2, and m_3 represent the mass of florfenicol, PEG 400 and water, correspondingly. M_1, M_2, and M_3 represent the relative molecular mass of florfenicol, PEG 400 and water, respectively.

The mean percentage deviation (*MPD*) defined in the following equation was used to estimate the agreement between the experimental and calculated solubility data.

$$MPD = \frac{100}{N}\sum \frac{\left|x_1 - x_1^{cal}\right|}{x_1} \quad (3)$$

The overall mean percentage deviation (*OMPD*) was given by the following equation in order to assess the accuracy and predictability of the fitted model.

$$OMPD = \frac{100}{n}\sum_{1}^{n} MPD \quad (4)$$

where *n* is the number of *MPD*.

3. Results and discussion

3.1. Experimental and ideal solubility

The solubility of florfenicol in PEG 400 + water solvent mixture at the temperature ranging from 293.15 K to 316.25 K were presented in Table 2, as well as the calculated solubility (x_1^{cal}) obtained from Eqs. (5), (7) and (8). From Table 2, it is obvious that the solubility in the solvent mixture with the maximal mole fraction of PEG 400 (0.0458) was markedly greater than that in any solvent mixture at each temperature. Therefore, in order to obtain a intuitive judgment for the lower solubilities, another logarithmic form of solubility ($\ln x_1$), which could show a positive correlation between $\ln x_1$ and x_1, was graphically plotted in Fig. 2. From Fig. 2, it can be seen that the solubility of florfenicol in selected solvent mixture increased with increasing temperature, which denoted a endothermic solution process for florfenicol in the selected experimental

Table 1
Characteristics of chemicals used in this study.

Chemical name	Source	Initial mass fraction purity	Purification method	Final mass fraction purity	Analysis method
Methanol	Tianjin Kermel Chemical poReagent Co., Ltd.	≥99.8%≥99.8%	None	–	–
PEG 400		≥98.5%	None	–	–
Florfenicol	Hubei Zhongmu Anda Pharmaceutical Co., Ltd.		Purified by recrystallization from acetone three times, and dried at 343.15 K for 24 h	≥99.6%	UV[a]
Water	Double-distilled water prepared by the laboratory	–	none	–	–

[a] Ultraviolet spectrophotometry.