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Thermodynamic models for determination of the solid-liquid equilibrium of istradefylline in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures

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ABSTRACT

In this paper, we focused on solubility and solution thermodynamics of istradefylline. Herein, we investigated the solubility and solution thermodynamics of istradefylline in binary solvent mixtures by gravimetric method. The solubility of istradefylline in (ethyl acetate + isopropanol), (ethyl acetate + tetrahydrofuran) and (ethyl acetate + acetone) was measured in the temperature range of 278.15 K–333.15 K under atmospheric pressure. In order to correlate the solubility of istradefylline, we employed the modified Apelblat equation, general cosolvency model and Jouyban-Acree model. Computational results showed that the modified Apelblat equation and general cosolvency model have low mean deviation. As calculated by van't Hoff equation, the values of thermodynamic properties such as Gibbs energy, enthalpy, and entropy proved that the dissolution process is endothermic.

1. Introduction

Istradefylline (CASRN:155270-99-8, MW = 384.43, Fig 1), as a drug for treatment of Parkinson, has been developed by Kyowa Hakko Kirin Co., Ltd. Istradefylline has been received much attention in medicine due to it is a kind of selective A2a receptor antagonist and can be used to treat Parkinson's disease [1]. As a novel anti-parkinson drug, it plays an important role in selectively blocking the brain's adenosine A2a receptor. With levodopa in combination, it also can extend the duration of action and improve the dyskinesia symptoms of the patient.

Crystallization or recrystallization is commonly used as a purification step in its production process [2].Owing to the reason known to all, purity is a significant data into industrial production and the recrystallization process of istradefylline requires the solubility data. The solubility of organic compounds in different solvents plays an important role for understanding the (solid + liquid) equilibria (SLE) or phase equilibria in the development or a crystallization process in (liquid + liquid) equilibria and in extraction of azeotropic distillation process. At present, it needs to be purified by dissolution, crystallization and separation. So it is important to know the solubility data to select the best solvent for recrystallization in industrial production. As far as we know, we find no reports on the solubility of istradefylline in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures.

In this work, the solubility of istradefylline in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures was measured from 278.15 K to 333.15 K under atmospheric pressure. The experimental data were related to the modified Apelblat equation, general cosolvency model and Jouyban-Acree model. This is the first attempt on modeling the solubility of istradefylline in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures using these specific thermodynamic models. The thermodynamic properties of the dissolution process, including enthalpy, entropy and Gibbs energy, were calculated by means of the van't Hoff analysis and Gibbs equation.

2. Experimental

2.1. Materials

Istradefylline (mass fraction purity ≥ 99%) was purchased from Aladdin (China). All solvents (Shanghai Shenbo Chemical Co., Ltd)

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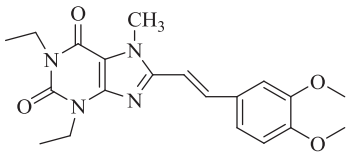

Fig. 1. Chemical structure of istradefylline.

used for experiments were of analytical reagents grade and their mass fraction purity were higher than 99%.The properties of these solvents are listed in Table 1.

2.2. Apparatus and procedures

The solubility of istradefylline was determined by a static equilibrium method as described in the literature [3–5]. A jacketed vessel with magnetic stirrer and Pyrex glass flask were used to measure the solubility. The flask was maintained in a jacket vessel full of water at desired temperature through circulating water, whose temperature was controlled by a thermostat with an accuracy of ±0.01 K that was supplied with a constant-temperature water-bath (type HWC-52, Shanghai Cany Precision Instrument Co., Ltd). And the actual temperature was measured by a thermometer (uncertainty of ±0.1 K) inside the vessel. For each measurement, some excess istradefylline were added to a known volume of solvent mixtures. Continuous stirring was achieved for fully mixing the suspension using a magnetic stirrer at the required temperature. The stirring continued for about 24 h to ensure the solid-liquid equilibrium and the solution was allowed to settle for 12 h or more before sampling for achieving a static state [6–8].To prevent the evaporation of the solvent, a condenser vessel was used during the measurement. An analytical balance (Sartorius, BS210s, Germany) with an uncertainty of 0.0001 g was used and a certain volume of the saturated solution was pipetted and transferred to a volumetric flask, then appropriately diluted to the desired volume. All beakers were made available for a dryer at room temperature and weighed weekly until reaching a constant weight. The water-bath, balance and measuring cylinder in the experiment were calibrated. All measurements were done three times to check reproducibility and then an average value was given [8–10].

Consequently, the experimental saturated mole fraction solubility of istradefylline (x) in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures is calculated by Eq. (1) [11,12]. The mole fraction of ethyl acetate (x_A) in the binary solvent mixtures is calculated by Eq. (2).

$$x = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \tag{1}$$

$$x_A = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \tag{2}$$

where m_1 and M_1 represent the mass and the molar mass of solute, respectively. The m_2 and M_2 represent the mass and the molar mass of the ethyl acetate respectively. The m_3 and M_3 represent the mass and the molar mass of the other solvent.

3. Result and discussion

3.1. Solubility data and thermodynamic models

The solubility data of istradefylline (x) in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures with the temperature ranging from 278.15 K to 333.15 K is presented in Tables 2–4 , and vividly showed in Figs. 2–4. From Tables 2–4 and Figs. 2–4, it can be found that the solubility of istradefylline in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures is a function of temperature and solvent composition. More specifically, the solubility of istradefylline in ethyl acetate plus (isopropanol, tetrahydrofuran, acetone) binary solvent mixtures increases with the rise of temperature, and it increases with increasing ethyl acetate content at constant temperature. In addition, the solubility of istradefylline at the highest ethyl acetate contents is higher. Furthermore, the dissolution process is a thermodynamic process. Istradefylline molecules escape from the crystal, and then combined with solvent molecules. The standard enthalpies for dissolution of istradefylline in the three mixed solvents are all positive, which shows that the dissolution process is endothermic.

3.2. Modified Apelblat equation

The changing trends of solubility against temperature in the solvent with the same ratio are described by modified Apelblat equation. This model is firstly used by Apelblat, which can give a relatively accurate correlation with three parameters [13,14].

$$\ln x = A + \frac{B}{T/\mathrm{K}} + C\ln(T/\mathrm{K}) \tag{3}$$

where x represents the mole fraction solubility of istradefylline, T is the experimental temperature in K, and A, B and C are the regression curve parameters in the equation which is listed in Table 5.

3.3. General cosolvency model

The relationship between the experimental isothermal mole fraction solubility and binary solvent compositions is described by the Combined Nearly Ideal Binary Solvent/Redich-Kister (CNIBS/R-K) model [15], which is one of the theoretical models for calculating the solute solubility in binary solvents and represented in Eq. (4)

$$\ln x = x_A \ln X_A + x_B \ln X_B + x_A x_B \sum_{i=0}^{N} S_i (x_A - x_B)^i \tag{4}$$

Table 1
Information about the materials used in this work.

Compound	Source	Mass fraction purity	Purification method	Analysis method	CAS RN
Intrafydelline	Aladdin Reagent Co. Ltd	≥0.990	Re-crystallization	HPLC[a]	155270-99-8
Ethyl acetate	Shenbo Chemical	≥0.995	None	GC[b]	141-78-6
Isopropanol	Shenbo Chemical	≥0.997	None	GC[b]	67-63-0
Tetrahydrofuran	Shenbo Chemical	≥0.995	None	GC[b]	109-99-9
Acetone	Shenbo Chemical	≥0.997	None	GC[b]	67-64-1

Both the analytical method and the mass fraction purity were provided by the suppliers.
[a] High performance liquid chromatography.
[b] Gas liquid chromatography.