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Thermodynamic analysis and correlation of solubility of Cefaclor in different solvents from 278.15 to 313.15 K

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ABSTRACT

The solubility of Cefaclor in water, methanol, ethanol and acetone was studied under atmospheric pressure in the 278.15–313.15 K temperature range using a dynamic laser method. The modified Apelblat model and a polynomial equation were used to model the experimental data, and both models provided good fits ($R^2 > 0.99$). The changes in the standard enthalpy, entropy and Gibbs free energy upon dissolution of Cefaclor were calculated to obtain thermodynamics data related to Cefaclor crystallisation. The results show that the dissolution process was endothermic and nonspontaneous, and that the main contributing force was the enthalpy in methanol, ethanol and acetone solvents.

1. Introduction

Cefaclor (CAS No.: 70356-03-5), as the second generation of cephalosporin antibiotics, is widely used to treat infections caused by various Gram-positive and Gram-negative bacteria, such as *Haemophilus influenzae* and *Klebsiella* species. Cefaclor is also capable of producing stable β-lactamases [1–5]. The structural formula of Cefaclor is shown in Fig. 1. It contains a 2-amino-4-pheylacetamido, an α-methoxamine and some highly electronegative groups (e.g. amino and carboxyl groups), and is therefore highly polar [6].

In the pharmaceutical industry, drugs are always subjected to several purification and separation processes to remove side-products and other impurities. One of the last and most important processes is the crystallisation process. The solubility behaviour [7] of a drug in various solvents is essential for the design and optimisation of a reasonable crystallisation process, as well as when the drug is given to humans. Thus, solubility data for Cefaclor in different solvents are needed. In this study, water, methanol and ethanol are polar protic solvents, and acetone is a dipolar aprotic solvent, meanwhile, they are common solvents in industry. Primary experiments in our labs show that water, methanol, ethanol, acetone are good potential solvents or anti-solvents for crystallization or recrystallization for Cefaclor. Therefore, the solubility data of Cefaclor in these solvents are essential for further developing and optimizing the crystallization process of Cefaclor.

In the present study, a laser monitoring observation technique was employed to determine the solubility of Cefaclor in four solvents – water, methanol, ethanol and acetone – in the 278.15–313.15 K temperature range at atmospheric pressure. Two mathematical models (reference to Section 3.2) were used to fit the solubilities of Cefaclor in different solvents. The results ($R^2 > 0.99$ and the $\sigma_x < 10^{-5}$) show that the two mathematical models are good fit with the experiment data. The enthalpy, entropy and Gibbs free energy for dissolution of Cefaclor were estimated on the basis of the regression of solubility data using the modified Apelblat model and the van 't Hoff equation.

2. Materials and methods

2.1. Materials and reagents

Cefaclor, the molcular structure of which shows in Fig. 1, with mass fraction purity greater than 99.6%, as determined by HPLC [8], was supplied by the North China Pharmaceutical Company Ltd. Furthermore, deionised water was used in all experiments. Descriptions of the chemicals used in the experiments are provided in Table 1.

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Nomenclature

List of symbols

x_A	Molar fraction of solute
m_A,m_B	The mass of solute and solvent, respectively, g
M_A, M_B	Molecular weights of solute and solvent, respectively, g mol^{-1}
A, B, C	Semi-empirical constants (of Eq. (2))
T	Absolute temperature, K (as a variable in Eqs. (2) and (4)–(9))
σ_x	Root-mean-square deviation
x_i^{exp}, x_i^{cal}	Experimental value and calculated value, respectively
n	The number of experimental data points
B_0, B_1, B_2, B_3, B_4	Semi-empirical constants (of Eq. (4))
ΔH_{sol}	Enthalpy of solution, kJ mol^{-1} (defined in Eq. (5), regard as a variable in Eqs. (8) and (9))
ΔS_{sol}	Entropy of solution, J mol^{-1} K^{-1}
ΔG_{sol}	Gibbs free energy of solution, kJ mol^{-1}
R	Gas constant, J mol^{-1} K^{-1}
$\%\zeta_H$	Partial enthalpy contribution
$\%\zeta_{TS}$	Partial entropy contribution

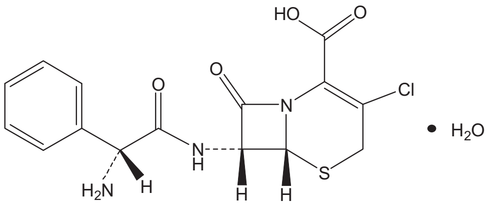

Fig. 1. Molecular structure of Cefaclor [10].

2.2. Apparatus and procedure

From various measurement method of solubility [11–14], a laser monitoring observation technique [15–24] whose rapid and efficient, was used to determine the solubility of Cefaclor. The measuring apparatus are shown in Fig. 2. A 100 mL jacketed vessel with water circulating from a water bath was used as the dissolver, and the temperature was controlled (to within 0.05 K) using a thermostated bath.

The inner solution was fully mixed via a magnetic stirrer. The temperature in the chamber was monitored by a mercury-in-glass thermometer with an uncertainty of ±0.01 K. The dissolution of the solute was examined by the laser beam penetrating the vessel. The laser monitoring system comprised a laser generator, photoelectric transformer and light-intensity recorder. An injector was used to discretely supplement solvent. All the masses of the solute and solvent were weighed using an analytical balance (Mettler Toledo AB204-N, Switzerland) with an uncertainty of ±0.0001 g.

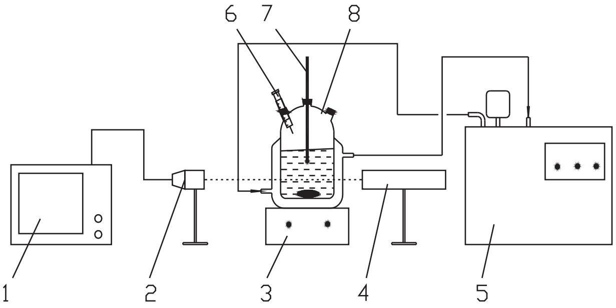

Fig. 2. Schematic setup for the solubility determination: (1) light-intensity recorder; (2) photoelectric transformer; (3) magnetic stirrer; (4) laser generator; (5) superthermostatic bath; (6) injector; (7) thermometer and (8) dissolver.

During the experiments, the fluid in the glass vessel was monitored by a laser beam. Predetermined excess amounts of Cefaclor as well as solvent of known mass were placed in the inner chamber of the jacketed vessel. The contents of the vessel were stirred continuously at a set temperature for 1 h. The corresponding solvent was then added dropwise to the vessel via the injector at a dropping rate of 2–3 g/h (weighed by analytical balance with an uncertainty of ±0.0001 g). The penetrating light intensity was recorded at the same time. The penetrating light intensity slowly increased. With the addition of the solvent and the dissolution of the solute, the penetrating light intensity slowly increased. When the last portion of the solute disappeared, the intensity of the laser beam penetrating the vessel reached its maximum, and the solvent mass consumed during the measurement was recorded [25]. This mass, together with the mass of the solute, allowed the calculation of the solubility. In most cases, the supplemented solvents were approximately 5–10 g (weighed by analytical balance with an uncertainty of ±0.0001 g), and one experiment lasted approximately 7–9 h. The same solubility experiment was conducted three times, and the mean values were used to calculate the molar fraction solubility. The relative standard uncertainty of the solubility measurement was less than 3%, as calculated from the standard deviations of repeated experimental measurements.

3. Results and discussion

3.1. Solubility data

The molar fraction solubility of Cefaclor in different solvents was calculated using Eq. (1):

$$x_A = \frac{m_A/M_A}{m_A/M_A + m_B/M_B} \tag{1}$$

where m_A and m_B refer to the masses of Cefaclor and the solvent, respectively; and M_A and M_B represent the molecular weights of Cefaclor and the solvent, respectively.

Table 1
Source and important physical properties of chemicals [9,10].[a]

Chemical name	CAS Registry No.	Source	Formula weight	Boiling point (K)	Dielectric constant	Mass purity	Purification method
Cefaclor	[70356-03-5]	North China Pharmaceutical Co.	385.82			≥99.6%	Recrystallization
Methanol	[67-56-1]	Tianjin Chemical Reagent Co.	32.04	337.85	33.00	≥99.5%	Method I[b]
Ethanol	[64-17-5]	Tianjin Chemical Reagent Co.	46.07	351.45	25.30	≥99.7%	Method I[b]
Acetone	[67-64-1]	Tianjin Chemical Reagent Co.	58.08	329.15	21.00	≥99.5%	Method I[b]
Water	[7732-18-5]		18.02	373.15	78.30		Distilled

[a] The properties of chemicals were obtained under 100 ± 2 kPa, and all the studied experiments as follows were measured under 100 ± 2 kPa.

[b] Analytical grade reagent and dehydrated with molecular sieves.