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Solubility and polymorphic forms of antibiotic lasalocid sodium in different organic solvents

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ABSTRACT

The solubilities of lasalocid sodium in five organic solvents including methanol, ethanol, propan-2-ol, ethyl acetate and acetone were determined at temperatures ranging from 283.15 K to 323.15 K at atmospheric pressure using a gravimetric method and three novel polymorphic forms of lasaolocid sodium were observed. van't Hoff equation was used to correlate the experimental solubility data. The calculated values of van't Hoff equation were found to be in good agreement with the experimental data. Further, the dissolution enthalpy and entropy of lasalocid sodium in the corresponding solvents were calculated.

1. Introduction

In pharmaceutical industry, active pharmaceutical ingredients (APIs) go through several separation and purification processes, among which, solution crystallization is one of the crucial steps. However, when dealing with APIs numerous organic solvents are available. Given this situation, accurate solubility data of APIs in potential solvents are of overwhelming importance for screening of solvents to obtain products with desired qualities [1]. Solubility information is also extremely valuable for estimation of crystal characteristics (such as polymorph), toxicity, bioavailability of the APIs of interest. Although the solubility of APIs in organic solvents can be referred in a vast amount of literatures [2–5], many more combinations of solvent and solute remain to be investigated.

Lasalocid sodium (molecular weight 206.02, CAS No. 25999-20-6) is an antibiotic and a coccidiostat, which is produced by strains of streptomyces lasaliensis. As a carboxylic acid ionophore, lasalocid sodium is able to make neutral complexes with monovalent and divalent cations and transport them through apolar phase (including lipid bilayer membranes). It can also transport big organic cations like dopamine [6]. Fig. 1 shows the chemical structure of lasalocid sodium. In industrial manufacturing, lasalocid sodium is refined through solution crystallization. Solubility determination of lasalocid sodium in the potential organic solvents is then crucial to select the proper solvent and further to optimize the crystallization process. However, solubility of lasalocid sodium has not been reported so far in literatures.

In this work, solubility of lasalocid sodium in five potential organic solvents including methanol, ethanol, propan-2-ol, ethyl acetate and acetone was measured at temperatures ranging from 283.15 K to 323.15 K at atmospheric pressure using a gravimetric method. The dissolution enthalpy and entropy of lasalocid sodium were calculated from the solubility data using van't Hoff equation. Moreover, microcopy and XRD analysis was performed to characterize the habit and structure of lasalocid sodium crystals equilibrated in organic solvents mentioned above.

2. Experimental

2.1. Materials

Lasalocid sodium (supplied by Hisun Co., Ltd., China) was recrystallized one time from acetone using cooling crystallization. Its purity was analyzed by an automatic titration system and the mass fraction purity is > 99.5%. The methanol, ethanol, propan-2-ol, ethyl acetate and acetone used for experiments were all supplied by

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x_1	solubility of the solute (mol mol^{-1})
x_1^{exp}	experimental solubility of the solute (mol mol^{-1})
x_1^{cal}	calculated solubility of the solute (mol mol^{-1})
T	absolute temperature (K)
T_m	the melting temperature (K)
R^2	coefficient of correlation
R	gas constant (J mol^{-1} K^{-1})
ΔG_d	Gibbs energy (kJ mol^{-1})
ΔH_d	dissolution enthalpy (kJ mol^{-1})
ΔH_m	the enthalpy of melting of HEDP (kJ mol^{-1})
ΔH_{mix}	enthalpy of mixing (kJ mol^{-1})
ΔS_d	dissolution entropy (J mol^{-1} K^{-1})

Shanghai Lingfeng Chemical Reagent Co., with purity higher than 99% (Table 1).

2.2. Experimental apparatus

Powder x-ray diffraction (PXRD, D/MAX 2500) analysis was used to characterize the polymorphic lasalocid sodium and to verify the form of the equilibrated solid. A diffractometer with a Cu $K\alpha$ radiation source (1.5405 Å, 40 kV, 100 mA) was used to collect powder diffraction patterns with 2θ increasing at the rate of 8°/min. The patterns were recorded between 5 and 40° in 2θ with steps of 0.05° and a dwelling time of 1 s/step.

The crystal habits were observed using an optical microscope (BX51 Olympus) with a magnification of 100×.

2.3. Procedure

The solubility of lasalocid sodium in five organic solvents was measured by gravimetric method. The experiments were performed in a 50 ml-vessel with a double jacket through which oil from a thermostated oil bath (FT 32, Julabo Labortechnik, Gmbh, Germany) was circulated and the process temperature was measured by a probe with an accuracy of ±0.05 K. Mixing was provided by a magnetic stirrer rotating at 300 rpm. Then, excess amount of lasalocid sodium was suspended in corresponding solvent at a certain temperature under stirring for at least 12 h, the stirring was stopped, and the solution was kept still for 2 h to allow complete sedimentation of the fine crystals. Three samples of 10 ml each were carefully withdrawn from the clear solution using a 10 ml pipettes equipped with a filter on top so as to make sure that fine crystals were completely removed and preserved in the weighted watch glass. Further, the watch glass was weighted to record the mass of solution and then the solvent was dried for more than 12 h under vacuum circumstance at 323.15 K. After drying, the watch glass was reweighed to determine the mass of residue solid and the evaporated solvent. The mean values of three samples were used to calculate the mole fraction solubility x_1 of lasalocid sodium in different solvents. The relative uncertainty of the experimental solubility values is within 0.06% [7]. Moreover, the equilibrated solid was extracted and characterized using PXRD and microscopy to verify the form of solid present at equilibrium.

3. Results and discussions

3.1. Solubility determination

Table 2 represents the measured lasalocid sodium solubility in five organic solvents. The temperature dependence of mole fraction equilibrium solubility of crystalline can be described by the van't Hoff equation, which relates the logarithm of mole fraction of a solute as a linear function of the reciprocal of the absolute temperature [7]:

$$\ln x_1 = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \quad (1)$$

where T is solution temperature (K), ΔH_d and ΔS_d are the dissolution enthalpy and entropy, respectively. R is the gas constant (8.314 J mol^{-1} K^{-1}). The calculated solubility data and values of dissolution enthalpy and entropy of lasalocid sodium in different solvents are presented in Tables 2 and 3, respectively. The coincidence of experimental solubility and calculated solubility reveals the experimental results and correlation equation in this work can be applied for solvent screening and further the calculation of crystallization kinetics of lasalocid sodium to confirm the optimization operation parameters of crystallization process.

Moreover, as listed in Table 2, it can be noticed that, for all cases, lasalocid sodium exhibits increasing solubility with increasing temperature although the rate of the increase varies

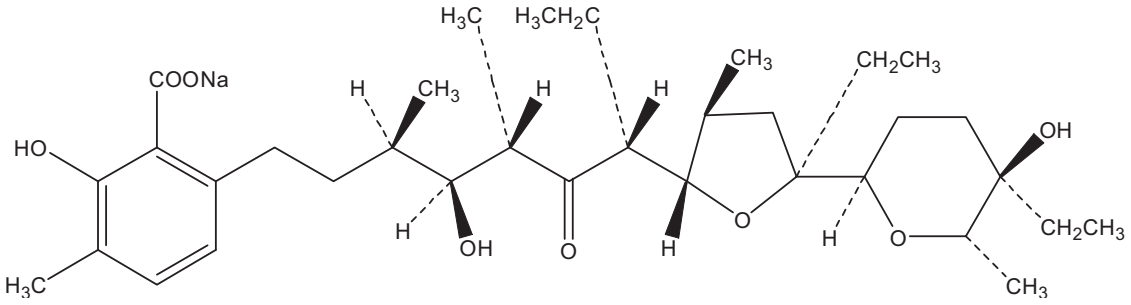

Fig. 1. Molecular structure of lasalocid sodium.

Table 1
Sample table.

Chemical name	Source	Mass purity	Purification method	Analysis method
Lasalocid sodium	Hisun Pharmaceutical	0.995	Recrystallized	Titration
Methanol	Shanghai Chemical	0.99	None	HPLC
Ethanol	Shanghai Chemical	0.99	None	HPLC
Propan-2-ol	Shanghai Chemical	0.99	None	HPLC
Ethyl acetate	Shanghai Chemical	0.99	None	HPLC
Acetone	Shanghai Chemical	0.99	None	HPLC