

Determination and correlation of solubility and solution thermodynamics of valnemulin hydrogen tartrate in different pure solvents

Jinbo Ouyang^{a,b}, Jingkang Wang^{a,b}, Hongxun Hao^{a,b,*}, Xin Huang^a, Yuan Gao^a, Ying Bao^{a,b}, Yongli Wang^{a,b}, Qiuxiang Yin^{a,b}

^a State Key Laboratory of Chemical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, PR China

^b Collaborative Innovation Center of Chemical Science and Chemical Engineering, Tianjin 300072, PR China

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ABSTRACT

The solubility of valnemulin hydrogen tartrate in five pure solvents was determined in temperature range of 278.15 K to 333.15 K by using a static analytical method. Five thermodynamic models were used to correlate the experimental solubility data. The correlated results were analyzed and compared with experimental results. It was found that the correlated results were in good agreement with the experimental results. By using the Van't Hoff equation, the dissolution enthalpy and entropy of valnemulin hydrogen tartrate in different solvents were calculated. The mixing thermodynamic properties of valnemulin hydrogen tartrate, including the mixing Gibbs energy, the mixing enthalpy and entropy, as well as the infinite-dilution activity coefficient and the excess enthalpy, were determined by using the Wilson model and the experimental solubility data.

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1. Introduction

Valnemulin is a new semi-synthetic pleuromutilin derivative, which is effective in the treatment of mycoplasma and brachyspira [1]. Valnemulin hydrogen tartrate has been proposed for an oral administration to pigs for the treatment and prevention of swine dysentery, clinical signs of porcine colonic and swine enzootic pneumonia in the European Union [2]. The chemical structure of valnemulin hydrogen tartrate is shown in Fig. 1. Given its high bioactivity, valnemulin hydrogen tartrate is often used as antimicrobial agent in veterinary medicine to treat the above-described infections nowadays [2,3].

The synthesis of valnemulin hydrogen tartrate has been well investigated by many researchers, with a few trying to develop manufacturing methods to obtain products with high stability and high purity. During the manufacturing of valnemulin, solution crystallization, which is an important separation and purification process and will affect the quality of the final product in the

pharmaceutical industry [4], is also one of the key steps. The development and design of the crystallization process strongly relies on accurate equilibrium solubility data which will vary with temperature and solution compositions [5]. In order to better understand the crystallization process and design an optimum crystallization step for valnemulin hydrogen tartrate, it is essential to establish the accurate solid–liquid equilibrium relationship of valnemulin hydrogen tartrate in different solvents. However, from literatures review, no reports about the thermodynamics, especially solubility of valnemulin hydrogen tartrate, can be found. In this work, the experimental solubility data of valnemulin hydrogen tartrate in pure ethanol, water, 2-propanol, *n*-butanol and acetone in the temperature range of 278.15 K to 333.15 K were experimentally measured by using a gravimetric method [6]. The experimental data were correlated with the modified Apelblat equation, the Van't Hoff equation, the λh equation and two local composition models (Wilson and NRTL models). The melting temperature and the enthalpy of fusion of valnemulin hydrogen tartrate were also determined by differential scanning calorimetry (DSC). In addition, in order to make sure that the same crystal form of valnemulin hydrogen tartrate is used in all experiments, the identification of the valnemulin hydrogen tartrate crystal was verified by using different X-ray powder diffraction (XRPD). By utilizing the solubility data and the Van't Hoff equations, the dissolution enthalpy and entropy, the

* Corresponding author at: State Key Laboratory of Chemical Engineering, School of Chemical Engineering and Technology, 92, Weijin Road, Nankai District, Tianjin 300072, PR China. Tel.: +86 22 27405754; fax: +86 22 27374971.

E-mail addresses: hxx73@hotmail.com, hongxunhao@tju.edu.cn (H. Hao).

T_m	melting temperature of the solute (K)
$\Delta_{\text{fus}}H_1$	fusion of enthalpy of the solute (J mol^{-1})
x_1	solubility of the solute (mol mol^{-1})
m_1	the mass of the solute (g)
m_2	the mass of the solvent (g)
M_1	the molecular mass of the solute (g mol^{-1})
M_2	the molecular mass of the solvent (g mol^{-1})
A	empirical constant for the modified Apelblat equation
B	empirical constant for the modified Apelblat equation
C	empirical constant for the modified Apelblat equation
λ	empirical constant for the λh equation
h	empirical constant for the λh equation (K)
N	number of experimental points in each solvent
R	gas constant ($\text{J mol}^{-1} \text{K}^{-1}$)
γ_1	activity coefficient
T	absolute temperature (K)
P	pressure (Pa)
ΔC_p	the difference between the molar heat capacity of the melting and solid states of the solute ($\text{J mol}^{-1} \text{K}^{-1}$)
$\Delta\lambda_{12}$	empirical constant for the Wilson equation
$\Delta\lambda_{21}$	empirical constant for the Wilson equation
u_1	mole volume of the solute ($\text{cm}^3 \text{mol}^{-1}$)
u_2	mole volume of the solvent ($\text{cm}^3 \text{mol}^{-1}$)
Δg_{12}	empirical constant for the NRTL equation (J mol^{-1})
Δg_{21}	empirical constant for the NRTL equation (J mol^{-1})
ΔH_d	dissolution enthalpy (J mol^{-1})
ΔS_d	dissolution entropy ($\text{J mol}^{-1} \text{K}^{-1}$)
ΔG_{id}	molar Gibbs energy of ideal solution (J mol^{-1})
ΔS_{id}	dissolution entropy of ideal solution ($\text{J mol}^{-1} \text{K}^{-1}$)
ΔH_{id}	dissolution enthalpy of ideal solution (J mol^{-1})
G_E	excess molar Gibbs energy (J mol^{-1})
S_E	excess molar dissolution entropy ($\text{J mol}^{-1} \text{K}^{-1}$)
H_E	excess molar dissolution enthalpy (J mol^{-1})
γ_1^∞	activity coefficient of infinite-dilution solution
$H_1^{E,\infty}$	excess enthalpy of infinite-dilution solution (J mol^{-1})
AAD	average absolute deviation between experimental and calculated x_1
x^{cal}	calculated solubility of the solute (mol mol^{-1})

Subscripts

1	solute
2	selected solvent
E	excess
id	ideal
d	dissolution
fus	fusion
m	melt

Superscripts

cal	calculated
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mixing properties of the solute in the solution systems, such as the activity coefficient, the mixing Gibbs energy, the mixing enthalpy and entropy, the infinite-dilution activity coefficient and excess enthalpy, were also determined.

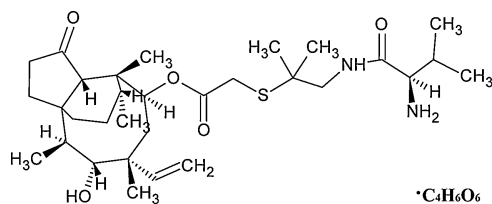


Fig. 1. Chemical structure of valnemulin hydrogen tartrate.

2. Experimental

2.1. Materials

Valnemulin hydrogen tartrate with mass fraction purity higher than 0.98 was supplied by Hubei Longxiang Pharmaceutical Co. Ltd. of China. The solvents, including ethanol, 2-propanol, *n*-butanol and acetone, are analytical grade reagents and were obtained from Tianjin Kewei Chemical Reagent Co. Ltd. of China and were used without any further purification. Distilled–deionized water (conductivities $< 0.5 \mu\text{s cm}^{-1}$) was prepared in our laboratory and used throughout. More detailed information about the materials use in this paper is given in Table 1.

2.2. X-ray powder diffraction

In order to identify the crystal form of valnemulin hydrogen tartrate used in the experiments, the X-ray powder diffraction (XRPD) patterns of the experimental samples were measured by the $\text{Cu K}\alpha$ radiation (1.5405 \AA) in the $2-\theta$ range from 2° to 30° . And the data collection was carried out on Rigaku D/max-2500 (Rigaku, Japan) with scanning rate of 1 step/s .

2.3. Differential scanning calorimetry

The melting temperature T_{melt} and enthalpy of fusion $\Delta_{\text{fus}}H_1$ of valnemulin hydrogen tartrate were measured by DSC (DSC 1/500, Mettler-Toledo, Switzerland) under protection of nitrogen. The sample amount was about 5.0 mg. The heating rate was set at 10 K/min . The measurement uncertainties were estimated to be approximately $\pm 2\%$.

2.4. Solubility measurements

The solubility of valnemulin hydrogen tartrate in different pure solvents was determined by using the gravimetric method. The details about the principle and apparatus of this method were described in the literatures [6–9]. The experimental process could be briefly described as follows. To start, excess amount of the solute and selected solvents were added into a jacketed glass vessel and agitated by a magnetic stirrer for about 3 h to reach the solid–liquid equilibrium. The temperature of the jacketed glass vessel was controlled by a thermostat (Julabo CF41, Germany) with uncertainty of $\pm 0.01 \text{ K}$. Then, the agitation was stopped and the solution was kept still for 2 h to allow the undissolved particles to settle down. After that the upper clear solution was withdrawn, filtered, and poured into a glass dish which was weighed beforehand. And then the total weight was measured immediately. Finally, the glass dish was placed into a vacuum oven and the mass of the dish was recorded periodically until the total weight did not change any more. All samples were weighed by an electronic analytic balance (Mettler Toledo ML204, Switzerland) with uncertainty of $\pm 0.0001 \text{ g}$. The process was repeated three times and the average value of the data was used to calculate the mole fraction solubility.

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