



Solubility and pseudopolymorphic transitions in mixed solvent: Meropenem in methanol–water solution



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ABSTRACT

Meropenem exists in the solid state as trihydrate and methyrate. In the present work, the solubility data of meropenem in mixed methanol–water solvent ranging from 273.15 K to 288.15 K were measured and pseudopolymorphic transitions of meropenem were first observed. The transition points were determined at various temperatures. The corresponding water/methanol activities at transition points were calculated using Wilson equation, and correlated by van't Hoff equation. The results show that the ratio of water activity to methanol activity plays a crucial role in determining the thermodynamic stability of trihydrate and methyrate of meropenem at a specific temperature. The result can be extended to the application of other pseudopolymorphic systems.

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1. Introduction

Crystallization as a unit operation in the pharmaceutical industry serves the dual purpose of separation and purification of the active pharmaceutical ingredients (APIs). Considering the compounds of interest are often labile, solution crystallization is primarily employed [1]. However, a wide variety of solvents are available when dealing with pharmaceuticals and in many cases, these solvents molecules can incorporate into the crystal structure in a specific stoichiometric ratio forming solvates or hydrates [2]. As such changes also occur when some crystalline species form polymorphs (chemical species with the same molecular formula, but different crystal structures), solvates are often called pseudopolymorphs [3]. Transformations among pseudopolymorphic forms often lead to variations in chemical and physical properties including solubility, density, dissolution rate, and bioavailability. These changes subsequently show impacts on the downstream processing during manufacturing, and furthermore, the safety and efficacy of final product. For example, due to the aqueous solubility differences between anhydrous and trihydrated form of ampicillin, blood serum concentrations of the anhydrous form are higher and reach optimal levels earlier than those of the trihydrated form [4]. Thus, a comprehensive understanding of the ability of solvents to form pseudopolymorphs with pharmaceutical compounds and

pseudopolymorphic transitions is crucial to developing reliable and stable pharmaceuticals.

Formation of pseudopolymorphs depends on a number of factors such as temperature and solvent selected. Changes on operating variables during crystallization may then result in pseudopolymorphic transitions and even discovery of new forms. Recent studies on different systems including theophylline, ampicillin, and sodium naproxen have demonstrated that water activity in mixed solvent is the major factor in determining the phase transformation between hydrate and anhydrate [5–8]. For a given temperature, there exists a transformation water activity, at which the solubility curves of the hydrate and anhydrate intersect, representing the transition point of the two forms. At this point, the solubility and thus the stability of the two forms are identical. Any deviation from the transformation water activity will lead to phase transformation, either from hydrate to anhydrate or vice versa [9].

Meropenem (MERO) was selected as a model system in this work. The chemical structure of MERO is shown in Fig. 1. MERO is a parenteral carbapenem antibiotic with a very broad spectrum of antibacterial activity against the majority of gram-positive and gram-negative pathogens [10]. Up to now, no paper addresses the solubility data of MERO in mixed methanol–water solvent and only the form of trihydrate meropenem (monoclinic, belongs to space group P21) was reported [11], which is believed to be a stable form at ambient temperature and pressure.

In our preliminary experiments, a new solvate form of methyrate was observed. The main goals of this study were to measure the solubility of MERO in methanol–water solvent and provide quantitative descriptions of the pseudopolymorphic transformation in

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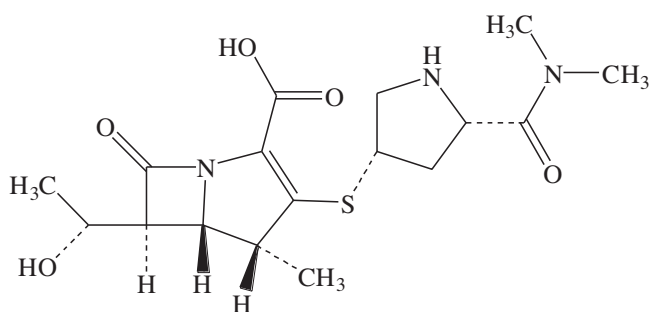
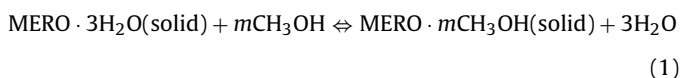


Fig. 1. Chemical structure of Meropenem.

the mixed solvent. Knowing the accurate solubility data of MERO in water–methanol solution and the factors affecting the pseudopolymorph transition can determine a robust operating region for the production of pure hydrate or solvate, which are essential to the process and product design.

2. Theoretical section

Commonly, the stability of hydrate/methylate in mixed solvent mainly depends on temperature and solvent composition. Namely, under a specific temperature, a change of solvent composition may trigger the occurrence of phase transition. With respect to MERO in mixed methanol–water solvent, the formation of methylate from trihydrate may be represented by the following equations:



$$K_h = \frac{a[\text{MERO} \cdot m\text{CH}_3\text{OH}(\text{solid})] \cdot a[\text{H}_2\text{O}]^3}{a[\text{MERO} \cdot 3\text{H}_2\text{O}(\text{solid})] \cdot a[\text{CH}_3\text{OH}]^m} \quad (2)$$

where K_h is the equilibrium constant of the reaction shown in Eq. (1), $a[\text{MERO} \cdot 3\text{H}_2\text{O}(\text{solid})]$, $a[\text{CH}_3\text{OH}]$, $a[\text{MERO} \cdot m\text{CH}_3\text{OH}(\text{solid})]$ and $a[\text{H}_2\text{O}]$ are the activities of the trihydrate, methanol, methylate and water, respectively. m is the stoichiometric number of methanol in methylate. If the pure solid is in its stable crystal form and at atmospheric pressure, the activity can be assumed to be unity. Thus, Eq. (2) reduces to

$$K_h = \frac{a[\text{H}_2\text{O}]^3}{a[\text{CH}_3\text{OH}]^m} \quad (3)$$

The equation suggests that the pseudopolymorphic transition is dependent on both the solvent activity and the temperature of the solution. At a given temperature, it can be obtained that there exists a transformation ratio of water activity to methanol activity where solvent ratios higher than the transformation ratio one form is more stable and at lower level another form is more stable.

Values of the water and methanol activities at the transition point can be calculated by the equations as followed:

$$\begin{aligned} a_W &= \gamma_W \cdot x_W \\ a_M &= \gamma_M \cdot x_M \end{aligned} \quad (4)$$

where subscript W and M are the abbreviations of water and methanol, respectively. γ_i and x_i denote the activity coefficient and the mole fraction of component i .

The main methods available for the calculation of activity coefficient in multicomponent mixtures include Flory–Huggins, Margules, Wilson, NRTL, UNIFAC etc. Among them, as a versatile and reasonably accurate model, Wilson equation is suitable for

both polar and nonpolar systems, especially for alcohol systems. Moreover, the parameters in Wilson equation are temperature dependent which provides more accurate prediction. For a ternary system, assuming the solute does not affect the solvent activities due to its slight solubility, the activity coefficients are provided by

$$\begin{aligned} \ln \gamma_1 &= -\ln(x_1 + \Lambda_{12}x_2) + x_2 \left(\frac{\Lambda_{12}}{x_1 + \Lambda_{12}x_2} - \frac{\Lambda_{21}}{x_2 + \Lambda_{21}x_1} \right) \\ \ln \gamma_2 &= -\ln(x_2 + \Lambda_{21}x_1) - x_1 \left(\frac{\Lambda_{12}}{x_1 + \Lambda_{12}x_2} - \frac{\Lambda_{21}}{x_2 + \Lambda_{21}x_1} \right) \end{aligned} \quad (5)$$

where

$$\begin{aligned} \Lambda_{12} &= \frac{V_2}{V_1} \exp \left(-\frac{\lambda_{12} - \lambda_{11}}{RT} \right) \\ \Lambda_{21} &= \frac{V_1}{V_2} \exp \left(-\frac{\lambda_{21} - \lambda_{22}}{RT} \right) \end{aligned} \quad (6)$$

where V_i is the molar volume at T of the pure component i , the parameters of $(\lambda_{12} - \lambda_{11})$ and $(\lambda_{21} - \lambda_{22})$, which are determined from experimental data, can be found in Vapor–Liquid Equilibrium Data Collection [12].

The equilibrium constant of the reaction can also be used to evaluate the enthalpy (ΔH_t) and entropy (ΔS_t) of the transition using van't Hoff equation written in the form

$$\ln K_h = -\frac{\Delta H_t}{RT} + \frac{\Delta S_t}{R} \quad (7)$$

On substituting the value of K_h from Eq. (3) in Eq. (7)

$$\ln(a_W^3 a_M^{-m}) = -\frac{\Delta H_t}{RT} + \frac{\Delta S_t}{R} \quad (8)$$

Eq. (8) can be used to predict the dependence of $\ln(a_W^3 a_M^{-m})$ on $1/T$. This linear dependence enables to calculate the values of enthalpy and entropy of the transition from the slope and intercept, respectively.

3. Experiments

3.1. Materials

MERO reference standard (99.9% in mass fraction) was purchased from Academia Sinica. Trihydrate (99.3% in mass fraction) and methylate MERO (99.5% in mass fraction) were recrystallized from raw material (obtained from Hisun Pharmaceutical Co., Ltd.) in water–methanol solutions at different compositions. Methanol (99.9% in mass fraction) was supplied by Kewei Chemical Reagent Co. at chromatographic grade. Ultrapure water (Milli-Q UF-Plus, Millipore) was used to prepare all solutions for the HPLC method and double-distilled water was used to prepare all mixed solvent. Relevant information of the materials concerned is summarized in Table 1.

3.2. Experimental apparatus

An Agilent high-performance liquid chromatography (HPLC) was used off-line to determine the concentration of MERO. The chromatographic column was Shiseido C18 (250 mm \times 4.6 mm, 5 μm). The mobile phase was a buffer solution of triethylamine and methanol (5:1, v/v), and the pH value of the triethylamine solution was adjusted by 0.1% phosphoric acid to 5.0 ± 0.1 . The velocity of mobile phase was set to be 1.5 ml/min, and the analysis was conducted at 298.15 K and 300 nm UV light. Peak at around 6.3 min was used for the analysis of MERO.

Headspace gas chromatography (HGC) with a FID detector (Agilent 7890 America) was used off-line to determine the crystal form of the solid product. The capillary chromatographic column used is

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