Crystallization kinetics of citric acid anhydrate

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ABSTRACT

The solubility curve, metastable zone width (MSZW) and Crystallization kinetics (nucleation and growth) were measured and estimated during batch crystallization of citric acid anhydrate (CAA). The solubility of citric acid in pure water was measured over the temperature range from 15 to 60 °C using a refractometer. The experimental data were correlated by the modified Apelblat equation. The MSZW was determined under four cooling rates for different citric acid concentrations by means of an ultrasonic technique. The primary nucleation kinetics of CAA was calculated based on these data and the polythermal method of Nyvlt. It was found that the MSZW obtained is in good agreement with literature. Crystal growth rates were calculated by two methods. The first one used seeded isothermal growth experiments (desupersaturation curve) and the derivatives method of Garside. The second method used the measurement of the dimension change of a single crystal in a microscopic cell at different supersaturation levels.

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1. Introduction

Crystallization is an important step in the purification of Active Pharmaceutical Ingredients (API) during the development process. Over 80% of drug products are produced by at least one crystallization step [1]. Two major steps govern the crystallization process, nucleation and crystal growth. The driving force for both steps is supersaturation defined as the difference between the actual concentration of the solute and the saturation concentration (solubility).The region between the solubility curve and the onset of nucleation phenomenon, called metastable zone width (MSZW), defines an operating boundary during crystallization process [2]. The MSZW depends on different process variables such as cooling rate, solvent composition, stirring rate and impurities [3]. Accurate modeling of crystallization kinetics, in particular the solubility curve, MSZW and the nucleation is an essential prerequisite to the design and control of a given crystallization process [4].

Citric acid plays an exceptional role, among the fruit acids used in beverage, food, pharmaceutical, textile, metal, chemical and other industries. Worldwide, citric acid is commercially produced in million tones with a steady annual increase in consumption and production [5]. At room temperature, citric acid exists in a white crystalline powder either in anhydrous form (CAA) or monohydrate form (CAM). Anhydrous citric acid differs from the

monohydrate in terms of solubility, bioavailability and crystal packing. The transition from the anhydrous to the monohydrate polymorphic form occurs in the range $34 - 36$ °C [6–8]. Citric acid monohydrate crystallization has been extensively studied in several research papers, but only few have been interested to the anhydrous form. Laguerie et al. [9] reported the solubility and other physical properties of CAM aqueous solutions. Nyvlt and Vaclavu [2] investigated the crystal growth of a CAM monocrystal at 32 and 12 °C. The growth order ranged from 1.9 to 2 depending on the operating conditions. Laguerie and Angelino [10] and Laguerie et al. [11] investigated the growth kinetics of large CAM crystals (> 1.4 mm) in a fluidized bed at 25 °C and found a growth order equal to 1.04. Sikdar and Randolph [12] studied very small crystals (70 μm) in mixed crystallizer and obtained a growth rate order equal to 0.65. Bravi et al. [13] performed solubility and primary nucleation kinetics of pure and selectively impure CAM solutions. In order to provide a critical comparison of the available data, Bravi et al. [14] have studied, in another paper, the crystal growth of CAM in a fluidized bed crystallizer or in the cell of a laser light diffraction granulometer, using seed sizes intermediate between those adopted by previous researchers [11,12]. The crystallization and dissolution behavior of the system citric acid-water has been previously studied using temperature-programmed and isothermal batch experiments [15]. In this last work, the mother-phase supersaturation and turbidity have been monitored on-line via simultaneous measurements using attenuated total reflection (ATR) Fourier transform infrared (FTIR) spectroscopy and optical turbidometric detection, respectively. The study reveals through the phase diagram a very wide MSZW width and

Nomenclature

A, B, C	Adjustable Apelblat equation parameters (dimensionless)
A_{T0}	Specific surface area per 100 g of solvent (cm^2/100 g solvent)
b	Cooling rate (K/h)
C	Concentration (wt%), (g/100 g solvent)
C^*	Saturation concentration (wt%), (g/100 g solvent)
$\arg\max\limits_{\mathbf{W,z,u}} \prod_{v\in T} P(\mathbf{v})$	Maximum supersaturation (wt%), (g/100g solvent)
ΔC_0	Initial supersaturation (g/100g solvent)
$\Delta \dot{C}_0$, $\Delta \ddot{C}_0$	First and second derivatives of the desupersaturation curve at t = 0 (g/100g solvent)
ΔC_{pf}	Heat capacity (J/Kg K)
$\frac{dC^*}{dT}$	Slope of solubility (wt%/°C)
F	Overall shape factor (dimensionless)
G	Linear growth rate (cm/min)
g	Order of growth (dimensionless)
ΔG_{sol}	Gibbs energy (J/mol)
ΔH_f	Enthalpy of fusion (J/mol)
K_g	Mass flux coefficient (g/ cm^2min (g/100 g solvent)^g)
k_g	Crystal growth rate coefficient (cm/min (g/100 g solvent)^g)
K_m	Nucleation constant (#/cm^3min)
l_0	Mean size of the seed crystals at t = 0 (cm)
m	Exponent of supersaturation in nucleation (dimensionless)
N_m	Nucleation rate (#/cm^3min)
R	Gas constant (J mol^{-1} K^{-1})
RI	Refractive index
ΔS_{sol}	Molar entropy (J/mol)
T	Temperature (°C), (K)
ΔT_{max}	Maximum undercooling (°C)
T_f	Melting temperature (K)
v	Ultrasonic velocity (m/s)
x	Mole fraction of the solute (mol/mol)
t	Time (min)
ρ	Density (g/cm^3)

that anhydrate phase crystallized by temperature-programmed runs while the monohydrate was formed by isothermal batch crystallization experiments. Batch seeded isothermal crystallization of monohydrate citric acid in water was also investigated as the first stage of a wider study devoted to the modeling of the anhydrous to monohydrate phase transition of citric acid at 15 °C (i.e., below the transition point of the system.) [16]. More recently, Helmdach et al. [6] evaluated the applicability of the ultrasonic technique in determining the solubility and the MSZW of 12 organic and inorganic compounds including some pharmaceutical ones. Among these substances citric acid has shown an excellent applicability. In another paper, Helmdach and coworkers [17] have demonstrated that the ultrasound technique, a cheap and robust method, allows the detection of the metastable zone width and an in-line control of supersaturation as well as the indirect control of phase transition in the system citric acid-water.

The characterization of crystallization process starts by measuring the solubility curve and the MSZW. Their knowledge, in the entire range of concentration and temperature is essential. Various experimental techniques can be used [3,18–21]. In this study the crystallization kinetics (nucleation and growth) of system CAA-water is investigated using a batch cooling crystallizer. The nucleation point (MSZW) was measured by an ultrasonic sensor, while the solubility points at various solute concentrations of CAA over the temperature range from 15 to 60 °C were determined by using a refractometer. The experimental solubility data were correlated with the Apelblat equation. The dissolution enthalpy, dissolution entropy and molar Gibbs energy of CAA-water solutions were derived using the parameters of modified Apelblat equation.

To calculate nucleation kinetic parameters knowing the MSZW, various theoretical approaches can be used [22–25], here, the classical Nyvlt approach [22] was selected.

Crystal growth kinetics of CAA-water system was evaluated by two methods. In the first one, the desupersaturation profile is monitored as a function of time. This method, introduced by Garside et al. [26], used by Glade et al. [27] and by Mohan et al. [28], assumes that no nucleation occurs and that the solution concentration change is only due to the crystal growth. The second method was based on the characteristic length observation of a single crystal in a microscopic cell.

Crystal growth kinetics was calculated by fitting the crystal growth measurements according to the power law relation.

2. Theory

Nucleation and growth are the major steps which control crystallization process. Both steps are typically related to supersaturation ΔC.

$$\Delta C = C - C^* \tag{1}$$

C and C^* are the concentration of solution and the saturation concentration at operation temperature, respectively.

2.1. Primary nucleation rate modeling

Primary nucleation is the 'classical' form of nucleation. It occurs mainly at high levels of supersaturation and is thus most prevalent during unseeded crystallization. The nucleation rate is the number of new particles formed per unit time and per unit of volume of solid free mother liquor [29].

According to Nyvlt [22], the relationship between the maximum permitted supersaturation ΔC_{max} and maximum permitted undercooling ΔT_{max} is given by:

$$\Delta C_{max} = \left(\frac{dC^*}{dT}\right)\Delta T_{max} \tag{2}$$

The nucleation rate N_m is related to the solution supersaturation by the power-law relation

$$N_m = K_m (\Delta C)^m \tag{3}$$

With the cooling rate $b = \frac{\Delta T}{\Delta t}$

$$N_m = b \left(\frac{dC^*}{dT}\right) \tag{4}$$

From Eq. (2) in Eq. (3) and equating Eqs. (3) and (4), one obtains