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Growth rates of ibuprofen crystals grown from ethanol and aqueous ethanol

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A B S T R A C T

To quantify the crystallization of racemic ibuprofen [2-(4-isobutyl-phenyl)-propionic acid] from aqueous ethanol it is necessary to know the growth rate kinetics. Growth rates were measured by adding SPG (size proportional growth) seed crystals to an isothermal non-nucleating batch crystallization and sampling during the batch. The supersaturation was measured by refractive index and the crystal size by laser light scattering (Malvern). To ensure the batch was non-nucleating the supersaturation was kept within the narrow secondary MZ (metastable zone). Measurements were made at three temperatures, 10, 25 and 40 °C. The growth rate was proportional (first order kinetics) to the solution supersaturation, expressed in mass ratio of ibuprofen to ethanol units. Despite the narrow MZ, the initial growth rates were substantial (up to 1 μm/min). Temperature has a large effect on growth rate with an activation energy of 13.7 kJ/mol. The water content affects the growth rate coefficient differently depending on the temperature.

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1. Introduction

Ibuprofen [2-(4-isobutyl-phenyl)-propionic acid] is a widely used anti-inflammatory drug. It is insoluble in water but soluble in many organics (Gracin and Rasmuson, 2002; Garzon and Martinez, 2004). It may be purified by crystallization. We will consider here crystallization from ethanol, which has not been fully studied previously. The solubility of ibuprofen in ethanol, which varies substantially with temperature, is given by Gracin and Rasmuson (2002) and Rashid et al. (2008). Measurements of the corresponding nucleation metastable zone widths (MZW) for primary and secondary nucleation were undertaken by Rashid et al. (2009), and showed that the MZ for secondary nucleation is quite small, typically corresponding to a subcooling of about 1 °C. Thus care is required in attempting to crystallize in the secondary MZ. This paper gives measurements of the crystal growth rates using isothermal non-nucleating seeded batch crystallization.

2. Experimental procedure

2.1. Materials

Pharmaceutical grade ibuprofen (CAS Registry Number 15687-27-1) purchased from Professional Compounding Chemists of Australia Pty Ltd (Matraville, NSW), was a high purity racemate of (R)/(S)-(±)-[2-(4-isobutyl-phenyl)-propionic acid] with the empirical formula C₁₃H₁₈O₂ and molecular weight 206.27.

2.2. Seed preparation

Many crystallization systems exhibit GRD (growth rate dispersion) where crystals of the same size can grow with different rates. In anticipation that ibuprofen growing from ethanol might display GRD, SPG (size proportional growth) seed was prepared. SPG crystal is that where the size is directly proportional to the growth rate. SPG seed crystals may be prepared

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