Demonstrating the influence of solvent choice, supersaturation and nucleation temperature on Phenacetin crystallization

Denise M. Croker, B. Kieran Hodnett, Åke C. Rasmuson

Synthesis & Solid State Pharmaceutical Centre, Science & Engineering Faculty, University of Limerick, Ireland.

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ABSTRACT

Phenacetin was used as a model pharmaceutical compound to demonstrate the impact of solvent choice and crystallization conditions on product crystal shape and size distribution. The BDFH crystal morphology was generated using Mercury ™ software and presented as 3-dimensional hexagonal blocks. Crystallization from solution was used to prepare a series of crystals from different solvents and investigate the impact of the crystallization solvent on the crystal shape of phenacetin. 15 solvents were tested: 1, 4-dioxane, 1-propanol, 1-butanol, toluene, ethyl acetate, ethanol, 2-propanol,butanone, acetonitrile, acetone, methanol, MTBE, dichloromethane, diethyl ether, n-pentane. In 12 of 15 experiments, needle shaped product crystals were recovered. Ethyl acetate and butanone yielded brittle plate shaped crystals and flat blocks were recovered from dichloromethane. Phenacetin solubility was measured in 5 solvents from 10 – 70 ^{o}C using a gravimetric method to allow for the design of crystallization experiments. Cooling crystallization experiments at constant nucleation temperature (30^{o}C) were used to investigate the influence of supersaturation on phenacetin crystallization in ethanol. Solution concentration was tracked in-situ using a React IR™ PAT probe. At higher supersaturation, smaller, thinner needles were recovered suggesting that growth in the needle direction is favored. The desupersaturation profiles recorded with the React IR™ illustrated

that as supersaturation increases, the onset of nucleation is faster and the subsequent desupersaturation curve is steeper. Cooling crystallizations were also attempted using constant supersaturation at three different nucleation temperatures – 15, 30, and 55 ^{o}C. Needles were recovred in all experiments, with thicker needles observed at high nucleation temperature. It is hypothesized that this is due to a combination of greater availability of solute at increased temperature (due to experiment design and inherent dependence of solubility on temperature) and also greater growth in the direction orthogonal to the needle direction. It is surmised that the activation energy for growth in the direction orthogonal to the needle direction is decreased to a greater extent that the activation energy for growth in the needle direction at high temperatures. The desupersaturation profiles show a faster onset of nucleation at higher temperature also, as would be expected. Evaporative crystallization was attempted in toluene, ethanol and acetone. Crystals approximating the BDFH-predicted hexagonal block were recovered from ethanol and acetone, suggesting thermodynamic growth can be realized at very low supersaturation.