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Polymorphic behavior of isonicotinamide in cooling crystallization from various solvents

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Abstract

In this work the nucleation of different polymorphs of isonicotinamide (INA) from different solvents has been studied. The metastable zone width of INA in cooling crystallization from five different solvents has been investigated and attempts have been made to reveal the link between the INA molecular self-association to the polymorphism of the nucleated crystals using ATR FT-IR (Attenuated Total Reflectance Fourier Transform Infrared) and Raman spectroscopy. Raman and IR spectra of INA dissolved in different solvents have demonstrated that the INA molecules might associate in different configurations, whereas, the link between the structure of the molecular self-association and the structure of the nucleated polymorph is complicated by the influence of INA concentration. This is consistent with our previous study with piroxicam. The cooling crystallization of INA from five different solvents resulted in two different polymorphs depending on the initial concentration of the solution. The results obtained in the present work showed that information about self-association of an API (Active Pharmaceutical Ingredient) in a given solvent is not sufficient to predict the polymorphic behavior in all scenarios.

Keywords: A1 Crystal Morphology, A1 Solubility, A1 Solvents, A1 Nucleation

1. Introduction

The crystal structure, or polymorph, of active pharmaceutical ingredients (APIs) is of great importance[1][2][3] as it has been found to greatly impact many of the factors that decide a drug's effectiveness, solubility, dissolution rate and storage stability[4].Therefore, the importance of polymorphic control of products is of increasing importance and various forms of spectroscopy have been employed with feedback control[5][6][7] to ensure the desired form with a high purity. For an API that is capable of forming different polymorphs and/or solvates, it is common that the thermodynamically most stable form is selected and used in development and formulation. In some circumstances though, a metastable form can be selected due to the preferred properties, such as the solubility and dissolution rate, stability and processability in down-stream operations. Nowadays the aqueous solubility of new drug candidates is dramatically decreasing[8][9] with the introduction of combinatorial chemistry approaches and high throughput receptor based screens to drug design and discovery. One of the most efficient