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Exploring the Effect of Solution Speciation on Crystallization Outcome

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ABSTRACT

In the field of pharmaceuticals, the crystallization process significantly impacts the purity, morphology and polymorphism of active pharmaceutical ingredients (API), all of which are important in drug development. Polymorphism is the existence of more than one solid-state form of the same chemical entity. Tolfenamic acid (TFA), a Non-Steroid Anti-inflammatory drug (NSAID), has been shown to exhibit a unique physical phenomenon called concomitant polymorphism, whereby two polymorphs crystallize from the solution simultaneously. From previous work, it has been established that solution speciation i.e. the presence of monomers or dimers of TFA in solution is concentration and temperature dependent. This study correlates this existing solution speciation with the crystallization outcome by analyzing the ratio of polymorphs obtained at different temperatures at a fixed concentration. Polymorphic purity was examined using powder X-ray diffraction. Crystallization experiments were performed at 10°C, 37°C, and 55°C at a constant supersaturation ratio of 1.95. Samples were taken at various time points in the recrystallization process. These samples were examined using Infrared spectroscopy for solid-state composition and quantified using a calibration curve. Pure polymorphs of TFA have been obtained and a calibration curve to quantify phase composition has been established. The initial recrystallization results suggest that the conformation of the crystals in solution is decided by the composition of the initial crystals formed, however more experimentation is necessary. Ongoing work involving recrystallization experiments under different temperature conditions would lead to a much better understanding of the role of solution speciation in the nucleation and crystallization processes.

KEYWORDS

Crystallization, Pharmaceuticals, Polymorphs, Solid-State, Tolfenamic Acid, Nucleation

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