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Crystallization of APIs in a Continuously Seeded Tubular Crystallizer

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Particle shape and size have an influence on the solubility of an API-particle and hence on the bioavailability of the substance. Thus, bulk properties such as the crystal size distribution (CSD) are important quality attributes of powders. Furthermore, downstream processes (e. g., filtering, washing, drying etc.) and the handling abilities (e. g., flowability, tabletability) of the particles are positively affected by narrow CSDs. In order to obtain product crystals with desired features it is important to control numerous parameters during a crystallization process.

We present a versatile, continuously operated tubular crystallizer system, which is based on the growth of seeds to product particles in a tube. Due to the tubular appearance and the small inner dimensions of the crystallizer in the few millimeter range, it is possible to adjust the temperatures along the tubing according to the needs of the crystallization. Thus, the product can be manipulated under controlled conditions [1–3]. Parameters that can be altered in the crystallization process include seed loadings, temperatures, solution concentrations, and flow rates of the suspension in the tubing. As a model system we have chosen the crystallization of acetylsalicylic acid (ASA) in ethanol (EtOH).

The effects of various process parameters on product characteristics have been investigated. All experiments resulted in significant crystal growth despite short residence times in the few minute range. Moreover, crystal masses increased by a few g/min and steady-state conditions were obtained in less than 5 minutes. Suppression of nucleation events by avoiding rapid cooling, thus high levels of supersaturation allowed successful achievement of narrow CSDs.

Additionally, simulations regarding the temperature gradients and the crystal growth have been performed and compared to the experimental results.

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