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Crystallization of 4-Acetaminophen (Paracetamol) Through Continuous Slug Flow Crystallizer

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ABSTRACT

One of the most demanding processes in the pharmaceutical industry is crystallization. Although batch crystallizers have been used and improved for several decades, they are typically challenging to control the product attributes. Developing a continuous crystallizer design that helps control the various attributes such as crystal size, purity, yield, and polymorphism, is an ongoing challenge. Mixed suspension mixed product removal, continuous oscillatory baffled crystallizer, and tubular flow are some of the continuous crystallizer designs studied extensively. A few continuous slug flow crystallizer (CSFC) designs with the ability to generate crystals of various polymorphs, higher yield, and narrow size distribution are described in this work. CSFC used in this work has three main zones, each for a specific function, i.e. slug formation, crystal nucleation, and crystal growth. Slugs are generated in the slug formation zone by feeding two liquids coaxially. The nucleation zone generates crystal nuclei by maintaining high supersaturation. The growth zone promotes crystal growth at a supersaturation lower than the nucleation zone. In this work, various CSFC design configurations have been used to produce the crystals of 4-acetaminophen. Relative liquid flow rates, supersaturation, and residence time have been regulated to alter the crystals' size, yield, and polymorphic form. The morphology, size, and crystal polymorphism of produced crystals are analyzed using microscopic images and PXRD analysis. We demonstrate the capability of CSFC to generate polymorphic pure crystals with a narrow crystal size distribution.

Keywords: Crystallization, Continuous crystallizer, Slug-flow, paracetamol

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