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Novel Impinging Jet and Continuous Crystallizer Design for Rapid Reactive Crystallization of Pharmaceuticals

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Abstract

Reactive crystallization is an important operation in the pharmaceutical industry for the production of the active pharmaceutical ingredients (APIs), but has not been as widely studied as cooling or anti-solvent crystallization. Reactive crystallization has many unique features that make them different from cooling or anti-solvent crystallization, even leading to some concepts and methods not directly applicable to the former. Literature survey reveals that previous research on reactive crystallization has mainly been conducted for inorganic materials which are known to be simpler than crystallization of organic molecules. The focus of this research project was to carry out research on the process design and optimization of organic reactive crystallization. The objective was to research on novel crystallizer designs that suit and take advantages of the features of reactive crystallization, and on advanced modeling and optimization techniques with the aim of manufacturing high quality products. Process analytical technology was used as a supporting tool to achieve the above stated objectives. The results showed that by using novel impinging jet design, the product had uniform size distribution and superior crystallinity. In addition, continuous process design can achieve a greater amount of product handling and reduce the batch-to-batch variation.

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Keywords: Rapid reactive crystallization; Continuous process design; Process analytical technology; Impinging jet; Scale-up

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1. Introduction

Crystallization is widely used in many industries including pharmaceutical, biopharmaceutical, agrochemical, healthcare, energy, material, food and various personal consumer products. In the pharmaceutical industry, over 80 % of all forms of products including tablets, aerosols, capsules, suspensions and suppositories contain crystalline components, making crystallization a very important step of the primary manufacturing stage. The quality of crystals produced is of critical importance since it has a major impact on secondary manufacturing processes such as filtration and milling, as well as on the end-use performance, transport and storage [1,2].

Compared with cooling and anti-solvent crystallization processes, reactive crystallization has been less studied and less well understood, and previous work has been mainly about inorganic materials with exceptions of complex rapid reaction. In fact, many active pharmaceutical ingredients (APIs) are obtained through the rapid reactive crystallization. Reactive crystallization has many unique features that make them different from cooling or anti-solvent crystallization. The difference even leads to some concepts and methods not directly applicable to the reactive crystallization process. Firstly, the metastable zone theory may not be applicable because the generated product is often insoluble in the solvent. If the solubility is close to zero, the supersaturation can be near infinity and the metastable zone will no longer exist. Secondly, under such large supersaturation, in theory secondary nucleation might be dominated. As a result, some researchers have questioned the applicability of the traditional crystal interface growth theory, and proposed new mechanisms. For example, some researchers believe that it is the aggregation that dominates the crystal growth process [3,4].

In this study, synthesis of sodium cefuroxime was chosen as a representative organic reactive crystallization process. The aim of this study is to develop a novel continuous process for this organic reactive crystallization synthesis. Firstly, the solubility of sodium cefuroxime was investigated by on-line attenuated total reflection-Fourier transform InfraRed (ATR-FTIR) spectroscopy (Mettler Toledo Co., Ltd, is an FTIR-based in situ reaction analysis system designed specifically for the organic process). Secondly, by using process analytical technology (PAT) technique, combined with particle characterization methods using imaging instrument Morphologi G3 and XRD, the impinging jets mixer design such as the angles and spacing of the two jet nozzles were optimized. Finally, by studying the residence time distribution (RTD) of the reaction and crystal growth during the synthesis of sodium cefuroxime, the novel continuous crystallizer was designed and tested in 1L rig. The ultimate performance of this novel process was judged by the product's performance in stability and processability.

2. Materials and experiment

2.1. Materials

Cefuroxime is a valuable broad spectrum antibiotic, which has high activity against a wide range of gram-positive and gram-negative micro-organisms. However, its poor stability has been a cause of widespread concern during industrial production. In the storage and transportation processes, it tends to deepen solid color, reduce solubility and become sticky.

The reactants are cefuroxime acid (water content < 0.2 %) and 60 % w/w sodium lactate aqueous solution (Fisher Scientific UK Ltd). The seed, sodium cefuroxime crystals (> 92 %, water content < 0.24 %), was produced by an anti-solvent re-crystallization process. Ethanol (95 % v/v) and activated carbon were obtained from Fisher Scientific UK Ltd, acetone was obtained from Sigma and the distilled water produced in our own laboratory was also used in the process.

2.2. Method and apparatus

The unique features of rapid reactive crystallization processes make it questionable whether the traditional stirred tank crystallizer is still a favored option. A major advantage of traditional stirred tank crystallizers is that they are easy to operate and able to produce large particles with low surface area. However, the mixing of such crystallizer is often poor. Several mixing models have been proposed and investigated in reactive crystallization processes. The most widely used method to shorten the mixing time in a crystallizer is to use a mixer design that reduces the initial