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

Wen J. Liu[a], Cai Y. Ma[a], Xue Z, Wang[a,b,*]

[a]*Institute of Particle Science and Engineering, School of Process, Environmental and Materials Engineering, University of Leeds, Leeds LS2 9JT, United Kingdom*

[b] *School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, China*

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

* Corresponding author. Tel.: +44 113 343 2427; fax: +44 113 343 2384.
E-mail address: x.z.wang@leeds.ac.uk

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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.

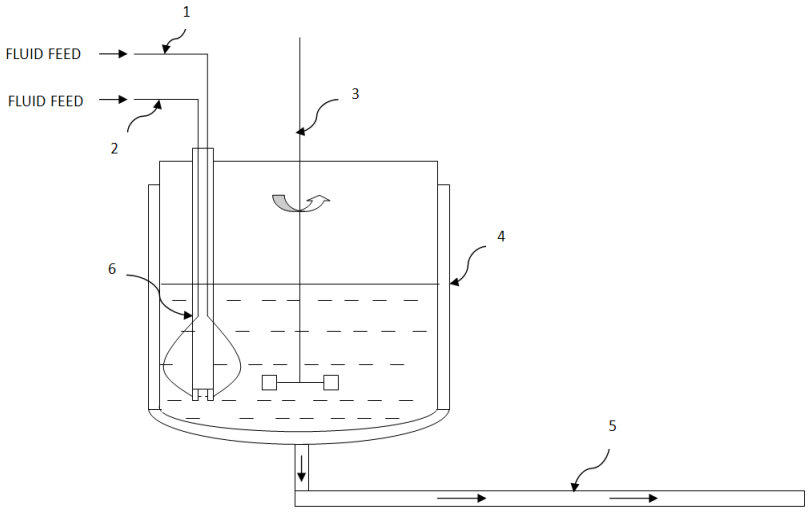
2.2. Method and apparatus

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

time of contact between the incoming fluids. The impinging jet mixer is one such technique in which two liquid streams in the form of narrow, coplanar jets at high velocities impinge upon each other inside a small mixing zone. Jet mixing is a relatively new field to researchers in crystallization and limited reports are available in literature so far. Midler et al [5,6] tested a jet mixer for rapid precipitation of several pharmaceutical compounds. They concluded that the mixing intensity in the jet mixer was helpful in rapidly achieving good mixing and uniformly high supersaturation environment, which led to a high quality final product with superior crystallinity and purity.

To improve the conventional crystallizer, the novel crystallizer we proposed relate to a tank reactor (reaction/nucleation area) along with impinging jet mixer to achieve intensity mixing of reactants so as to form a homogeneous compound before nucleation and a tubular reactor (crystal growth area) with suitable length to meet the required crystal growth time so as to form uniform crystal size distribution in a continuous reactive crystallization process. The two parts, tank reactor and tubular reactor, are divided according to the specific attributes and requirements of nucleation and crystal growth contents in a reactive crystallization process. For nucleation, mixed flow is preferred. The driving force, supersaturation, produced by reaction required thorough mixing. Tank reactor plus impinging jet mixer provide perfect prerequisites to form a homogeneous compound before nucleation. For crystal growth, plug flow is preferred. No back mixing means that the crystals grow under uniform conditions, and consistent residence time means uniform crystal size distribution.

The 1L novel continuous process with impinging jet mixer used for reactive crystallization process optimization is illustrated in Fig. 1. The reaction solutions were prepared as follows: 9.0 *g* 60 *%* w/w sodium lactate aqueous solution was added into the mixed solvent of 40 *mL* acetone and 50 *mL* 95 *%* ethanol at 20 - 25 ^{o}C, then this sodium lactate solution was filtered and washed with 10 *mL* 95 *%* ethanol into a beaker. Next, 10 *g* acid cefuroxime was dissolved in the mixed solvent of 246 *mL* acetone and 124 *mL* 95 *%* ethanol. The activated carbon was added in the acid cefuroxime solution and this mixture was stirred for 10 - 15 minutes at 38 - 42 ^{o}C, then filtered. The activated carbon needed to be washed with 30 *mL* acetone. Finally, the obtained product, sodium cefuroxime, was filtered and washed by the mixture of acetone and 95 *%* ethanol (1.8 : 1) until the pH value reached 8.0. After 24 hours vacuum drying in a vacuum oven (DZF-6030B), the final product can be obtained.



(a)

(b)

Fig. 1. 1L novel continuous crystallizer with impinging jet mixer: (a) the schematic diagram (1 – the sodium lactate solution feeding; 2 – the acid cefuroxime solution feeding; 3 – the IKA EUROSTAR digital stirrer; 4 – the 1L tank reactor with a jacket; 5 – the tubular reactor; 6 – the novel impinging jet mixer); (b) the impinging jet mixer.

2.3. Analytical characterization

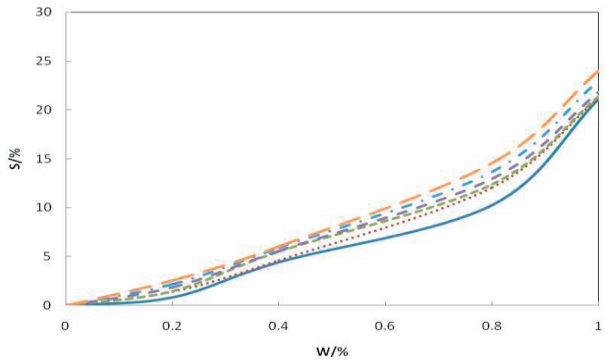
X-ray diffraction data were collected using Bruker D8 advance (CuKα1, λ = 1.540598Å). Yttria (Y_2O_3) was used as standard for the estimation of instrumental peak broadening. The size distribution data were collected using Morphologi G3 particle size and particle shape analyzer from Malvern. The Morphologi G3 measures the size and shape of particles using the technique of static image analysis. Fully automation with integrated dry sample preparation makes it the ideal replacement for costly and time-consuming manual microscopy measurements.

3. Results and discussion

3.1. Solubility of sodium cefuroxime

In Pharmacopeia, sodium cefuroxime is freely soluble in water and buffer solvent (*pH* 7.0, *pH* 4.5 and *pH* 1.2), soluble in methanol and very slightly soluble in ethyl acetate, diethyl ether, octanol, benzene and chloroform [7]. It was also found that sodium cefuroxime is insoluble in acetone [8]. However, there was research focused on neither the influence of *pH* value on solubility of sodium cefuroxime nor provided any data. In order to investigate the effect of both temperature and *pH* value on the solubility of sodium cefuroxime, on the basis of the conditions of industrial production, the test temperature range was set to be 24 to 35 ^oC, and the test *pH* value range was 5 to 7. Acetic acid was used to adjust the *pH* value because it showed no effect on sodium cefuroxime.

It can be seen from Fig. 2 that the solubility of sodium cefuroxime was relatively insensitive to temperature variations but sensitive to the *pH* values. The solubility of sodium cefuroxime increased with the increase of temperature, but the extent of growth was relatively limited. Subsequently, the solubility of sodium cefuroxime in 95 % (v/v) ethanol was investigated under the same conditions. It was found that sodium cefuroxime was slightly soluble in pure ethanol (0.05 %), but the solubility in 95 % (v/v) ethanol was 1.14 % at 25 ^oC and *pH* 7. The solubility had little change with the temperature and *pH* values in 95 % (v/v) ethanol, so compared with the solubility in the water, the change can be ignored.



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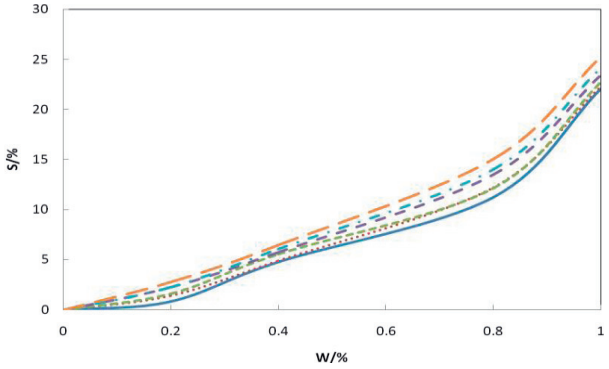

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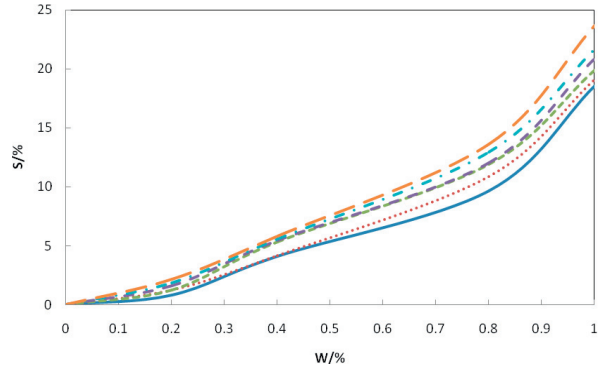


(c)

Fig. 2. The experimental solubility profiles of sodium cefuroxime in binary solvent (ethanol and water): (a) *pH*=7; (b) *pH*=6; (c) *pH*=5. (Solid line – T = 24 *°C*; Round Dot line – T = 25 *°C*; Square Dot line – T = 26 *°C*; Dash line – T = 27 *°C*; Dash Dot line – T = 28 *°C*; Long Dash line – T = 29 *°C*).

3.2. Impinging jet mixer

The use of jets was to create impinging fluid jet streams and achieve high intensity micromixing and reaction of the fluids prior to nucleation in a crystallization process. To decide the best angle and spacing of the jet, three angles and two spacing (6.78 *mm*, 11.76 *mm*) were chosen. Taking into account the working range of the pump, we selected 10 *m/s*, 15 *m/s*, 20 *m/s* as the feeding speed tests (Table 1).

Table 1. Design parameters of the impinging jet mixer.

Angle	Column A (*mm*)	Feeding rate (*m/s*)
10^o upward	6.87	10
Parallel	11.76	15
10^o downward		20

- 10^o upward jets

Many works have done on investigating the impinging jet crystallization, but almost no one chosen the 10^o upward jets. On the one hand, this might because the upward jets would make an increase impact of gravity on fluid linear speed, and cause a faster speed slow down. On the other hand, many previous researches preferred the suspended impinging jet design. If the jet was upward, it would be more difficult to control operation, or even be a security risk. However, for our reaction system, the impinging jet was submersed in the organic solvent with the pre-input seeds, which caused the fluid outflow would encounter greater resistance than in the air. In order to also maintain a high degree of mixing, the spacing between two jets was designed closer, which made the attempt of 10^o upward jets possible.

- Parallel

Parallel jets were introduced by many papers and patents, and also used in many experimental processes. Theoretically, this feeding method can guarantee the two fluids a frontal collision with maximum speed, resulting in the best mixing effectiveness. However, for the synthesis process of sodium cefuroxime or other drugs, the biggest drawback was that parallel jets were easy to cause clogging. The main reason was that the two fluid feeding amounts were not the same. Since the feeding volume ratio of this two fluids was 1 : 4 (sodium lactate: acid cefuroxime), under the same feeding speed, the momentum of the less amount fluid was significantly smaller than the larger one, which caused the meeting point gradually moved to the inlet of the less amount fluid, eventually leading to the product accumulated slowly at the inlet and then clogging.

- 10^o downward jets

To avoid clogging, 10^o downward jets were the selected feeding jets in most of the literature. This feeding way can avoid the two fluids frontal crash directly. Although the collision rate would decline, when the momentum difference was large between the two fluids, it could avoid one fluid squeeze the meeting point to the other one.

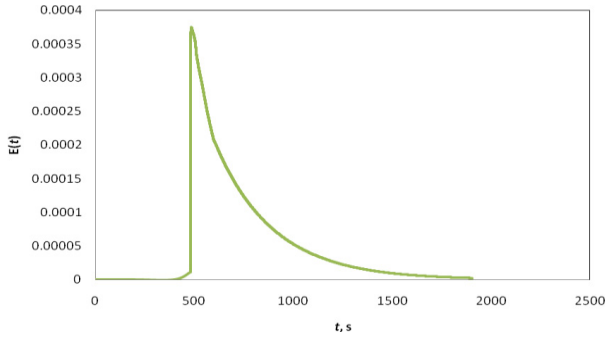
The best product can be obtained from 10^o downward jets with the spacing of 6.87 *mm* and feeding rate of 10 *m/s*. As mentioned in literature [9,10], a high linear velocity could produce crystals with higher crystallinity. However, our conclusion was that a slower feeding speed was a better choice for obtaining crystals with higher crystallinity, which might be because that the mechanism of sodium cefuroxime crystal growth is different. Sodium cefuroxime synthesis process, the combination of the reaction process and the crystallization process, is such a process which conducts under high levels of supersaturation. The huge supersaturation was firstly generated by the reaction because the product cannot be dissolved in solvents completely, and then the nuclei were generated, and further the growth process happened when the nuclei met the crystal seeds in the crystallizer. Besides the competition between the nucleation process and the growth process during this crystallization process, the kinetic of the reaction itself also directly affects the whole process by varying the supersaturation.

In a traditional stirred tank crystallizer, the nucleation and growth processes were carried out at the same time and the same place. The continuous process with impinging jet mixer designed in this study was to avoid the simultaneous existence of nucleation and growth processes by confining the nucleation process and the growth process within the corresponding tank reactor (nucleation area) and tubular reactor (growth area). In the nucleation area, the novel impinging jet mixer was used to achieve fully mixing of reactants for reaction and to generate small nuclei. Then the impeller drove these small nuclei from the nucleation area to the growth area where the nuclei contact with the crystal seeds in the crystallizer for growth.

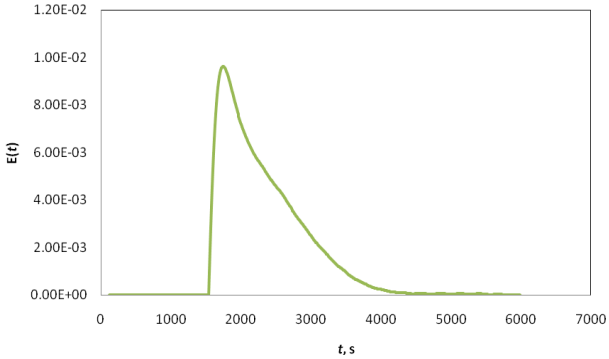
3.3. Novel continuous crystallizer

The residence time of a reactor can be measure by injecting a little inert substance into the stability fluid within the reactor and monitoring the concentration change of this inert substance at the outlet of the reactor. The results of

residence time distribution for novel process design can be seen in Fig. 3. The concentration data should be normalized firstly, and then the function E (*t*) could be obtained. The variance σ^2 of the tank reactor and the tubular reactor were 0.93 and 0.07, respectively. The variance σ^2 result of tank reactor indicated that the 10^o downward nozzles could provide the best mixing and also indicated that the design that adding impinging jet mixer and the stirrer into reactor made this tank reactor closer to the ideal mixed flow reactor. The variance σ^2 result of tubular reactor indicated that this design made the tubular reactor closer to the ideal plug flow reactor.



(a)

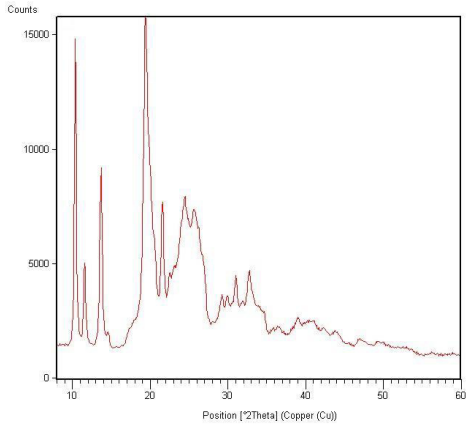


(b)

Fig. 3. Residence time distribution for novel process design: (a) the tank reactor; (b) the tubular reactor.

3.4. Product analytical profile

As can been seen from the XRD results in Fig. 4, the crystallinity of product obtained from novel continuous process were better than the product from conversional reactor. And it can be seen from the Morphologi G3 results in Fig. 5, the crystal size distribution of products obtained from novel continuous process were become much better than it of the products obtained from the conventional reactor. The mean size was good and there was no bimodal phenomenon.



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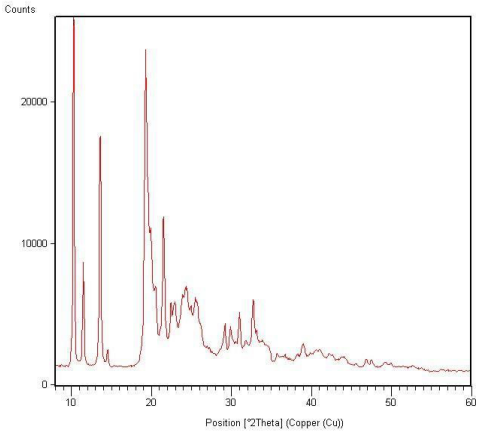
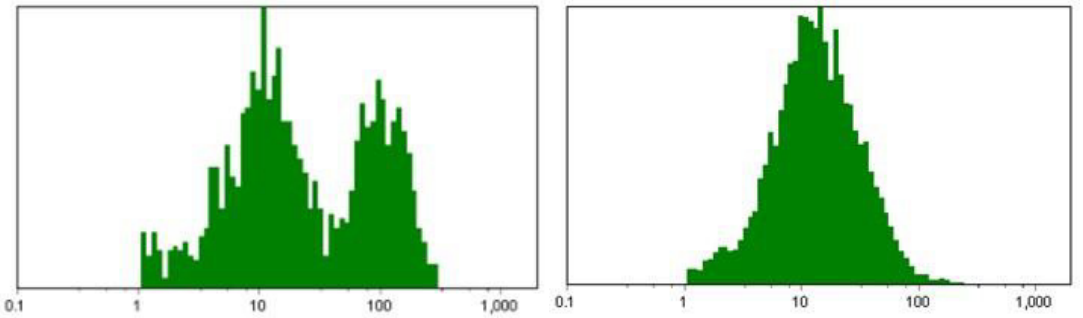


(b)

Fig. 4. The XRD patterns of sodium cefuroxime: (a) product from the conversional reactor; (b) product obtained from the novel continuous process.



(a) (b)

Fig. 5. The Morphologi G3 results of sodium cefuroxime (the horizontal axes are Size Classes, *μm*; the vertical axes are Volume Density, *%*): (a) product from the conversional reactor; (b) product obtained from the novel continuous process.

4. Conclusion

In this paper, a novel process for continuous organic reactive crystallization synthesis was designed. It provided two reactors, a tank reactor and a tubular reactor, in series for conducting a rapid reactive crystallization process of pharmaceutical compounds. This novel process separated the reaction and crystal growth processes with the tank reactor (reaction/nucleation area) and the tubular reactor (crystal growth area) in series based on their respective characteristics, hence achieves a continuous operation. Impinging jet mixers are used in the tank reactor to mix the reactants sufficiently and quickly before nucleation. The crystals obtained from this novel process have uniform size distribution and longer shelf-life. Moreover, continuous process design can achieve a greater amount of product handling and reduce the batch-to-batch variation.

Acknowledgements

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