Engineering 3 (2017) 354–364

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Research
Green Chemical Engineering—Review

Progress of Pharmaceutical Continuous Crystallization

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ARTICLE INFO

Article history:
Received 25 March 2017
Revised 10 May 2017
Accepted 11 May 2017
Available online 19 June 2017

Keywords:
Continuous crystallization
Pharmaceutical
MSMPR
Tubular crystallizer
Control strategy

ABSTRACT

Crystallization is an important unit operation in the pharmaceutical industry. At present, most pharmaceutical crystallization processes are performed in batches. However, due to product variability from batch to batch and to the low productivity of batch crystallization, continuous crystallization is gaining increasing attention. In the past few years, progress has been made to allow the products of continuous crystallization to meet different requirements. This review summarizes the progress in pharmaceutical continuous crystallization from a product engineering perspective. The advantages and disadvantages of different types of continuous crystallization are compared, with the main difference between the two main types of crystallizers being their difference in residence time distribution. Approaches that use continuous crystallization to meet different quality requirements are summarized. Continuous crystallization has advantages in terms of size and morphology control. However, it also has the problem of a process yield that may be lower than that of a batch process, especially in the production of chirality crystals. Finally, different control strategies are compared.

1. Introduction

Crystallization, which can be used to determine numerous product properties in the solid-liquid separation process, is not only a separation and purification process but also a refining process in the pharmaceutical industry [1–3]. Of active pharmaceutical ingredients (APIs), 90% are crystals of small organic molecules [4]. At present, most crystallization processes in the pharmaceutical industry are performed in batches [5]. Although batch crystallization has been widely studied, the problems of batch-to-batch variability and processing inefficiency are still present [6]. As a means of dealing with these problems, continuous crystallization has received increasing attention due to its characteristics of constant conditions at the steady state and high product efficiency [7–9]. Continuous crystallization is a unit operation in which the mother liquid is continuously flowed in, and the slurry is continuously withdrawn. According to an analysis by Schaber et al. [10], the continuous crystallization process can save 9% to 40% of the production cost. In this review, we discuss how to meet the different pharmaceutical quality requirements using continuous crystallization, and outline the different control strategies that are used in continuous crystallization.

2. Comparison between two types of continuous crystallization

There are two main types of continuous crystallizer: the mixed-suspension mixed-product removal (MSMPR) crystallizer and the continuous tubular crystallizer [11]. Fig. 1 shows a schematic diagram of the two general types of crystallizer.

The residence time distribution in the MSMPR crystallizer is relatively wide and long, compared with the tubular crystallizer, in which it is relatively narrow and short. Table 1 [6] provides a comparison of these two types of crystallizers.

3. General requirements for crystal products

Numerous studies have been carried out on converting batch

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http://dx.doi.org/10.1016/J.ENG.2017.03.023

crystallization processes into continuous crystallization ones [6,11,12]. In order for a continuous crystallization process to substitute for a batch crystallization process, the quality of the continuous products should meet the quality that is achievable in batch products [13].

As shown in Fig. 2, the general quality requirements for pharmaceutical crystallization are yield, purity, size, morphology, polymorphism, and chirality [11]. However, the process of continuous crystallization is different from a batch process [14], and must be carefully designed and controlled. In general, two problems must be solved in order to employ a continuous process in pharmaceutical crystallization: The first is the design problem, which determines whether a new designed crystallization process is able to produce the desired crystals; and the second is the control problem, which determines whether a continuous crystallization process can produce the desired crystals in a stable manner. In the past few years, a certain amount of progress has been made to allow the products of continuous crystallization to meet the abovementioned requirements. The following sections discuss this progress from a product engineering perspective.

4. Continuous MSMPR crystallizers in pharmaceutical crystallization

The MSMPR crystallizer is one of the most commonly used continuous crystallizers. In general, the MSMPR crystallizer is assumed to be well-mixed. In this crystallizer, supersaturation, which is created by means of processes such as cooling, evaporation, or a reaction, is the driving force for nucleation and growth. A high degree of supersaturation will accelerate the nucleation and growth rate, and will consequently increase the total crystal surface in the crystallizer. In turn, a large total crystal surface will accelerate the supersaturation consumption rate, thus creating a feedback loop. The MSMPR crystallizer will eventually achieve a steady state, except under special circumstances.

Many studies have been performed on the MSMPR crystallizer, and this type of crystallizer has been used to produce inorganic salts. Since inorganic salts are relatively simple, issues of polymorphism and chirality may not exist or may not be important for their crystallization. In addition, the requirements of inorganic crystals, such as crystal size distribution, purity, and yield, may differ from the requirements of pharmaceutical crystallization. Therefore, the design and control processes in pharmaceutical continuous crystallization are often different from those in the continuous crystallization of inorganic salts.

4.1. Using MSMPR crystallizers to meet purity and yield requirements in pharmaceutical crystallization

Purity and yield are the basic requirements for a crystallization process, since they directly influence the process economy. However, as a characteristic of continuous crystallization, the process must be operated at a certain degree of supersaturation [15]; hence, the yield of a single pass of a continuous crystallization process is lower than the yield of a single batch process. To overcome this problem, many researchers have modified MSMPR crystallizers into different forms. Table 2 [7,13,15–18] compares different approaches for increasing product yield.

In order to reduce the residual supersaturation, the simplest approach is to extend the residence time [11,16,17,19]. The attainable yield can be calculated according to the population and mass balance equations. However, this method would lead to low productivity. In addition, a long residence time may lead to a low purity. As shown in Ref. [16], given a long enough residence time, a maximum yield can be achieved, but the purity is then at its lowest, at about 97.6%.

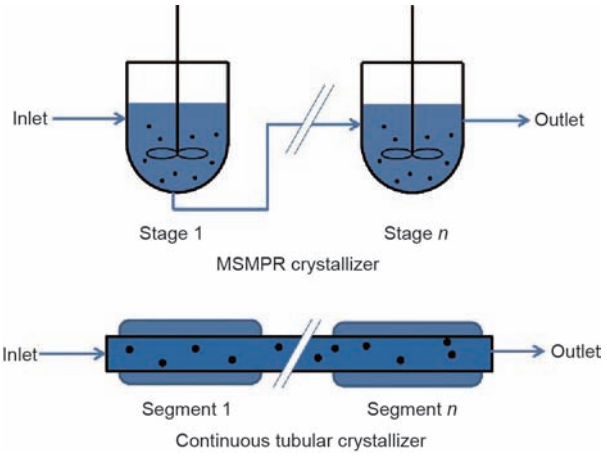

Fig. 1. Schematic diagram of two types of continuous crystallizer: the MSMPR crystallizer and the continuous tubular crystallizer.

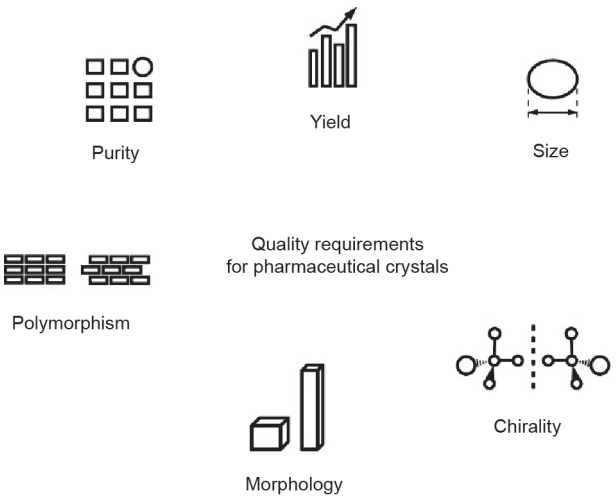

Fig. 2. General quality requirements for pharmaceutical crystals.

Table 1
Comparison of the MSMPR and tubular crystallizers [6].

Type	Advantages	Disadvantages
MSMPR crystallizer	• Easier to convert from batch crystallizer	• Less efficient than tubular crystallizer
	• Lower maintenance cost	• May lead to non-stable behavior
	• Equipment is simpler	• Startup process may be relatively long
	• Easier maintenance	• Relatively hard to scale up
Tubular crystallizer	• Higher efficiency than an MSMPR crystallizer of the same volume	• Maintenance is expensive and complex
	• Narrow residence time distribution	• Easier to cause fouling
	• Easier to scale up	• Equipment is relatively complex