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Review

# Recent progress of continuous crystallization

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ABSTRACT

Continuous crystallization has always been a hot topic in industrial crystallization. Many efforts have been made to improve the continuous crystallization, either by designing novel continuous crystallizers or by proposing improved design and operation of conventional continuous crystallizers. Some new models for continuous crystallization processes have also been proposed and tested in recent years. In this work, the development of continuous crystallization in recent years, including novel crystallizers, control strategies, models and some assistive technologies, is summarized. Promising as it is, continuous crystallization is still not as universal as batch crystallization due to the existence of the drawbacks, such as blockage and encrustation. Therefore, further efforts are needed before wider application of continuous crystallization.

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## Contents

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## Introduction

Crystallization is one of the most important separation and purification processes in chemical engineering industries, especially in pharmaceutical industries. It is believed that approximately 90% of the active pharmaceutical ingredients (APIs) are organic crystals and crystallization process is one of key unite operations which determine the products' final qualities [1]. In crystallization industry, batch crystallization has been the most frequently used technique for many years. However, batch crystallization has some drawbacks, such as variation of product quality, low capacity, high requirements of human intervention, high facility cost, *etc.* [2]. In contrast, continuous process provides many advantages, such as consistence of the product quality, improved yield and capacity, and lower facility cost and space requirement [3,4]. Hence, it is attracting the interests of more and more researchers in recent years, especially in the field of pharmaceutical crystallization.

After Randolph and Larson [5] introduced the concept of population balance to crystallization, continuous crystallization process could be more precisely controlled than ever. Though promising, continuous crystallization is still not as universal as batch crystallization in industries. Problems, such as blockage and encrustation, need to be solved by some cost-effective solutions before wider application of continuous crystallization [6]. Besides, mixed suspension and mixed product removal (MSMPR) crystallizer, one of the typical continuous crystallizers, often causes cyclical oscillations in the crystal size distribution (CSD), which is also challenging for continuous crystallization.

In this work, the progresseses of continuous crystallization in recent years, especially in pharmaceutical area, are summarized to give a brief review on the state of art and future research directions of continuous crystallization. Theoretical models of continuous crystallization are firstly introduced. Then, continuous crystallizers and their applications are summarized. Furthermore, new emerged assistive technologies for continuous crystallization are also outlined and discussed.

## Theoretical models for continuous crystallization

### Population balance equation (PBE) model

Population balance equation (PBE) models are the most common models for the simulation of continuous crystallization. If a PBE model is applied to describe the crystal size distribution in a stirred tank, the model can be specially expressed as [7]:

$$\frac{\partial n}{\partial t}+\frac{\partial(Gn)}{\partial L}+n\frac{d(logV)}{dt}=B-D-\Sigma_k\frac{n_kQ_k}{V} \tag{1}$$

where $n$ is the population of crystals, which is relative to time and particle size, $G$ is the linear growth rate of crystal, $L$ is the size of the crystal and $V$ is the volume of the solution. $B$ and $D$ represents the birth and death rates of the crystal due to aggregation and breakage, respectively. $Q_k$ is the flow rate of influent and effluent streams.

Based on the following assumptions: (1) the grow rate is independent of the crystal size; (2) there are no seeds in feed flow; (3) the whole system maintains a steady state; (4) the solution in the tank is well mixed, which means that, the crystal population and size distribution are the same anywhere inside the tank and the condition of the withdraw flow is the same with the suspension in the tank; (5) the crystal size distribution curve in the system is continuous; (6) aggregation and breakage are ignored; (7) the mean resident time can be described by $\tau = V/Q_k$,

$B = D = 0$, $\tau = V/Q_k$,$n_{\text{inlet}} = 0$, and the right-hand side of Eq. (1) can be changed as:

$$\Sigma_k\frac{n_kQ_k}{V}=\frac{n}{\tau} \tag{2}$$

When the system reaches a steady state, $n$ and $V$ would not change with time, then

$$\frac{\partial n}{\partial t}=n\frac{d(logV)}{dt}=0 \tag{3}$$

Finally, the model can be simplified as:

$$\frac{d(Gn)}{dL}+\frac{n}{\tau}=0 \tag{4}$$

If the crystal growth is assumed to be independent of particle size, Eq. (4) can be further simplified into Eq. (5).

$$\frac{Gdn}{dL}+\frac{n}{\tau}=0 \tag{5}$$

Therefore, it can be solved by integration as:

$$n=n_0\exp\left(-\frac{L}{G\tau}\right) \tag{6}$$

Eq. (6) is the final form of the basic PBE model, in which $n_0$ is the population of nucleus. On the basis of Eq. (6), the fluctuation of the CSD in the stirred tank during the process can be monitored and thus operating conditions can be adjusted in time to control the process.

Since 1980s, the PBE models have been used for crystallization process modeling [8], such as the simulation of CSD, the nucleation process [9–11], the design of continuous crystallizers [12,13], the optimization of operating conditions [14,15], and the avoidance of unwanted problems such like fouling [16], *etc.* Because the conditions in the crystallizers are not always as ideal as assumptions, the neglect of some variables, such as breakage, aggregation and growth rate dispersion, might result in inaccuracy of the models. On the other hand, too many variables will lead to a highly-complicated simulation, which is also not desirable. Fortunately, due to the assistance of high-performance computers, new algorithms have been proposed [17–22], and models concerning factors such like aggregation and breakage could be solved effectively [23–26]. Fevotte and Fevotte [27] studied the effects of industrial impurities on the crystallization of citric acid using the PBE model. The impacts of the unsteady-state behavior of the absorption of impurities on the yield and CSD of the product were simulated and the results were used for the design of the model-based control strategies.

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