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REVIEW ARTICLE

State-of-the-art review on various mathematical approaches towards solving population balanced equations in pharmaceutical crystallization process

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Crystal growth

Abstract Crystallization is an important process, which possesses an undeniable role in many chemical industries. In recent years, significant endeavors have been made to increase the efficiency of this process via designing novel crystallizers. Development of numerical models and their efficient solutions is known as an important approach to justify the behavior of contributed mechanism in crystallization process. The emergence of various complexities towards the modeling of crystallization process is due to the existence of disparate mechanisms such as crystal birth, growth, and death processes. The prominent purpose of this study is to review various employed models to justify crystal birth, death, and growth in the crystallization process. Additionally, various numerical approaches like method of moments (MOM), discretized sizing technique (DST) and method of weighted residuals (MOWR) are presented in this review paper and their advantages and disadvantages to solve PBE are discussed in detail. At the end, future perspectives towards increasing the efficiency of various employed approaches foe solving population balance equation (PBE) in the crystallization process are presented, which can be of great interest for expert readers as well as non-expert investigators to be more acquainted with the undeniable role of mathematical modeling approaches in the crystallization process.

1. Introduction

One of the most important chemical operations for separating solid materials is crystallization. This process includes two prominent steps including nucleation and subsequent crystal growth (Omar and Rohani, 2017; Auer and Kashchiev, 2022; Tavare, 2013; Cao, 2021). Primary nucleation often takes place from the super-saturated solution in the non-existence of pre-existing crystals, while secondary nucleation happens through the generation of new crystals in the presence

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of parent crystals. In comparison with primary nucleation, secondary nucleation needs a lower amount of energy owing to the fact that this process requires less super-saturation. Secondary nucleation possesses great potential of application in various industrial crystallizers (Kodera et al., 2019; Zhang, 2021; Agarwal and Gupta, 2022; Marjani, 2020). Employed operations in crystallization process are able to be implemented to control momentous parameters such as crystal size distribution (CSD), morphology and so on. (Sun, 2018; Roelands, 2006; Myerson et al., 2002). The CSD is of great importance in pharmaceutical industry due to its undeniable effect on some operational factors including process flow characteristics, bioaccessibility and tablet pressing properties (Wen et al., 2015; Abu Bakar, 2009; Zhang et al., 2013; Cao et al., 2021). A crystalline product may include various crystalline particles with disparate sizes. CSD is an important product property of a solid, which not only influences the suspension manner in the crystallizer, but also specifies the efficacy of the liquid–solid separation and subsequently drying step. Numerical solution of the CSD has been accelerated by the development of population balance equation (PBE) in the 1960 s (Randolph, 1962). Fig. 1 schematically demonstrates the CSD determination in the batch crystallization process.

Temperature is considered as a momentous parameter in the crystallization process of biological macromolecules due to its undeniable impact on the nucleation and crystal growth (Christopher et al., 1998; Liu, 2019; Nguyen, 2022). Moreover, temperature has recently illustrated its important role in membrane protein crystallization. Therefore, suitable control of this important parameter during the optimization/manufacturing process of crystals would be of great importance for successful crystal growth of proteins. (McPherson, 2017; Caffrey, 2003; Babanezhad, 2021). It has been reported that increment or decrement of temperature significantly influences quantity, size, and crystals quality. An important advantage of temperature is the creation of rapid, accurate and reversible control of supersaturation. Apart from the application of standard crystallization variables, the use of temperature may significantly improve the possibility of crystals production for a sample (Kwon, 2014).

Recently, the emergence of mathematical modeling/computational-based approaches following with advancement in the particle size measurement techniques have significantly improved the interest of many researchers all over the world to employ PBEs for crystallization processes and other industries (Borchert, 2009; Farias, 2019; Bhoi and Sarkar, 2020; Marjani, 2021). PBEs is a well-known mathematical approach to deal with particulate systems. This technique includes formation, growth, breakage and aggregation of particles and possesses great ability of application in disparate industries such as polymerization, crystallization, aerosol reactors, biological processes, membrane-based separation, chemical reaction and fermentation (Costa et al., 2007; Pinar, 2021; Zhang et al., 2022; Pishnamazi, 2020; Babanezhad, 2020; Elveny, 2021; Babanezhad, 2020). The majority of crystalline entities existed in different industries (i.e., pharmaceutical) illustrate anisotropic morphologies (Ma et al., 2002). The PBEs interpreting these types of crystallization processes can be considered multi-dimensional. Mathematical-based solution of multi-dimensional PBEs is one of the greatest challenges in crystallization process, which results in the appearance of noteworthy difficulties towards appropriate control of this process. Owing to the accessibility of new computing tools, scientific investigations on PBEs have been revolutionized recently for various applications (Ma and Wang, 2008).

In this review paper, various approaches like MOM which is so-called method of moments, discretized sizing technique (DST), and Method of weighted residuals (MOWR) towards solving PBE in the crystallization process accompanying with their advantages and disadvantages are aimed to be discussed. Up to the knowledge of the authors, very few papers have comprehensively investigated all current advancements for solving PBEs in the crystallization process. Therefore, this paper may open new horizon for better perception of the indisputable role of mathematical-based modeling approaches to justify disparate contributed mechanisms in crystallization process and increase its efficiency and performance.

2. Population balance model (PBM)

Estimation of product quality in crystallization process needs comprehensive information about CSD. With the aim of achieving this knowledge, PBE must be solved to explain the progression of size distribution in the process. The main perception of PBE has been initially presented in 1962 (Randolph, 1962). Equation 1 presents the generalized PBE applied for computing the number distribution of the crystals as follows (Lewis, 2015):

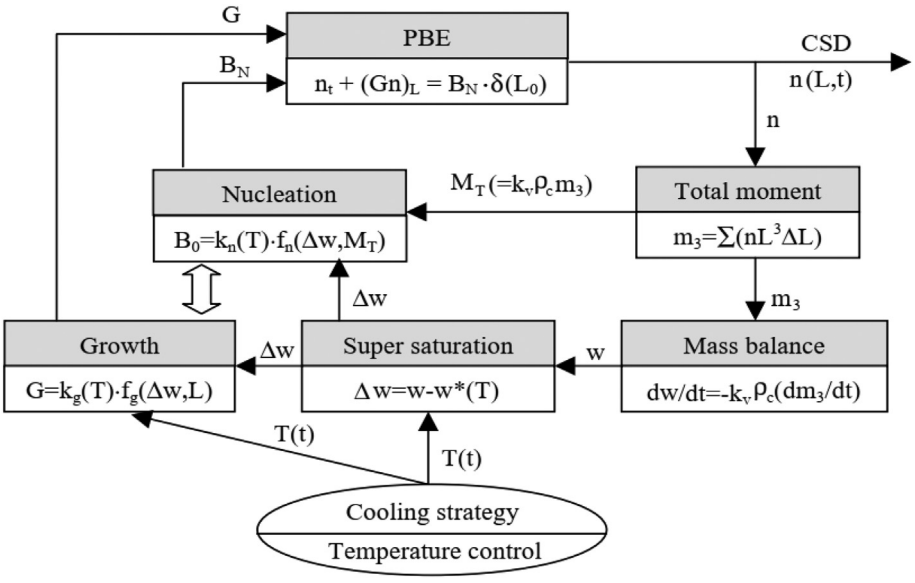

Fig. 1 Schematic illustration of CSD determination in the batch crystallization process. Reprinted from (Lim, 2002) with permission from Elsevier.

$$\frac{\partial(n(L,t)V(t))}{\partial t} = -V\frac{\partial(G_L(L,t)n(L,t))}{\partial L} + B(L,t)V - D(L,t)V + \sum_{j=1}^{m}\varphi_{v,in,j}(t)n_{in,j}(L,t) - \sum_{k=1}^{n}\varphi_{v,out,k}(t)h_{out,k}(L,t)n(L,t) \quad (1)$$

In this equation, the crystals' amount and size are respectively defined in case of number density (n (L, t)) and crystal length (L). Additionally, in the abovementioned equation, V, φ_v and G_L (L,t) are defined as the crystallizer volume, volumetric flow rates and linear size dependent growth rate. Finally, *D* and *B* can be respectively expressed as death and birth rates. In a batch operational process, the initial distribution may be physically appertained to a seed population, while in an operationally continuous process, this factor would be the seed population or the population of outgrown nuclei. Despite the fact that the occurrence of secondary nucleation may be to the attrition of the larger crystals, this parameter is excluded in the PBE.$\frac{\partial(G_L(L,t)n(L,t))}{\partial L}$, which interprets the size-dependent growth of crystals is another parameter in the PBE that can explain disparate physical processes takes place within crystallization. In the condition of the growth rate independency to crystal length, $\frac{\partial(G_L(L,t)n(L,t))}{\partial L}$ is modified to $\frac{G_L(t)dn(L,t)}{dL}$. $B(L,t)V - D(L,t)V$ is an important term in PBE, which indicates the crystals birth and death due to agglomeration,

breakage and nucleation. The terms $\sum_{j=1}^{m}\varphi_{v,in,j}(t)n_{in,j}(L,t)$ and $\sum_{k=1}^{n}\varphi_{v,out,k}(t)h_{out,k}(L,t)n(L,t)$ in equation 1 are respectively denoted as the arbitrary number of inlet and outlet streams.

Owing to the first-order nature of PBE regarding to time and length of crystal, a boundary condition following with an initial condition are needed to mathematically solve the PBE. Equations 2 and 3 present the boundary and initial conditions, respectively.

$$n(L,t) = \frac{B_0(t)}{G_L(0,t)} \quad (2)$$

$$n(L,0) = INITIALDISTRIBUTON \quad (3)$$

With the aim of solving PBE, the zero-size nucleation ratio can be applied as the boundary condition. By description of nucleation process via new crystals formation (B(L, t)) in a determined crystals size range ($0 \le L \le y$), the birth term in equation 2 can be obtained using Equation 4 as follows:

$$B_0(t) = \int_0^y B(L,t)dL \quad (4)$$

2.1. The PBE for agglomeration and breakage

Agglomeration is an important mechanism in crystallization process. Although this mechanism significantly affects the particles number, it doesn't change the overall volume of the particles. Fig. 2 schematically illustrates major steps of agglomeration.

Therefore, formulation of PBE in the attendance of agglomeration regarding to volume coordinates isn't challengeable. The agglomeration rate (r_{agg}) relies on some momentous factors like the number of existed particles (n),

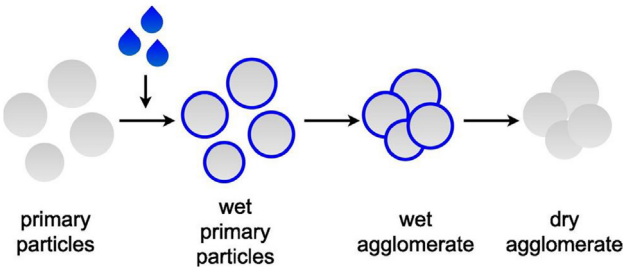

Fig. 2 Schematic demonstration of major steps of agglomeration including wetting, collision and drying. Reprinted from (Otto, 2021) with permission from Elsevier.

the particles size participated in the process (v), the relative super-saturation (σ) and the power input P_0 and can be derived by the following equation:

$$r_{agg}(v_1,v_2) = \beta_{agg}(v_1,v_2,\sigma,P_0)n(v_1)n(v_2) \quad (5)$$

In this equation, β_{agg} is a constant rate for agglomeration known as agglomeration kernel. By knowing the concept of the agglomeration mechanism in crystallization process, the following equations can be derived to define birth and death terms:

$$B(v) = \frac{1}{2}\int_0^v \beta_{agg}(\varepsilon, v-\varepsilon)n(\varepsilon)n(v-\varepsilon)d\varepsilon \quad (6)$$

$$D(v) = n(v)\int_0^\infty \beta_{agg}(\varepsilon, v)n(\varepsilon)d\varepsilon \quad (7)$$

The number $\frac{1}{2}$ in the birth equation is identified as a correction factor because of the integration of ε from 0 to v. Substitution of the abovementioned equations for the birth and death rates with a determined size into the general form of PBE results in the derivation of the following equation for a system without any significant growth or breakage:

$$\frac{\partial(n(v,t)V(t))}{\partial t} = \left[\frac{1}{2}\int_0^v \beta_{agg}(\varepsilon, v-\varepsilon)n(\varepsilon,t)n(v-\varepsilon,t)d\varepsilon - n(v,t)\int_0^\infty \beta_{agg}(\varepsilon,v)n(\varepsilon,t)d\varepsilon\right]V + \sum_{j=1}^{m}\varphi_{v,in,j}(t)n_{in,j}(v,t) - \sum_{k=1}^{n}\varphi_{v,out,k}(t)h_{out,k}(v,t)n(v,t) \quad (8)$$

As pointed out before, crystals breakage hardly ever takes place. Breakage is an important mechanism in crystallization process, which significantly affects the particles number in a system, but doesn't have any effect on volume. The kinetics of breakage can be expressed via D(v, t) and B(v, t) functions, which rely on the selection function (S(v)) and breakage constant (b(ε, v)) as follows:

$$B(v) = \int_v^\infty b(\varepsilon,v)S(\varepsilon,t)n(\varepsilon,t)d\varepsilon \quad (9)$$

$$D(v,t) = S(v,t).n(v,t) \quad (10)$$

Substitution of equations 9 and 10 in the generalized form of PBE causes the derivation of Equation 11 for breakage:

$$\frac{\partial(n(v,t)V(t))}{\partial t} = \left[\int_v^{\infty} b(\varepsilon,v)S(\varepsilon,t)n(\varepsilon,t)d\varepsilon - S(v,t).n(v,t)\right]V + \sum_{j=1}^{m}\varphi_{v,in,j}(t)n_{in,j}(v,t) - \sum_{k=1}^{n}\varphi_{v,out,k}(t)h_{out,k}(v,t)n(v,t) \quad (11)$$

Disparate forms of the agglomeration and breakage kernel models can be presented in Table 1.

Table 1 Agglomeration and breakage Kernel Models.

Agglomeration	Expression	Ref.
	$\beta(x,x') = \beta_0$	(Qamar et al., 2009)
	$\beta(x,x') = \beta_0(x,x')$	(Scott, 1968)
	$\beta(L,L') = \beta_0(L^3,L'^3)$	(Lister et al., 1995)
	$\beta(L,L') = \beta_0(L,L')(L^{-1},L'^{-1})$	(Friedlander and Smoke, 1977)
	$\beta = k_\beta G^h B_0^p \tau^q$	(Tavare and Patwardhan, 1992)
Breakage	$b = 1$	(Marchisio et al., 2003)
	$b = L^a$	
	$b = \exp(\delta L^3)$	(Falola et al., 2013)
	$b = L^3$	

3. Crystallization models

Crystallization models express disparate procedures of crystals generation, destruction and growth. Numerous formations of these equations are existed, which are usually derived applying a semiempirical technique. Fig. 3 schematically renders a flowchart illustrating all of the mechanisms related to crystals birth and death.

3.1. Crystal birth

3.1.1. Primary nucleation (PN)

PN takes place from the solution of its own kind at high supersaturation (Viedma, 2004). The relationship between PN and super-saturation is completely non-linear. It is near 0 when the level of super-saturation is negligible and quickly enhances by reaching the level of super-saturation to a specific critical value (Garside, 1985). Owing to the existence of weak reproducibility, appropriate control of PN is significantly hard. Poor reproducibility can be described by two main facets. The first aspect is based on the assumption of the deterministic essence of PN mechanism, which results in the occurrence of poor reproducibility owing to great sensitivity of the experimental circumstances. Hence, precise control of experimental conditions can eventuate in the appropriate control of nucleation. The second facet is according to the assumption of the stochastic nature of the nucleation process (Maggioni and

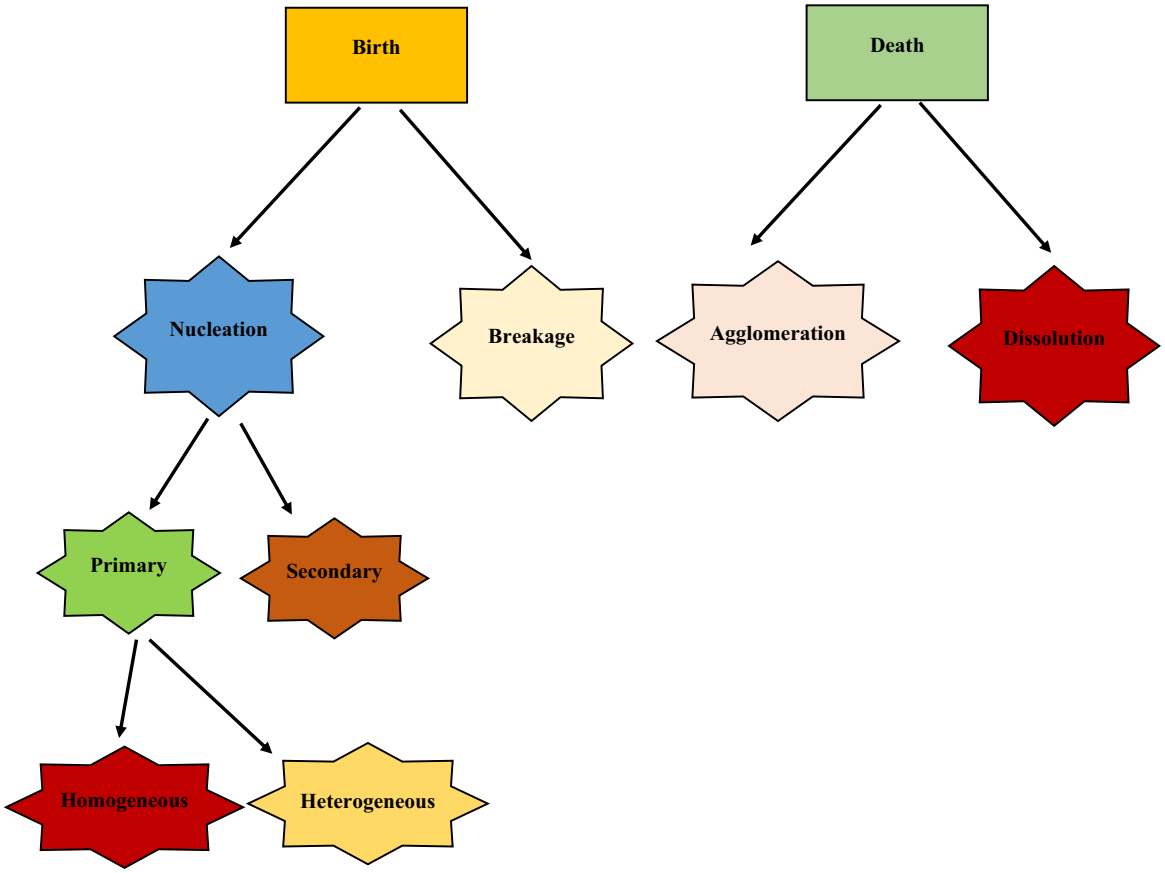

Fig. 3 Schematic illustration of the mechanisms related to crystals birth and death. (). Adopted from Omar and Rohani, 2017; El-Yafi and El-Zein, 2015

Mazzotti, 2015; Sear, 2014; Sullivan, 2014). Classical nucleation theory (CNT) possesses great ability to provide an insight about the circumstance of nuclei formation from the solution (Cooper, 1974; Langer and k. Schwartz, 1980). Albeit various conducted experiments in recent years are basically different from the predictions provided by CNT. One of the most interesting theories, which has been recently of great attraction is the two-step nucleation theory (TSNT) (Vekilov, 2004; Vekilov, 2010). In CNT, a critical size exists, which profoundly relies on the super-saturation. In this theory, the cluster is of great stability and grows to a macroscopic size. In contrast, in TSNT, the recognition of molecules into a regular structure takes place with the aim of generating a nucleus after the cluster formation of solute molecules (Erdemir et al., 2009). Karthika et al has comprehensively evaluated both CNT and TSNT. They concluded that according to both evaluated theories, those operational parameters that influence the cluster formation may help or inhibit the process of PN. For instance, cluster formation can be declined or enhanced based on the intensity of mixing (Karthika et al., 2016). In an investigation, Forsyth et al. corroborated the significant impact of fluid shear on the PN mechanism. Based on their investigation, PN and growth rates were both relied on the shear rate. Additionally, they concluded that increment in the amount of average shear rate significantly declined the mean induction time (Forsyth, 2015). Application of acoustic cavitation (AC) with the aim of motivating PN mechanism is identified as another technique to influence cluster formation. This technique has been proposed by Virone et al. They concluded from their investigation that the presence of AC decreased the sensitivity against the average super-saturation. The derived pressure owing to the cavitation enforces a high local super-saturation that positively affects PN (Virone, 2006). About the ultrasound intensity, it is worth pointing out that low amounts of ultrasound irradiation restrains PN mechanism, while its high amounts motivates the PN process (Kurotani, 2009). Moreover, PN mechanism may be classified into two major divisions including homogeneous nucleation (HON) and heterogeneous nucleation (HEN). HON is defined as the spontaneous generation of nuclei from the solution. The pathway of HON is still ambiguous, which can be attributed to the great difficulty in direct observation. CNT doesn't have eligibility to appropriately describe the nucleation process. In an experiment, Tan et al. demonstrated the insignificant role of density fluctuations to increase nucleation in HON (Tan et al., 2014). HEN process takes place in the existence of impurities (i.e., particles) that help the generation of a seed for a nucleus. HEN is more prevalent than HON owing to the requirement of low amount of energy to create the nuclei. Wall roughness and impurity type are among the most important operational factors that can control the presence of HEN (Omar and Rohani, 2017).

3.1.2. Secondary nucleation (SN)

SN takes place when pre-existing crystals exist. PN mechanism precedes SN (Viedma, 2004). SN mechanism can overcome the PN mechanism when the number of crystals reached to a sufficient amount. SN process takes place by two main mechanisms including shear and collision (Agrawal and Paterson, 2015). Fig. 4 demonstrates the mechanisms of SN process. The pre-existing crystals may be regarded as the nuclei source. Opposite of other mechanisms, attrition doesn't have any dependency to the super-saturation. Various types of crystal can be formed on the surface of the pre-existing crystals by early removal of layer in the process. Albeit, by passing a sufficiently-long time,

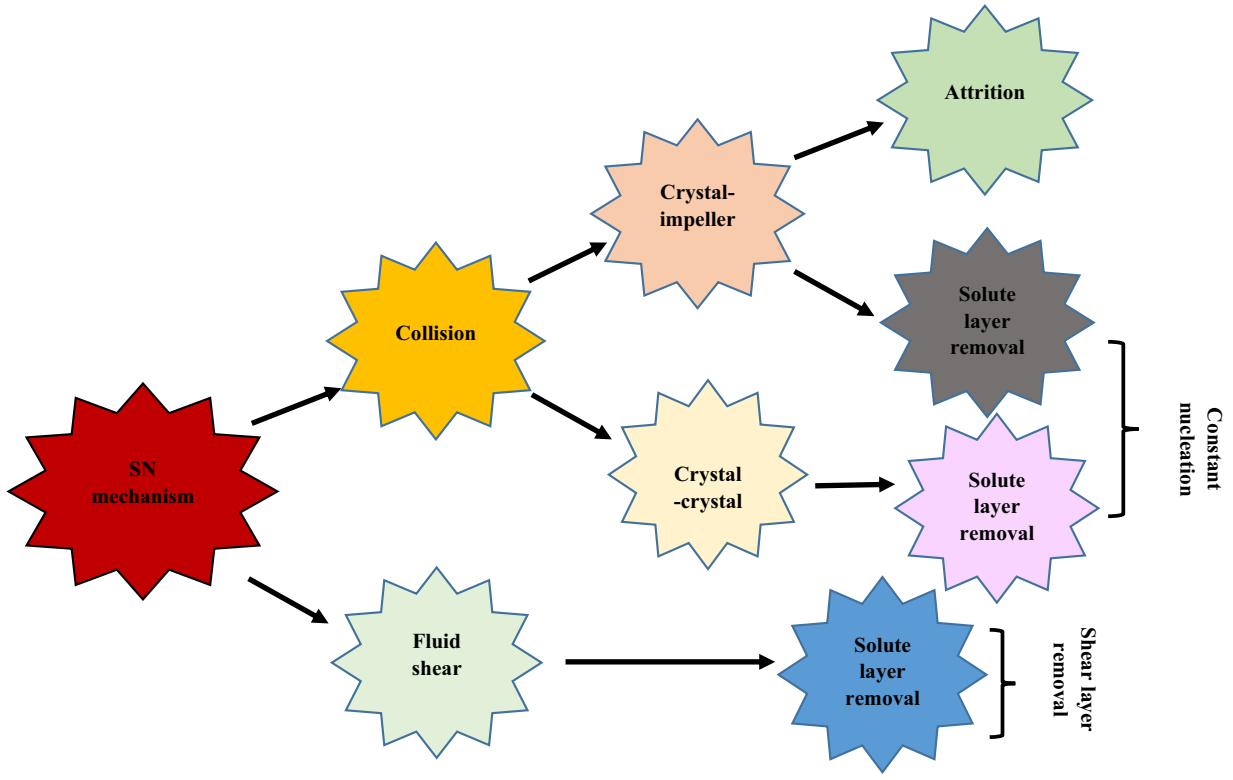

Fig. 4 Principal mechanisms of SN process. (). Adopted from Agrawal and Paterson, 2015

the solute layer can accept the shape of the seed crystal and therefore, the crystal configuration is similar to the seed (Agrawal and Paterson, 2015). The number of manufactured secondary nuclei within the contact nucleation process is in direct relation with the super-saturation and the contact energy (Denk and Botsaris, 1972). Review of various scientific papers illustrates the fact that faster growing materials increases the efficiency of nuclei (Tai et al., 1975). Contact nucleation possesses great potential of application as a suitable procedure to control the crystal size. In this procedure, the secondary nuclei size is able to be controlled via the flow rate of the feed solution (Wong et al., 2013). The occurrence of shear nucleation is exactly similar to contact nucleation mechanism. As like as contact nucleation mechanism, the removal of crystals surface layer results in its action as nuclei (Sung et al., 1973).

3.1.3. Breakage and attrition

Attrition / breakage is known as dissociation process of a particle into smaller compartments due to the induction of a physical force which could occur in the process of crystallization. These compartments act as nuclei and possess the potential of growth into bigger crystals (Omar and Rohani, 2017). The prominent discrepancy between breakage and contact nucleation is that in contact nucleation, the parent crystal doesn't break, while in attrition process, the parent crystal is fractured into numerous segments in irreversible form. One of the most important parameters in crystal attrition mechanism is time. In an investigation, Mazzarotta et al. investigated the influence of time on attrition in a mixing tank. Based on their investigation, in the first minute, numerous small segments were manufactured, but rapidly after that the production process of small fragments became insignificant (Mazzarotta et al., 1996). Asakuma et al. applied momentous parameters of micro-hardness such as roundness and fracture strength to estimate attrition behavior. These factors had been applied to compute fracture energy and attrition coefficient that are of great importance in the estimation of attrition value (Asakuma, 2007). Crystal morphology/shape are two important parameters, which their investigation is of great importance. Compared to crystals with low aspect ratios, those with higher aspect ratios can be easier broken (Sato, 2008; Briesen, 2009). In a numerical study, Briesen developed a two-dimensional (size and shape of the crystals) model based on PBE that for shape dependent crystal attrition. They resulted that the PBE has great potential of application to mathematically model shape dependence (Briesen, 2009). Guo et al. studied the impact of ultrasound on attrition/breakage of crystals. Based on their investigations, ultrasound can influence the crystals in two different ways as follows (Guo, 2007):

1) Ultrasound enhances the collision rate between crystals and results in the contribution of cavitation to breakage.

2) Ultrasound possesses great potential to be applied in the nucleation process. If the ultrasound process lasts too long, it results in the breakage of crystal and consequently alteration in the obtained CSD.

3.2. Crystal death

3.2.1. Dissolution

Dissolution is a mechanism which takes place by reducing the relative super-saturation to an amount less than 1. Numerous functional/operational parameters of crystals such as growth, configuration, size and form along with the chemical essence of both crystal and solvent can have significant effect on dissolution mechanism (Blagden, 2007). The mechanism of dissolution takes place in two major steps including 1) surface reaction and detachment 2) Crystal-to-bulk solution mass transfer of components. Relying on the crystal solubility, either mass transfer or surface detachment of the species may be propounded as the rate-limiting step (Nagy et al., 2011). Shan et al. proposed a mathematical model for dissolution mechanism by considering both mass transfer and molecules detachment on the surface of crystal (Shan et al., 2002). In another study, Mangin et al. applied PBE to investigate dissolution mechanism in a stirred tank vessel. They concluded that at the time near the occurrence of dissolution mechanism, disaggregation agglomerated particles significantly accelerate the dissolution process (Mangin, 2006).

3.2.2. Aggregation and agglomeration

In crystallization process, the phenomenon of agglomeration is the process of contacting particles for an adequately long time with the aim of enabling the growth of a crystalline bridge between the particles (Lewis, 2015). Agglomeration of particles plays a vital role in the creation of bigger particles and therefore, is of great importance for industrial crystallization (Hollander, 2002). Aggregation is defined as the pre-nucleation process of molecules formation to supramolecular structures (Nichols, 2002). Based on the definition, aggregation can result in agglomeration. The occurrence of agglomeration is based on different steps, which can be explained as follows:

1) Proximity of two particles for the growth of an agglomerative bond; and.

2) Generation of the agglomerative bond.

In the second step, the bond is reinforced by passing the time but may be broken by other collisions. Surface configuration, quiddity of agglomerative bond, hydrodynamic and super-saturation effects and orientation of collisions can be considered as important parameters that affect agglomeration (Brunsteiner, 2005). Formation of the agglomerates is in close relationship with the size. If crystals have large sizes, the addition of a single crystal can increase the agglomerates size but if crystals have small size, the addition of smaller agglomerates can enhance the agglomerates size (David et al., 1995). David et al. proposed a new interpretation for agglomeration mechanism by mixing fluid mechanics with crystal engineering. They concluded based on employing their developed equation that agglomeration is a size-dependent mechanism and crystals with small size can favorably stick to large crystals in comparison with those crystals with similar size (David, 1991).

3.3. Crystal growth

Crystal growth is an important mechanism in crystallization process, which profoundly depends on the solute super-saturation. Appropriate control of super-saturation is an important process in crystal growth mechanism, which is possible employing some methods such as cooling of the supersaturated solution, addition of an anti-solvent, evaporation and change of the pH value. The prevalently employed mathematical model for crystal growth can be presented applying the power law relationship as follows (Briesen, 2006; Gunawan et al., 2004; Morris, 2015):

$$G = k_G S^a \tag{12}$$

In this equation, k_G and a are respectively expressed as the growth rate kinetic parameter and an empirical constant.

Impurities in mother liquor are considered as an important parameter, which significantly influence the crystal growth rate. Various impurities in mother liquor are of great importance in industrial crystallization owing to their unavoidable presence. Numerous investigations have been recently conducted to evaluate the impact of various impurities on the growth trend of pharmaceutical crystals (Garnier et al., 2002; Chong-Hui and Grant, 2002). Moreover, application of various types of additives may be beneficial for controlling crystal morphology. In an investigation, Thompson et al. studies the effect of additives on the growth/morphology of paracetamol crystals. They corroborated that the impurities' structure possesses great importance on the growth process of crystals relying on the functional groups of the crystal faces (Thompson, 2004). Zhang et al. evaluated the influence of impurities via the development of a two-dimensional population balance model. They concluded the great performance of PBEs on solving population balance model for determining the shape evolution during crystal growth (Zhang, 2015). Fig. 5 schematically demonstrates the crystal growth mechanism of doped Ag_2O_3-ZnO NCs generated by wet-chemical process.

4. Numerical approaches for PBE solution

4.1. Method of moments (MOM)

Three principal techniques for analyzing the PBE are the MOM, the discretization of the size domain interval (DSDI) and the weighted residuals (WRs) (Costa et al., 2007; Davidson and Aberle, 2004; Babanezhad, 2020). The MOM is identified as an old numerical approach that can convert the PBE into a series of ODEs via multiplying the PBE by L^j and integrating it. This numerical process results in deriving the following equations. Solution of these equations presents the moments of particle distribution as function of t (Ranodolph, 2012):

$$\int_0^\infty L^j \left[\frac{\partial n}{\partial t} + \frac{\partial}{\partial L}(Gn) + D - B\right] = 0 \tag{13}$$

$$\frac{d\mu_0}{dt} = B_0 + \bar{B} - \bar{D} \tag{14}$$

$$\frac{d\mu_1}{dt} = \mu_0 G + \bar{B} - \bar{D}$$

$$\frac{d\mu_2}{dt} = 2\mu_1 G + \bar{B} - \bar{D}$$

$$\frac{d\mu_3}{dt} = 3\mu_2 G + \bar{B} - \bar{D}$$

In the above-mentioned equations, B_0 is expressed as the nucleation rate. By consideration of only nucleation and growth mechanisms, the moments is able to be created via the ordinary differential equation (ODEs) as follows:

$$\frac{d\mu_j}{dt} = 0^j B_0 + jG\mu_{j-1} \tag{15}$$

The derivation process of ODEs when PBE is 2D is easy and can be obtained as follows:

$$\frac{d\mu_{00}}{dt} = B_0 \tag{16}$$

$$\frac{d\mu_{ij}}{dt} = iG_1\mu_{(i-1)j} + jG_2\mu_{i(j-1)} \mathrm{i} + \mathrm{j} > 0$$

One of the prominent drawbacks of MOM is the complication of equations if the growth rate is size-dependent. In this situation, application of moments and an orthogonal polynomial with the aim of simulating the population density function may be considered as an appropriate alternative to simplify mathematical equations. By contribution of aggregation and breakage, the simplification of moment equations isn't feasible. Apart from this important disadvantage, the existence of numerical unstability towards rebuilding the real distribution from its moments can be another drawback of MOM approach, which eventuates in the emergence of serious problems in model application (Costa et al., 2007; Rigopoulos and Jones, 2003).

4.2. Discretized sizing technique (DST)

The discretization approach, known as DST, discretizes independent variable in various intervals and apply the mean-

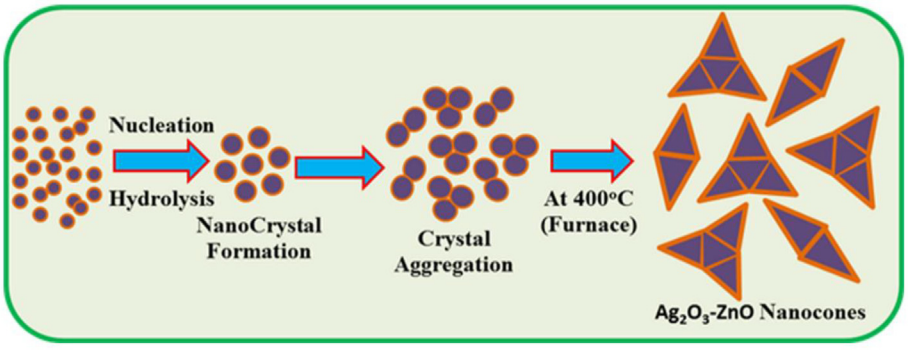

Fig. 5 Schematic demonstration of crystal growth mechanism of doped Ag_2O_3-ZnO NCs generated via wet-chemical process. Reprinted from (Rahman, 2014).

value theorem to convert the continuous PBE into a series of equations. DSDI possesses the ability to turn the PBE to discretized population balance (DPB) (Costa et al., 2007; Kotsiantis and Kanellopoulos, 2006; Abbas and Romagnoli, 2007). The endeavors towards mathematical-based solution can be significantly declined by the assumption of a geometric progression for grids owing to significant decrement of the number of particles combinations required to evaluate the aggregation terms (Rigopoulos and Jones, 2003). Moreover, coarse discretization procedures are of great amenability to control applications due to its great speed to recognize, which method should be achieved particularly when fronts and discontinuities are not existed (Ramkrishna and Mahoney, 2002). Two momentous disadvantages can be highlighted during the implementation of this method as follows (Mahoney and Ramkrishna, 2002):

1) Both conservation in the mass and particles number is just warranted in the limit of infinite resolution
2) Creation of a sharp discontinuity, which rapidly develops via numerical diffusion in simulation.

Marchal et al. developed the Method of Classes (MOC) to numerically solve the agglomeration, breakage and length-dependent growth rate. This technique divides the size domain interval in some grids to create granulometric bins (C_i). MOC considers a fixed amount for the density function in each bin (Marchal, 1988). The main disadvantage of the MOC is the dependency of its density functions on the adopted grid. In recent years, Self-adaptive discretization (SAD) method has been developed to decline the number of differential equations considering no impact on results. Strong dependency of computation feasibility on the difficulty of the death and birth rates can be identified as another major disadvantages of MOC process (Costa et al., 2007). Puel et al. broadened the MOC procedure to 2D PBE and interpreted that some systems haven't been of great potential to be rendered individually by one characteristic dimension. The bi-dimensional MOC estimates the time-variation of the crystal habit, which needs to be under profound attention in some applications. They offered the performance of an adaptive bi-dimensional algorithm to enhance the precision of the computation. They employed the LSODAR to solve the obtained ODEs (Puel et al., 2003).

4.3. Method of weighted residuals (MOWR)

Method based on weighted residuals contain some procedures that retake the distribution by predicting the solution with a series of trial functions (Finlayson, 2013). The weighted residuals are classified into two major procedures including weighted residuals with global functions (WRWGF) and finite element (FE). WRWGF method has been among the oldest techniques in PBE numerical solution. Despite its soon recognition in the field of PBE numerical solution, its application in the numerical solution of PBE has been limited due to showing sharp changes and discontinuities (Braatz, 2002). FE technique predict the solution via piecewise low-order polynomials that are flexible and qualified of taking highly irregular solutions (Rigopoulos and Jones, 2003). In WRWGF procedure, the population density function can be approximated using the following equation:

$$n(L,t) = \sum_{i=1}^{\infty} a_i(t)\Psi_i(L) \tag{17}$$

Where, Ψ_i is a basis function. Moreover, the ambiguous a_i's can be obtained by placing former equation into the general PBE to define a residual R (L, t). The main objective of weighted residuals is to find those ai's that compel the orthogonal residual to an opted set of weighting functions via the following equation:

$$\int_0^{\infty} \Psi_i(L)R(L,t)dL = 0 \tag{18}$$

Feasible options of the weighting functions consists of either Dirac's delta functions (leads to collocation procedures) or the basis functions (leads to Galerkin's methods) (Mahoney and Ramkrishna, 2002). In FE techniques, the infinite domain is shortened to a finite domain. This shortened domain is compartmentalized to discrete subdomains. For all $L \in (L_a, L_b]$, a linear combination of interpolation functions can be applied for the approximation of PBE solution as follows (Nicmanis and Hounslow, 1996; Nicmanis and Hounslow, 1998):

$$n(L) = n_h^e(L) = \sum_{j=1}^{n_e} n_j^e \Psi_j^e(L) \forall L \in (L_a^e, L_b^e] \tag{19}$$

In an investigation, Nicmanis and Hounslow employed Collocation and Galerkin FE algorithms to solve PBE steady state mode of operation applying Lagrange cubic interpolation polynomials and spaced nodes inside each element. They corroborated that this algorithm possesses great efficiency to precisely estimate the number density with small numbers of elements. Despite great efficiency, Galerkin algorithm needs additional integrations that results in increasing the computational price of this method compared to collocation method (Nicmanis and Hounslow, 1996; Nicmanis and Hounslow, 1998). The orthogonal collocation on finite elements (OCFE) is considered as another procedure applied by numerous investigators in the scientific field of emulsion polymerization. This numerical method applies Lagrange and Legendre interpolation polynomials (Doyle et al., 2003; Immanuel, 2002; Immanuel and Doyle Iii, 2003).

In a study, Mahoney and Ramkrishna applied two modifications in the Galerkin's procedure on FE to solve PBEs for precipitation process with the aim of decreasing its traditional disadvantages as follows (Costa et al., 2007; Mahoney and Ramkrishna, 2002):

1) Choosing linear basis functions to overcome the difficulties towards managing discontinuities that are usually emerged in simulations of seeded crystallizers.
2) Precise adjustment of invariant integrals of separable aggregation models is an appropriate way to decline computational prices.

5. Conclusion and future outlook

The significant role of numerical modeling approaches in crystallization process and crystallizer control has motivated researchers all over the world to develop more efficient, economical and precise solutions to solve population balance equations. In recent decades, various types of numerical procedures have been evaluated to solve PBE. MOM is identified as one of the most common types of crystal popular solution

that consists of the conversion of PBEs to ODEs applying a moment transformation. Application of MOM results in obtaining the mean particle sizes and distribution coefficient. DST is another commonly applied technique that provides the distribution. Despite its good performance to solve PBEs, high computational costs have restricted its extensive application in crystallization process. MOM technique possesses great ability of application as coupled with CFD software and especially when rapid calculations of the average crystal size are of great importance. The main purpose of this review paper is to present a state-of-the-art review in the mathematical-based solution of PBE in crystallization process and discuss the challenges towards solving it in the presence of disparate contributed mechanisms such as nucleation, growth, agglomeration, and attrition. This review paper presents the advantages and disadvantages of commonly employed approaches such as MOM, DST and MOWR for solving PBE in crystallization process. More investigations on PBEs have illustrated significant progression. As an outlook, more investigations must be carried out to evaluate the potential of phenomenological models instead of the semiempirical models. Additionally, development of more efficient aggregation/agglomeration and breakage kernels is of great importance for more appropriate description of the underlying processes. Furthermore, application of quantum mechanics modeling to solve PBE is a novel idea that can be evaluated by investigators in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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