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Inside the Phenomenological Aspects of Wet Granulation: Role of Process Parameters

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Abstract

Granulation is a size-enlargement process by which small particles are bonded, by means of various techniques, in coherent and stable masses (granules), in which the original particles are still identifiable. In wet granulation processes, the powder particles are aggregated through the use of a liquid phase called binder. The main purposes of size-enlargement process of a powder or mixture of powders are to improve technological properties and/or to realize suitable forms of commercial products. A modern and rational approach in the production of granular structures with tailored features (in terms of size and size distribution, flowability, mechanical and release properties, etc.) requires a deep understanding of phenomena involved during granules formation. By this knowledge, suitable predictive tools can be developed with the aim to choose right process conditions to be used in developing new formulations by avoiding or reducing costs for new tests. In this chapter, after introductory notes on granulation process, the phenomenological aspects involved in the formation of the granules with respect to the main process parameters are presented by experimental demonstration. Possible mathematical approaches in the granulation process description are also presented and the one involving the population mass balances equations is detailed.

Keywords: granular materials, wet granulation process parameters, granule growing, granule breakage, granulation mathematical description

1. Introduction

Granulation, also known as agglomeration, pelletization, or balling, is a “size-enlargement process” of small particles into larger coherent and stable masses (granules), in which the original particles are still identifiable [1]. The aim of the granulation process is to improve the properties of the final product compared to the powder form, such as giving better flow properties for safer and cheaper transport and storage, lowering of caking and lump formation (especially for hygroscopic materials), improving heat transfer features, obtaining a more uniform distribution of the active molecule, lowering powder dispersion in the environment, linked to a reduced inhalation, handling and explosion risks hazard [1, 2]. Granules have, therefore, received a great interest in many industrial fields, from mineral processing to agricultural products, detergents, pharmaceuticals, foodstuffs, nutraceuticals, cosmetics and zootechnical products [3].

In pharmaceutical field, solid dosage forms remain an important part of the overall drug market, despite the success and the development of new pharmaceutical forms. The oral solid dosage forms market was of \$571 million in 2011 and projected to reach \$870 million at the end of 2018 [4]. In particular, among novel drugs approved by FDA, 46% in 2014 and 32% in 2016 were solid dosage products [5], most of them made of granules. The most important pharmaceutical industries, such as Patheon, Aesica, Rottendorf Pharma GmbH, Catalent Pharma, continually do investments in oral solid manufacturing solutions, including the development of granulation processing methods [6]. Granulated products are also highly used in the fertilizers field: about 90% of fertilizers are applied as solids, less as powder, more in granular form. The global demand for fertilizer nutrients was estimated to be 184.02 million tons in 2015, and it is forecast to reach 201.66 million tons by the end of 2020 [7]. The animal feed additives global market was estimated at 256.8 kilo tons in 2015, and in particular, industries aim to develop new technologies [8], very often based on granulation principles, to provide stabilization and effective protection of the active components in the finished products [9].

In spite of its great importance and over 40 years of research, granulation process is still based on practical experience, i.e., there is a qualitative understanding of both the granule growth mechanisms and the effects of different variables on agglomeration phenomena. This constitutes a great problem for industries exploiting many and frequently changing formulations with widely varying properties (e.g., food, pharmaceuticals and agricultural chemicals). Thus, new formulations always need expensive and lengthy laboratory and pilot-scale testing. Moreover, even when pilot-scale testing is ok, there is still a significant failure rate during scale up to the industrial production [10]. Over the past decade, however, design, scale-up, and operation of granulation processes have been considered as quantitative engineering and significant advances have been made to quantify the granulation processes [3]. Firstly, granulation must be recognized as an example of “powder particle design”: granule final features are controlled by a perfect combination of formulation design, i.e., choice of the feed-material properties, and process design, i.e., choice of equipment type and operating conditions [11, 12]. The granule final properties are also determined by the interaction of phenomena coexisting in the granulation process simultaneously [1]: physical transformations of the powder particles with

relevant kinetic mechanisms (wetting and nucleation, consolidation and growth, and breakage and attrition) and aggregation rate are controlled by operating conditions and feeding material properties [3]. Therefore, for the quantitative analysis of the granulation process, both a careful characterization of the feed-material properties and knowledge of operating parameters and phenomenological aspects are needed [3, 13]. Basically, the granulation methods are divided into dry and wet ones. Dry granulation is based on the use of mechanical compression (slugs) or compaction (roller compaction), while the wet granulation exploits a granulation liquid phase called “binder” to agglomerate powder particles by formation of a wet mass by adhesion. This second process involves a final step of granules stabilization by removal of the wetting phase to make the relevant bonds permanent. Among these two techniques, wet granulation is the most widely used [2, 10, 14]. To produce granular structures with tailored features (in terms of size and size distribution, flowability, mechanical and release properties, etc...), a deep understanding of phenomena involved during granule formation is required. This can also lead to optimized processes in terms of production costs and other types of resources involved.

The purpose of this chapter is to emphasize the phenomenological aspects involved in the formation of the granules with respect to the main parameters of the wet granulation process. To this aim, experimental demonstrative campaigns of wet granulation runs were performed by changing several formulations and process parameters to detail the effect of each single parameter both on the granulation stages and on the obtained granular materials features. Mathematical modeling approaches’ description of granulation process was then presented. Usually, in literature, the approach to the granulation process is based on either experimental tests (to study granules properties) or on modeling studies. The novelty of this work is the integrated approach exploiting both experimental studies to understand the involved basic phenomena in powders aggregation, with the aim to optimize the process, and modeling aspects to verify and predict the experimental results.

2. Wet granulation process: apparatus and process parameters

2.1. Apparatus features

As briefly introduced, the wet granulation technique allows the formation of granules through the addition of a binding phase to a powder bed. It is usually performed in four steps: (1) homogenization of dry powders, (2) wetting by binder addition, (3) wet massing when liquid feeding system switches off, and (4) drying of the finished product [15]. The most common apparatuses used for granules production are: tumbling granulators, both batch and continuous low and high shear mixers, fluid bed granulators [16]. In tumbling granulators (including discs, drums, pans, and similar equipment), the particles motion is assured by the tumbling action caused by the balance between gravity and centrifugal forces. In particular, the powder feed is fed to the disc, typically at the edge of the rotating granular bed, and the binder is added through a series of nozzles distributed across the face of the bed. Discs and drums generally operate continuously and have large throughputs; thus, they are extensively used in

mineral processing and fertilizer granulation [17]. Low and high shear mixers are mechanically agitated containers that promote an efficient mixing, especially of cohesive materials. Such mixers exert intense local shear force actions on the powder, which break the small cohesive aggregates, promoting good dispersion of the liquid and effective consolidation of the product [15]. In fluid bed granulators, the powder bed is first fluidized by a flow of air injected upward through a distributor plate at the base of the granulator, and then the liquid binder is sprayed through a nozzle onto the fluidized bed to agglomerate powder in granules. When binder spraying is stopped, the granules continue to dry in the fluidizing airstream, avoiding the use of a following drying step [18]. This type of granulator is flexible, relatively easy to scale, difficult for cohesive powders, and good for coating applications [16]. Wet granulation has also witnessed various technical and technological innovations such as steam granulation, moist granulation, thermal adhesion granulation, melt granulation, freeze granulation, foamed binder granulation, and reverse wet granulation. For example, steam granulation exploits water steam as binder, providing a more rapid diffusion into the powder and a more favorable thermal balance during the drying step [14].

In general, three fundamental sets of rate processes determine wet granulation behavior: (1) wetting and nucleation, (2) consolidation and growth, (3) breakage and attrition (see schematization in **Figure 1**). Wetting/nucleation is the initial step where the liquid binder comes in contact with the dry powder bed causing the adhesion among particles to obtain a distribution of small aggregates (nuclei). During the consolidation and growth phase, the particles collide in the granulator and the nuclei begin to grow (particles increase in size and volume) for the deposition of additional material on the nuclei surface. Finally, attrition and breakage phase is characterized by the rupture of granules with relevant formation of small particles, due to both the impacts in the granulator and product handling. These mechanisms coexist in all the wet granulation processes, even if their importance is related to the process type. For example, in the fluid-bed granulation, the wetting phase prevails while in the high-shear

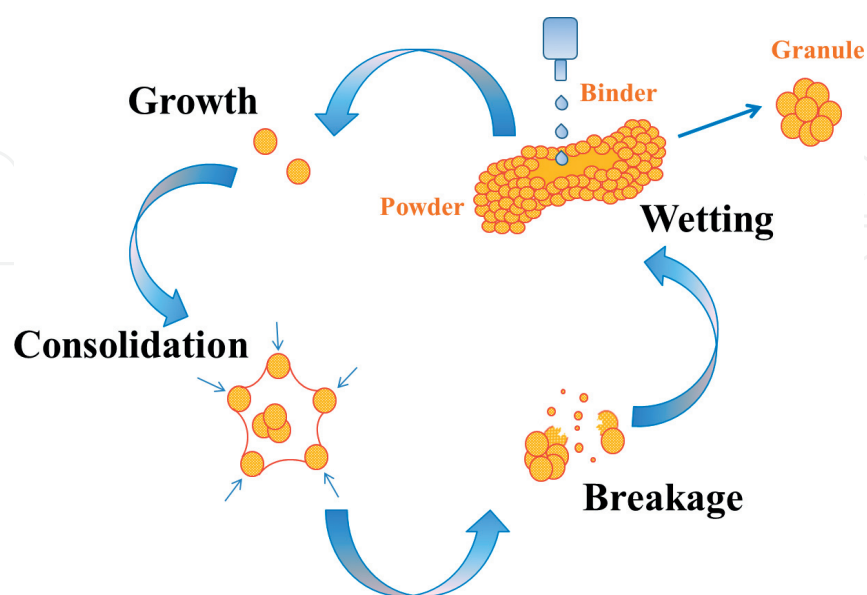


Figure 1. Mechanisms involved in wet granulation.

granulation, the consolidation step is predominant. To estimate what will be the characteristics of the granules, it is necessary to know that each of the phases presented has a fundamental role that must be predictable. In fact, once these processes have been analyzed, it is possible to predict, at least theoretically, the type of equipment and operating conditions to be used to obtain a good granulation [2].

2.2. Effect of process parameters

Several parameters can play a fundamental role on the basic mechanisms of wet granulation and therefore on the product final properties [19]. In particular, granule features depend on ingredients formulation (binder and powder properties and their interaction and proportion), process, and equipment parameters, these last two depending on the kind of the used apparatus. Thus, both material and operating variables together define the kinetic mechanisms and rate constants of wetting, growth, consolidation, and attrition [16].

2.2.1. Formulation parameters

2.2.1.1. Effect of binder addition rate

Due to the use of a liquid phase as binder, the ratio between the liquid and solid phases would affect the granule final properties [20]. If the liquid/solid ratio increases (due to a high amount of used liquid), nucleation is favored, but at the same time, it is possible that overwetting phenomena may occur, with consequent formation of a mixture and not granules. Moreover, as the quantity of the added liquid increases, the granule saturation, i.e., the ratio between the liquid volume and the interstitial granule volume, changes. However, the addition of too much liquid implies a larger granule size because of a high saturation; in the same way, a low saturation does not allow the granules to growth. The needed amount of liquid must be increased as the size of the powder particles decreases [19, 21–23].

2.2.1.2. Effect of binder delivery method

The addition of the wetting phase can take place in three different ways, i.e., by pouring, by spraying, or by making it melt, and it is closely linked to the nucleation regime, which has in turn a substantial effect on the product final features [24, 25]. A uniform liquid spray with small droplets size will have the greatest coverage throughout the powder bed and will prevent localized overwetting of the granules, which can result in oversized particles [16]. Moreover, both when pouring and when spraying, the particles size distribution (PSD) is initially bimodal and it tends to be unimodal for high granulation times [26]. In melting technique, however, the obtained granules will be less coarse and only for high granulation times a bimodal distribution will develop [19, 27].

2.2.1.3. Effect of binder properties

Binder viscosity and surface tension are the properties, which more influence the granulation process because the collision energy necessary to agglomerate particles depends on them [28–31]. In particular, a higher binder solution viscosity could lead to larger granule size and less needed

binder amount to start the granule growth in both high-shear [32, 33] and fluid-bed [34] granulation processes. This is due to the fact that a high liquid viscosity requires more energy to break up the liquid droplets (less binder spreadability); hence, larger droplets are formed, which consequently give larger granules. However, at too high viscosity, droplets will be unable to spread throughout the bed causing the reduction in collisions and relevant growth [35]. Surface tension and capillary forces always act to pull particles together, and their magnitudes depend on the liquid bridge formed between the particles [36]. Reducing binder surface tension causes the decrease in the capillary suction pressure and friction resistance, leading therefore to an improved wettability and spreading efficiency [10]. Moreover, also the solvent used for the formulation of the binder solution (only water, alcoholic, or hydroalcoholic solutions are usually used) could significantly change granule properties for its impact on binder wettability and spreadability [28].

2.2.1.4. Effect of powder particles' size and solubility

Powder particles' size influences the amount of binder to be used: a larger liquid amount is required to establish liquid bridges between the powders of lower size, thus with a high surface area [37, 38]. Moreover, the high surface area allows the availability of more contact points between colliding particles bringing as final result to stronger granules, which, however, have a more porous structure [10, 29, 30]. Perhaps the larger surface area allows also a higher growth tendency of the smaller particle fraction probably due to a more efficient nucleation and coalescence [39]. Moreover, a larger solubility of the solid excipient in the granulating solvent is able to decrease the solvent amount needed for granule formation, and granules with uniform particle size distribution and a reduced friability will be formed [28].

2.2.2. Equipment and process parameters

In general, equipment and process variables impact on mixing, agglomerating, and drying operations. For example, equipment variables in fluid bed granulators are related to the apparatus design with the aim to fluidize, thus granulate and dry the product. Therefore, air distribution plate must be appropriately designed depending on the powder properties. For example, a product with low bulk density will require a low fluidizing velocity, thus a distributor plate having a small open area. Moreover, a blower with appropriate pressure drop will fluidize the process material adequately. A proper use and cleaning of filters to retain entrained particles also must be carried out in fluidized bed [16]. However, for both mixers and fluid beds, the bowl geometry is also considered a factor with large impact on the agglomeration process. Moreover, for low and high shear mixers, the impeller and chopper design affects the flow patterns and powder flow dynamics in the bowl, by varying the volume of powder mixture swept out by the impeller itself: a high-swept volume provokes high densification of the agglomerates and narrow granule size distributions [40].

Process variables in fluid bed granulators agglomeration is highly dependent on: process inlet air temperature, atomization air pressure, fluidization air velocity and volume, liquid spray rate, nozzle position and number of spray heads, and product and exhaust air temperature [41]. Inlet-process air temperature depends on both the binder type and the heat sensitivity of

powder bed. For example, higher temperatures will cause binder faster evaporation with the relevant production of smaller and friable granules [42]. Process variables in high/low-shear mixers are essentially related to the impeller and chopper relative speed, granulating solution addition rate, both global granulation and wet-massing time [43]. In general, we can conclude that for all types of apparatuses, both equipment and process parameters define the two most important operating conditions in wet granulation process, i.e., mixing performance and residence time.

3. Inside wet granulation runs: experimental evidences

The impact that the aforementioned process parameters have on final granule properties is continuously studied to predict the final product quality. A possible approach to study the wet granulation process was that of a recent study conducted by [44], devoted to first planning experiments by the design of experiments (DoEs) and then to use the results to give correlations between product properties and process parameters. In particular, the central composite design (CCD) statistical protocol was applied for planning the experimental campaign about the production of hydroxypropyl methylcellulose (HPMC 20, Pentachem Srl, San Clemente RN-Italy) granules with distilled water as the binder phase and using a bench scale low-shear granulator apparatus. In brief, a given amount of HPMC 20 powder was placed in the low-shear granulator, and then the addition of the binder phase was carried out by spraying it by an ultrasonic device. The produced granulates were stabilized by dynamic drying, using hot air (65°C) for 1 h, collected, and then separated by a manual sieving with cut-off sizes as follows: 2 mm, 0.45 mm, and a metal collection pan. Three particles fractions were obtained: a fraction of “big scrap,” i.e., particles with size larger than 2 mm, a fraction of “small scrap,” i.e., particles with size smaller than 0.45 mm, and a fraction of “useful,” i.e., particles with size between 0.45–2 mm. The range size 0.45–2 mm was considered as the fraction of interest being a size typical range of commercial granulated food, pharmaceutical, and zootechnical products. Finally, only the fraction of useful was subjected to characterization protocols carried out by adopting the American Society for Testing and Materials (ASTM) standards.

Firstly, screening experiments were performed in order to determine the independent variables and their interactions playing a significant role on the dependent variables, i.e., on the final features of granulated product, such as granulation yield (defined as mass percentage of dry granules with size between 0.45 and 2 mm) and flowability properties (Carr Index, Hausner Ratio and Angle of Repose). The screening work showed that some parameters can be fixed, such as the powder mass (50 g) and the process time of 20 min (by observing that longer times caused granule-breaking phenomena). Instead, the impeller rotation speed, the binder volume at constant mass, and the binder flow rate were the parameters (factors) with larger influence on the final granule properties. The factors have a values limited range: high binder volume (greater than 100 ml) or high binder flow rate (greater than 58 ml/min) involved overwetting phenomena, low amounts of liquid (lesser than 50 ml) did not form granules, high impeller rotation speed (greater than 112 rpm) generated solid particulate breaking. At this point, for each factor, three intensities (levels) were used, i.e., the minimum, medium, and maximum

values, and combined by the CCD method. The performed runs have underlined that there are process operating conditions, which combined together can produce granules with size smaller than the requested one, i.e., failure of the aggregation phenomena (**Figure 2A**).

Others, instead, can achieve clusters of powder and binder, i.e., overwetting phenomena, that is a condition to avoid (**Figure 2C**). The best conditions of granulation, able to produce granules with a defined size (0.45–2 mm) and good flowability together with a high granulation process yield, were obtained by working with a high impeller rotation speed, i.e., 112 rpm, a high binder volume, i.e., 100 ml, and a low binder flow rate, i.e., 17 ml/min (**Figure 2B**). Then, semiempirical correlations between granule properties and process parameters were developed by describing the experimental data with several model equations. Akaike information criterion and R-square calculations showed that the best comparison between experimental data and model predicted values was attained by using the second-order polynomial equation. The proposed correlations were then validated by new granulation tests, not included in the work plan, underlining their ability to predict the granule final properties in terms of flowability and granulation yield. It is important to note that several studies in the literature describe the correlations between process parameters and granule properties; however, they use different apparatuses and final products (tablets). It was the first time that, for such similar granulation systems, semiempirical correlations were able to give the combined effect of impeller rotation speed, binder volume, and binder flow rate on granulation yield and flowability [44].

The found combination of process parameters (for granules better final properties) is thus used in the production of loaded granules, with the aim to evaluate the effect of two formulation variables, molecule solubility and binder type, on their physical, mechanical, and release properties. First of all, the best loading method for a hydrophilic molecule, vitamin B12, in HPMC granules was investigated. Vitamin B12 was incorporated in the HPMC granules by two different loading methods: according to the method 1, it was dissolved in the liquid binder phase (here, the binder was a solution of water and vitamin B12); according to the method 2, the vitamin B12 was premixed with HPMC powders at an impeller rotation rate of 78 rpm for 10 min. It was observed that the loading method did not have significant effects on either the

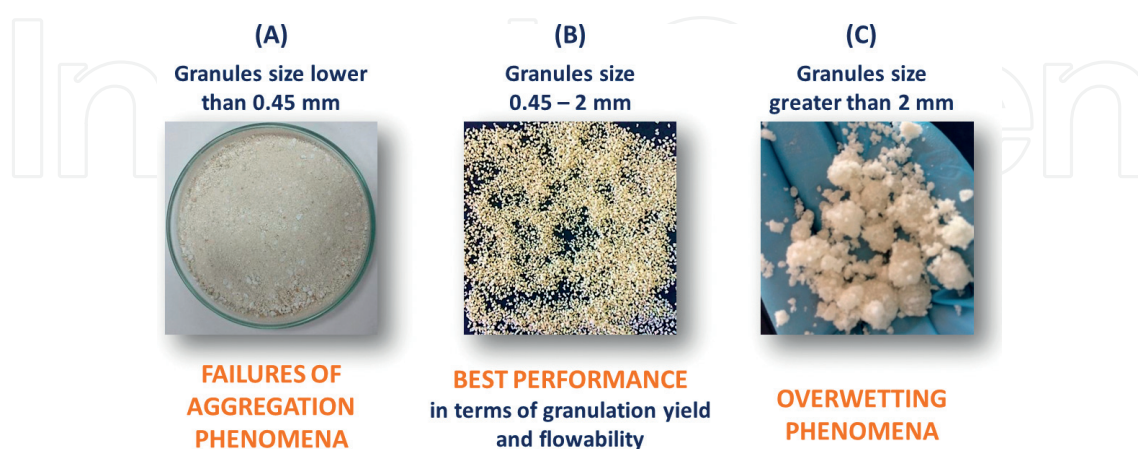


Figure 2. Granules obtained with different combination of factors and levels: (A) particles with size smaller than 0.45 mm, (B) particles with size between 0.45 and 2 mm, that is the size range required, and (C) particles with size larger than 2 mm.

granules flowability or the yield, but a better dispersion of vitamin B12 inside the HPMC polymer matrix was achieved by the method 1, perhaps thanks to the high solubility of this vitamin in the binder and the relevant uniform spray by the ultrasonic atomization device [45]. Thus, by exploiting the most successful method 1, three different payloads of B12 (1, 2.3, and 5% w/w) were tested. It was observed that a high vitamin load (5%) reduced the granulation yield and brought to the formation of more rigid granules if compared to unloaded ones and those loaded at 1 and 2.3% of B12. Vitamin release kinetics was slower when it was added with a 1% load, thus suggesting a better incorporation. Moreover, by comparing kinetics of fresh and 1 month-aged granules, they showed similar trends, thus no effect of the storage on release properties of loaded granules was observed [45].

Moreover, the effect of the incorporation of a lipophilic vitamin was also tested by using the loading method 1. Due to its lipophilic properties, a binder composed of a solution made by distilled water and ethanol was used. Results showed that the use of ethanol gave a reduced granulation yield and granules with less defined shape, smaller dimensions, more friable structure, worse flowability, and slightly faster polymer erosion. It was demonstrated that the molecule solubility did not affect either granules' physical or mechanical properties, but it had effect on the molecule release mechanism (diffusion for the hydrophilic molecule and erosion for the lipophilic one) [46].

A deep understanding of the phenomena involved during the wet granulation process can lead to optimized processes that obtain the maximum benefits without increasing the production costs. In light of that, studies on the evolution of particle size distribution (PSD) during the granulation process were performed by using an ad hoc dynamic image analysis (DIA) device, based on the free falling particle scheme of particles per unit of volume. It resulted evident that nucleation, agglomeration, and breakage phenomena occur simultaneously during all the process time [47], phenomena that therefore must be taken into account in the modeling approach.

4. Mathematical approach to describe the phenomena involved in granulation process

Mathematical modeling of the granulation process can play a dual role: can help to understand and to underline the observed physical phenomena and to predict properties (size and size distribution) of granular materials. It is important to note that the predictive ability is a powerful way to define suitable process conditions, which can minimize costs and optimize process yields, avoiding onerous experimental tests.

Modeling approaches mainly consist in three types:

- Empirical models: they are obtained from the regression of large set of experimental data, most of the time derived from the design of experiments statistic technique [44, 48, 49]. Empirical models have the advantages of being very simple (often polynomial equations), easy to obtain (regression of data), quite reliable within the investigated range. The drawback of this approach is that it is a black box approach: it provides very little (or none) information on the underlying mechanisms.

- Discrete element method (DEM) models: this is the most detailed type of mathematical model for particulate systems [50]. Thanks to mass and momentum balances on each particle of the powder bulk, DEM models aim to describe the evolution of the analyzed system. The advantage is that the description is very detailed (at a single particle level), but it is so computational power demanding that rarely it is applied to systems of more than hundreds of thousand particles. They are often used to obtain parameters useful for higher scale models [51].
- Population balance equation (PBE)-based models: the powder bulk is described as a population with a distribution of certain characteristics (internal coordinates i.e., size, binder content) that can vary in space (external coordinates) and time [52]. Therefore, the PBE-based models describe the evolution of the number of particles of a given characteristic in time and space [53]. The advantages of such an approach, with respect to DEM models, are enormous in terms of computational power requirement, despite the complexity of the involved equations (integro-differential). Nowadays, this is still the most used approach in modeling granulation processes and several numerical methods have been developed to “easily” solve the PBEs. Among them, the discretization of the PBEs (DPBEs) in classes (multiclass method) is the most used to describe the evolution of the distribution of the internal variables (i.e., size: particle size distribution) [54–58]. Less computational demanding methods, like the method of moment (which focus only on the moments of distributions), are preferred when the PBE has to be combined with computational fluid dynamics (CFD) models to describe the multiphase flow (i.e., the movements inside the granulator) [59].

4.1. Discretized population balance equations modeling

4.1.1. From the continuous to the discretized form of PBEs

In the following, a modeling approach based on the one-dimensional (one internal coordinate: particle size) discretized PBEs (DPBEs) will be shown. Such kind of models turns to be the best choice when dealing with granulation processes, being very descriptive, since the evolution of the entire size distribution is considered, including all the phenomena that cause variation of the particle size distribution, and computational efficient (with the modern computational power), which allows to integrate them in flow sheet models of entire processes.

Considering the entire granulator as control volume, the PBEs do not depend on spatial variables (external coordinates), and it can be written as [60]:

$$\begin{aligned}
 \frac{\partial n(v, t)}{\partial t} &= \frac{\dot{Q}_{in}}{V} n_{in}(v) - \frac{\dot{Q}_{out}}{V} n_{out}(v) - \frac{\partial[(G - A)n(v, t)]}{\partial v} \\
 &+ B_{Nuc}(v, t) + B_{Agg}(v, t) - D_{Agg}(v, t) + B_{Br}(v, t) - D_{Br}(v, t) I.C. \quad n(v, 0) \\
 &= n_0(v) B.C. \quad n(0, t) = 0
 \end{aligned} \tag{1}$$

where $n(v, t)$ is the probability density function [$b^{-1} x^{-1}$], with “b” basis of calculation that can be the total mass of powder [kg] or the total volume [m^3] and x the particle volume [m^3] or particle diameter [m], depending on the internal coordinate chosen. Indeed, this last v [x] can

be the particles volume v [m³] or the particles diameter l [m]. \dot{Q}_{in} and \dot{Q}_{out} are the flow rate of the inlet and outlet currents [b t⁻¹], V is the volume or mass in the granulator [b], and G and A are the growth as layering and the attrition [x t⁻¹], respectively. B_{Nuc} is the birth by nucleation [b⁻¹ x⁻¹ t⁻¹], which creates particles within the PSD of interest. B_{Agg} and D_{Agg} are the birth and death by agglomeration of particle of size v , and analogously B_{Br} and D_{Br} are the birth and death by breakage phenomena of particle of size v . Disregarding layering and the attrition phenomena, for a batch granulator:

$$\frac{\partial n(v, t)}{\partial t} = B_{Nuc}(v, t) + B_{Agg}(v, t) - D_{Agg}(v, t) + B_{Br}(v, t) - D_{Br}(v, t) \quad (2)$$

I.C. $n(v, 0) = n_0(v)$

The nucleation, agglomeration, and the breakage phenomena are described by the equations:

$$B_{Nuc}(v, t) = K\delta(v) \quad (3)$$

$$B_{Agg}(v, t) = \frac{1}{2} \int_0^v \beta(u, v-u) n(u, t) n(v-u, t) du \quad (4)$$

$$D_{Agg}(v, t) = \int_0^\infty \beta(u, v) n(u, t) n(v, t) du \quad (5)$$

$$B_{Br}(v, t) = \int_v^\infty b(u, v) S(u) n(u, t) du \quad (6)$$

$$D_{Br}(v, t) = S(v) n(v, t) \quad (7)$$

where K is a constant that multiply a function of the internal coordinate v (i.e., Dirac delta function). β is the coalescence kernel [b t⁻¹], which describes the frequency of collision between particles of internal coordinate u and v and the influence of the internal coordinates on the efficiency of agglomeration. On the other hand, b is the breakage function [x⁻¹], which describes the probability of formation of particles of internal coordinates v from the collision and breakage of particles of internal coordinates u ($u > v$). S is a selection function [t⁻¹], which describes the frequency at which particles of a given internal coordinates are broken.

To solve Eq. (2), a numerical method has to be used: the class methods of zero order [61],

$$N_i = \int_{v'_i}^{v'_{i+1}} n(v) dv = n_i(v'_{i+1} - v'_i) \quad (8)$$

where N_i is the number of particles per unit base [b⁻¹] within a class with size range $[v'_i, v'_{i+1}]$. The characteristic size of each class is v_i : $v'_i \leq v_i \leq v'_{i+1}$. With this approach, instead of solving for a continuous (particle size) distribution, a system of ordinary differential equations (ODEs) is generated to describe the evolution of the number of particles within the classes. Increasing the number of classes, the number of ODEs increases as well as the computational power requirements: the most used discretization uses a geometric progression with common ratio $v'_{i+1}/v'_i = 2^{1/q}$ (or equivalently $l'_{i+1}/l'_i = \sqrt[q]{2}$), where q is an integer ≥ 1 .

4.1.2. Modeling the agglomeration phenomena

The most used discretized form of the agglomeration phenomena is the one proposed by Hounslow et al. [55] ($v'_{i+1}/v'_i = 2$), updated by Litster et al. [62] to consider geometric progression with $q \geq 1$ ($v'_{i+1}/v'_i = 2^{1/q}$). The described agglomeration phenomenon is binary (interaction between two particles), and the birth terms are due to the collisions and coalescence between particles of lower dimensions with respect to the considered class. The death terms account for the interactions and coalescence of particles belonging to the considered class, producing their disappearance (and their birth in upper classes).

$$\begin{aligned}
 B_{Agg_i}(t) - D_{Agg_i}(t) = & \sum_{j=1}^{i-S(q)-1} \frac{2^{\frac{j-i+1}{q}}}{2^{\frac{1}{q}} - 1} \beta(i-1, j) N_{i-1} N_j + \\
 & + \sum_{k=2}^q \sum_{j=i-S(q-k+2)-k+1}^{i-S(q-k+1)-k} \frac{2^{\frac{j-i+1}{q}} - 1 + 2^{\frac{-k+1}{q}}}{2^{\frac{1}{q}} - 1} \beta(i-k, j) N_{i-1} N_j + \\
 & + 0.5 \beta(i-q, i-q) N_{i-q}^2 + \\
 & + \sum_{k=2}^q \sum_{j=i-S(q-k+2)-k+2}^{i-S(q-k+1)-k+1} \frac{2^{\frac{j-i}{q}} - 2^{\frac{-k+1}{q}} + 2^{\frac{1}{q}}}{2^{\frac{1}{q}} - 1} \beta(i-k+1, j) N_{i-k+1} N_j + \\
 & - \sum_{j=1}^{i-S(q)} \frac{2^{\frac{j-i}{q}}}{2^{\frac{1}{q}} - 1} \beta(i, j) N_i N_j - \sum_{j=1-S(q)+1}^h \beta(i, j) N_i N_j
 \end{aligned} \tag{9}$$

where $S(q) = \sum_{p=1}^q p$. For $q = 1$, the Hounslow discretization can be obtained.

4.1.2.1. The kernel of coalescence

The coalescence kernel is the most important parameter when describing granulation processes. A body of literature is present on this kernel, proposing several expressions ranging from purely empirical, semiempirical, and model-based kernels. In general, the coalescence kernel is split into two parts:

$$\beta(u, v, t) = \beta_0(t) \beta(u, v) \tag{10}$$

where the first is the “aggregation rate” term and the latter describes the dependence of the coalescence kernel on the dimensions of the granules. In the first term, various system parameters are incorporated (i.e., granulator geometry, operating conditions, formulation properties, etc.).

The nature of $\beta(u, v)$, most of the time an homogeneous function, establishes how the agglomeration modify the internal coordinate, in particular whether or not the transformation is self-preserving in PSD and whether or not a gelling behavior should be expected. Analyzing the

degree of homogeneity λ ($\beta(cu, cv) = c^\lambda \beta(u, v)$), which expresses the strength of the dependence of $\beta(u, v)$ on its argument, it is possible to distinguish between nongelling and leading to a self-preserving size distribution kernels ($\lambda \leq 1$) and gelling (and non-self-preserving PSD) kernels ($\lambda > 1$) [46]. **The most used kernel in literature is the equikinetic energy (EKE) kernel, which is a nongelling** and leading to a self-preserving size distribution kernels, as it can be seen from **Table 1**. In **Figure 3**, the (normalized) EKE kernel is reported: as it can be seen the maximum probability of coalescence in a binary process is between a big particle (high classes) and a small particle (low classes).

4.1.3. Modeling the breakage phenomena

The discretized form of the breakage phenomena can be obtained by substituting continuous with discrete functions and by using Eq. (8):

$$B_{Bri}(t) - D_{Bri}(t) = \sum_{j=i+1}^{\infty} b(v_i, v_j) S(v_j) N_j \Delta v'_j - S_i N_i \quad (11)$$

However, as suggested in Vanni [63], to satisfy the mass conservation (valid for both agglomeration and breakage), for all the possible discretizations (i.e., for a geometric progression of the type $v'_{i+1}/v'_i = 2^{1/q}$), the equation has to be corrected:

$$B_{Bri}(t) - D_{Bri}(t) = \sum_{j=i+1}^{\infty} \Gamma_{i,j} S_j N_j C_j^{(1)} - C_i^{(2)} S_i N_i \quad (12)$$

where

$$C_i^{(1)} = \frac{v_i}{\sum_{j=1}^{i-1} v_j \Gamma_{ji}} C_i^{(2)} \quad (13)$$

$$C_i^{(2)} = 1 - \frac{1}{v'_{i+1} - v'_i} \int_{v'_i}^{v'_{i+1}} \left[\int_v^{v'_{i+1}} b(v, q) dq \right] dv \quad (14)$$

Kernel	Equation	λ
Constant kernel	$\beta(u, v) = 1$	0
Sum kernel	$\beta(u, v) = u + v$	1
Product kernel	$\beta(u, v) = u v$	2
Coagulation kernel	$\beta(u, v) = u^{\frac{2}{3}} + v^{\frac{2}{3}}$	2/3
Equikinetic energy kernel	$\beta(u, v) = \left(u^{\frac{1}{3}} + v^{\frac{1}{3}} \right)^2 \sqrt{\frac{1}{u} + \frac{1}{v}}$	1/6

Table 1. Examples of coalescence kernels and degrees of homogeneity.

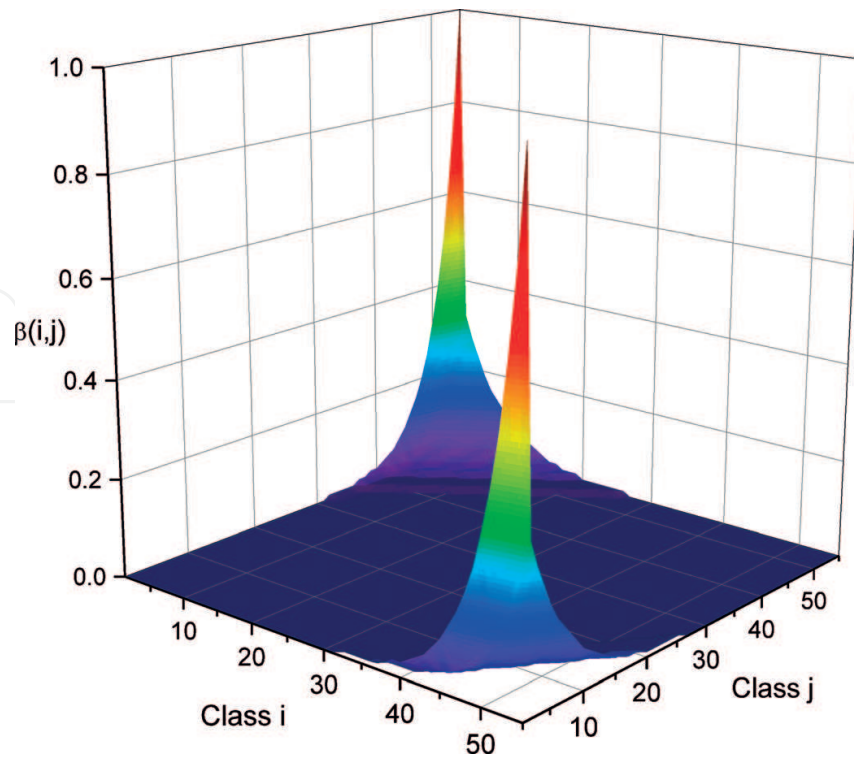


Figure 3. Equikinetic energy coalescence kernel.

$$\Gamma_{ij} = \int_{v'_i}^{v'_{i+1}} b(v_i, v_j) dv \quad (15)$$

with $C_1^{(2)} = 0$ and v_i the characteristic size x of the class in volume [m^3]. In case the distribution density function has been obtained ($n(l, t)$) and discretized ($N_i = n_i(l'_{i+1} - l'_i)$) with the diameter l_i as characteristic size, the relation $v_i \sim l_i^3$ can be used to adapt Eqs. (13), (14), and (15).

4.1.3.1. The selection and breakage function

Several functions can be chosen for the selection function and breakage function (continuous or discrete), usually of semiempirical nature: the breakage theory is not well developed as the agglomeration theory [63].

An example of selection function can be the power law form: $S_i = kv_i^\gamma$, where k and γ ($1/3 \leq \gamma \leq 2$) are adjustable parameters.

A flexible form of the breakage function is the parabolic form:

$$b(v_i, v_j) = \frac{C}{v_j - 1} + \left(1 - \frac{C}{2}\right) \left[\frac{8(3v_i^2 - 3v_i + 1)}{(v_j - 1)^3} - \frac{12(2v_i - 1)}{(v_j - 1)^2} + \frac{6}{v_j - 1} \right] \quad (16)$$

that, depending on C , can simulate different behaviors: concave parabola ($0 \leq C < 2$), it is more likely the formation of unequal fragments, convex parabola ($2 < C < 3$), it is more likely

the formation of equal fragments, and uniform distribution ($C = 2$), in which it is equally likely to form a child particle of any size.

4.1.4. Modeling the nucleation phenomenon

Nucleation phenomenon occurs because small particles lower than the considered minimum size class can suddenly form granules (i.e., due to the action of binder droplets) within the considered size range. In light of this, it is clear that nucleation is not a mass conservative mechanism. It can be modeled as:

$$B_{Nuc_i}(t) = k(t)f(i) \quad (17)$$

where $k(t)$ is a function of time, describing for how long this phenomenon is present. $f(i)$ is a function of the size class and it individuates the class interested by nucleation.

4.1.5. Model results

The resulting DPBE is a system of ordinary differential equations:

$$\begin{aligned} \frac{dN_i}{dt} &= B_{Agg_i}(t) - D_{Agg_i}(t) + B_{Bri}(t) - D_{Bri}(t) + B_{Nuc_i}(t) \\ I.C.N_i(0) &= N_{i0}, \end{aligned} \quad (18)$$

which can be solved numerically with the well-known discretization techniques (i.e., explicit Runge-Kutta). The results give the evolution of N_i during the granulation process, allowing to follow the (discretized) particles size distribution (**Figure 4**).

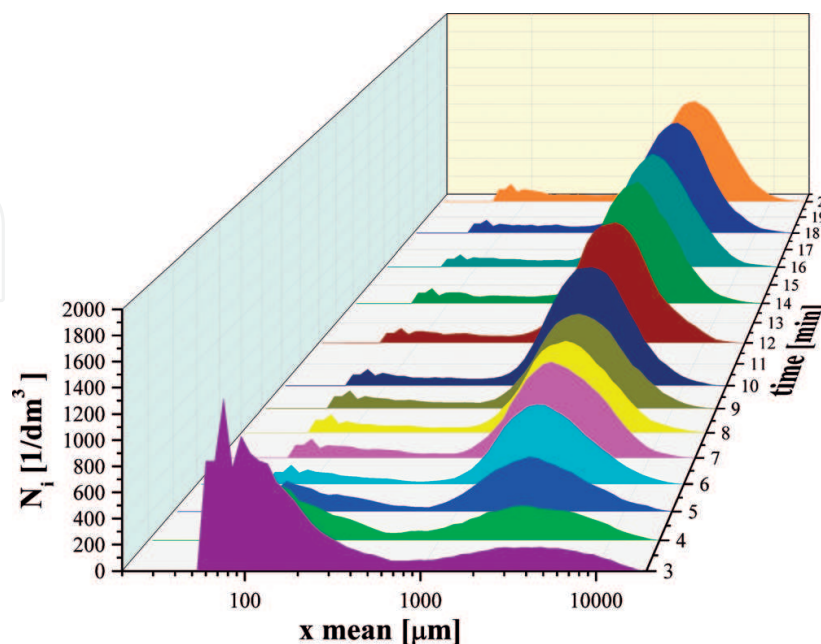


Figure 4. Time evolution of the PSD in terms of number of particle per unit volume N_i (impeller rotation speed of 93 rpm and liquid binder flow rate of 17 ml/min).

The agglomeration process leads to the lowering and translation toward higher dimension of the PSD, because the particles diminish in number increasing their size. On the contrary, breakage phenomena lead to an increase of the number of particles per unit volume, with a translation toward lower dimensions of the PSD. Finally, nucleation locally increases the number of particles per unit volume.

5. Conclusions

Granular materials represent a relevant form of commercial products on the worldwide market. A rational organization of manufacturing, based on phenomenological knowledge rather than practical trials, can allow high granulation performance in terms of yields, product features, and manufacturing costs.

In this chapter, wet granulation process is described presenting the role of several factors, such as apparatus features, formulation, and operative parameters on granules final features.

Experimental campaigns of wet granulation runs, performed by using a low-shear granulator, changing several formulation and process parameters, have been performed to detail each single parameter effect both on the granulation stages and on the obtained granular materials features.

Mathematical modeling approaches of the granulation process have been thus introduced with the aim both to understand and underline the observed physical phenomena, and to propose predictive tools able to forecast granulation results in terms of size and size distribution of obtained granular materials. The predictive ability is a powerful way to define suitable process conditions, which can minimize costs and optimize process yields, avoiding onerous experimental tests. In this work, particular attention was given to models based on population balance equations (PBEs), for which appropriate mathematical descriptive functions have been presented.

Conflict of interest

The authors declare that they have no conflict of interests.

Abbreviations

ASTM	American society for testing and materials
CCD	central composite design
CFD	computational fluid dynamics

DEM	discrete element method
DIA	dynamic image analysis
DoE	design of experiments
DPBE	discretized population balance equation
EKE	equi kinetic energy
HPMC	hydroxypropyl methylcellulose
ODE	ordinary differential equation
PBE	population balance equation
PSD	particle size distribution
Symbols	
β	coalescence kernel
A	attrition
b	breakage function
B_{Agg}	birth by agglomeration phenomena of particle of size v
B_{Nuc}	birth by nucleation phenomena
B_{Br}	birth by breakage phenomena of particle of size v
D_{Br}	death by breakage phenomena of particle of size v
D_{Agg}	death by agglomeration phenomena of particle of size v
G	growth as layering
K	constant that multiply a function of the internal coordinate v
n	probability density function
N_i	number of particles for class “i” per unit of volume of solid
q	integer ≥ 1
\dot{Q}_{in}	flow rate of the inlet currents
\dot{Q}_{out}	flow rate of the outlet currents
S	selection function
v	internal coordinate (particle volume or particle diameter)
V	volume or mass in the granulator

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