Expert Opinion

informa
healthcare

Spray granulation for drug formulation

Zhi Hui Loh, Dawn ZL Er, Lai Wah Chan, Celine V Liew & Paul WS Heng[†]
[†]*National University of Singapore, Department of Pharmacy, Faculty of Science, Singapore*

Introduction: Granulation is a key unit process in the production of pharmaceutical solid dosage forms and involves the agglomeration of fine particles with the aid of a binding agent. Fluidized bed granulation, a classic example of spray granulation, is a technique of particle agglomeration brought about by the spray addition of the binding liquid onto a stationary bed of powder particles that is transformed to a fluid-like state by the passage of air through it.

Areas covered: The basic working principles, equipment set-up, advantages and challenges of fluidized bed granulation are introduced in this review. This is followed by an overview of the formulation and process-related variables affecting granulation performance. Technological advances, particularly in the application of process analytical tools, in the field of fluidized bed granulation research are also discussed.

Expert opinion: Fluidized bed granulation is a popular technique for pharmaceutical production, as it is a highly economical and efficient one-pot process. The research and development of process analytical technologies (PAT) has allowed greater process understanding and control to be achieved, even for the lesser known fluidized bed techniques, such as bottom spray and fluidized hot melt granulation. In view of its consistent mixing, as well as continuous and concurrent wetting and drying occurring throughout processing, fluidized bed granulation shows great potential for continuous production although more research is required to fully implement, validate and integrate the PAT tools in a production line.

Keywords: fluidized bed granulation, granulation, pharmaceutical manufacturing, process analytical technology, solid dosage forms

Expert Opin. Drug Deliv. (2011) 8(12):1645-1661

1. Introduction

The production of pharmaceutical dosage forms is a complex multi-stage process involving numerous unit operations. Granulation, one of the key operations, is a size-enlargement process where small particles are gathered into larger masses with the aid of a binding agent added either in liquid or solid form. The product formed is termed granules and they often possess desirable size and microstructural characteristics. Granules are polydisperse and typically fall within the size range of 0.1 – 3 mm [1]. In most cases, granules are intermediate products and are used subsequently for the production of tablets or caplets. The active ingredient may first be granulated on its own and then blended with other excipients prior to tablet compaction or capsule filling. Alternatively, the active ingredient may be co-granulated with most or all of the excipients. Granules may also be subsequently coated and filled into capsules [2].

Granules are more desirable than fine powders as granulated powders resist segregation, flow better and ensure that granules flow well through chutes and hoppers into tablet dies without significant variation in weight. Dust is reduced and this

10.1517/17425247.2011.610304 ISSN 1742-5247

Article highlights.

- Fluidized bed granulation is a technique of particle agglomeration brought about by the spray addition of a binding liquid onto a bed of powder particles that is transformed to a fluid-like state by the passage of air through it. It can be considered a 'one-pot process' with dry mixing, wet massing and drying all integrated in a single unit.
- As the efficiency of mixing and fluidization in a fluidized bed process is highly dependent on the nature and characteristics of the powder particles, the fluidized bed granulation process is inherently more sensitive to the properties of the starting materials than other commonly known techniques of wet granulation such as high shear granulation.
- The outcome of fluidized bed granulation is affected by myriad material and process-related variables. The complex interplay amongst these variables affect the droplet size of the binding liquid and powder bed humidity both of which are recognized as critical scaling parameters that should be maintained during the process scale-up.
- Recent advances in fluidized bed granulation include the application of chemometric and numerical simulation tools to model agglomerate growth at a microscopic level as well as the adoption of continuous or semi-continuous granulation strategies to mitigate scale-up problems.
- The adoption of process analytical technologies (PAT) in fluidized bed granulation include the application of near infrared (NIR) and Raman spectroscopic techniques for real-time monitoring of the moisture content of the powder bed at different stages of the fluidized bed process, agglomerate growth and attrition, changes in material distribution with time as well as solid state transformations of active principles and excipients.

This box summarizes key points contained in the article.

minimizes material losses and the handling hazards of toxic materials. The increase in bulk density of powders after granulation renders storage and transport more convenient. The compaction characteristics and appearance of granulated powders are also improved compared with fine powders [3]. Granules are more easily compacted and produce stronger tablets due to the presence of well-distributed binding agents within the granular structure.

Modified release granules may also be produced. Researchers have shown that controlled release of drugs such as theophylline, ibuprofen, ketoprofen and paracetamol from tablet matrices may be achieved by granulating these drugs with various polymeric excipients [4-7]. Promising results have similarly been obtained in studies on rapid release granules, with reports on the enhancement in dissolution of poorly aqueous soluble or hydrophobic drugs such as ibuprofen, naproxen, ketoprofen, indomethacin, testosterone, phenacetin and progesterone after granulation [8-10]. In addition to formulation development, the advent of novel granulation techniques such as steam granulation [11], melt granulation [12-15] and ultrasonic spray congealing [16] for the preparation of rapid release granules have also gained considerable attention in recent years.

Several manufacturing techniques are used for producing granules, and they can be broadly classified into dry and wet granulation processes. In dry granulation, the binding agents are incorporated in solid form and the resultant powder mixtures are agglomerated by mechanical force. Granule formation is reliant on interparticulate bond formation between primary particles and this reduces the need for wetting agents such as water or organic solvents [17]. Hence, this process is useful for the granulation of moisture or heat sensitive drugs. Furthermore, as drying is no longer required, significant savings in cost and process time may be achieved. Typical dry granulation processes include slugging and roller compaction, of which the latter is more widely studied.

In wet granulation, primary powder particles are agglomerated using a granulating liquid. The binding agent may either be incorporated in the granulating liquid forming what is commonly termed as a 'binding liquid', or as solid particles forming part of the feed material. Compared with dry granulation processes, wet granulation provides better control of drug content uniformity, product bulk density and compactibility [18]. The main deterrent to the adoption of wet granulation processes is that they are relatively more complicated and costly. This is because of the increased demands for labor, time, equipment, energy and space. The additional steps involved in the preparation of the binding liquid and drying of granules add complexity during process validation and control [19]. Furthermore, the stability of moisture and heat sensitive drugs may be affected by wet granulation. Wet granulation of pharmaceutical formulations comprising significant proportions of hydrophobic drugs will conceivably pose a major challenge due to the inferior wetting characteristics of these compounds. This represents an important area in granulation research in view of the marked hydrophobicities of new chemical entities coming through the drug discovery pipeline. In view of this, investigations into the granulation of hydrophobic formulations have intensified in recent years. Hapgood and co-workers have conducted extensive investigations on the high shear wet granulation of model hydrophobic materials that included glass beads and pharmaceutical active principles such as salicylic acid and 2-ethoxybenzamide. They observed that nucleation and granule growth occurred via solid spreading during which the hydrophobic particles coated or encapsulated droplets of aqueous binding liquid, forming liquid marbles that eventually dried to form hollow granules with interesting microstructural characteristics [20,21]. In spite of these challenges, there remains widespread use of wet granulation in the pharmaceutical industry in view of its attractive offerings and advances in equipment design and technology.

Some common examples of wet granulation processes include wet massing, high shear granulation, pan granulation, extrusion-spheronization and fluidized bed granulation. Spray

granulation describes a specific technique of wet granulation and involves the spraying of the granulating/binding liquid onto primary powder particles as they are agitated in a mixing device. Spray granulation is exemplified by the fluidized bed granulation technique which constitutes the focus of this review.

2. Fluidized bed granulation as a technique of spray granulation

Fluidized bed technology dates as far back as the 1920s when it was first employed in the chemical industry. In the 1940s, this technology was adopted by the pharmaceutical industry and since its successful implementation for pharmaceutical coating by Wurster [22], this air suspension technique became widely used for drying and granulation processes. In this method of granulation, a bed of powder particles, supported over a fluid distribution plate, is made to behave like a liquid by the passage of a fluid, typically air, at a flow rate above a critical value. The phenomenon of imparting the properties of this fluid to the bed of particulate solids by passing the fluid through the latter at a velocity which brings the stationary bed to its loosest possible state just before its transformation into a fluid-like state is termed fluidization [23].

There are several key components to a fluidized bed processor (**Figure 1**). These include a control system, air handling unit, product chamber, air expansion chamber, exhaust filters, exhaust blower, air distribution plate, spray nozzle and lastly, a delivery system for the binding liquid [24]. During granulation, the powder particles circulate within the product chamber and provide a constant flow of particles through a defined spray granulation zone. At the spray granulation zone, a fine spray of the binding liquid is usually atomized and deposited onto the fluidized particles. Particle wetting brings about granule formation. Partial drying of the wetted particles by the fluidizing air occurs continuously during granulation. When the required amount of binding liquid has been sprayed, rapid drying of the granules in the hot air stream occurs and complete drying is often achieved.

Several types of spray nozzle systems are available for use in the fluidized bed processor. They include the hydraulic, ultrasonic and air atomizing/two-fluid nozzle systems. The two-fluid nozzle system, where the binding liquid is atomized by compressed air, is most popular as it is capable of functioning at very slow liquid flow rates [25] and allows the control of droplet size independently of flow rate. Although the effect of spray drying is more pronounced with this nozzle type, it is not a severe problem when aqueous granulating liquids are employed. Fluidized bed granulation processes may further be classified according to the orientation of the spray nozzle. The orientation determines not only the spray pattern of the binding liquid, but also the impingement and subsequent spread of the sprayed droplets on the powder particles. Consequently, this will exert an impact on the characteristics of the granules formed.

The different orientations of the spray nozzle include:

Top-spray: Top-spray granulation is one of the most recognized and well-studied technique of fluidized bed granulation since the 1960s [26]. As depicted in **Figure 2A**, the spray nozzle is positioned at the top of the product chamber and the binding liquid is sprayed onto the fluidized solid particles, counter-current to the airflow. Granules produced from top-spray granulation are characterized by low bulk density and porous surfaces that promote wicking of liquid into the interstitial voids of the granules, thereby promoting their dispersion and disintegration [27].

Tangential-spray: The tangential-spray technique was conceived for producing denser granules than typically possible in fluidized bed granulation [28]. The spray nozzle is introduced at the side of the product chamber and is embedded in the powder bed during processing (**Figure 2B**). More commonly known as rotary processing, this rotating plate granulator combines centrifugal, high intensity mixing with the efficiency of fluidized bed drying [29]. The rotating plate of the granulator provides a centrifugal force, which forces the particles toward the wall of the processing chamber at the periphery of the product chamber. The fluidizing air, introduced via a slit, provides a vertical force that lifts the particles upward before gravitational force causes particles to fall down onto the disc [30]. As the granules formed are spherical, denser and less porous than granules produced from the top-spray technique, rotary processing is suitable for producing granules that are to be coated [31].

Bottom-spray: In this configuration, the spray nozzle is positioned in the middle of the air distribution plate at the base of the product chamber (**Figure 2C**). A partition column is frequently installed and its presence regulates the fluidization and flow of particles into the spray granulation zone [32]. The binding liquid is sprayed in the same direction as the airflow. Essentially employed for coating purposes and less so for granulation [33], there were few reports on its use for pharmaceutical granulation in the 1990s [34,35]. Nonetheless, interest remains among some researchers [36,37] in the use of the bottom-spray technique for granulation. The development of improved bottom-spray processors in recent years [38] also provided new impetus for this granulation technique.

3. Advantages and challenges of fluidized bed granulation

Fluidized bed granulation is an efficient and convenient process, offering many advantages over the multistage process of conventional wet granulation [26]. As the powders can be mixed, granulated and dried *in situ*, product transfers and cross-contamination are minimized and these factors greatly simplify the process. In addition, the fluidized bed enhances heat and mass transfer between the fluidizing air and solid particles, leading to uniform temperature distribution within the product bed and relatively short processing times [39]. High process yields of 97 – 100% w/w with less than 1%

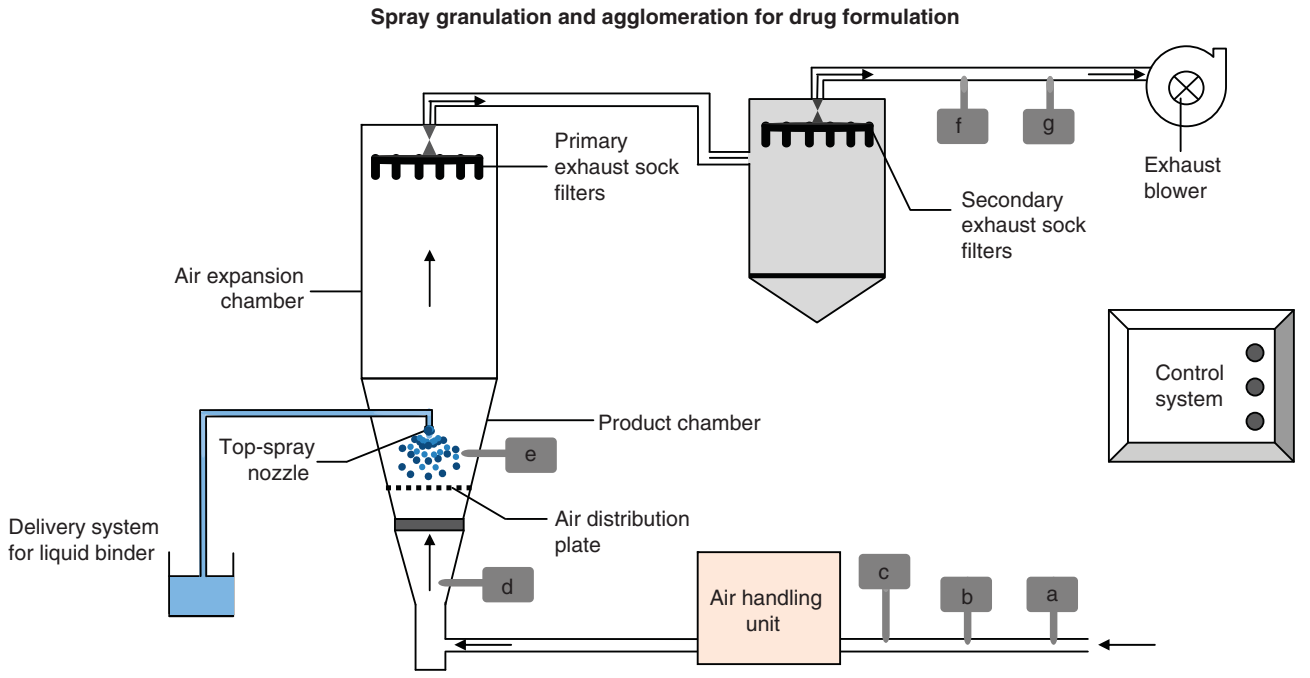

Figure 1. Diagram of a MP-1 air handling system showing the parts and locations at which the following process parameters were measured: (a) ambient temperature, (b) inlet air relative humidity, (c) airflow rate, (d) inlet air temperature, (e) granule bed temperature, (f) outlet air relative humidity and (g) outlet air temperature. Arrows indicate the direction of airflow.

w/w fines and 3% w/w lumps can be attained [40]. In comparison with high shear granulation, another popular wet granulation process, the size distribution of granules produced from the fluidized bed technique is often narrower, with the absence of oversized granules. This reduces the need for regranulation and accelerates drying. Fluidized bed granules have also been reported to be more porous, less dense and more compressible than granules produced from high shear wet granulation [41-44].

The type of filler material was reported to have a more pronounced effect on the properties of granules produced in the conventional fluidized bed granulator than in the rotary processor [45]. It has also been shown that a wider range of feed material could be tolerated in rotary processing [46] and high shear granulation [47] as compared with the fluidized bed process.

The optimal particle size for fluidization ranges from 50 to 2000 µm. For fine particles less than 50 µm and particles which are not amenable to fluidization when moistened, vibratory forces have to be applied to the powder bed, increasing equipment, cleaning and maintenance costs [48]. The critical size limit below which common pharmaceutical powders cannot be discretely processed is approximately 20 µm. Below this limit, steady fluidization without any retardation is difficult as indicated by Geldart's fluidization map [49]. Processing powder mixtures comprising components of vastly different densities poses yet another challenge, as disparities in fluidization behavior of the different formulation components may result in bed segregation and non-uniform mixing. Apart from powder properties, the spreading ability of the droplets of the binding liquid in the powder bed is also critical in fluidized bed granulation, as unlike other wet granulation processes, distribution of liquid is unaided by mechanical forces. As such, agglomeration in the fluidized bed process is highly dependent on the phenomenon of liquid spreading [50].

Evidently, fluidized bed granulation is an intricate process and apart from material-related factors such as the nature and characteristics of the ingredients in the formulation, process factors related to the granulation and drying stages of the process also influence process outcomes. These factors are elucidated in the following sections.

4. Material and process-related factors influencing fluidized bed granulation

4.1 Material-related factors

Wetting properties of solid particles: As aforementioned, wetting of the solid particles by the binding liquid is important for it affects the initial formation of liquid bonds between the particles and subsequent agglomerate growth. The feed powder must possess reasonably good wetting properties in order to ensure uniform distribution of the binding liquid. In fluidized bed granulation, the initial spreading of the binding liquid in the powder bed is very crucial [50]. This is attributed to the presence of relatively low shear forces during processing which largely restricts particle densification, saturation level of liquid

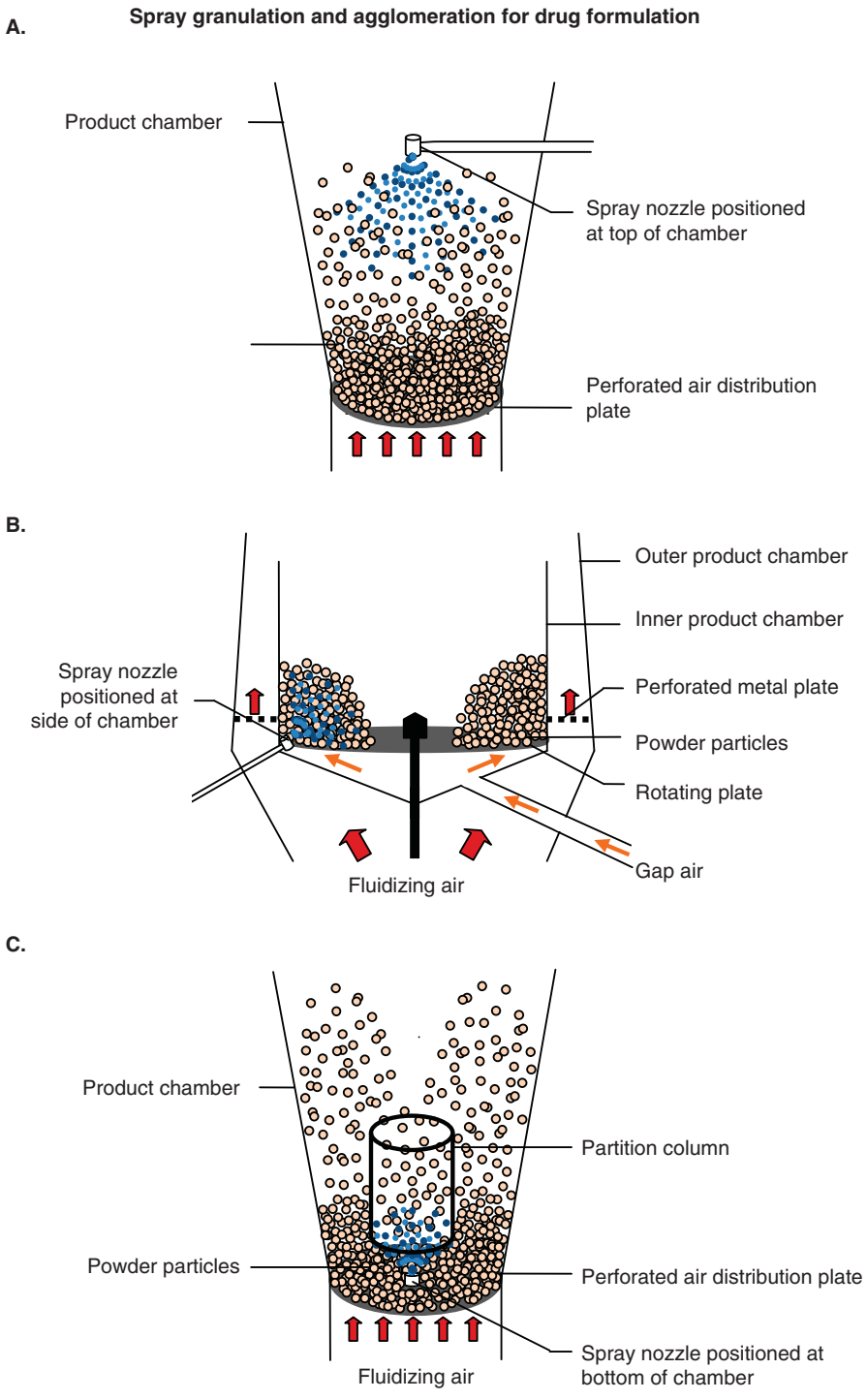

Figure 2. Schematic diagrams of (A) top-spray granulator, **(B)** tangential-spray granulator: double chamber rotary processor and **(C)** bottom-spray granulator. Arrows represent the direction of airflow.

in the agglomerates and consequently, granule growth by coalescence. It has been emphasized by several groups of researchers that wetting of the powder by the binding liquid critically determines the size distribution of resultant granules. In the studies by Pont and co-workers [51,52] where glass beads and sand particles of varying hydrophobicities were granulated using 1 – 3% w/w sodium carboxymethylcellulose solution as the binder, it was shown that granule growth was favored with a decrease in contact angle between the particles and binding liquid. It was also reported elsewhere that

mechanically stronger lactose granules of lower porosities were formed when the adhesion tension of hydroxypropylcellulose solution, employed as the binding liquid, was increased [53]. The spreading coefficients of binding liquids containing dissolved hydroxypropylmethylcellulose or polyvinylpyrrolidone over pentoxyphylline, acyclovir or lactose particles were similarly observed to be in good correlation with the friability of the resultant granules [54].

Solubility of powder particles: The solubility of powder particles in the binding liquid also affects resultant granule properties. It has been observed in early studies by Wan and Lim [55] that surface dissolution of lactose followed by its recrystallization during drying reinforced the mechanical strength of the granules as the recrystallized lactose was proposed to behave as a secondary binding agent. Similar results were obtained by Danjo and co-workers [53], where an increase in hardness and decrease in pore volume of granules was observed when the solubility of lactose particles in the solvent used to prepare the binding liquid was increased. These findings are echoed in another study by Rohera and Zahir [56] where lactose, alone or in combination with microcrystalline cellulose, were granulated with polyvinylpyrrolidone, acacia and gelatin as binding agents. It was noted that the partial dissolution of excipients in the granulating liquid was desirable for granule growth and contributed significantly to the size distribution of resultant granules.

Type, load and micromeritic properties of powder: The type and load of powder also influenced granulation outcomes. A larger load to binding agent ratio reduced the extent of particle wetting and resulted in the production of smaller-sized granules [57,58]. Using population balance modeling, the different deformation behaviors of lactose and cornstarch were reported to affect granule coalescence and kinetics of agglomeration [59]. At a microscopic level, the size, shape and roughness of particles critically affect resultant granule properties. Interestingly, in the study by Hemati and co-workers [52] where sand particles were wet granulated with either a solution of sodium chloride or carboxymethylcellulose used at 1% w/w, a decrease in the mean primary particle size increased agglomerate growth rate. When the mean size of the particles exceeded 350 μm, agglomerate growth proceeded predominantly by layering. It was further concluded that there was greater surface area for interparticulate contact between irregularly shaped sand particles as compared with spherical glass beads and this contributed to differing kinetics of agglomerate growth between the two types of primary particles. Using numerical simulations, the particle surface roughness of four commonly used pharmaceutical excipients (mannitol, lactose, microcrystalline cellulose and calcium phosphate) were reported to exert a strong influence on the distribution and more critically, the availability of binder on granule surfaces. The latter contributed to disparities in granulation kinetics amongst the four test materials under identical processing conditions [60].

Properties of binding agent: Apart from the filler, the properties of the binding agent also play an important role. Powder mixtures comprising lactose, starch, microcrystalline cellulose and microfine cellulose were granulated using 9% w/w aqueous solutions of polyvinylpyrrolidone K90, pregelatinized starch or gelatin. Amongst the three types of granules, those prepared using polyvinylpyrrolidone K30 were observed to possess the lowest friability [61]. To reiterate the findings of the study by Rohera and Zahir [56], where polyvinylpyrrolidone, acacia and gelatin were compared as binding agents, it was found that binders of synthetic and natural origins exerted varying influences on granule growth.

Several studies have reported that when the binding agent was introduced as a liquid, increasing the concentration and viscosity of the binding liquid increased the mean size and mechanical strength of the granules. The types of binding agents investigated in these reports included gelatin, acacia, polyvinylpyrrolidones and celluloses [56,62-69]. When mannitol, anhydrous calcium hydrogen phosphate and their blends were granulated using hydroxypropylcellulose solutions at concentrations ranging from 5 to 15%, different agglomerate growth regimes were observed at different binder concentrations. It was believed that the poorer aqueous solubility of anhydrous calcium hydrogen phosphate resulted in the formation of weaker interparticulate bridges that retarded agglomerate growth. This contributed to disparities in the morphologies and porosities of resultant granules [70]. In another study, the use of different molecular weights (K29/32 and K90) and concentrations (2.5 – 7.5% w/w) of polyvinylpyrrolidone affected not just the physical characteristics, but also the drug release profiles of granules [71].

The mode of addition of the binding agent, whether suspended/dissolved in the granulating liquid or dry mixed in the powder, was observed to affect resultant granule properties. Kokubo and co-workers [67,68] studied the fluidized bed granulation of powder blends comprising lactose and cornstarch. Different types of cellulose ethers such as hydroxypropylcellulose, hydropropylmethylcellulose and methylcellulose were employed as binders. The authors reported that compared with the 'dry mixing' method of binder addition, introducing the binder as a solution narrowed the size distribution of the granules and improved the uniformity of binder distribution amongst the different granule size fractions. The 'dry mixing' method, on the other hand, resulted in higher binder concentrations in the coarser granule fractions. Disparities in binding efficiencies amongst the different cellulose ethers were also less pronounced when the binder was introduced in solution form.

Regardless of the mode of binder addition, the solubility of the binder as well as other components of the formulation in the binding liquid constitutes the single most critical factor influencing binder distribution in the different size fractions of granules. The solvation capacity of the binding liquid also dictated the volume of liquid required for successful agglomeration. In two separate studies involving the fluidized bed granulation of lactose-based propranolol hydrochloride [66] and theophylline [72] formulations using aqueous solutions

of polyvinylpyrrolidone, increasing the amount of binding solution led to the production of larger [66] and stronger granules with longer disintegration times [72]. Both findings were likely to be attributed to enhance interparticulate binding. However, the influence of the amount of binding liquid is not confined to the granulation process *per se*. As was observed by Niskanen and Yliruusu [73], the amount of binding liquid employed may also affect granule attrition during subsequent drying which must be taken into consideration.

4.2 Process-related factors during granulation

The humidity of the product bed has been identified by several researchers as a critical factor influencing overall process reliability [74-76]. Bed humidity is an indication of the availability of binding liquid on the surfaces of the particles. A more humid bed indicates an increased availability of liquid on the particle surface and this enhances nucleation and growth. Conversely, if the moisture content of the granule bed exceeds a critical limit, the poor fluidizing capacity of the overly wetted mass might result in the collapse of the product bed [77]. The moisture content of the powder bed critically affects the physicochemical properties of resultant granules. Various processing parameters interplay to either directly influence the addition of the binding liquid to the solid particles, or indirectly affect the moisture content of the powder bed during granulation. For instance, the size of the spray droplets is one key factor that influences the moisture content of the product bed and agglomerate growth. Bigger spray droplets were found to produce more granules in the larger mass size fractions [78], and this can be attributed to a direct relationship between the size of the sprayed droplets and granule size at the early stages of granule growth. However, it should be borne in mind that the size of the spray droplets is an indirect result of various processing parameters, namely spray rate of binding liquid, atomizing air pressure and design of spray nozzle. The effects of these specific parameters as well as other important process factors are further elucidated below:

Spray rate of binding liquid: At the outset, the spray rate of the binding liquid will affect the moisture content of the powder bed. A higher amount of binding liquid is available to the solid particles when the spray rate is increased and this results in a more humid bed. Under these conditions, granules of larger size and lower bulk density are formed [43,52,58,69,79-83]. Pulsed spraying of the binding liquid has been attempted by Ehlers and co-workers as a method to control granule growth [84].

Atomizing air pressure: The degree of atomization of the binding liquid depends on the air-to-liquid mass ratio at the nozzle head. A decrease in atomizing air pressure was shown to result in granules of larger size and lower bulk density. This is due to the decreased air-to-liquid mass ratio that caused the formation of bigger spray droplets [43,69,72,80,85]. Gao *et al.* [43] found that granules prepared at an atomizing air pressure of 1.5 bars produced more fines (20 – 34.5%) compared with those prepared using 0.5 bars (11%). High level of atomizing air pressure (2.5 bars) used in a fractional factorial study was reported to attain target mass median diameter (300 – 500 µm) in granule batches produced, whereas lower levels of atomizing air pressure (2 – 1.5 bars) were reported to produce batches with undesirably larger mass median diameters that ranged approximately from 504 to 612 µm [85]. The degree of atomization was observed to affect the structure and mechanical strength of granules [36]. In another study by Wan and co-workers [86], an optimum pressure was found to be necessary in promoting the uniform distribution of a low-dose drug that was incorporated in the binding liquid.

Properties of the spray nozzle: The position of the spray nozzle in the top-spray technique was reported to significantly influence the growth and friability of granules [79,80,85]. The nearer the nozzle was to the powder bed, the larger were the granules formed. A wider nozzle tip diameter caused larger spray droplets to be formed which promoted granule growth [85]. The spray nozzle tip protrusion from air cap determined the angle at which the granulating liquid was sprayed onto the powder bed. It was also found that a higher protrusion resulted in a higher yield with more granules falling in the smaller size range [85].

Geometry of the product chamber: The shape of the product chamber is an important consideration during process design as it may affect the pattern of particle flow and distribution during processing. Schaafsma *et al.* observed that the geometry in tapered product beds induced gulf-streaming, and gave rise to a central region of high bubble activity and particle up-flow [87]. However, Yang *et al.* reported that the effect of chamber geometry had little influence on the drug release rates of products prepared in a Strea-I™ machine. This small difference was believed to have arisen from the small sizes of the chambers (granulation chamber, coating chamber and Wurster chamber) investigated, which allowed easy maintenance of bed spouting. Nonetheless, the authors suggested that this might not be the case for larger chambers of larger fluidized bed machines [88].

Airflow rate: Smaller granules were formed when the airflow rate was increased [58]. The geometric mean diameter of the product increased from 610 to 966 µm when the airflow rate was decreased from 8 to 4 m/s in a study [69]. This was attributed to the higher shear forces arising from the higher airflow rate, which limited the granule growth rate. It was also found by Wang and co-workers [36] that airflow rate affected granule size and process yield.

Inlet air temperature: A rise in inlet air temperature brought about greater evaporative moisture losses from the wetted particles. This reduced the layer of free moisture surrounding the powder particles and decreased the likelihood of agglomerate growth by coalescence [82,89].

4.3 Process-related factors during drying

Drying is performed to reduce the residual moisture of the granules to a level best suited for the stability of the

constituent actives and requirements of the ensuing downstream process. Inefficient or poor control of the drying process will lead to products of variable quality. For instance, attrition of the formed granules was reported to occur paradoxically, resulting in unwanted size reduction [73]. Excessive generation of fines as a result of attrition can affect granule flow and should be avoided [90]. The key parameters influencing the fluidized bed drying process are discussed below.

Humidity and temperature of inlet air: It has long been established that the humidity of the inlet air influenced the drying rate of aqueous-based granulations [91]. This was because it affected the concentration gradient established at the solid–air interface over which diffusion of water vapor from the granule surface to the surrounding fluidizing air could occur. Studies have shown that an increase in inlet air humidity resulted in higher product temperatures [92,93]. A linear temperature increase of 10°C was observed in the powder bed when the absolute inlet air humidity was increased from 4.5 to 23.4 g/m^3 during the liquid addition phase [92]. Thus, if the attainment of a specific product temperature was used as the end point of drying, the dried granules may contain an undesirably high amount of residual moisture which may adversely affect product quality. These findings are particularly important in the granulation of heat- and moisture-sensitive materials. The use of higher inlet air temperatures was reported to enhance evaporation rate; the evaporation rate increased approximately from 56 to 78 g/s when inlet air temperature was raised from 90 to 120°C at a fixed airflow rate of 4000 scfm [94]. Expectedly, the equilibrium moisture content of the resultant granules was higher when the temperature of the inlet air was lower [94].

Airflow rate: Increments in airflow rate had also been observed to enhance moisture evaporation and drying of granules. The use of higher airflow rate (4000 – 5000 scfm) reduced time taken to attain equilibrium moisture content from the range of 70 – 80 min to approximately 60 min, as compared with the use of lower airflow rate (3000 scfm) [94]. In practice however, modifying airflow rates to enhance evaporation may not be feasible due to its potential influence on the particle size distribution of granules [50]. Excessively high airflow rates may result in an unacceptable level of attrition.

Atomizing air pressure: The atomizing air should be deactivated after the required amount of granulating liquid has been added as a high atomizing air pressure maintained during the drying phase was shown to contribute substantially to granule breakage [69]. The atomizing air may also disrupt the fountain-like flow of the granules in the fluidized bed.

Duration of drying: The duration of drying was shown to affect granule size [26]. Prolonged drying may result in excessive granule attrition. The drying time was reported in a recent fractional factorial study to influence the residual moisture content, bulk and tapped density of granules [95].

5. Recent advances in fluidized bed granulation

In the last decade, there had been a rising number of publications on the scale-up of fluidized bed granulation and how continuous manufacturing strategies may mitigate potential issues and problems associated with process scale-up. New analytical tools for *in-line* process monitoring of granulation and new genres of granulation methods have also surfaced in literature. Those pertinent to the field of fluidized bed granulation research are discussed below.

5.1 Scale-up of fluidized bed granulation

Fluidized bed granulation is widely employed in the pharmaceutical industry as a 'one-pot process' for the production of solid dosage forms. Scaling up the process from the laboratory scale to commercial production has generated immense interest amongst scientists, engineers, regulators, equipment manufacturers and academics alike. As described in Section 4, the outcome of fluidized bed granulation is affected by myriad formulation and process-related factors. As the formulation of a product often remains a constant feature in any scale-up project, successful scale-up hinges on an in-depth understanding of equipment design as well as its associated equipment and process-related variables which mutually interact with one another or with material variables to affect final product quality.

Amongst the three steps involved in fluidized bed agglomeration, namely, dry mixing, spray agglomeration and drying, the spray agglomeration step is deemed most critical [96]. During this phase, granule growth and attrition occur concurrently with solvent evaporation and these processes are affected by a complex interplay amongst equipment variables such as the type and size of equipment, as well as process variables like bed humidity, spray rate, atomization pressure, droplet size, spray pattern, inlet air temperature and location of spray nozzle. Based on the studies that were conducted, it was concluded that successful scale-up require fine tuning of process variables to achieve a desired droplet size and bed humidity which are considered as the two universal scaling parameters that should be kept consistent across the different scales of fluidized bed granulation [97]. As bed humidity depends on the balance between the supply of the binding liquid during the agglomerative phase and its evaporation during drying, it is also important to maintain consistent drying efficiencies between laboratory and production equipment.

However, successful scale-up will not only require a prudent selection of appropriate processing and equipment variables. Experience, together with a mix of educated guesses and approximations on part of the operator, are often needed. In view of this, computational and modeling techniques offer an attractive alternative to the traditional method of trial and error experimentation. Multivariate statistical tools may be adopted which offer a more rational approach to the scale-up process, minimizing guesswork.

These approaches allow identification of the critical formulation and process parameters that influence key product attributes as well as the modeling of processes within a reasonable time frame. These critical parameters can then be monitored preferentially to yield high quality products consistently on a large scale. In a paper published this year by Otsuka *et al.* [98], principal component analysis was successfully applied for the identification of critical process and formulation parameters affecting fluidized bed granulation, with further optimization of the process to yield granules with superior tableting properties.

In the last decade, mathematical models of fluidized bed granulation processes have been constructed largely via the application of population balances which track changes in particle size distributions during granulation. With the advent of high-speed computers, population balance equations are now combined with numerical simulation tools such as computational flow dynamics to better understand granular flow behavior and agglomerate growth processes at the micro-level in bottom spray fluidized bed granulators [99]. These simulation tools, which are deemed more cost-effective and flexible than physical testing methods, can be likened to virtual experimentation and represent the interface between laboratory experiments and theory. They offer quantifiable results and precise visualization of the mechanistic aspects of granulation [100]. In the introduction section of his research article, Fries *et al.* presented a concise and comprehensive review of the different computational and mathematical approaches employed for the modeling of fluidized bed granulation [101].

Another method to mitigate scale-up efforts is to adopt a continuous manufacturing strategy. Fundamentally, continuous manufacturing entails feeding a constant stream of raw materials into a process that runs continuously at a steady, optimized state for an extended period of time until a finished product is obtained. It is particularly suited for high volume products and has been widely applied in the petrochemical, chemical, cosmetics and food industries to improve manufacturing and cost efficiencies. In recent years, the US Food and Drug Administration (FDA) has also recognized that continuous manufacturing has an important role to play in improving the efficiencies and managing the variabilities of pharmaceutical processes. Equipment companies such as Glatt (GF and AGT series) and GEA Niro Pharma Systems (Vibro-Fluidizer) offer numerous solutions for continuous fluidized bed granulation [102]. These equipment differ significantly in their configuration, method of material transfer as well as production rates. Scale-up to commercial production may also be achieved based on a semi-continuous mode of processing. In this mode, highly efficient, small-scale unit processors are operated repeatedly and in parallel fashion until the desired lot size has been accumulated. Although semi-continuous fluidized bed technologies are available from Glatt (MultiCell) and GEA Niro Pharma Systems (Supercell), further equipment modifications are necessary as these processors have been designed specifically for the drying of granules and tablet coating, respectively.

Continuous or semi-continuous granulation cannot rely on end-product testing to determine quality. Hence, real-time monitoring of the critical process parameters and in-line analysis of intermediary products are essential to continuously ensure quality during production. By its very nature, continuous processing lends itself to in-process monitoring and control and is compatible with FDA's process analytical technologies (PAT) initiative as well as the agency's overall move to a risk- and science-based approach to pharmaceutical manufacturing and quality-by-design principles. Thus, PAT should be implemented hand-in-hand with continuous processing in the pharmaceutical industry. These are further described below.

5.2 Process analytical technology in fluidized bed granulation

As a result of the PAT initiative by the US FDA, there has been a surge in interest in process science and understanding within the pharmaceutical industry. PAT is defined as 'a system for designing, analyzing and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality'. At the heart of PAT is building quality by design through a deep and thorough understanding of the manufacturing process with minimal reliance on end-product testing for quality assurance [103].

Many different PAT tools have been proposed to enable scientific, risk-managed pharmaceutical development and manufacture using the fluidized bed process. Traditionally, control of fluidized bed granulation was based on indirect measurements, for example, by monitoring the temperatures of the inlet and outlet air as well as the product [93,104-105]. Vibrational spectroscopic techniques such as near infrared (NIR) and Raman spectroscopy are now available, providing rapid, direct and real-time information on the entire granulation process. These techniques are non-destructive and with the sample interface located in the process stream, information may be derived *in-line*. *On-line* techniques involve automated sampling and transfer of the sample to an automated analyzer. Both *at-line* and *off-line* techniques require manual sampling and are differentiated from each other in terms of the physical proximity of the testing laboratory to the manufacturing area [106]. To date, the application of PAT in fluidized bed granulation has been focused on the following areas:

Moisture content: For process understanding and drying end-point determination, several researchers have employed NIR spectroscopy for in-line moisture determination of the powders at different stages of fluidized bed processing [107-112]. By combining NIR moisture measurements with temperature and humidity data, Rantanen and co-workers [113] have identified different granulation patterns attributed to the

formulation differences of the powder mixtures. NIR technology could be employed for predicting the liquid requirements of multi-component powder formulations during granulation [114]. The different phases of fluidized bed drying have also been distinguished by Nieuwmeyer and co-workers [115] based on a similar technique. However, due to the low penetration depth of NIR waves, measurements are restricted to moisture present on the surfaces of the materials. This has led to the emergence of microwave resonance technology for in-line moisture determination [116]. The higher penetration depth of microwaves increased the accuracy of moisture measurement and enabled continuous and density-independent moisture monitoring of the powder bed. Researchers may also gain further insights into the molecular level phenomena of dehydration.

Particle size: In-line NIR monitoring of moisture content and particle size are often conducted simultaneously to improve process control and end-point determination in fluidized bed granulation [108,112]. Particle size is an important attribute because it affects the flow, drug release, compaction behavior and tableting properties of the granules. The NIR approach has shown promise in monitoring attrition effects during drying [115]. However, accurate *in-line* NIR particle size analysis is challenging because of the variation in scattering and absorptive properties of granules of different sizes. Furthermore, spectral pretreatment and chemometric modeling approaches are often required before meaningful particle size data may be obtained.

To overcome these difficulties, both *on-line* and *at-line* applications have been developed. They include i) image analysis systems where digital images of particles are first captured using a camera then subjected to analysis [117-120], ii) acoustic chemometric techniques that measure the vibrational characteristics of the system to provide information about the state of the system [121,122], iii) focused beam reflectance method [123] and spatial filtering technique [124] that determine the chord length of particles using special probes.

Material composition: Raman spectroscopy has been employed for the three-dimensional mapping of the concentration and chemical structure of particles in a fluidized bed, allowing *in situ,* real-time measurement of material composition as a function of time in three spatial dimensions [125,126]. The changes in relative content of the powder bed as a function of processing time have also been monitored using *off-line* NIR spectral analysis [127].

Solid-state transformations: During wet granulation, process-induced phase transformations may occur where polymorphs, hydrates or amorphous forms of a material interconvert [128]. Control of polymorphic transformations of active principles or excipients during processing is important because such transformations may adversely affect the therapeutic efficacy of the drug product. The presence of different polymorphs of theophylline [129], glycine [130], erythromycin [131] and piroxicam [132] during fluidized bed drying had been successfully quantified using NIR technology. Raman spectroscopy had also been employed to characterize the hydration states of risedronate during fluidized bed drying [133] and was shown to be more useful than NIR in the quantification of different forms of carbamazepine [132]. With in-process information obtained using an appropriate PAT tool and knowledge on the basic properties of the drug, processing conditions can be adjusted to anticipate and prevent potential polymorphic transformations.

5.3 New methods of fluidized bed granulation

Fluidized hot melt granulation: In general, melt granulation has gained considerable attention in recent years as it offers distinct advantages over the conventional wet granulation process. As its name suggests, this process involves the use of meltable binding agents instead of water or solvents to agglomerate fine particles. Hence, it is often referred to as a 'dry' process and is well suited for the granulation of moisture-sensitive bioactives [134,135]. Melt granulation can simply be carried out in a traditional heat-jacketed high shear or tumbling mixer. However, the melt granules produced are often too dense and hard as a result of the high shearing forces exerted by the impeller on the powder as well as material shrinkage on cooling. An industrial scale melt granulator also suffers the drawback of requiring excessively long cooling times for large volume batches, resulting in incomplete/insufficient cooling and potential thermal degradation of materials.

In an effort to overcome the pitfalls of high shear melt granulation, fluidized hot melt granulation was attempted by Kidokoro and co-workers [136]. It was observed that the heating/cooling cycles of the melt granulation process could be easily controlled by changing the temperature of the fluidizing air, resulting in the production of porous granules with good tableting properties. Rapidly disintegrating, effervescent granules and tablets have been successfully prepared using fluidized hot melt granulation [137]. In a recent study, an improvement in the bioavailability of ibuprofen was reported after it was melt granulated with lactose, polyethylene glycol 10000 and polyvinylpyrrolidone using the fluidized bed technique [138].

To facilitate process understanding, several researchers have studied the relationship between process and outcome variables in the fluidized hot melt granulation process. Similar to conventional fluidized bed granulation, the atomizing air pressure and rate of molten binding agent addition were found to influence granule properties [139]. Ansari and Stepanek [140] reported that in an *in situ* fluidized hot melt granulation process, the size of the resultant granules and binding agent particles were directly proportional. Systematic studies on the kinetics of fluidized hot melt granulation have been performed by Tan and co-workers [141-145]. Some authors have also evaluated the effects of the size of molten binding agent droplets and powder particles [146], massing time as well as binding agent concentration [147,148] on the mechanisms and kinetics of granule growth in fluidized hot melt granulation.

Modified Wurster processes: Top-spray fluidized bed granulation is the current gold standard in the industry. The bottom-spray fluidization technique, alternatively termed as Wurster processing, has been used primarily for pellet coating and less so for granulation. In the Wurster process, the granulating liquid is atomized and sprayed directly onto particles supported and suspended by an upwardly moving air stream [22].

The Wurster system was deemed to be capable of good process control, with the possibilities of *on-line* monitoring of granule quality and one-step processing of taste-masked and controlled release preparations (since the steps of granulation and coating can be carried out consecutively in the same equipment) [37]. Based on the Wurster process, Ichikawa and Fukumori [35] proposed the concept of microagglomeration, a technique where pulverized powders are converted into agglomerates 20 – 50 μm in size for subsequent microencapsulation by film coating. However, there is also rising interest in the use of the Wurster process for the production of larger granules. In a study by Wang and co-workers [36], artificial neural network was employed for process optimization and it was concluded that the stability of a moisture sensitive drug was poorer at conditions of high binding liquid spray rates. Recently, the impact of binding agent properties on granule morphology was examined and a methodology that combined both theoretical and experimental techniques was developed for analyzing granule growth in the Wurster process [70,99].

Since its introduction in the pharmaceutical industry, the design of the conventional Wurster process has been subjected to several significant modifications. These include the addition of draft tubes or partition columns [32,149], vibration [150-152] and conical-based and/or conically shaped chambers [153,154]. One of the latest modifications of the Wurster process is precision granulation, which uses a modified mode of air distribution to improve the fluid dynamics of the system [38].

Real-time control of operating conditions such as temperature, relative humidity and flow rate of the inlet/outlet air, product temperature as well as spray rate of the binding liquid can be performed during precision granulation, thus facilitating process monitoring and understanding [155]. The precision granulation process was proposed by Walter [38] to be capable of rapid drying and in the same year, Liew and co-workers [156] demonstrated the suitability of precision granulation for materials that are soluble, sticky or hygroscopic in nature. They compared the properties of granules produced from precision granulation, top-spray granulation and high shear granulation on an industrial scale and found that the porosity, strength and density of granules produced from precision granulation were intermediate between those produced from top-spray and high shear granulation processes. At equivalent tablet weight and hardness, tablets produced from precision granulation exhibited shorter disintegration times. The same group of researchers also studied precision and top-spray granulation of acetaminophen and observed that granules produced from precision granulation were generally less friable, smaller and had relatively smaller proportions of oversized particles compared with granules produced from top-spray granulation. It was also shown in subsequent studies that the highly ordered particle circulation pattern and unique fluid dynamics in precision granulation was advantageous for the wet granulation of moisture-sensitive and low-dose drugs [157,158].

6. Conclusion

Although fluidized bed processing first started out primarily as a method of drying pharmaceutical products, equipment improvements, technological innovations and proliferation of the fluidized bed technology in other industries over the last three decades have led to new possibilities in fluidized bed coating, granulation and even pelletization. As discussed in the review, the outcome of fluidized bed granulation is governed by the complex interplay amongst material and process-related variables. As the industry moves from batch-oriented processing to quasi-continuous or continuous systems, a deeper understanding and appreciation of these variables will have to be gained, and this will require the use of more sophisticated tools such as chemometric methods and PAT.

7. Expert opinion

Fluidized bed granulation, a highly economical and efficient one-pot process, is a popular technique in the pharmaceutical industry for achieving particle size enlargement. The popularity of this technique stems from good process scalability and highly desirable properties of the granules, which are often more porous and compressible than granules produced from other common techniques of granulation in the industry. The fundamental principles of fluidized bed granulation have been strongly established following decades of research in this area, with the majority of the efforts concentrated on the conventional top-spray technique. Formulation and process-related variables that influence the granulation process have been extensively studied and well understood. However, fluidized bed granulation still faces impending challenges related to the inherent sensitivity of the process and product instabilities associated with the use of binding liquids. As the process is very sensitive to its bed humidity, strict control of the condition of the fluidizing powder bed is of utmost importance for overall process reliability. Additionally, the use of binding liquids in this wet granulation technique may cause instability problems such as polymorphic transformations and degradation of drug during processing. This has provided the impetus for the development of new or modified spray granulation processes (e.g., bottom-spray granulation and fluidized bed melt granulation) and the incorporation

of PAT during fluidized bed granulation to improve process control and product quality.

The manufacturing of pharmaceutical dosage forms has traditionally been a batch-wise process. However, the industry is experiencing a paradigm shift toward continuous processing because of the many advantages that can be offered by such systems. For instance, an ideal continuous granulator would have a flexible batch size, and this would eliminate technology transfer, scale-up difficulties and optimization studies from laboratory-scale to large-scale granulators. Continuous processing offers opportunities for cost reduction in relation to personnel, time, equipment and overall equipment effectiveness. Additionally, continuous processing brings along advantages such as ease of automation, reduced material handling (hence reduced handling hazards and contamination risks) and lower risks of product sanction (since product quality has to be monitored real-time and tested *in-line*). Continuous processing builds quality into products by real-time monitoring of critical process parameters and *in-line* analysis of intermediates, diminishing the reliance on end-product testing.

Fluidized bed granulation shows great potential for continuous granulation. This stems not only from its consistent mixing, but also the continuous and concurrent wetting and drying occurring throughout the entire granulation process. As a result of the US FDA's PAT initiative, greater understanding of the fluidized bed granulation process has been achieved in recent years. Although much attention has been drawn to the research and development of suitable PAT tools (e.g., visiometric, NIR spectroscopy and Raman spectroscopy techniques) to control process conditions and characterize product attributes *in-line*, more work is required to fully implement and validate these PAT tools in a production line. Nonetheless, the recent work done on PAT research in the field of fluidized bed granulation field will prove to be timely and useful for the introduction of continuous fluidized bed granulation in the years to come.

Declaration of interest

The authors declare no conflict of interest. This work has been funded by the National University of Singapore.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Appelgren C. Recent advances in granulation technology and equipment. Drug Dev Ind Pharm 1985;11(2-3):725-41
2. Schwartz JB. Granulation. Drug Dev Ind Pharm 1988;14(14):2071-90
3. Stanley-Wood NG. Size enlargement. In: Rhodes MJ. editor. Principles of powder technology. John Wiley and Sons; Chichester; 1990. p. 193-226
4. Radtke G, Knop K, Lippold BC. Manufacture of slow-release matrix granules by wet granulation with an aqueous dispersion of quaternary poly (meth)acrylates in the fluidized bed. Drug Dev Ind Pharm 2002;28(10):1295-302
5. Sakkinen M, Seppala U, Heinanen P, et al. In vitro evaluation of microcrystalline chitosan (MCCh) as gel-forming excipient in matrix granules. Eur J Pharm Biopharm 2002;54(1):33-40
6. Vaithiyalingam SR, Tuliani P, Wilber W, et al. Formulation and stability evaluation of ketoprofen sustained-release tablets prepared by fluid bed granulation with Carbopol (R) 971P solution. Drug Dev Ind Pharm 2002;28(10):1231-40
7. Mukhopadhyay D, Reid M, Saville D, et al. Cross-linking of dried paracetamol alginate granules - Part 1. The effect of the cross-linking process variables. Int J Pharm 2005;299(1-2):134-45
8. Ghorab MK, Adeyeye MC. Enhancement of ibuprofen dissolution via wet granulation with beta-cyclodextrin. Pharm Dev Technol 2001;6(3):305-14
9. Gupta MK, Goldman D, Bogner RH, et al. Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. Pharm Dev Technol 2001;6(4):563-72
10. Gupta MK, Tseng YC, Goldman D, et al. Hydrogen bonding with adsorbent during storage governs drug dissolution from solid-dispersion granules. Pharm Res 2002;19(11):1663-72
11. Rodriguez L, Cavallari C, Passerini N, et al. Preparation and characterization by morphological analysis of diclofenac/PEG 4000 granules obtained using three different techniques. Int J Pharm 2002;242(1-2):285-9
12. Perissutti B, Rubessa F, Moneghini M, et al. Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique. Int J Pharm 2003;256(1-2):53-63
13. Seo A, Holm P, Kristensen HG, et al. The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. Int J Pharm 2003;259(1-2):161-71
14. Vilhelmsen T, Eliasen H, Schaefer T. Effect of a melt agglomeration process on agglomerates containing solid dispersions. Int J Pharm 2005;303(1-2):132-42
15. Yang D, Kulkarni R, Behme RJ, et al. Effect of the melt granulation technique on the dissolution characteristics of griseofulvin. Int J Pharm 2007;329(1-2):72-80
16. Passerini N, Albertini B, Perissutti B, et al. Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel. Int J Pharm 2006;318(1-2):92-102
17. Kurihara K. Dry granulation. In: Swarbrick J, Boylan JC. editors. Encyclopedia of pharmaceutical technology. Marcel Dekker; New York; 1993. p. 423-47
18. Bacher C, Olsen PM, Bertelsen P, et al. Compressibility and compactibility of granules produced by wet and dry granulation. Int J Pharm 2008;358(1-2):69-74
19. Shangraw RF. Compressed tablets by direct compression. In: Lieberman HA, Lachman L, Schwartz JB. editors. Pharmaceutical dosage forms: tablets.

Marcel Dekker; New York; 1990. p. 195-245

20. Hapgood KP, Khanmohammadi B. Granulation of hydrophobic powders. Powder Technol 2009;189(2):253-62
21. Hapgood KP, Farber L, Michaels JN. Agglomeration of hydrophobic powders via solid spreading nucleation. Powder Technol 2009;188(3):248-54
22. Wurster DE. Air-suspension technique of coating drug particles - a preliminary report. J Am Pharm Assoc 1959;48(8):451-4

• **Article that pioneered the use of fluidized bed technology for pharmaceutical coating and granulation.**

23. Gupta CK, Sathiyamoorthy D. Generalities and basics of fluidization. In: Gupta CK, Sathiyamoorthy D. editors. Fluid bed technology in materials processing. CRC Press; Boca Raton; 1998. p. 1-111
24. Parikh DM, Mogavero M. Batch fluid bed granulation. In: Parikh DM. editor. Handbook of pharmaceutical granulation technology. Taylor and Francis; London; 2005. p. 247-309

•• **This chapter covers many diverse aspects of the fluidized bed granulation process and addresses practical issues which are particularly relevant to working professionals in pharmaceutical manufacturing.**

25. Olsen KW. Fluid bed equipment. In: Ghebre-Sellassie I. editor. Pharmaceutical pelletization technology. Marcel Dekker; New York; 1989. p. 39-70
26. Banks M, Aulton ME. Fluidized-bed granulation - a chronology. Drug Dev Ind Pharm 1991;17(11):1437-63
27. Jones DM. Factors to consider in fluid bed processing. Pharm Technol 1985;9:50-62
28. Jones D. Air suspension coating for multiparticulates. Drug Dev Ind Pharm 1994;20(20):3175-206
29. Gu L, Liew CV, Heng PWS. Wet spheronization by rotary processing - a multistage single-pot process for producing spheroids. Drug Dev Ind Pharm 2004;30(2):111-23
30. Goodhart FW. Centrifugal equipment. In: Ghebre-Sellassie I. editor. Pharmaceutical pelletization technology. Marcel Dekker; New York; 1989. p. 101-22
31. Rubino OP. Fluid-bed technology. Overview and criteria for process selection. Pharm Technol 1999;23(6):104-9
32. Ishida M, Shirai T. Circulation of solid particles within the fluidized bed with a draft tube-equilibrium bed heights when a fluidized bed and a fixed bed are connected through an opening. J Chem Eng Jap 1975;8:477-81
33. Dixit R, Puthli S. Fluidization technologies: aerodynamic principles and process engineering. J Pharm Sci 2009;98(11):3933-60

•• **Provides a detailed review on the fundamental principles of fluidization and equipment developments in fluidized bed processing.**

34. Flogel S, Egermann H. Fluid bed granulation of lactose using bottom spray method. Eur J Pharm Sci 1996;4(Suppl 1):S185
35. Ichikawa H, Fukumori Y. Microagglomeration of pulverized pharmaceutical powders using the Wurster process I. Preparation of highly drug-incorporated, subsieve-sized core particles for subsequent microencapsulation by film-coating. Int J Pharm 1999;180(2):195-210
36. Wang XY, Cui F, Yonezawa Y, et al. Preparation and evaluation of high drug content particles. Drug Dev Ind Pharm 2003;29(10):1109-18
37. Ho JS, Dumont H, Mancinelli C, et al. inventors. Process for granulating particles. US20080095850; 2005
38. Walter KT. inventor. Precision granulation. US6492024B1; 2002
39. Turton R, Tardos GI, Ennis BJ. Fluidized bed coating and granulation. In: Yang W. editor. Fluidization solids handling and processing: industrial applications. Noyes Publications; New Jersey; 1999. p. 331-434
40. Olsen KW. Fluid bed agglomerating and coating technology - state of the art. Int J Pharm Technol Prod Mfr 1985;6:18-24
41. Tobyn MJ, Staniforth JN, Baichwal AR, et al. Prediction of physical properties of a novel polysaccharide controlled release system. I. Int J Pharm 1996;128(1-2):113-22
42. Horisawa E, Danjo K, Sunada H. Influence of granulating method on physical and mechanical properties, compression behavior, and compactibility of lactose and microcrystalline cellulose granules. Drug Dev Ind Pharm 2000;26(6):583-93
43. Gao JZH, Jain A, Motheram R, et al. Fluid bed granulation of a poorly water soluble, low density, micronized drug: comparison with high shear granulation. Int J Pharm 2002;237(1-2):1-14
44. Hausman DS. Comparison of low shear, high shear, and fluid bed granulation during low dose tablet process development. Drug Dev Ind Pharm 2004;30(3):259-66
45. Kristensen J, Hansen VW. Wet granulation in rotary processor and fluid bed: Comparison of granule and tablet properties. AAPS PharmSciTech 2006;7(1):E22
46. Kawaguchi T, Sunada H, Yonezawa Y, et al. Granulation of acetaminophen by a rotating fluidized-bed granulator. Pharm Dev Technol 2000;5(2):141-51
47. Stahl H. Comparing different granulation techniques. Pharm Technol Eur 2004;16:23-33
48. Law CL, Mujumdar AS. Fluidized bed dryers. In: Mujumdar AS. editor. Handbook of industrial drying. CRC Press; Boca Raton; 2007. p. 173-201
49. Geldart D. Types of gas fluidization. Powder Technol 1973;7(5):285-92
50. Faure A, York P, Rowe RC. Process control and scale-up of pharmaceutical wet granulation processes: a review. Eur J Pharm Biopharm 2001;52(3):269-77
51. Pont V, Saleh K, Steinmetz D, et al. Influence of the physicochemical properties on the growth of solid particles by granulation in fluidized bed. Powder Technol 2001;120(1-2):97-104
52. Hemati A, Cherif R, Saleh K, et al. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. Powder Technol 2003;130(1-3):18-34

• **Article discusses the influences of several equipment and material-related variables on the fluidized bed granulation of powders which are water-insoluble.**

53. Danjo K, Kamiya A, Ikeda E, et al. Influence of granulating fluids in hydroxypropylcellulose binder solution on physical-properties of lactose granules.

Chem Pharm Bull (Tokyo) 1992;40(9):2505-9

54. Planinsek O, Pisek R, Trojak A, et al. The utilization of surface free-energy parameters for the selection of a suitable binder in fluidized bed granulation. Int J Pharm 2000;207(1-2):77-88
55. Wan LSC, Lim KS. Mode of action of polyvinylpyrrolidone as a binder on fluidized bed granulation of lactose and starch granules. STP Pharm Sci 1989;5:244-50
56. Rohera BD, Zahir A. Granulations in a fluidized-bed - effect of binders and their concentrations on granule growth and modeling the relationship between granule size and binder concentration. Drug Dev Ind Pharm 1993;19(7):773-92
57. Wan LSC, Lim KS. The effect of incorporating polyvinylpyrrolidone as a binder on fluidized bed granulations of lactose. STP Pharm Sci 1988;4:560-71
58. Cryer SA, Scherer PN. Observations and process parameter sensitivities in fluid-bed granulation. AIChE J 2003;49(11):2802-9
59. Abberger T. The effect of powder type, free moisture and deformation behaviour of granules on the kinetics of fluid-bed granulation. Eur J Pharm Biopharm 2001;52(3):327-36
60. Stepanek F, Rajniak P, Mancinelli C, et al. Distribution and accessibility of binder in wet granules. Powder Technol 2009;189(2):376-84
61. Yuksel N, Karatas A, Baykara T. Comparative evaluation of granules made with different binders by a fluidized bed method. Drug Dev Ind Pharm 2003;29(4):387-95
62. Davies WL, Gloor WT. Batch production of pharmaceutical granulations in a fluidized-bed. II. Effects of various binders and their concentrations on granulations and compressed tablets. J Pharm Sci 1972;61(4):618-22
63. Alkan MH, Yuksel A. Granulation in a fluidized-bed. II. Effect of binder amount on the final granules. Drug Dev Ind Pharm 1986;12(10):1529-43
64. Lim KS. Fluidized bed granulation. PhD thesis. National University of Singapore; 1989
65. Ling BL. Fluidized bed granulation and polymeric coating of particles. Master's thesis. National University of Singapore; 2009
66. Wan LSC, Heng PWS, Ling BL. Effect of polyvinylpyrrolidone solutions containing dissolved drug on characteristics of lactose fluidized bed granules. Int J Pharm 1996;141(1-2):161-70
67. Kokubo H, Nakamura S, Sunada H. Effect of several cellulosic binders on particle-size distribution in fluidized-bed granulation. Chem Pharm Bull (Tokyo) 1995;43(8):1402-6
68. Kokubo H, Nakashima C, Sunada H. Effect of several cellulosic binders and method of their addition on the properties and binder distribution of granules prepared in an agitating fluidized bed. Chem Pharm Bull (Tokyo) 1998;46(3):488-93
69. Bouffard J, Kaster M, Dumont H. Influence of process variable and physicochemical properties on the granulation mechanism of mannitol in a fluid bed top spray granulator. Drug Dev Ind Pharm 2005;31(9):923-33
70. Rajniak P, Mancinelli C, Chern RT, et al. Experimental study of wet granulation in fluidized bed: impact of the binder properties on the granule morphology. Int J Pharm 2007;334(1-2):92-102
71. Haldar R, Gangadharan B, Martin D, et al. Fluid bed granulation of ibuprofen. Drug Dev Ind Pharm 1989;15(14-16):2675-9
72. Merkku P, Lindqvist AS, Leiviska K, et al. Influence of granulation and compression process variables on flow-rate of granules and on tablet properties, with special reference to weight variation. Int J Pharm 1994;102(1-3):117-25
73. Niskanen T, Yliruusi J. Attrition of theophylline granules during drying in a fluidized-bed granulator. Pharm Ind 1994;56(3):282-5
74. Kokubo H, Sunada H. Effect of process variables on the properties and binder distribution of granules prepared in a fluidized bed. Chem Pharm Bull (Tokyo) 1997;45(6):1069-72
75. Watano S, Takashima H, Miyanami K. Scale-up of agitation fluidized bed granulation. V. Effect of moisture content on scale-up characteristics. Chem Pharm Bull (Tokyo) 1997;45(4):710-14
76. Hu XH, Cunningham J, Winstead D. Understanding and predicting bed humidity in fluidized bed granulation. J Pharm Sci 2008;97(4):1564-77
77. Schaafsma SH, Kossen NWF, Mos MT, et al. Effects and control of humidity and particle mixing in fluid-bad granulation. AIChE J 1999;45(6):1202-10
78. Schaafsma SH, Vonk P, Kossen NWF. Fluid bed agglomeration with a narrow droplet size distribution. Int J Pharm 2000;193(2):175-87
79. Rankell AS, Battista JV, Lieberma HA, et al. Continuous production of tablet granulations in fluidized bed. II. Operation and performance of equipment. J Pharm Sci 1964;53(3):320-4
80. Davies WL, Gloor WT. Batch production of pharmaceutical granulations in a fluidized bed. 1. Effects of process variables on physical properties of final granulation. J Pharm Sci 1971;60(12):1869-74
81. Wan LSC, Heng PWS, Liew CV. The influence of liquid spray rate and atomizing pressure on the size of spray droplets and spheroids. Int J Pharm 1995;118(2):213-19
82. Lipps DM, Sakr AM. Characterization of wet granulation process parameters using response-surface methodology. I. Top-spray fluidized-bed. J Pharm Sci 1994;83(7):937-47
83. Menon A, Dhodi N, Mandella W, et al. Identifying fluid-bed parameters affecting product variability. Int J Pharm 1996;140(2):207-18
84. Ehlers H, Liu AC, Raikkonen H, et al. Granule size control and targeting in pulsed spray fluid bed granulation. Int J Pharm 2009;377(1-2):9-15
85. Rambali B, Baert L, Thone D, et al. Using experimental design to optimize the process parameters in fluidized bed granulation. Drug Dev Ind Pharm 2001;27(1):47-55
86. Wan LSC, Heng PWS, Muhuri G. Incorporation and distribution of a low-dose drug in granules. Int J Pharm 1992;88(1-3):159-63
87. Schaafsma SH, Marx T, Hoffmann AC. Investigation of the particle flowpattern and segregation in tapered fluidized bed

granulators. Chem Eng Sci 2006;61(14):4467-75

88. Yang ST, Vansavage G, Weiss J, et al. The effect of spray mode and chamber geometry of fluid-bed coating equipment and other parameters on an aqueous-based ethylcellulose coating. Int J Pharm 1992;86(2-3):247-57

89. Schinzinger O, Schmidt PC. Comparison of the granulation behavior of three different excipients in a laboratory fluidized bed granulator using statistical methods. Pharm Dev Technol 2005;10(2):175-88

90. Nieuwmeyer FJS, Maarschalk KV, Vromans H. Granule breakage during drying processes. Int J Pharm 2007;329(1-2):81-7

91. Zoglio MA, Streng WH, Carstensen JT. Diffusion-model for fluidized-bed drying. J Pharm Sci 1975;64(11):1869-73

92. Lipsanen T, Antikainen O, Raikkonen H, et al. Novel description of a design space for fluidised bed granulation. Int J Pharm 2007;345(1-2):101-7

93. Lipsanen T, Antikainen O, Raikkonen H, et al. Effect of fluidisation activity on end-point detection of a fluid bed drying process. Int J Pharm 2008;357(1-2):37-43

94. Hlinak AJ, Saleki-Gerhardt A. An evaluation of fluid bed drying of aqueous granulations. Pharm Dev Technol 2000;5(1):11-17

95. Tomuta I, Alecu C, Rus LL, et al. Optimization of fluid bed formulations of metoprolol granules and tablets using an experimental design. Drug Dev Ind Pharm 2009;35(9):1072-81

96. Yamamoto K, Shao ZJ. Process development, optimization and scale-up: fluid-bed granulation. In: Qiu Y, Chen Y, Zhang GGZ, Liu L, Porter WR, editors, Developing solid oral dosage forms: pharmaceutical theory and practice. Part III: Design, development and scale up of formulation and process. Academic Press, New York; 2008; p. 701-14

97. Rambali B, Baert L, Massart DL. Scaling up of the fluidized bed granulation process. Int J Pharm 2003;252(1-2):197-206

98. Otsuka T, Iwao Y, Miyagishima A, et al. Application of principal component analysis enables to effectively find important physical variables for optimization of fluid bed granulator conditions. Int J Pharm 2011;409(1-2):81-8

99. Rajniak P, Stepanek F, Dhanasekharan K, et al. A combined experimental and computational study of wet granulation in a Wurster fluid bed granulator. Powder Technol 2009;189(2):190-201

100. Ng BH, Ding YL, Ghadiri M. Modelling of dense and complex granular flow in high shear mixer granulator-A CFD approach. Chem Eng Sci 2009;64(16):3622-32

101. Fries L, Antonyuk S, Heinrich S, et al. DEM-CFD modeling of a fluidized bed spray granulator. Chem Eng Sci 2011;66(11):2340-55

102. Vervaet C, Remon JP. Continuous granulation in the pharmaceutical industry. Chem Eng Sci 2005;60(14):3949-57

103. United States Food and Drug Administration. Guidance for industry: PAT - a framework for innovative pharmaceutical development, manufacturing and quality assurance. 2004

104. Alden M, Torkington P, Strutt ACR. Control and instrumentation of a fluidized-bed drier using the temperature-difference technique. I. Development of a working model. Powder Technol 1988;54(1):15-25

105. Wostheinrich K, Schmidt PC. Evaluation and validation of a fully instrumented Huttlin HKC 05-TJ laboratory-scale fluidized bed granulator. Drug Dev Ind Pharm 2000;26(6):621-33

106. Hassell DC, Bowman EM. Process analytical chemistry for spectroscopists. Appl Spectrosc 1998;52(1):18A-29A

107. Watano S, Takashima H, Sato Y, et al. Measurement of moisture content by IR sensor in fluidized bed granulation. Effects of operating variables on the relationship between granule moisture content and absorbance of IR spectra. Chem Pharm Bull (Tokyo) 1996;44(6):1267-9

108. Frake P, Greenhalgh D, Grierson SM, et al. Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy. Int J Pharm 1997;151(1):75-80

109. Morris KR, Stowell JG, Byrn SR, et al. Accelerated fluid bed drying using NIR monitoring and phenomenological modeling. Drug Dev Ind Pharm 2000;26(9):985-8

110. Rantanen J, Kansakoski M, Suhonen J. Next generation fluidized bed granulator automation. AAPS PharmSciTech 2000;1:E10

111. Wildfong PLD, Samy AS, Corfa J, et al. Accelerated fluid bed drying using NIR monitoring and phenomenological modeling: Method assessment and formulation suitability. J Pharm Sci 2002;91(3):631-9

112. Findlay WP, Peck GR, Morris KR. Determination of fluidized bed granulation end point using near-infrared spectroscopy and phenomenological analysis. J Pharm Sci 2005;94(3):604-12

113. Rantanen J, Jorgensen A, Rasanen E. Process analysis of fluidized bed granulation. AAPS PharmSciTech 2001;2(4):E21

114. Miwa A, Yajima T, Ikuta H, et al. Prediction of suitable amounts of water in fluidized bed granulation of pharmaceutical formulations using corresponding values of components. Int J Pharm 2008;352(1-2):202-8

115. Nieuwmeyer FJS, Damen M, Gerich A, et al. Granule characterization during fluid bed drying by development of a near infrared method to determine water content and median granule size. Pharm Res 2007;24(10):1854-61

116. Buschmuller C, Wiedey W, Doscher C, et al. In-line monitoring of granule moisture in fluidized-bed dryers using microwave resonance technology. Eur J Pharm Biopharm 2008;69(1):380-7

117. Watano S, Miyanami K. Image-processing for online monitoring of granule size distribution and shape in fluidized-bed granulation. Powder Technol 1995;83(1):55-60

118. Watano S. Direct control of wet granulation processes by image processing system. Powder Technol 2001;117(1-2):163-72

119. Laitinen N, Antikainen O, Rantanen J, et al. New perspectives for visual characterization of pharmaceutical solids. J Pharm Sci 2004;93(1):165-76

120. Naervanen T, Seppaelae K, Antikainen O, et al. A new rapid on-line imaging method to determine particle

size distribution of granules. AAPS PharmSciTech 2008;9(1):282-7

121. Halstensen M, Esbensen K. New developments in acoustic chemometric prediction of particle size distribution - 'the problem is the solution'. J Chemometr 2000;14(5-6):463-81

122. Halstensen M, de Bakker P, Esbensen KH. Acoustic chemometric monitoring of an industrial granulation production process - a PAT feasibility study. Chemometr Intell Lab Syst 2006;84(1-2):88-97

123. Hu XH, Cunningham JC, Winstead D. Study growth kinetics in fluidized bed granulation with at-line FBRM. Int J Pharm 2008;347(1-2):54-61

124. Narvanen T, Lipsanen T, Antikainen O, et al. Gaining fluid bed process understanding by in-line particle size analysis. J Pharm Sci 2009;98(3):1110-17

125. Walker G, Bell SEJ, Vann M, et al. Fluidised bed characterisation using Raman spectroscopy: applications to pharmaceutical processing. Chem Eng Sci 2007;62(14):3832-8

126. Walker GM, Bell SEJ, Greene K, et al. Characterisation of fluidised bed granulation processes using in-situ Raman spectroscopy. Chem Eng Sci 2009;64(1):91-8

127. Li WY, Cunningham J, Rasmussen H, et al. A qualitative method for monitoring of nucleation and granule growth in fluid bed wet granulation by reflectance near-infrared spectroscopy. J Pharm Sci 2007;96(12):3470-7

128. Zhang GGZ, Law D, Schmitt EA, et al. Phase transformation considerations during process development and manufacture of solid oral dosage forms. Adv Drug Deliv Rev 2004;56(3):371-90

•• **Provides an excellent account of the basic principles of solid state transformations and their methods of characterization as well as how such transformations may be brought about by the various unit processes involved in pharmaceutical manufacture.**

129. Rasanen E, Rantanen J, Jorgensen A, et al. Novel identification of pseudopolymorphic changes of theophylline during wet granulation using near infrared spectroscopy. J Pharm Sci 2001;90(3):389-96

130. Davis TD, Peck GE, Stowell JG, et al. Modeling and monitoring of polymorphic transformations during the drying phase of wet granulation. Pharm Res 2004;21(5):860-6

131. Romer M, Heinamaki J, Miroshnyk I, et al. Phase transformation of erythromycin a dihydrate during fluid bed drying. J Pharm Sci 2008;97(9):4020-9

132. Kogermann K, Aaltonen J, Strachan CJ, et al. Establishing quantitative in-line analysis of multiple solid-state transformations during dehydration. J Pharm Sci 2008;97(11):4983-99

133. Hausman DS, Cambron RT, Sakr A. Application of on-line Raman spectroscopy for characterizing relationships between drug hydration state and tablet physical stability. Int J Pharm 2005;299(1-2):19-33

134. Thies R, Kleinebudde P. Melt pelletisation of a hygroscopic drug in a high shear mixer Part 1. Influence of process variables. Int J Pharm 1999;188(2):131-43

135. Kowalski J, Kalb O, Joshi YM, et al. Application of melt granulation technology to enhance stability of a moisture sensitive immediate-release drug product. Int J Pharm 2009;381(1):56-61

136. Kidokoro M, Haramiishi Y, Sagasaki S, et al. Application of fluidized hot-melt granulation (FHMG) for the preparation of granules for tableting; Properties of granules and tablets prepared by FHMG. Drug Dev Ind Pharm 2002;28(1):67-76

137. Yanze FM, Duru C, Jacob M. A process to produce effervescent tablets: Fluidized bed dryer melt granulation. Drug Dev Ind Pharm 2000;26(11):1167-76

138. Walker GM, Bell SEJ, Andrews G, et al. Co-melt fluidised bed granulation of pharmaceuticial powders: Improvements in drug bioavailability. Chem Eng Sci 2007;62(1-2):451-62

139. Borini GB, Andrade TC, Freitas LAP. Hot melt granulation of coarse pharmaceutical powders in a spouted bed. Powder Technol 2009;189(3):520-7

140. Ansari MA, Stepanek F. Formation of hollow core granules by fluid bed in situ melt granulation: Modelling and experiments. Int J Pharm 2006;321(1-2):108-16

141. Tan HS, Salman AD, Hounslow M. Kinetics of fluidised bed melt granulation - IV. Selecting the breakage model. Powder Technol 2004;143:65-83

142. Tan HS, Salman AD, Hounslow M. Kinetics of fluidised bed melt granulation III: tracer studies. Chem Eng Sci 2005;60(14):3835-45

143. Tan HS, Salman AD, Hounslow MJ. Kinetics of fluidised bed melt granulation V: simultaneous modelling of aggregation and breakage. Chem Eng Sci 2005;60(14):3847-66

144. Tan HS, Salman AD, Hounslow MJ. Kinetics of fluidised bed melt granulation I: the effect of process variables. Chem Eng Sci 2006;61(5):1585-601

145. Tan HS, Salman AD, Hounslow MJ. Kinetics of fluidized bed melt granulation - II: modelling the net rate of growth. Chem Eng Sci 2006;61(12):3930-41

146. Abberger T, Seo A, Schaefer T. The effect of droplet size and powder particle size on the mechanisms of nucleation and growth in fluid bed melt agglomeration. Int J Pharm 2002;249(1-2):185-97

147. Walker GM, Holland CR, Ahmad MMN, et al. Influence of process parameters on fluidised hot-melt granulation and tablet pressing of pharmaceutical powders. Chem Eng Sci 2005;60(14):3867-77

148. Walker GM, Andrews G, Jones D. Effect of process parameters on the melt granulation of pharmaceutical powders. Powder Technol 2006;165(3):161-6

149. Song BH, Kim YT, Kim SD. Circulation of solids and gas bypassing in an internally circulating fluidized bed with a draft tube. Chem Eng J 1997;68(2-3):115-22

150. Noda K, Mawatari Y, Uchida S. Flow patterns of fine particles in a vibrated fluidized bed under atmospheric or reduced pressure. Powder Technol 1998;99(1):11-14

151. Levy EK, Celeste B. Combined effects of mechanical and acoustic vibrations on fluidization of cohesive powders. Powder Technol 2006;163(1-2):41-50

152. Silva-Moris VA, Rocha SCS. Vibrofluidized bed drying of adipic acid. Drying Technol 2006;24(3):303-13

153. Bi HT. A discussion on minimum spout velocity and jet penetration length. Can J Chem Eng 2004;82(1):4-10

154. Wormsbecker M, van Ommen R, Nijenhuis J, et al. The influence of vessel geometry on fluidized bed dryer hydrodynamics. Powder Technol 2009;194(1-2):115-25

155. Walter KT, Liew C, Brzeczko AW. Fluidized bed precision granulation with real time process determination. Presented at: Americal Association of Pharmaceutical Scientists (AAPS) Annual Meeting. Salt Lake City, Utah, US, 2003

156. Liew C, Walter K, Wigmore A, et al. Precision granulation as an alternative granulation method. Presented at: AAPS poster presentation. Toronto, Ontario, Canada, 2002

157. Liew CV, Er DZL, Heng PWS. Air-dictated bottom spray process: impact of fluid dynamics on granule growth and morphology. Drug Dev Ind Pharm 2009;35(7):866-76

158. Er DZL, Liew CV, Heng PWS. Layered growth with bottom-spray granulation for spray deposition of drug. Int J Pharm 2009;377(1-2):16-24

Affiliation

Zhi Hui Loh[1] PhD, Dawn ZL Er[4] PhD, Lai Wah Chan[2], Celine V Liew[3] & Paul WS Heng[†2] PhD
[†]Author for correspondence
[1]Instructor,
National University of Singapore,
Department of Pharmacy,
Faculty of Science,
Block S4, 18 Science Drive 4, 117543,
Singapore
[2]Associate Professor,
National University of Singapore,
Department of Pharmacy,
Faculty of Science,
Block S4, 18 Science Drive 4, 117543,
Singapore
Tel: +65 6516 2930; Fax: +65 6775 2265;
E-mail: phapaulh@nus.edu.sg
[3]Assistant Professor,
National University of Singapore,
Department of Pharmacy,
Faculty of Science,
Block S4, 18 Science Drive 4, 117543,
Singapore
[4]Medical editor,
National University of Singapore,
CMPMedica Asia Pte Ltd,
3, Lim Teck Kim Road, #10-01,
Singapore Technologies Building, 088934,
Singapore