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Multiphase versus Single Pot Granulation Process: Influence of Process and Granulation Parameters on Granules Properties

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ABSTRACT High-shear wet granulation is widely used for the production of pharmaceutical dosage forms. Different equipment is available for high-shear granulation and drying. This review focuses on two main processes for granules production: multiphase consisting of high-shear granulation followed by drying in a separate apparatus, and single pot granulation/drying. At present, formulas are specifically developed with regard to the production equipment, which raises many problems when different industrial manufacturing equipment is used. Indeed, final granules properties are likely to depend on equipment design, process, and formulation parameters. Therefore, a good understanding of these parameters is essential to facilitate equipment changes.

The aim of this review is to present the influence of equipment, process, and formulation parameters on granules properties, considering both the granulation and the drying steps of multiphase and single pot processes.

KEYWORDS Wet granulation, High-shear, Single pot, Drying, Process, Formulation, Granules properties

INTRODUCTION

Wet granulation, which consists in the agglomeration of powder particles, is a major unit operation in the production of most pharmaceutical dosage forms. It is primarily used to improve the physical and rheological properties of the powder and therefore facilitates handling and further processing into tablets. It is also often required to achieve acceptable content uniformity. High-shear force mixers are widely used for wet granulation because they provide short granulation time, high density, and high strength granules.

Various high-shear wet granulation/drying processes are available to pharmaceutical manufacturers, each presenting different strengths and weaknesses. Multiphase processes remain the most common configuration. In particular, high-shear granulation followed by fluid bed drying is largely used for the production of granules. However, single pot granulators-dryers, that is to say

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mixer-granulators that dry granules in the same equipment, have also been seen as an interesting alternative.

At this time, pharmaceutical formulas are specifically developed with regard to the granulation equipment, i.e., a formula does not generally allow for the use of a different manufacturing equipment without major changes. It is therefore necessary for international industrial development with different equipment to deposit several marketing authorizations. Moreover, when switching from one equipment to another, many problems are raised due to the numerous process and formulation parameters that must be taken into account. A good understanding of these parameters is therefore of a high importance to facilitate equipment changes.

In the first part of this review, different apparatus available for high-shear granulation and drying will be presented. Then, in the second part, the major process and formulation parameters affecting the quality of the granules will be investigated as reported in the literature. This review will focus on two main production processes used to manufacture granules via a wet granulation process: high-shear mixer/fluid bed dryer and single pot equipment. Therefore, the following subjects will be excluded: spray drying, fluid bed granulation, melt granulation, steam granulation, foam granulation, processes scale-up, equipment cleanability and containment, shock pressure resistance of equipment, initial mixing, and final treatment such as sieving or grinding as well as sustained release formulations.

MULTIPHASE OR SINGLE POT EQUIPMENT AND PROCESS

High-shear Granulation and Drying Processes

High-shear Granulation

High-shear granulation can be performed in a high-shear mixer-granulator as part of a multiphase granulation process or in a single pot mixer-granulator-dryer.

During high-shear granulation, a binder solution is added to the mechanically blended powder mix which results in particle size enlargement by the formation of liquid bridges between primary particles. The binder solution can also be obtained inside the bowl when the binder is in a dry form and a solvent is added.

Granulation is commonly described as a combination of three different steps (Chulia, 1990; Ennis, 1996; Iveson et al., 2001a; Mort T. Tardos, 1999; Tardos et al., 1997; Vialatte, 1998; Waruters et al., 2002): wetting and nucleation, consolidation and coalescence, attrition and breakage (Fig. 1).

- Wetting and nucleation: The binder solution distributes through the dry powder bed and nuclei are formed.
- Macroscopic interactions between a liquid and a powder are classically divided into four main successive states (Fig. 2) (Deleuil, 1990; Goldszal & Bousquet, 2001; Newitt & Conway-Jones, 1958; York & Rowe, 1994):
  - The pendular state. Liquid bridges start forming between the particles following the addition of a binder solution or solvent.
  - The funicular state. Interparticle spaces are filled with binder solution. Particle agglomerates are formed.
  - The capillary state. Interparticle spaces are saturated. Further addition of liquid creates bridges between the agglomerates.

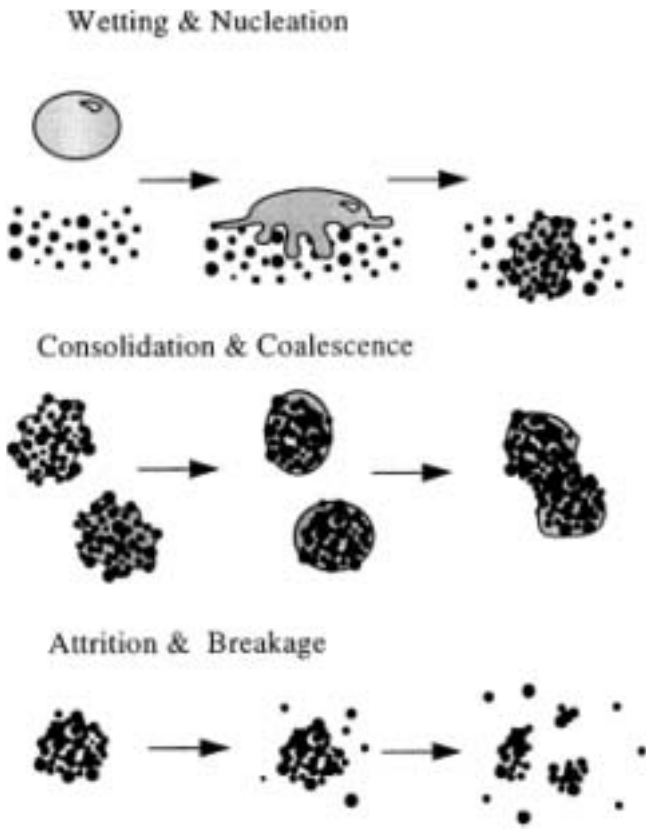


FIGURE 1 **Wet Granulation Steps (Iveson et al., 2001a).**

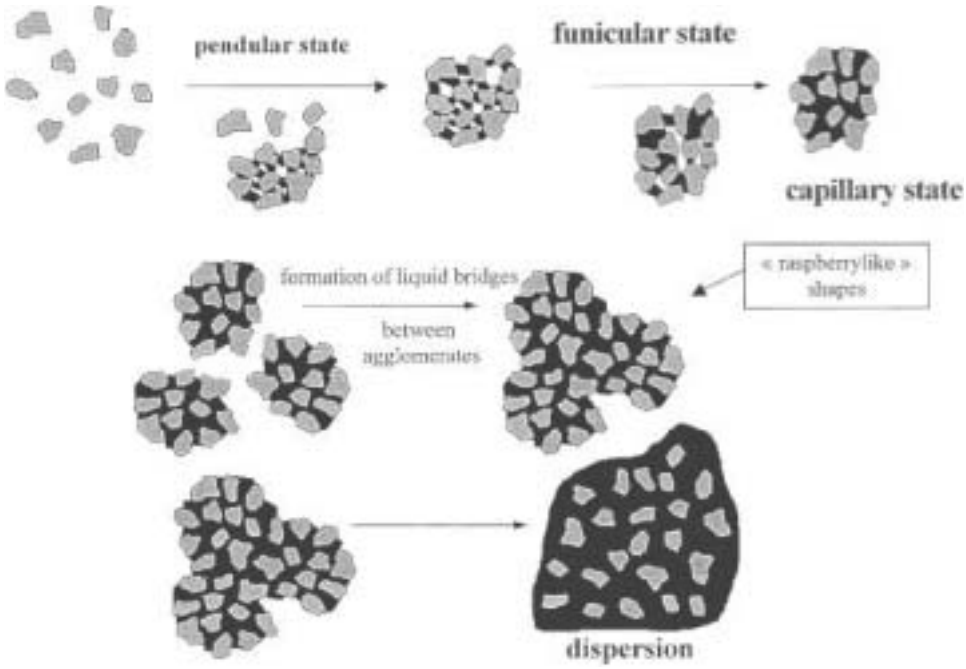


FIGURE 2 **Successive States Resulting from Macroscopic Interactions Between a Liquid and a Powder (Goldszal & Bousquet, 2001).**

- The dispersion state. The space between the agglomerates has been filled and a solid-liquid dispersion state is finally obtained by overwetting.

- In the granulation process, wetting is stopped when the funicular state is reached and particle agglomerates are formed. Wetting is performed under high-shear mixing and at high chopper speed to avoid the formation of lumps.
- Consolidation and coalescence: Collisions between nuclei, between nuclei and native agglomerates, or between nuclei and the equipment wall lead to granule compaction and growth. After wetting, high-shear mixing is pursued for consolidation and growth of the granules.
- Attrition and breakage: Granules may break due to impacts against other granules, the granulator wall, or the impeller (Fig. 3). After wetting, the chopper speed is reduced to limit attrition and breakage.

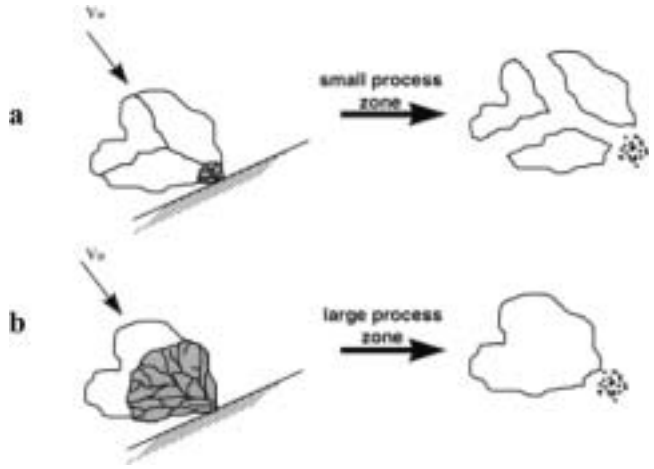


FIGURE 3 **Breakage by (a) Fracture, and (b) Erosion/attrition (Iveson, 2001a).**

Drying

Drying is performed after wet granulation to obtain suitable moisture content for further processing and to enhance the stability of the final products. However, a residual amount of moisture in the granules remains necessary to preserve cohesion, to maintain the ingredients in a hydrated state, and to reduce static electric charges on the particles.

Drying is not a uniform phenomenon but can be divided into three distinct phases (Fig. 4):

- Phase I: Heating phase. Heat is usually transferred to the granule by convection and/or conduction and from there further into the granule by conduction.
- Phase II: Constant evaporation rate phase. An equilibrium between evaporation and migration at

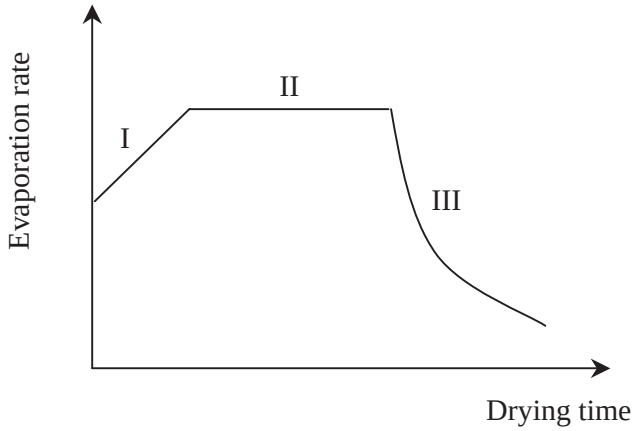


FIGURE 4 **Different Phases of the Drying Cycle (Rosetto, 1998).**

constant temperature is reached. Water is drawn to the surface by capillary forces. Dehydration reactions are influenced by a number of factors, including crystal packing, moisture content, temperature, hydrogen bonding, and porosity (Airaksinen et al., 2004). As the liquid bridges in the wet granules are transformed into dry bonds during the drying process, drying is obviously a critical point for the properties of the final granules (Cruaud et al., 1980).

- Phase III: Falling rate of evaporation phase. Temperature increases because the heat transferred to the granules is no longer used for water evaporation.

The number of gas molecules vaporized by time unit during drying is given by the following equation.

$$m = \frac{K.S.(F-h)}{P.t}$$

where m is the number of gas molecules vaporised by time unit, K is the constant, S is the surface in contact with the drying fluid, F is the saturated vapor tension, h is the vapor tension in the ambient atmosphere, P is the pressure, and t is the drying time.

So, drying time can be shortened by increasing evaporation surface (mixing during drying), increasing temperature and decreasing relative humidity, and decreasing pressure (drying under vacuum).

However, drying under stress conditions, such as a high shearing speed, can be responsible for granule breakage. Indeed, it can favor collisions leading to fractures or attrition of the granules (Kiekens et al., 1999).

Although organic solvents remain commonly used, water has become the preferred solvent for granulation for safety reasons. However, because of the relatively high heat of vaporization and low vapor pressure of water, it is sometimes difficult to dry granules obtained from aqueous granulation (Hausman, 2004, Hlinak & Salezi-Gerhardt, 2000).

In a multiphase process, granulation in a high-shear mixer is followed by drying in a separate apparatus whereas in a single pot, granulation and drying are performed in the same apparatus. Table 1 summarizes the characteristics of the drying processes described below.

Drying as a part of a multiphase process

- Tray drying in a hot oven is a conventional method used for drying pharmaceutical granules. Wet granules are placed on large sheets of paper on shallow wire trays and placed in a drying oven with a circulating air current and thermostatic heat control. However, this process is slow and difficult to be controlled (Carstensen & Zoglio, 1982; Hunter, 1992; Mandal, 1995; Mbali-Pemba et al., 1996; Travers, 1975).
- In fluid bed drying, particles are suspended in a vertical column with a rising air stream.
- Increasing the inlet air temperature and the process air flow rate can improve the evaporation rate (Gao et al., 2000). The air flow rate must be optimized to ensure a proper fluidization of the granules (Magnet, 1996). When increasing product temperature, it is necessary to verify that no degradation occurs.

TABLE 1 **Comparison of Drying Processes**

	Multiphase process		Single pot	
	Tray drying	Fluidized bed	Double jacket/vacuum	Double jacket/vacuum/microwaves
Heat transfer	convection	convection	conduction	conduction/radiation
Static/dynamic system	static	dynamic	dynamic	dynamic
Contact between granules	high	low	high	high

- Heat transfer to the granules by convection is very efficient (Joulié, 1994; Hlinak & Salezi-Gerhardt, 2000; Paschos, 1987). The fluidized bed process possesses a major advantage to be much faster than conventional tray drying. However, it is dusty with a risk of dust explosion (Kristensen & Schaefer, 1987), and its energy consumption is high (Hunter, 1992).

Drying in a single pot apparatus

- Single pots are equipped with a double jacket bowl. Drying efficiency is related to time and surface contact between the granules and the heated apparatus wall.
- One drawback is that drying time remains rather long with simply double jacket drying (Bauer & Vadagnini, 1997; Pearlswig et al., 1994; Poska, 1991; Robin et al., 1994; Stahl, 2000, 2004).
- Vacuum drying is therefore systematically associated to double jacket drying in order to obtain faster drying or to allow drying at lower temperatures which may be useful for thermosensitive products (Bauer & Vadagnini, 1997).
- In order to optimize drying efficiency, various additional solutions have been developed, such as an optimization of the bowl design in order to improve surface contact between the heated double jacket and the product (Le Lan, 1978; Rosetto, 1998), the use of a swinging bowl (Van Vaerenbergh, 2001), or the addition of a gas stripping system which consists in a small, controlled and diffused injection of gas through the powder mass (see the Section in Single Pot Apparatus).

Moreover, in addition to double jacket vacuum drying, microwaves can be applied also in single pot apparatus to shorten drying times further. Another advantage of microwave drying is that it allows linear scale up in single-pot apparatus which is not possible when the heated wall is the only source of drying energy since the wall surface area/product contact ratio decreases as the bowl size increases (Niro, 2005; Stahl, 2004). In microwave drying, the friction of water molecules generates heat. The resulting steam pushes moisture out of the granule (Péré, 1999; Péré & Rodier, 2002; Poska, 1991; Smart, 1996; Stahl, 2004). However, the stability of all components exposed to microwave energy, which provides deep highly energetic radiation penetration, must be evaluated to avoid the risk of chemical degradation or even of a thermal runaway (Bauer & Vadagnini, 1997; Stahl, 2004). An effective fail-safe end-point control system is therefore essential for microwave drying since as soon as all water molecules are removed, the energy becomes concentrated on the next most excitable molecule. This can lead to a rapid and irreversible degradation of an ingredient in the mix (Baillon, 1996; Bauer & Vadagnini, 1997; Hunter, 1992). The dielectric properties of the pharmaceutical products are very important characteristics regarding the suitability and efficiency of microwave drying. Mixing is essential during and after the drying phase to improve the dielectric heating efficiency.

Description of Multiphase and Single Pot Equipment

High-shear Granulation Apparatus Used in a Multiphase Process

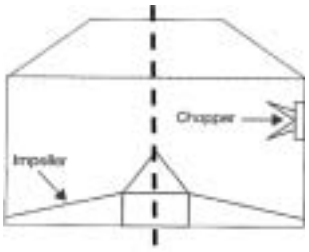
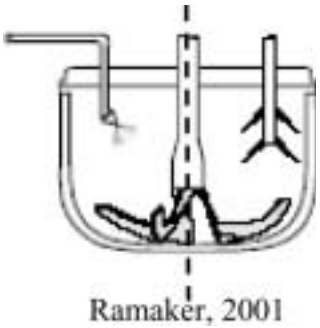
High-shear mixer-granulator apparatus are commonly mentioned in the literature in the material section but few technical syntheses of the different existing equipment are actually available (Faure, et al., 2001; Levin, 2004; Stahl, 2004). Table 2 describes the most frequently used apparatus.

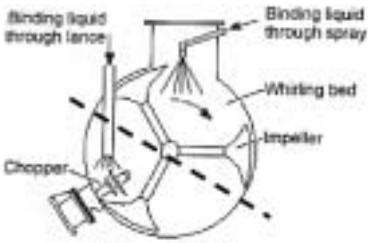
The mixing chamber and the impeller are simultaneously designed to ensure the best movement of the particles inside the bowl. This movement depends on the bowl (Fig. 5) and impeller (Fig. 6) geometry. The geometry of the impeller is adapted to the bowl shape in order to improve the volume of powder swept by the mixing tool and to decrease wall adhesion and dead zone. Moreover, the movement of the powder blend inside the bowl depends on the impeller speed. At low speed, the impeller gives the powder a bumping movement, whereas at high speed the powder is submitted to a rotational movement (Fig. 7).

The presence of a chopper in the bowl is also required to break coarser agglomerates and control granules distribution (Le Lan, 1978; Stahl, 2004). As for the impeller, the geometry and rate of the chopper differ from one apparatus to another (Fig. 6). Therefore, the chopper is likely to disturb the flow pattern of the mass depending on its design and running speed.

The rotation speed, the size, and the shape of the mixing tools are likely to have an influence on the powder bed temperature. Holm (1987), Kristensen & Schaefer, (1987), and Schaefer et al. (1986, 1987) showed that the energy consumed in a high shear

TABLE 2 **Examples of Marketed Vertical and Horizontal Shaft High-shear Mixer-granulators**

Vertical shaft high-shear mixer-granulators			
Supplier	Equipment capacity	References	Presentation
Diosna	P1™ to P1250™ (1 to 1250 L)	Becker et al., 1997; Bock & Kraas, 2001; Hausman, 2004; Schaefer et al., 1986	 Plank, 2003
GEA (Aeromatic-Fielder)	GP1SP™ (3 to 10 L) PMA10™ to PMA 1800™ (10 to 1800 L)	Badawy et al., 2000a and 2000b; Chaplin et al., 2004; Faure et al., 1999; Landin et al., 1996a, 1996b; Mackaplow et al., 2000; Plank et al., 2003; Rekhi et al., 1996; Schaefer et al., 1986	
Glatt-Powrex	VG-1™ to VG-3000™ (1 to 3000 L)	Horisawa et al., 2000; Kokubo & Sunada, 1996; Konishi et al., 1996; Miyamoto et al., 1998	
Loedige	MGT 30™ to 1200™ (30 to 1200 L)	Timko et al., 1986, 1987	
GEA (Collette NV)	Ultima Gral™ (10 to 1200 L), successor of Gral™ (10 to 600 L)	Ameye et al., 2002; Gao et al., 2001; Hausman, 2004; Hlinak et al., 2000; Schaefer et al., 1986; Van Den Dries et al., 2002, 2003; Van Vaerenbergh, 2001; Zuurman et al., 1995	 Ramaker, 2001
Pro-C-epT	4M8™ (100 to 700 g) Mi Pro™ (15 to 1000 g)	Ameye et al., 2002; Bouwman et al., 2004; Jorgensen et al., 2004a, 2004b; Kiekens et al., 1999	
Hüttlin	HMG 5™ to 1200™ (9 to 1776 L)		
Key International	KG-5™ (125 to 3000 g)	Badawy et al., 2000ab	

Horizontal shaft high-shear mixer-granulators			
Supplier	Equipment capacity	References	Presentation
Littleford Loedige	5 to 30000 L L5™ to L10™ M5™ to M20™ FKM130D™ to FKM30000D™ FKM130 direct™ to FKM2000 direct™	Benkerrour et al., 1982; Delacourte et al., 1992; Ertel et al., 1990; Hoornaert et al., 1998; Li et al., 1996; Lister et al., 2004; Schaefer et al., 1986	 Lister, 2004

mixer was converted into heat in the moist mass. This phenomenon has to be taken into account as it may induce problems when working on thermosensitive products (Le Lan, 1978; Stahl, 2004).

The shaft in the bowl can be either vertical (Fig. 8a) or horizontal (Fig. 8b). When the shaft is vertical, the influence of gravity forces on the powder bed is higher.

FIGURE 5 High-shear Mixer-granulators with Different Mixing Chamber Design (Gaillard, 1990, Ramaker, 2001).

Drying Equipment as Part of a Multiphase Process

After a wet granulation in a high shear mixer is used as a part of a multiphase process, drying is usually performed in a fluid bed dryer or in a forced hot air dryer. As seen previously for multiphase granulation equipment, few studies describe the marketed equipments. Table 3 proposed a synthesis of technical characteristics of the most frequently used apparatus.

Single Pot Apparatus

A single pot is a double jacket bowl apparatus equipped with an impeller and a chopper which allows mixing, granulating, and drying in the same apparatus without discharging (Fig. 9). Therefore, it improves handling (no wet milling prior to drying) and it decreases the risk of cross contamination in accordance with Good Manufacturing Practice (GMP) requirements (Bauer, 1997; Pearlswig et al., 1994). Nevertheless, care must be taken to avoid the formation of lumps, as they cannot be broken before drying. Moreover, drying phase is known to be longer in single pot compared to fluid bed drying (Stahl, 2004).

Vacuum is always associated to double jacket drying. In addition to vacuum double jacket drying, manufacturers have developed various solutions to further improve drying efficiency: spherical bowl, tilting bowl, gas stripping, and microwaves.

For example, the spherical design of the bowl is likely to improve the movement of the product inside the bowl and increase the contact surface between the product and the heated wall (Le Lan, 1978; Rosetto, 1998). The spherical design of the bowl also improves the distribution of the binder solution through the powder blend, thus diminishing the quantity of wetting liquid necessary for granulation (Le Lan, 1978; Rosetto, 1998).

Additionally, Van Vaerenbergh (2001) demonstrated that the use of a swinging bowl during vacuum drying had a positive influence on drying times. It was observed that drying time was 15% shorter when using a swinging bowl as a result of the increase in the surface contact between the product and the apparatus wall.

Furthermore, the use of a gas stripping system, such as developed by Zanchetta™, Böhle™, and Collette™, allows faster drying by applying a gas flow through the powder bed (Bauer & Vadagnini, 1997; Duschler et al., 1997; Stahl, 2004). Under vacuum conditions, the injected gas expands inside the bowl and acts as a vapor carrier (Zanchetta, 1992).

Microwaves can also improve drying times in single pot apparatus. Pearlswig et al. (1994), who worked on a Collette Vactron™ single pot, observed that drying time was three times shorter with the combination of vacuum and microwaves compared to vacuum drying alone.

Table 4 proposed a synthesis of single pot mixer-granulator-dryers commercialised at present time.

Granule characteristics are likely to depend on both the granulation and the drying processes. Therefore, final granule properties will depend on the choice of the apparatus and process and of formulation parameters.

INFLUENCE OF HIGH-SHEAR GRANULATION EQUIPMENT AND PROCESS AS WELL AS FORMULATION PARAMETERS ON GRANULE PROPERTIES

Influence of Apparatus and Impeller Design

A few studies have described the impact of the bowl (shape, shaft, material), of the impeller geometry, and of the chopper design on granules properties (Holm, 1987; Hunter & Ganderton, 1973; Le Lan, 1978; Schaefer et al., 1986, 1987; Schaefer, 1988). Growth mechanism, final particle size distribution, and porosity of the granules were found to be directly related to

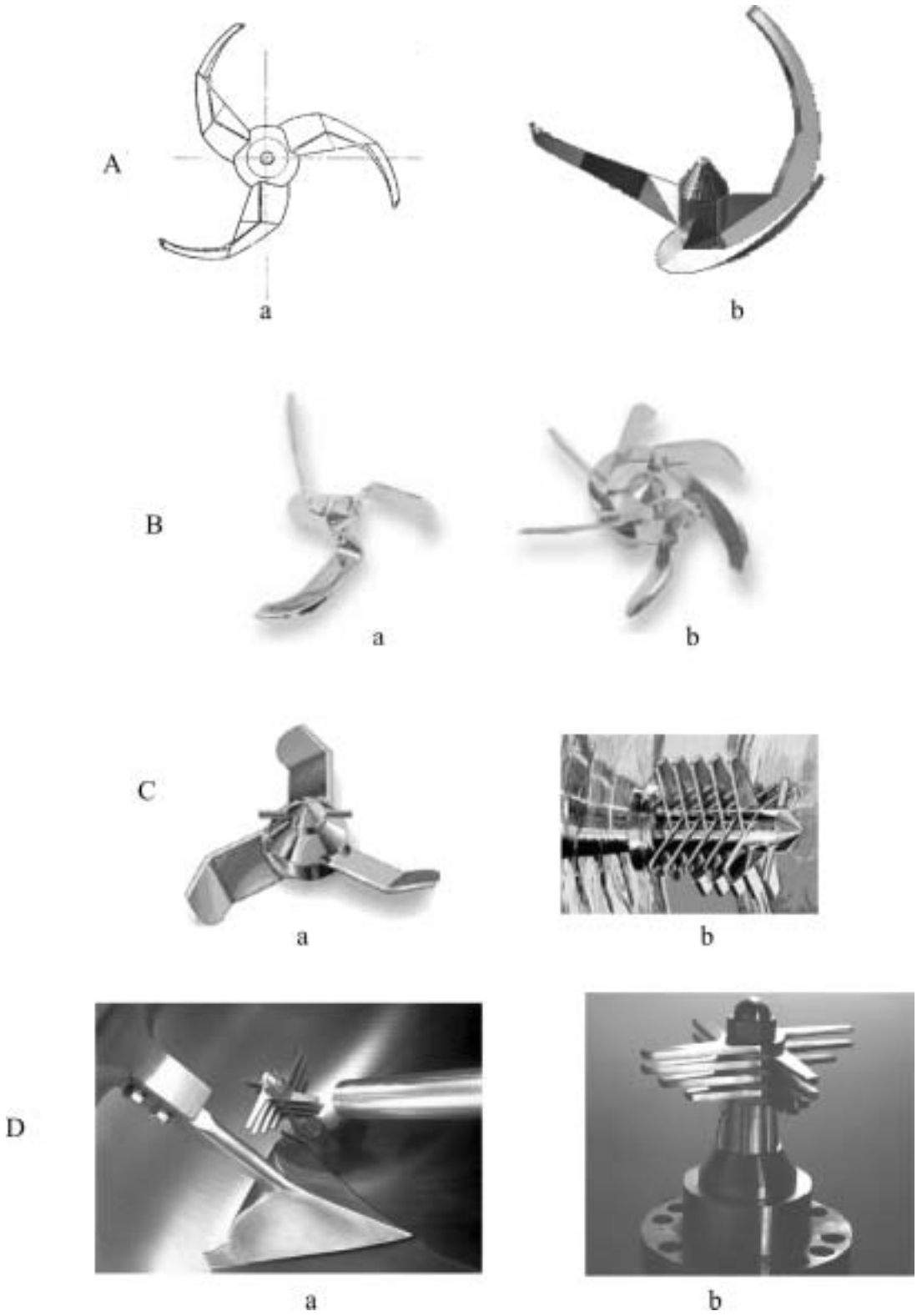


FIGURE 6 **Examples of Impellers and Choppers Shapes. A. Three Blades Impeller for Spherical Mixer: Moritz Turbosphere™ (a. Le Lan, 1978, b. Guerin, 2005); B. Standard Mixing Blades (a) and Collette Ultima Pro™ Mixing Blades (b) (Collette, 2005); C. "z" Rotor and Chopper of a Glatt Vertical Granulator™ (VG) (Glatt, 2005); D. Ploughshare Impeller (a) and Chopper (b) (Loedige, 2005).**

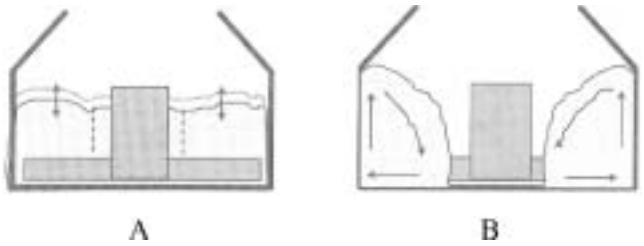


FIGURE 7 **Flow Regimes in Fielder™ Mixer Granulators: Bumping at Low Speed (A) and Roping at High Speed (B) (Lister et al., 2004).**

the distribution of the binder solution inside the powder mix. Indeed, it was observed (Mort & Tardos, 1999; Plank et al., 2003; Reynolds et al., 2004) that an inhomogeneity in binder distribution led to a wider size distribution of the granules with both fine and coarse fractions. Additionally, granules were more porous and less mechanically stable in fractions with low binder concentration. It is therefore necessary to optimize the distribution of the wetting liquid inside the powder mix (Delacourte et al., 1992; Fu et al., 2004; Holm et al., 1984; Kokubo & Sunada, 1996; Laicher et al., 1997). According to Le Lan (1978) and Rosetto (1998), when the bowl is designed with a spherical shape, the movement of the ingredients and the distribution of the binding liquid through the powder bed are facilitated.

The shaft in the bowl can be either vertical or horizontal. The use of a vertical shaft can result in an increase in granule density due to a higher influence of gravity forces on the powder bed (Kristensen & Schaefer, 1987).

In a research study, Bouwman et al. (2004) suggested that granulation behavior (mainly initial nucleation) was determined by the balance between the contact angle of the vessel wall and the sorption rate of the powder blend. When the vessel is made of a low contact angle material such as glass or stainless steel, a layer of liquid can be formed on the wall that will not be involved immediately in the nucleation process. Bouwman et al. (2004) showed that this phenomenon could be responsible for an inhomogeneity in the liquid distribution which led to a wide size distribution of the nuclei and, consequently, of the final granules. On the contrary, the authors observed that when the vessel was made of a high contact angle material, such as PMMA (polymethyl methacrylate) or PTFE (polytetrafluoroethylene), a narrow size distribution of the granules was obtained. The degree of influence of the

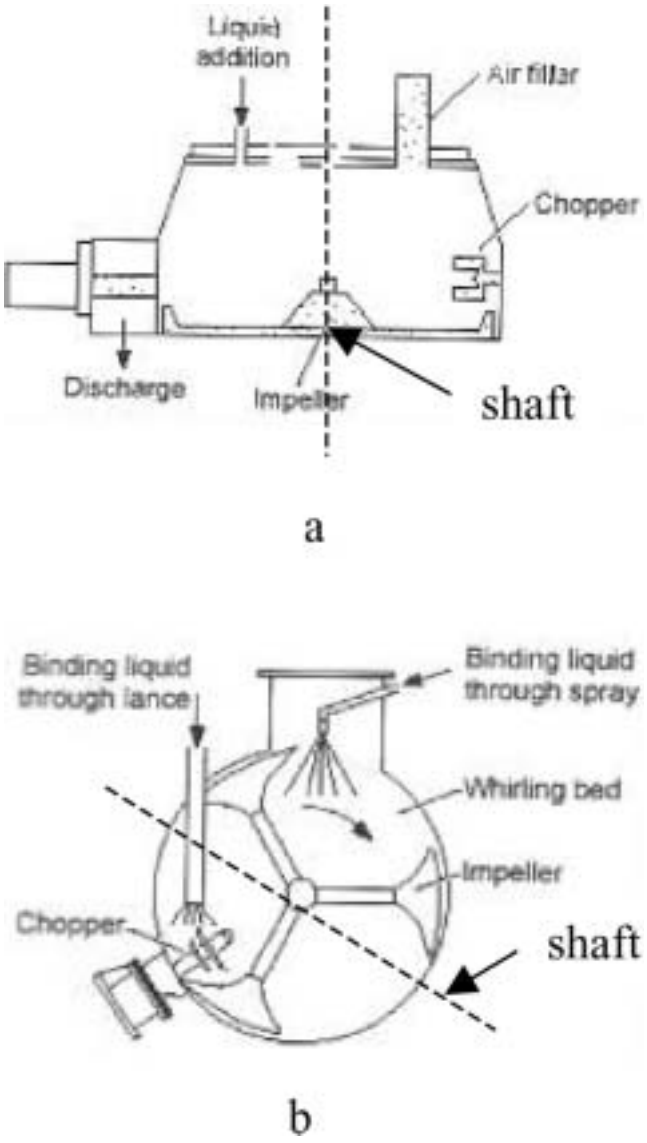


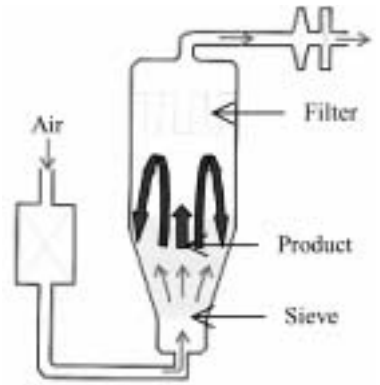
FIGURE 8 **Vertical Shaft (a), Horizontal Shaft (b) (Lister et al., 2004).**

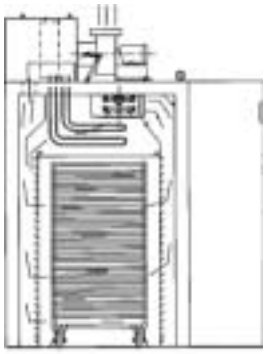
vessel material is related to the nature of the filler used. Granulation involving microfine cellulose and lactose which are "slow imbibing" powders will tend to be more influenced by the type of vessel than microcrystalline cellulose which is a "fast imbibing" powder.

However, it was observed that for larger equipments the impact of the nature of the vessel wall material was lower because of a smaller proportion of powder in contact with the wall (Faure et al., 1999). Above all, production equipment does not allow for a large choice in vessel material and stainless steel is usually used.

Holm (1987), Schaefer et al. (1986, 1987), and Schaefer (1988) described the influence of the impeller

TABLE 3 **Examples of Marketed Fluid Bed and Forced Hot Air Dryers**

Fluidized bed dryer			
Supplier	Equipment/capacity	References	Presentation
Aeromatic-Fielder (GEA-Niro)	MP-Micro™ (50 to 200 g) Aeromatic Fielder 5™ to 1550™ (10 L to 3100 L)	Delacourte et al., 1992; Gao et al., 2000; Li et al., 2003	 (adapted from Rosetto, 1998)
Hüttlin	Mycrolab™: 50 to 300 g Unilab™: 2 to 6 kg Pilotlab™: 7 to 32 kg HD-100™ to HD-3000™ (245 to 10553 L)		
Chin Yi Machinery	FBD-2™ to FBD-500™ (7 to 1600 L)		
Diosna	Mini-Lab™: 3.5 to 8 L CA 25™ to CA 2400™ (25 to 2400 L)		
Fitzpatrick	FitzAire™ (25 kg to 900 kg)		
Glatt	GPCG™ Series WST / WSG™ Series (5 kg to 1.5 t)	GPCG™ Series: Benkerrour et al., 1982; Chaplin et al., 2004; Hausman, 2004; Gotthardt et al., 1999 WST/WSG™ Series: Kokubo & Sunada, 1996	
Karnavati engineering	KELFBD-10™ to KELFBD-120™ (35 to 430 L)		
Vector Corporation	MFL01™: 50 mL FL-1™ to FL-500™ (4 to 1450 L)		

Forced hot air dryers			
Supplier	Equipment/capacity	References	Presentation
Gruenberg	TI8H28™ to TI8H476™ (15 to 800 cubic feet/42 to 2265 L)		 Gruenberg, 2005
Karnavati engineering	KELDO-24™ to KELDO-96™ (24 to 96 t)		
VWR international	VWR™ vacuum oven Model 1410™: 17 L Model 1430™: 48.1 L Model 1450™: 127.4 L	Badawy et al., 2000b	

on granule density using, as a criteria, the relative volume of powder swept out by the impeller, i.e., the volume swept out by the impeller blades per second divided by the volume of the bowl. Experiments were conducted in different apparatus, equipped with impellers of various design and blade angles at different impeller speeds. The authors concluded that a high swept volume caused high densification of the agglomerates and narrowed granule size distribution by crushing of largest agglomerates.

Holm (1987) also studied the influence of the chopper on granules density using the relative swept volume as a criterion. He demonstrated that the chopper size and rotation rate had no effect upon the granule size distribution. He suggested that the primary function of the chopper was to disturb the uniform flow

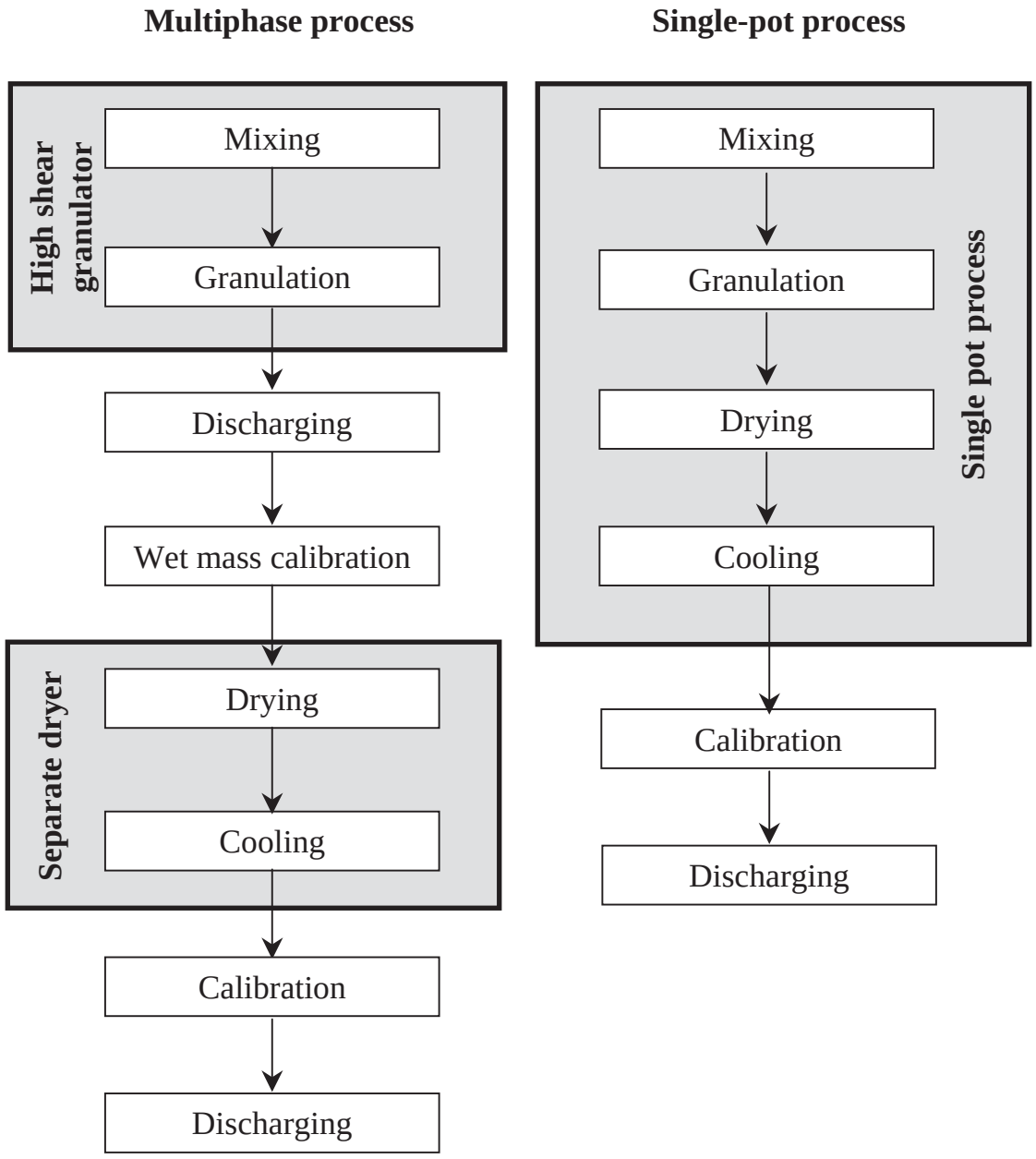


FIGURE 9 **Granulating Process: Multiphase Versus Single-pot.**

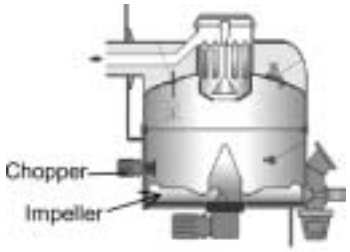
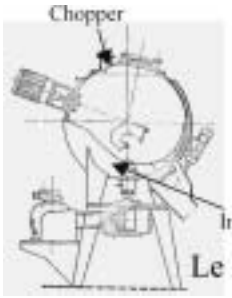
pattern of the mass. Lister et al. (2004) observed that the effect of the chopper on granules attributes, such as density, was higher when a large proportion of the mass powder was pushed through the chopper region, i.e., when the chopper was relatively large.

Because the size and shape of mixing chambers, impellers and choppers can differ significantly according to the equipment, equipment switch cannot easily be performed (Rekhi et al., 1996).

Schaefer et al. (1986) worked on different apparatus (Loedige™, GEA™, Diosna™, and Fielder™ equipment). Their first aim was to compare same size/different suppliers granulators. Their second objective was to compare same supplier/different sizes apparatus. In both cases, they found major differences in granule properties when smaller scales equipments were used.

Because the design of the bowl, impeller, and chopper is fixed for a given granulator and cannot be adapted for each type of granulation, the control of the granule properties has to be achieved by the optimization of the process and formulation parameters.

TABLE 4 **Examples of Marketed Single Pot Apparatus**

Single pot equipments			
Supplier	Equipment capacity and drying method	References	Presentation
Böhle	VMA 70™ (70 L) Double jacket, vacuum, gas stripping	Steffens et al., 1995	 Böhle, 2005
Diosna	VAC 20™ to 1200™ (20 to 1200 L) Double jacket, gas stripping		
GEA (Collette NV)	UltimaPro™ (10 to 1200 L), succesor of Vactron™ Double jacket, vacuum, tilting bowl, gas stripping	Dushler et al., 1995; Killeen, 1999; Pearlswig et al., 1994; Robin et al., 1994; Van Vaerenbergh, 2001	
Zanchetta Romaco	Rotolab™ (2 L) Roto P10™ to P2000™ (10 to 2000 L) Roto E 100™ to E1200™ (100 to 1200 L) Roto Cube 12™ to 1200™ (12 to 1200 L) Double jacket, vacuum, tilting bowl, gas stripping	Albertini et al., 2003; Bauer & Vadagnini, 1997; Cavallari et al., 2002; Fu et al., 2004; Robin et al., 1994; Stahl, 2000, Scott, 2000	 Tilting Collette, 2005
GEA (Aeromatic-Fielder)	Spectrum GP™ (1 to hundreds of kg) Double jacket, vacuum, microwaves	Badawy et al., 2000a and 2000b; Gauthier, 1993; Poska, 1991; Robin et al., 1996; Smart, 1996; White, 1994	
Pro-C-epT	Mi Pro™ Double jacket, vacuum (15 to 1000 g) Mi-Mi-Pro™ Double jacket, vacuum, microwaves (100 to 800 g)	Kiekens et al., 1999	 Niro, 2005
Moritz (Bio Inox/ Pierre Guerin)	Turbosphere 10™ to 2000™ (10 to 2000 L) Double jacket, vacuum, spherical bowl, microwaves	André et al., 1990; Gaillard et al., 1989; Le Lan, 1978; Poska, 1991; Robin et al., 1994	 Le Lan, 1978

Influence of Process Parameters

The following process parameters have been found to be of a high importance (Fu et al., 2004; Schaefer, 1988): binder solution or solvent addition mode, wet massing time, impeller and chopper speed, and temperature.

Method of Addition of Binder Solution and Wetting

The binder solution may be added either directly to the powder mix or in binder solution. Holm and coworkers (1984), who performed granulations in a Fielder PMAT 25™, noticed that the binder distribution

was not homogeneous when dry binder was used and a solvent was added. Therefore, the study recommended the addition of a binder solution to the powder mix. On the other hand, Laicher et al. (1997) and Delacourte et al. (1992), who respectively performed granulations in a Diosna P10™ and a Loedige M5™, chose to use a dry binder because it allowed granulation at high binder concentrations, while a corresponding binder solution would have been too viscous for spraying. However, since these experiments were not conducted under the same conditions in terms of equipment and formulation, the influence of the method of binder addition on the observed results cannot be ruled out.

Some authors (Holm et al., 1983; Fu et al., 2004; Knight et al., 1998, 2000; Kristensen & Schaefer, 1987; Kokubo & Sunada, 1996; Scott et al., 2000) observed that the atomization of the wetting liquid improved its distribution inside the powder blend. Liquid addition without atomization led to an inhomogeneous liquid distribution especially at low impeller speed. Lister et al. (2001) showed that size distribution and shape of nuclei were dependent on spray flux. Higher spray flux values led to larger surfaces of wetted powder. Spray flux needed to be optimized to perform controlled nucleation and obtain a narrow size distribution. Schaefer et al. (1986) did not observe any significant influence of the size of the atomized droplets on granule quality. On the other hand, Iveson et al. (2001a) demonstrated that the nucleation formation mechanism depended on the relative sizes of the droplets and of the primary particles (Fig. 10). It was observed that when droplets were smaller than solid particles, they distributed onto the surface of the particles and granules grew by coalescence (Fig. 10a). On the contrary, when droplets were larger than solid particles, immersion of the small particles in the liquid was noted (Fig. 10b).

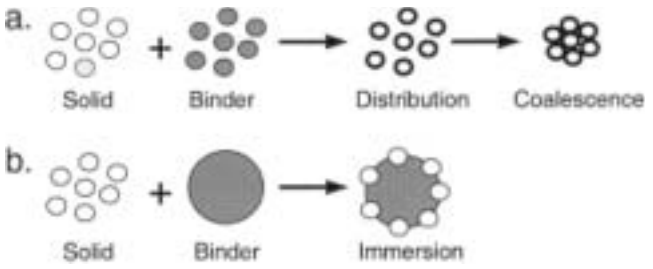


FIGURE 10 Distribution Mechanism (a), Immersion Mechanism (b) (Iveson et al., 2001a).

Impeller and Chopper Speed and Granulation Time

In a specific study, Uribarri et al. (2003) noticed a decrease in the mean granulated particle size when a chopper was used in comparison with granulation performed without the use of a chopper. However, many authors reported that the speed of the chopper had no significant influence on granule properties (Holm et al., 1983, 1984; Levin, 2004; Westerhuis et al., 1997). Therefore, while the presence of a chopper could have an influence on granule properties, its speed is not likely to be of importance.

Two parameters, impeller speed and granulation time, were found to influence concomitantly the following granule properties: size distribution (Biggs et al., 2003; Kristensen et al., 1987; Kokubo & Sunada, 1996; Uribarri et al., 2003), shape (Knight et al., 2000), porosity, and friability (Badawy et al., 2000a; Kiekens et al.,1999; Oulahna et al., 2003).

For high impeller speed, the distribution of the binder solution in the powder mix is improved. Consequently, a lower amount of binder solution is required to obtain granules with a narrow size distribution (Bardin et al., 2004; Knight et al., 2000; Holm et al., 1983, 1984; Schaefer et al., 1986). However, if the impeller speed becomes too high, fine particles can be generated from granule breakage due to mechanical stress. This can produce two major fractions in granule size distribution: a coarse agglomerated fraction on one side and a fine powder fraction on the other side (Knight et al., 2000; Kokubo & Sunada, 1996; Oulahna et al., 2003; Vromans, 1994). Similarly, increasing granulation time increases granule mean size. However, after a certain time, breakage creates fine particles and leads to a wider size distribution (Kokubo & Sunada, 1996; Uribarri et al., 2003).

When the speed of the impeller is too low, the inefficient distribution of the binder solution may lead to a wide particle size distribution and to the presence of ungranulated particles (Holm et al., 1983, 1984; Schaefer et al., 1986). Additionally, a short granulation time can be responsible for the poor distribution of the components. In particular, Kokubo & Sunada, (1996), in the case of a dry binder, showed that, at extremely short granulation times, the distribution of the solvent in the powder mass was not homogeneous

decreasing the binder dispersion. Because of insufficient dispersion, weakly bonded particles were formed, thus raising breaking susceptibility.

Impeller speed was also found to have an influence on granule shape. Knight et al. (2000) observed that granules produced at high impeller speed for a short granulation time were less spherical than granules obtained at low impeller speed for a long granulation time. He concluded that the impeller speed and granulation time had to be optimized in order to obtain spherical granules.

Moreover, the impeller speed and granulation time can modify granule porosity. For high impeller speed and/or long granulation time, granules are submitted to high-shear forces which leads to their densification, i.e., decrease of intragranular porosity and decrease of friability (Badawy et al., 2000a; Kiekens et al., 1999; Oulahna et al., 2003; Tobyn et al., 1996). However, Ameye et al. (2002) observed that the impeller speed had no influence on granule friability in Mi Pro™ high-shear mixers at whatever the scale (from 250 mL to 5 L bowls).

Based on these findings, impeller speed and granulation time must be concomitantly chosen to ensure to the resulting granules the required properties to facilitate further processing into tablets, i.e., optimized sphericity, density, porosity, and size distribution.

Influence of Formulation Parameters

Physical Properties of Raw Materials

Obviously, wet granule characteristics are expected to be related to the physical properties of raw materials. The most important physical properties are: primary particle size and morphology, wettability and solubility.

Badawy et al. (2000b), Cruaud et al. (1980) and Kristensen & Schaefer, (1987) highlighted an effect of primary particle size on granule growth rate and on wet granule size distribution. Coarser powders led to a faster growth rate and larger final wet granules. Therefore coarser powder required a shorter granulation time. However, these authors observed that granulation time could be optimized to limit the effect of primary particle size.

Furthermore, an influence of primary particles size on porosity was observed. Coarser powders led to weaker liquid bridges between primary particles. Growth by coalescence and/or crushing and layering were favored. The resulting granules were more deformable, friable, and less porous (Mackaplow et al., 2000; Ritala & Virtanen, 1991). In addition, the surface of the granules appeared smoother as the primary particles size was reduced. It is probable that granules with smaller primary particles were probably less readily damaged in the high-shear environment (Fu et al., 2004).

An effect of primary particles size on the amount of granulating liquid required was also demonstrated (Hunter & Ganderton, 1973; Johansen & Schaefer, 2001; Knight et al., 1998; Keningley et al., 1997; Westerhuis, 1997). Indeed, there is a direct relationship between primary particle size and shape and their surface area. Larger amounts of liquid are required when surface area increases.

Finally, a narrow size distribution of primary particles is recommended to limit segregation and avoid granule heterogeneity (Van Den Dries & Vroman, 2002; Vromans, 1994).

Wettability of the powder by the binder solution is related to the solid–liquid contact angle of the system. Iveson et al. (2001a and 2001b) and Jaiyeoba & Spring, (1980) observed that a low powder–liquid surface tension increased wettability and led to larger granules. Therefore, a good wettability of the powder enhances binder solution distribution onto the particles surface and granules agglomeration (Becker et al., 1997; Goldszal & Bousquet, 2001; Pont, 2000).

Moreover, in the case of a low powder–liquid contact angle, resulting granules presented good cohesive properties (Iveson et al., 2001a and 2001b).

Powder with good wettability also allows a lower amount of binder liquid and the use of a lower amount of binder liquid for granulation (Malamataris & Kiortsis, 1997).

As seen above, granule growth is initiated by the formation of liquid bridges between primary particles. The number and strength of such bridges not only depend on the powder–liquid surface tension but also on the solubility of the raw material. (Bardin et al., 2004; Jaiyeoba & Spring, 1980; Keningley et al., 1997). In particular, the solubility of the filler and of the drug substance in the binder solution is of high importance.

When the filler is soluble in the binder solution, granulation requires lower solvent volume (Holm et al., 1983, 1984). Benkerrour et al. (1982) and Faure et al. (1999) studied granulation with a soluble

and an insoluble filler (respectively, lactose and tricalcium phosphate). They observed that when lactose was used, it dissolved in the granulating liquid and recrystallization occurred. So, the resulting granules demonstrated a higher strength and a lower friability. Moreover, lactose granules were less porous than the tricalcium phosphate ones. In the case of lactose granules, macro-pores predominated while in the case of tricalcium phosphate granules, micro-pores were in high proportion (Benkerrour et al., 1982).

The solubility of the drug substance in the binder solution is also important as poor solubility may result in drug content heterogeneity (Wells & Walker, 1983). Miyamoto et al. (1998) studied a highly soluble drug (ascorbic acid) and a poorly soluble drug (ethenzamide). It was observed that the highly soluble ascorbic acid was homogeneously distributed in the granules whereas the poorly soluble ethenzamide was highly concentrated in smaller granules with both experiments being conducted under the same conditions.

Amount and Nature of Binder Solution

It is well known that the amount of granulating liquid affects granule growth; the greater the amount of granulating fluid, the higher the granule mean size (Kokubo & Sunada, 1996; Konishi et al., 1996; Uribarri et al., 2003).

The presence of a binder at the inter-granular interface improves both the plasticity of the mass and the inter-particulate bonding (Zuurman et al., 1995). Therefore, when the amount of binder is increased, granule porosity is lowered (Iveson et al., 1996; Knight et al., 1998; Konishi et al., 1996; Mackaplow et al., 2000). Moreover, Fu et al. (2004) observed that a too high or a too low binder concentration led to lower granule sphericity due to their deformability.

An optimal effect of the binder can be obtained for particles with a high inter-granular porosity because of an increase of the surface area over which the binder can act (Konishi et al., 1996; Zuurman et al., 1995). It is thus possible to use a lower amount of binder.

Increasing the amount of binder leads to an increase in binder solution viscosity if the amount of solvent remains unchanged. An increase in binder concentration was found to increase granule strength (Benkerrour et al., 1982). An increase in viscosity was found to limit drug migration during subsequent drying of the granules (Kapsidou et al., 2001; Warren & Price, 1977b). However, it was also observed that when the viscosity of the solution became too high, the granulating solution was not uniformly distributed in the powder blend thus inducing poor granule homogeneity (Keningley et al., 1997; Reading & Spring, 1984; Schaefer et al., 2004; Van Den Dries et al., 2003).

It was noticed that both the solubility of the raw materials in the wetting liquid and the liquid viscosity affected granule properties (see the section on Physical Properties of Raw Materials). Consequently, the nature of the solvent can also influence granule properties. Hausman (2004) performed granulations with water and methanol as solvents (at constant process parameters). The experiment showed that the nature of the granulating solvent modified granule size distribution and inter-granular porosity. In the case of water soluble fillers, granules with a larger size distribution and a higher density were obtained when water was used as granulating solvent (Kristensen & Schaefer, 1987; Wells & Walker, 1983).

Table 5 lists the apparatus, process, and formulation parameters that may have an influence on the characteristics of final granules.

Additional Considerations

The influence of the temperature increase during running of the process has to be mentioned. Betz et al. (2004) observed a linear relationship between product temperature and friction forces at interparticle contacts. Friction forces depended on powder blend properties, such as particle size, shape, surface, solubility (Betz et al., 2004), and flowability (Le Lan, 1978), and on the filling level of the bowl (Betz et al., 2004). Moreover, product temperature was found proportional to the relative swept volume which is linked to the design of the bowl and to the impeller speed (Kristensen & Schaefer, 1987; Le Lan, 1978; Levin, 2004).

Such an increase in powder blend temperature can lead to a loss of moisture because of evaporation (Holm, 1987; Schaefer et al., 1986, 1987; Schaefer, 1988). Evaporation of surface free liquid at high-energy

TABLE 5 **High-shear Granulation Apparatus Design, Process, and Formulation Parameters Likely to Have an Influence on Granule Properties**

Apparatus design	Process parameters	Formulation parameters
• Bowl (shape, material, shaft)	• Method of formation of binder solution	• Primary particles size and morphology
• Impeller (shape)	• Method of addition of binder solution or solvent	• Powder wettability by binder solution
• Chopper (presence)	• Impeller speed/granulation time	• Drug substance/filler solubility in binder solution
	• Chopper speed	• Amount and nature of binder solution
	• Temperature	

input is likely to decrease the potential for growth by coalescence (Albertini et al., 2003). Obviously, a good sealing of the bowl can prevent evaporation. On the contrary, granule growth depends on the solubility of the raw material in the binder solution, which can be improved when product temperature increases (see Physical Properties of Raw Materials).

Considering that generally the choice of the apparatus is imposed, it is essential to understand which process and formulation parameters are likely to have a major impact on final granules properties as summarized in Table 6.

Nevertheless, in order to minimize high-shear granulation process and formulation parameters contribution on granule properties, Li et al. (1996) and Hausman (2004) suggested to add extra-granular microcrystalline cellulose (MCC) Comparing the influence of intra- and extra-granular localization of MCC, it was found that the addition of MMC improved granule compressibility.

INFLUENCE OF DRYING EQUIPMENT AND RUNNING PROCESS PARAMETERS ON GRANULES PROPERTIES

The different drying techniques previously described may confer different textural and mechanical properties to granules. The influence of the choice of a drying process on granule properties, for multiphase and single pot equipment, is going to be presented.

Multiphase Drying Process

Forced Hot Air Drying

In forced hot air drying, the close contact between granules can facilitate solute migration towards the surface. This can favor caking when evaporation rate from the surface of the powder blend is faster than its

TABLE 6 **Influence of Main High-shear Granulation Process and Formulation Parameters on Granules Properties**

Increase in	Granules size	Narrowing of size distribution	Density	Sphericity	Granulation time	Control on granules size
Impeller speed	↘	↗↗	↗↗	↗	↗↗	↗
Temperature	↗	↘↘	↗	—	↘	↗↗
Binder concentration[1]	↗↗	↘↘	↗↗	↗	↗↗	↘↘
Primary particles size	↘	↘	↘	↘	↗	—

[1]Powder wettability and solubility are also linked to that parameter, because a high wettability and solubility can enhance the action of the binder.
Adapted from: Castel, Techniques de l'ingénieur.

internal diffusion. Warren & Price, (1977a) studied water soluble drug migration during tray drying of a lactose based wet granulation. They showed that variations in filler particle size resulted in differences in drug content uniformity. A decrease in lactose particle size led to a reduction in the pore size within the particles and to an increase in the contact area between particles. Therefore, drug inter-granular migration phenomenon was increased. A control of particle size of the major filler could therefore limit drug migration and improve granule uniformity (Kapsidou et al., 2001; Kiekens et al., 2000).

Davis et al. (2004) studied the polymorphic transformation of glycine during the drying phase following a wet granulation. Tray drying, a slow drying technique, was found to limit the polymorphic transformation of the drug substance as opposed to rapid fluid bed drying.

According to Pérez et al. (2002), tray dried granules presented lower fine proportions compared to fluidized bed dried granules. Indeed, as the product remains static during forced air tray drying, the granules are not submitted to aggressive mechanical phenomena responsible with attrition (Kokubo & Sunada, 1996).

Fluid Bed Drying

Contrary to slow drying in an oven, the rapid evaporation of water as a result of the turbulent motion during fluid bed drying limits the shrinkage of the granules and produces granules of high porosity and of large mean diameter. On the contrary, liquid evaporation occurs in a very slow manner when drying is conducted in an oven and so produces less porous granules (Bashaiwoldu et al., 2004).

In fluid bed drying, each granule is isolated from its neighbors by the heated air and inter-granular migration of solute is not possible. However, intra-granular migration, i.e., solute migration caused by the movement of liquid toward the surface of the granule due to capillary effects through intra-particulate spaces, can occur. In fact, fluidization produces greater solvent intra-granular migration as compared with other drying methods (forced hot air, microwaves, vacuum etc.) because of the important movement of the particles in the air flow and because drying kinetic is improved (Bashaiwoldu et al., 2004). A drug substance highly soluble in the granulating solvent is therefore likely to migrate to the granule surface generating heterogeneity with a higher concentration in the outer layer (Cruaud et al., 1980). Moreover, during fluid bed drying, inter-granular collisions and collisions with the dryer wall can decrease granules size by attrition (Paschos, 1987). In the same case, attrition of the solute-rich outer layer during fluidization and elution of dust can therefore result in an overall loss of drug substance (Travers, 1975).

There are various types of expanded beds (slugging, boiling, channeling, and spouting). The influence of the apparatus type on the effectiveness of heat transfer is not to be developed in this review. For further information, the following references can be consulted: Joulié (1994) Ormós (1994), and Parikh (1997).

Single Pot

Single pots are equipped with a double jacket bowl which is heated for drying. Drying efficiency is related to the time and surface contact between the granules and the heated apparatus wall. Therefore, drying is improved when agitation is performed. However, a high agitation can lead to attrition with the production of fines and can increase granule densification (Authelin et al., 1996; Stahl, 2004). The shape of the impeller has to be designed to limit as much as possible the attrition of the granules and facilitate mixing.

Vacuum drying is always associated to double jacket drying in order to perform faster drying.

Manufacturers have developed complementary solutions to improve drying efficiency in single pots: spherical chamber, gas stripping, tilting bowl, and microwaves. Obviously, these are likely to have an influence on final granules properties:

- When manufactured in a spherical mixing chamber, granules were found to present a higher sphericity and density. Moreover, a limited attrition was observed after drying due to the spherical shape of the bowl (Rosetto, 1998; Shi, 1996).
- Gas stripping consists in the injection of gas through the powder mass. Under vacuum conditions, the injected gas expands inside the bowl and acts as a vapor carrier, thus speeding up the drying process which consequently leads to a decrease in granules attrition and densification (Stahl, 2004; Zanchetta, 1992).

- The influence on granule properties of a swinging bowl, that is to say tilting during vacuum drying, was studied by Van Vaerenbergh (2001). The study observed an increase in granule size distribution with a reduction in fines production. These results were closer to those obtained by forced air drying. Consequently, the granules possessed better flow properties.
- Killeen (1999) compared granules dried in a conventional air-circulation oven and in a microwave oven after wet granulation. It was observed that the granule tapped density was higher and the porosity lower when dried with microwaves. Moreover, the shape of the granules dried by microwaves was more regular and their surface smoother. Kapsidou et al. (2001) studied the migration of various drug substances (prednisolone, propanolol hydrochloride, and salicylic acid) during drying processes. Drug migration was remarkably lower when dried in a microwave dryer compared to a conventional hot oven.

Influence of Running Process Parameters for a Given Drying Technique

For a given drying technique, a modification of one of the parameters influencing the process may also affect some of the granule properties.

Temperature and drying time are essential parameters. For example, Perez & Rabišková, (2002), who studied hot air oven, microwave oven, and fluid bed drying, observed that, for a same drying process, an increase in temperature led to a decrease in the diameter of the final granules due to a shrinking phenomenon. In single pot drying, complementary solutions (spherical chamber, tilting bowl, microwaves, and gas stripping) have been developed to reduce drying time and thus limit the attrition due to shearing (Le Lan, 1978; Rosetto, 1998; Shi, 1996; Stahl, 2004; Zanchetta, 1992; and see Single Pot).

Other parameters are also involved, such as impeller speed in single pot drying. Indeed, while an increase in impeller speed can improve drying efficiency, it can also cause attrition and lead to granule densification and to fines production (Authelin et al., 1996; Stahl, 2004). In fluid bed drying, air velocity has also to be optimized; it has to be high enough to allow a good fluidization without inducing important attrition (Paschos, 1987).

Therefore, granule properties depend on the optimization of several running process parameters.

Synthesis on the Influence of Drying Processes on Granules Properties

Table 7 summarizes the influence of different drying processes on granule properties (granule size distribution, density, and porosity) and on the migration of solute material.

The drying method proved to have a strong influence on the granule properties. Indeed, the high attrition phenomena during fluid bed drying leads to the production of fines. Attrition also occurs during double jacket/vacuum drying under shearing in a single pot apparatus. Densification of the granules happens

TABLE 7 **Influence of Different Drying Processes on Major Granules Properties**

	Multiphase		Single pot	
	Forced hot air drying	Fluidized bed	Double jacket/ Vacuum	Double jacket/ Vacuum/Microwaves
Granules size distribution	No change during drying except if caking occurs (formation of lumps)	High attrition (fines) Possible granulation continuation (size increase)	Attrition due to shearing (size reduction)	Attrition reduced with the decrease of drying time
Granules bulk and tapped density and porosity	No densification	Higher porosity	Densification due to shearing	Lower densification because drying time is reduced
Migration of solute material	High intra-granular migration. towards the surface with a risk of caking	High intra-granular migration. Migration and attrition can lead to over-dosed fines	Inter- and intra-granular migration	Low inter- and intra-granular migration

when drying is performed in a single pot due to shearing. This phenomenon can be limited when microwaves are added and as drying time is reduced. On the contrary, fluid bed drying produces granules with a high intra-granular porosity as a consequence of fluidization and of a short drying time.

It has been shown that inter- or intra-granular solute migration is likely to occur during drying depending on the process used. A drug substance highly soluble in the granulating solvent is therefore likely to migrate in the forming granules thus inducing content heterogeneity (Cruaud et al., 1980). Travers (1975) studied the migration of sodium chloride solution during different drying processes of kaolin granules. The solution migrated towards the surface of the granules due to capillarity through intra-granular spaces. Intra-granular migration was very important when drying was performed in a fluid bed dryer whereas there was nearly no migration during double jacket vacuum drying so the latest process led to granules with a better homogeneity (Travers, 1975). Migration was reduced when granules were dried by microwave drying. For comparison, in a ventilated oven, migration was also observed but was rather less important than in a fluid bed dryer (Cruaud et al., 1980).

CONCLUSION

Various equipments are available for wet granule production. Two main processes are granulation in a high-shear mixer-granulator followed by drying in a separate apparatus (hot oven tray or fluid bed dryer) and single pot granulation including drying.

Granulation parameters have a strong impact on final granule properties. These parameters can be related to the equipment, the process, and the formulation. Indeed, the design of the bowl and of the impeller has an effect on granule size distribution and density due to its influence on the hydrodynamic of the powder mass and on the distribution of the binding liquid. Moreover, the method of addition of the binder affects granule growth as it affects binder distribution. Impeller speed and granulation time need to be concomitantly adjusted to obtain granules with optimized sphericity, density, porosity, and size distribution. Granule size distribution also depends on process temperature. Finally, granule size distribution, porosity, friability, shape, homogeneity, and compressibility can differ significantly depending on the physical properties of the primary particles (size, shape, wettability, and solubility) and on the amount and nature of the binder solution.

After wet high-shear granulation, drying can be conducted in different ways. Heat transfer, mechanical stress, and intra/inter-granular solute migration are specific to each drying technique. Consequently, differences in granules size distribution, density, porosity, and homogeneity may be observed depending on the drying technique. Furthermore, for a given equipment, running process parameters also influence granules properties. Temperature and drying time are essential parameters. Moreover, in the case of single pot drying, complementary solutions (spherical chamber, tilting bowl, microwaves, and gas stripping) have been developed to reduce drying time and thus limit attrition. Other parameters are involved such as impeller speed in single pot drying or air velocity in fluid bed drying. The optimization of several parameters is required for proper end-use properties of granules.

In conclusion, granules properties depend on apparatus, process and formulation parameters during both the granulation and the drying step. Final granule properties result from the complex interaction between all these parameters. The right knowledge of their contribution is therefore essential to ensure reproducible granule quality and thus facilitate equipment changes or scale up.

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