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Review article

Process control and scale-up of pharmaceutical wet granulation processes: a review

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Abstract

In this paper the techniques for process control and scale-up of pharmaceutical wet granulation processes are reviewed. For wet granulation in high-shear mixers, specific methods based on the liquid saturation and the consistency of the wet mass are described. Both parameters can be used to quantify the deformability of the wet granules, and relate well with the particle size of the end granules. In practice, the power consumption of the high-shear mixer is used for the monitoring of the wet granulation process, whilst for scale-up, it is helpful to use the underlying relationship between power consumption and saturation level or wet mass consistency. In fluid bed granulation the granulation process is different and the moisture content in the bed is the key parameter to control. This can be monitored directly by near infrared probes or indirectly with temperature probes. As a large number of inter-related variables can be adjusted to modify the process, computerized techniques have become popular for fluid-bed process control – fuzzy logic, neural networks, and models based on experimental design techniques are several examples. In addition, engineering techniques based on particle size population balance modelling are under development for both fluid bed and high-shear granulation.

Keywords: Wet granulation; High-shear mixers; Fluid bed; Scale-up; Process control

1. Introduction

Wet granulation is a process still widely used in the pharmaceutical industry. It has not been replaced by direct compression technology, partly because of development cost considerations and habits, and partly because it remains in some cases an attractive technique. It provides better control of drug content uniformity at low drug concentrations, as well as control of product bulk density and ultimately compactibility (brittle fracture), even for high drug contents.

Processing takes place in one of two types of closed granulating systems: fluid bed granulators or high-shear mixers. The two techniques differ technically on the mode of solid agitation, and fundamentally on the mode of granule growth. In fluid bed granulation, the powder mix is maintained as a fluidized bed by a flow of air injected upwards through the bottom screen of the granulator. The binding solution is sprayed above the powder bed, in a direction opposite to the air flow. Other spraying directions can be used on the same equipment for solids coating. The granules result from the adhesion of solid particles to the liquid droplets that hit the bed. Partial drying by the fluidizing air occurs continuously during granulation. The process continues until all the powder has been agglomerated, and it needs to be stabilized as far as moisture balance is concerned. The equilibrium may not be constant, however, as the moisture content of the granules could be increasing slightly throughout the process, and the trajectories of the particles may change with changes in the density of the agglomerated powder bed. Complete drying is quickly achieved in the hot air stream when binder spraying is stopped.

In high-shear granulation, an impeller maintains the powder in agitation in a closed vessel, and here also a binder solution is sprayed from the top. As the liquid droplets disperse in the powder, they form the first nuclei of future granules. The agitation forces prevent the development of large agglomerates, because they would be too fragile to sustain the shear. However, as mixing and spraying proceed, the existing agglomerates undergo densification, whereby the internalized binder is squeezed out to the surface of the wet agglomerates. This has two consequences. It

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makes the agglomerates harder, and their surface more adhesive, and hence granule growth enters a new, more efficient phase. The process is stopped somewhere in this phase before an excess of liquid or excessive densification provokes a phase inversion, i.e. a slurry or uncontrollable growth ('balling' phenomenon). The drying step traditionally takes place after transferring the damp mass into another piece of equipment (fluid bed dryer), but the use of single-pot technology (drying in place) is now spreading. The granules formed are understandably denser than those obtained in fluid bed granulation.

By definition, process scale-up is the transfer of a controlled process from one scale to another. It implies that the process on the small scale is understood and controlled, and ideally that some basic rules can be followed to quickly obtain optimization and control of the process at the bigger scale. This paper will therefore review elements of process control as well as scale-up.

2. Which parameters need to be controlled?

Table 1 lists the main variables affecting the quality of the granules and eventually that of the tablets. For convenience, those variables have been classified in five groups. The first group is usually disregarded: the nature and characteristics of the ingredients entering the formulation are almost always fixed.

Category 2 regroups the process variables which are machine-dependent. In high-shear granulation, the fast dispersion of the binder is taken for granted. The spraying conditions are therefore not critical. The coalescence into granules is mainly affected by the mixing conditions and the proportion of liquid used. That the spraying conditions do not matter is not exactly true, but in practice the system usually 'recovers' even when the binder is added as a single event [1,2]. The principal difficulty with wet granulation in high-shear mixers is to decide 'when to stop': hence, the importance of control of the end-point.

In fluid bed granulation, the spreading of the binder liquid droplets in the powder bed is much more crucial, because it is this phenomenon that controls most of the agglomeration. Here droplet size, contact with the powder bed and humidity in the bed are key parameters. The situation is further complicated by the fact that the variables listed in category 2 for fluid bed granulation are very much inter-related. For example, bed temperature and humidity depend on the temperature and humidity of the inlet air, the temperature and amount of water sprayed, and the extent of evaporation observed, itself a function of droplet size, spray rate and air flow rate. The principal difficulty with wet granulation in fluid bed granulation is to obtain a stable regime by carefully balancing the different input variables.

The parameters from category 3 which are associated with the drying step of the wet granules have been given considerably less attention. Wet granules may be tray-dried, fluid bed-dried, or dried in the high-shear mixer using gas stripping (dry air or nitrogen), microwave drying, infrared drying or a combination thereof. Drying in fluid bed granulators is relatively simple, and the drying end-point is detected by a sudden rise in bed and outlet air temperature, and an equalization of the outlet air dew point to that of the inlet air. In single-pot high-shear granulation, it is reasonable to expect that some crushing and attrition could take place during drying. In this case the drying conditions would have to be considered in scaling-up the whole granulation process. A discussion on this issue is provided in the review paper from Stahl [3]. In most publications concerning the scale-up of wet granulation processes, drying conditions were fixed: wet granules produced at different scales were dried in the same conditions, e.g. small scale tray drying or fluid bed drying.

The granule properties represent the fourth category of variables. Granules have been systematically characterized in the dried state, and the effects of variables from categories 1 and 2 on the granule characteristics have been listed. The effect of variables from category 3 has nearly always been considered negligible.

The particle size distribution (PSD) of the granules is the main characteristic which has been examined. Because the ultimate application is tableting, bulk density and porosity are also considered [4,5]. Residual moisture content has its importance, as well as granule strength [6–8]. The drug content uniformity in the granules is not often considered. It would be nevertheless important to know if the drug is well incorporated into the agglomerates [9], especially in the cases where the drug content is very low, and for hydrophobic drug substances.

Finally, the post-drying treatment of the granules (category 5 variables) may affect the characteristics of the tablets. The granules may be sieved, and mixed with other excipients (e.g. a lubricant). Tableting conditions will clearly also affect the quality of the tablets. Ultimately, the tablet characteristics will be a function of the formulation, the conditions of granulation and tableting [10].

In summary, the scale transfer of a pharmaceutical granulation process involves the following parameters: (i) some fixed parameters: parameters related to the starting materials, type and size of agglomerating equipment; (ii) the input variables: spraying conditions, amount of solvent, mixing conditions (energy input and efficiency), and processing time. Assuming the drying step can be scaled-up easily, the properties of the dry granules become the output variables; most commonly those are the d_{50} and geometric standard deviation of the granule size distribution. The scale-up of the tableting operation is altogether a separate activity.

3. Process control and scale-up in high-shear mixers

Several approaches are available for controlling the process at one scale, and for scaling-up to another scale.

Table 1
Main variables affecting the quality of tablets obtained by wet granulation and tableting

1. Material parameters	2. Granulation conditions	3. Drying conditions	4. Granule properties	5. Tablet properties
Powder particle size distribution	In high-shear mixing:	In high-shear mixing:	Particle size distribution	Tableting conditions (compaction force and speed)
Wettability of the solid by the liquid	Mixing/collision generation levels	Extent of mixing	Bulk density and porosity	Extra-granular additions: e.g. lubrication, extra-granular disintigrant
Solid solubility and degree of swelling in binder liquid	Process time	Mode of drying (air stripping, microwave, infrared)	Moisture content	
Binder concentration and viscosity	Fill level	Energy input	[Flow: usually good, i.e. not discriminative]	
	Liquid spray rate	Process time	Drug content uniformity across the particle size distribution	
	Quantity of solvent	In fluid bed granulation:	Binder distribution	
	Temperature (+/− controlled)	Inlet air temperature and RH	Granule strength/friability	
	In fluid bed granulation:	Air flow rate		
	Spray droplet size	Process time		
	Spraying surface and rate			
	Quantity of solvent			
	Bed fluidity/air flow rate			
	Inlet air temperature and RH[a]			
	Equilibrium temperature and RH in bed			
	Process time			

[a] RH, % relative humidity.

Those strategies can be grouped as follows:

- methods based on the monitoring of one representative parameter: somehow the representative parameter relates back to one or more properties of the wet mass or of the dry granules, e.g. power consumption of the high-shear mixing, moisture and vibration sensor outputs;
- modelling the process using experimental design: once established, the models can estimate the quality of the granules produced when the process conditions are changed, within the domain studied;
- modelling the granule population balance: contrary to the previous models, some assumptions on the granulation regime are needed.

3.1. Using power consumption as a monitoring parameter

Monitoring the power consumption of the processing equipment during granulation is a widely used technique. Leuenberger [11] attributed the variations in power consumption during granulation to the evolution of the strength of the wet agglomerates. Monitoring of the impeller amperage, power consumption, torque or indirect torque are affiliated techniques. Pharmaceutical high-shear mixers are generally equipped with one device or another for such monitoring.

The relationships between power consumption, conditions of granulation and resulting agglomerate characteristics have been extensively studied [12–16]. In a series of papers, Kristensen and his collaborators have shown why the power consumption is a good choice for monitoring the granulation process in high-shear granulation. It has been demonstrated that the power consumption was related to the extent of densification of the wet mass: $P \propto (1 - \varepsilon)/\varepsilon$ [17]. Not only the densification but also the deformability of the wet granules affects the agglomeration growth rate. Lindberg et al. [18] and then Kristensen et al. [19] showed the link between power consumption and the saturation level S of the granules. The saturation level of an agglomerate is defined as the ratio of pore volume occupied by liquid to the total volume of pores available in the agglomerate.

$$S = \frac{H(1 - \varepsilon)}{\varepsilon}\rho$$

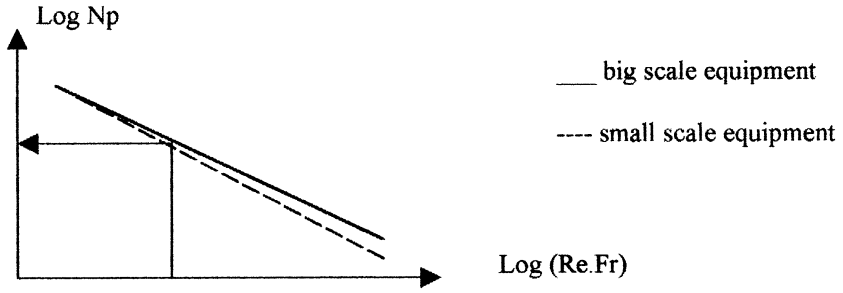
where H is the mass ratio of liquids to solids, ε is the intragranular porosity and ρ is the density of the particle relative to the density of the liquid.

Additionally, the saturation level could be related back to the average granule size for different sizes of one type of agglomerator [20], and for different sizes of starting powder material [21]. The relationships between the median granule diameter and the moisture content or the porosity of the wet granules remain equipment- and scale-dependent [22]: the saturation level provides the missing parameter to establish the link from one machine to another.

These highlighted articles have therefore laid the basis for relating the granule particle size to the saturation level achieved in the wet mass. This parameter can be more easily monitored following the power consumption with time rather than by retrieving samples for the determination of their saturation level, a measurement that remains somewhat delicate and time consuming [20].

Another group of researchers have followed a very similar approach, with two major refinements. Firstly, the saturation level is replaced by a parameter called the wet mass consistency which describes the rheological properties of the wet mass [23]. The consistency of the wet mass is dependent on the deformability of the wet granules, which is a function of the distribution of the liquid in the available pores [24]. A mixer torque rheometer is used to quantify the wet mass consistency of the granules. This technique is much easier to carry out than the determination of the saturation level of the sample, although the conditions of measurement have to be fixed [23,25]. In addition, the relationship between wet mass consistency and dry granule properties has been demonstrated [26]. The second refinement is in the establishment of a dimensionless relationship between the power consumption and the wet mass consistency. Being dimensionless, the relationship becomes general for a series of geometrically similar high-shear mixers regardless of their scale, i.e. the same machines with different sizes present the same relationship [27–30]. For process control, the procedure involves performing a series of granulation experiments to determine the wet mass consistency, μ, corresponding to the optimal granules, and at the same time establishing the dimensionless form of the relationship $\Delta P = f(\mu)$. The power consumption of the granulation end-point is the ΔP value that corresponds to the optimal wet mass consistency. For scale-up in a different size of the same granulator, the dimensionless relationship is once again used to determine the target ΔP at this new scale. An example is provided in Fig. 1. Scale-up in a different design of high-shear mixer (different scale or not) requires the establishment of the dimensionless relationship applicable for this type of equipment; otherwise the same optimal wet mass consistency value remains valid. Finally, it is interesting to note that the dimensionless relationships show a degree of formulation dependency [31], and also that they will depend on how the wet mass consistency is measured. The relationship between wet mass consistency and dry granule properties will be further affected by the conditions of treatment of the wet mass (screening, drying, etc.) which must be standardized for the different scales.

Power consumption considerations have also induced energy input considerations. The relative swept volume (RSV), representing the volume swept and displaced by the blades of the impeller per unit of time, has been correlated to the energy input of the mixer. This energy input is obtained by integration of the power consumption versus time function, relative to the batch load. The RSV could not, however, be related back to the d_{50} of the granules produced [32]. Additionally, neither the RSV nor the Froude number contain



The relationship can be used for scale-up purposes as follows :

	D	N	ρ	μ	ΔP	Re	Fr	Np
small scale	n/a	n/a	optimised	optimised	n/a	n/a	n/a	n/a
big scale	given	given	input (id. as small scale)	input (id. as small scale)	unknown (target)	calcu-lated	calcu-lated	read on the curve

n/a : not applicable (not needed)

retro-calculated
(ΔP is the only unknown)

Fig. 1. $\Delta P = f(\mu)$ is made dimensionless by using the form: $Np = f(Re,Fr)$ where

$Np = \frac{\Delta P}{\rho \cdot N^3 D^5}$ is the Power Number

$\mathrm{Re} = \frac{\rho N D^2}{\mu}$ is the Reynolds Number

$Fr = \frac{DN^2}{g}$ is the Froude Number

and ΔP is the net power consumption of the granulation; ρ is the wet mass bulk density; μ is the wet mass consistency; N is the rotational speed of the impeller; D is the radius of the impeller; g is the gravitational constant. The relationship $Np = f(Re,Fr)$ is established from data from granulation experiments in which: ΔP, ρ and μ have been measured, preferably on the scale at which transfer must be done. Alternatively a smaller scale machine can be used, provided the two pieces of equipment are geometrically similar and that the wall effects can be neglected, i.e. with bowl sizes of minimum 75–100 l usually.

elements describing the wet mass. They are therefore best considered for the scale-up of the machine rather than the process. Unfortunately, the scale-up of high-shear mixers can follow at most only one of the following rules: tip speed constant ($\propto ND$), Froude number constant ($\propto N^2D$) or RSV constant ($\propto ND^2$) where N is the rotational speed of the impeller and D is a dimension of the machine, e.g. blade diameter. Usually manufacturers propose variable speed machines for small capacity high-shear mixer-granulators (up to 100 l) with fixed speeds for larger scale, and the rule for design seems to have been keeping the Froude number constant. In those conditions it is impossible to also keep the RSV constant. The approach of Singh Rekhi et al. [33] is also difficult to follow: keep the tip speed constant, scale-up the liquid requirement linearly, and adjust the granulation time based on the ratio of impeller speeds between the two scales. Even if this was technically possible, the processing time would be extremely long, e.g. multiplied by a factor of nearly 3 for the scale-up from a 10 l to a 200 l bowl. The approach of Kristensen [22] seems much more practical: the impeller speed is fixed by the machine manufacturer, and it is known that less efficient mixing is generated as the bowl size increases. Therefore, one can expect less densification of the wet agglomerates to occur, i.e. the maximum saturation level reached will be less. It is possible to prevent this fall in saturation level by increasing the (relative) amount of liquid used in the granulation. This has the advantage of keeping the process within a reasonable timeframe.

Power consumption curves are notoriously unpredictable in high-shear granulation. Conditions for binder spraying and irregular wall adhesion in time make the curve of power consumption versus time fluctuate and decrease in reproducibility. Some authors have tried treating the signal (e.g. by fast Fourier transform (FFT) [34]. Otherwise it is possible but fastidious to analyze the dry granules obtained at different power consumption levels to determine at which level the best granule and the best yield are obtained [35]. There are then no rules for scale-up, except trial and error.

3.2. Monitoring parameters other than power consumption

Some attempts have been made with vibration probes.

Power consumption is known to oscillate with the amount of wet mass impacting the impeller blades (and thereby showing great variation when the wet mass is balling or chunks are collapsing from the wall to which they were adhering). Why not then develop a probe that would be better suited for measuring in situ the cohesion of the wet mass? The vibration probes tested were able to record a signal that reflected the level of densification achieved by the wet granules. Staniforth and Quincey [36] linked this signal to the Hausner ratio of the dried granules, while Ohike et al. [37] using the FFT of the signal were able to correlate the amplitude of the strongest peak with the d_{50} of the dry granules.

Moisture sensors have also been used to monitor the granulation process in high-shear granulation. A conductivity probe was used to assess water distribution in the wet mass [38]. Similarly, capacitance sensors [39,40] and also infrared sensors were investigated.

So far, only the methods based on the monitoring of one parameter, be it the power consumption or output signal from a probe, have been considered. There are, however, several methods that are not based on this principle, but on modelling.

3.3. Experimental designs for use in process control

The 'design of experiments' approach can be a powerful tool to model processes. It may be time consuming but it is simple and can lead to a working knowledge of the experimental domain studied. In the most common type of experimental designs, a number of input variables are selected (X_i) among the process conditions and material properties (e.g. impeller speed, binder concentration, mixing time…). A number of output variables are also selected (the Y_i), usually the granule and sometimes also the tablet properties. The principle is to determine for each Y_i a model (linear or not) involving each variable X_i and the interactions between variables. Variables and interactions which do not contribute significantly to the model, i.e. that do not affect the response to an extent that would unmistakingly not be confused with response noise, are withdrawn from the model. The models obtained are useful to control the granulation process at one scale. By comparison of the models (e.g. response surface methodology), it is possible to optimize the different variables X_i to obtain a compromise between the results of the Y_i wanted (there may be some constraints, e.g. a yield of workable granules of at least 90%, a certain range of granule density, etc.). When considering scale-up, however, the experimental work necessary to generate the models has to be repeated in the larger scale equipment, and only then can the models be compared. The new optimums for the variables X_i have to be found, and they may be quite different from scale to scale, depending on the choice of the range studied for each X_i, and whether the variables are used relatively or not, e.g. a w/w % of liquids to solids instead of a quantity of water. Some examples of experimental design for process control and/or optimization on another scale can be found in Refs. [41–46].

3.4. Use of population balance models

Another approach in modelling has received considerable attention over the last few years: it concerns the modelling of the granulate population balance. Compared to the models generated by experimental designs, the population balance models focus only on the PSD of the granules. The models are extremely complex and require several assumptions to be made for simplification and solving. They also require a certain understanding of the situation developing in the high-shear mixer, so as to make a reasonable estimate for the assumptions made. Fundamentally, the entire granule size distribution is divided in small intervals, and the model follows the evolution of the granule growth, allowing the computing at each time of how many granules exist in each size interval. At the core of the problem lies the estimation of the probability of coalescence when a granule or particle from size interval i collides with a granule or particle of size interval j. This probability of coalescence has been represented by a parameter β, the coalescence kernel. Although first taken to be a constant, this parameter has been later on considered as a function of the size of the granule on impact (i and j) and of time. This is to reflect the fact that the deformability of the granules upon impact will vary with their saturation, densification and presence or not of binder at the surface (according to the models of Kristensen and Schaefer [20], Ennis et al. [47] and Iveson and Lister [48]).

Cryer [49] lists several of the assumptions made for the function of β_{ij}. Some examples are also given in Refs. [50–53]. At the moment the models are used as a learning tool to understand processes and mechanisms taking place in high-shear mixers, plough shape granulators, drum granulators, etc., in various industries using wet granulation. The assumptions made on the granulation regime/probability of coalescence with time give model results which are compared to experimental data, thereby confirming the validity of the models or highlighting which assumptions are not valid. This approach looks promising for granulation process control, but to date there have not been any reports which use the models for scale-up. A good understanding of the granulation process on a micro-scale and a working model of the population balance in a small scale granulator should one day be extremely valuable for scale-up in larger machines.

4. Process control and scale-up in fluid bed granulators

4.1. Specificities of the fluid bed granulation process

As mentioned earlier, a problem in fluid bed granulation is to stabilize a process that is in slow progression. In high-shear granulation, the liquid distribution is considered fast,

although it is not altogether instantaneous [2,54]. In fluid bed granulation, the initial spreading of the binder in the powder bed is even more crucial. Owing to the much lower shear forces in fluid beds, the liquid within an agglomerate is less likely to be squeezed out, so coalescence will be limited. The initial wetting conditions are therefore determining for the future granule size distribution. Schaefer and Wørts [55] have studied the relationship between binder viscosity, mean droplet size and mean granule size. The relationship between droplet size and granule size, under constant process conditions, is affected by the binder-induced mechanical strength of the wet granule liquid bridges. Different binder solutions sprayed at the same mean droplet size can thus give different granular characteristics in the end product. Schaafsma et al. [56] have shown how the liquid of a given droplet may extend to all the surfaces of the particles wetted, providing for new liquid bridges with neighbouring particles, until the surface of the agglomerate formed is not wet enough to make successful collisions with other particles. The granules may dry to some extent in the bed, and may be sprayed once again. Predicting and modelling how the bed will evolve, in terms of the extent of drying and agglomerate circulation, as time goes by and as the bed density changes is extremely complex [57].

The component that seems easier to scale-up is the initial wetting of the powder. The spray droplet size and size distribution can be modelled and controlled [58,59]. The spraying zone depends on the spray angle of the nozzle and its position above the bed. It should be scaled-up to remain relatively constant [60], or at least the nozzle position should be such that clogging (nozzle too low) and wetting of the granulator walls (nozzle too high) are avoided [61]. In general, the number of nozzles is multiplied but the mean droplet size is kept constant for scale-up although this means little if the evaporation rate from the droplet is not under control. Spray drying of the binder solution makes the granulation process inefficient. Additionally, it is important to know how quickly the powder bed in the wetting zone is renewed, i.e. the ratio of the liquid addition rate to surface renewal [62], to avoid overwetting and potential bed collapse.

The initial nucleation that takes place as droplets hit the particle surfaces in the powder bed is characterized by a fast agglomerate growth rate. This phase is followed by a slower granule growth phase, a transition region, as the amount of fine, ungranulated powder has substantially decreased in the bed [63]. In this transition region, the slower growth kinetics enable easier process control, and the process end-point will most likely be found in this phase. Monitoring of the process is done sometimes by image processing, i.e. the on-line monitoring of granule size distribution within the bed [64]. More generally, and less ideally, the stability of the process is monitored with bed moisture and related parameters, and trial-and-error experiments are required to determine the time/amount of binder necessary to achieve the granule size targeted. Schaafsma [57] has studied the effect of the moisture content of the granules re-entering the wetting zone. If the agglomerates are not completely dried, re-wetting and further coalescence are favoured. The humidity of the bed is therefore a key factor to control. In practice, relative humidity probes can be inserted directly into the bed. It is also possible to simply monitor the equilibrium bed temperature, since this temperature is related to the inlet air temperature and the evaporation rate of the binder solution. More recently, infrared and near-infrared probes have been used [60,65–67]. The output from the probes serves to readjust the binder spray rate manually or automatically, although this will also affect the binder droplet size (two fluid nozzles). Other alternatives are to adjust the binder spraying frequency, that is spraying intermittently but always in the same conditions so that the droplet size remains unaffected [57], and to modify the inlet air temperature to adjust the evaporation rate. The drying capacity of the inlet air is also a function of its dew point, but in the pharmaceutical industry the size of the fluid beds usually allows for air dehumidification systems to be used, so that the inlet air humidity is generally under control. Finally, the air flow rate could also be adjusted for the change in the material flow pattern as granulation proceeds and agglomerates become larger and more influential for the air flow.

4.2. Methods used for process control and scale-up

The many interactions between the input variables (inlet air and spray rate related parameters) make the process difficult to optimize with the ‘one parameter at a time’ concept. This is therefore ideal ground for experimental designs and response surface methodology (e.g. Ref. [68]). Watano and co-workers have used fuzzy logic [64] and neural networks [69] to control granulation processes in agitation fluid bed granulators, where the standard fluid bed design is completed with an impeller blade rotating at the bottom of the bed, which improves the densification of the granules. These authors had previously demonstrated [70,71] the importance of the balance between the rotational speed of the impeller and the air velocity, as those parameters affect the kinetic energy of the particles via respectively its horizontal and vertical components. In the computer models generated, the output variables are the PSD of the granulate, and additionally, bulk density and shape factors of the agglomerates. PSD population balance modelling has also been tried on fluid bed granulators with a specific coalescence kernel [49]. Rantanen et al. [72] have used self-organizing maps (a kind of non-linear principal component analysis) to represent in two dimensions the effect of the different process variables over the evolution of the granulation process. With this technique the authors can visually detect deviations from the reference, e.g. validated process, and can take action to bring back the process on its normal pathway within the self-organizing map.

5. Conclusion

Building quality into production systems, starting at earlier and earlier stages during drug product development, has been a recent trend in the pharmaceutical industry. Wet granulation processes, as for other pharmaceutical manufacturing processes, are comprehensively documented and the technical solutions to 'what if' questions have been identified and tested (i.e. process robustness, edge of failure concepts). On a macro-scale, empirical techniques have been developed for process control and scale-up in high-shear mixers, while computing techniques (e.g. neural networks, fuzzy logic, self-organizing maps) are being generated for monitoring the more complex fluid bed granulation process. Interestingly, on a micro-scale, fundamental knowledge of the processes is progressing, with developments in areas such as granulation regime mapping and population balance modelling. This information provides extremely valuable information to support the macro-scale process monitoring approaches.

References

[1] K. Terashita, S. Watano, K. Miyanami, Determination of end-point by frequency analysis of power consumption in agitation granulation, Chem. Pharm. Bull. 38 (1990) 3120–3123.
[2] P.C. Knight, A. Johansen, H.G. Kristensen, T. Schaefer, J.P.K. Seville, An investigation of the effects on agglomeration of changing the speed of a mechanical mixer, Powder Technol. 110 (2000) 204–209.
[3] H. Stahl, Single-pot systems for drying pharmaceutical granules, Pharm. Technol. Eur. 12 (5) (2000) 23–29.
[4] A.M. Juppo, Change in porosity parameters of lactose, glucose and mannitol granules caused by low compression force, Int. J. Pharm. 130 (1996) 149–157.
[5] M. Pottman, B.A. Ogunnaike, A.A. Adetayo, B.J. Ennis, Model-based control of a granulation system, Powder Technol. 108 (2000) 192–201.
[6] K. Danjo, H. Kato, A. Otsuka, K. Ushimaru, Fundamental study on the evaluation of strength of granular particles, Chem. Pharm. Bull. 40 (6) (1994) 2598–2603.
[7] M.J. Adams, M.A. Mullier, J.P.K. Seville, Agglomerate strength measurement using an uniaxial confined compression test, Powder Technol. 78 (1994) 5–13.
[8] E. Horisawa, A. Komura, K. Danjo, A. Otsuka, Effect of granule strength on compressed tablet strength, Chem. Pharm. Bull. 43 (2) (1995) 2261–2263.
[9] R. Zelko, Z. Budavari, S. Marton, I. Racz, The effect of solid/liquid interactions on the migration of riboflavin in tray-dried granule beds, STP Pharma Sci. 9 (2) (1999) 215–217.
[10] J.A. Westerhuis, P.M.J. Coenegracht, C.F. Lerk, Multivariate modelling of the tablet manufacturing process with wet granulation for tablet optimisation and in-process control, Int. J. Pharm. 156 (1997) 109–117.
[11] H. Leuenberger, Granulation, new techniques, Pharma Acta Helv. 57 (3) (1982) 73–82.
[12] B.M. Hunter, D. Ganderton, The influence on pharmaceutical granulation of the type and capacity of mixers, J. Pharm. Pharmacol. 25 (Suppl.) (1973) 71P–78P.
[13] L. Paris, A. Stamm, Optimal massing liquid volume determination by energy consumption measurement: study of the influence of some physical properties of solvents and produced used, Drug Dev. Ind. Pharm. 11 (1985) 361–386.
[14] P. Holm, T. Schaefer, H.G. Kristensen, Granulation in high-speed mixers. Part V. Power consumption and temperature changes during granulation, Powder Technol. 43 (1985) 213–223.
[15] P. Holm, T. Schaefer, H.G. Kristensen, Granulation in high-speed mixers. Part VI. Effects of process conditions on power consumption and granule growth, Powder Technol. 43 (1985) 225–233.
[16] T. Schaefer, P. Holm, H.G. Kristensen, Wet granulation in a laboratory scale high shear mixer, Pharm. Ind. 52 (9) (1990) 1147–1153.
[17] M. Ritala, P. Holm, T. Schaefer, H.G. Kristensen, Influence of liquid bonding strength on power consumption during granulation in a high shear mixer, Drug Dev. Ind. Pharm. 14 (8) (1988) 1041–1060.
[18] N.O. Lindberg, L. Leander, B. Reenstierna, Instrumentation of a Kenwood major domestic-type mixer for studies of a granulation, Drug Dev. Ind. Pharm. 8 (5) (1982) 775–782.
[19] H.G. Kristensen, P. Holm, T. Schaefer, Mechanical properties of moist agglomerates in relation to granulation mechanisms. Part I. Deformability of moist, densified agglomerates, Powder Technol. 44 (1985) 227–237.
[20] H.G. Kristensen, T. Schaefer, Granulation. A review on pharmaceutical wet granulation, Drug Dev. Ind. Pharm. 13 (1987) 803–872.
[21] H.G. Kristensen, P. Holm, T. Schaefer, Mechanical properties of moist agglomerates in relation to granulation mechanisms. Part II. Effects of particle size distribution, Powder Technol. 44 (1985) 239–247.
[22] H.G. Kristensen, Particle agglomeration in high shear mixers, Powder Technol. 88 (1996) 197–202.
[23] M.D. Parker, R.C. Rowe, N.G. Upjohn, Mixer torque rheometry. A method for quantifying the consistency of wet granulations, Pharm. Tech. Int. 2 (8) (1990) 50–64.
[24] B.C. Hancock, P. York, R.C. Rowe, M.D. Parker, Characterisation of wet masses using a mixer torque rheometer 2. Mixing kinetics, Int. J. Pharm. 83 (1992) 147–153.
[25] M. Landin, R.C. Rowe, P. York, Characterization of wet powder masses with a mixer torque rheometer 3. Non linear effects of shaft speed and sample weight, J. Pharm. Sci. 84 (1995) 557–559.
[26] A. Faure, End-point control and scale-up in pharmaceutical mixer-granulators, Chapter 7, PhD thesis, University of Bradford, Bradford, 1998.
[27] M.J. Cliff, M.D. Parker, Scale-up of mixer-granulators, Proceedings of the 12th Interphex Conference, 5, Advanstar Communications, Boston, MA, 1990, pp. 17–32.
[28] M. Landin, P. York, M.J. Cliff, R.C. Rowe, A.J. Wigmore, Scale-up of a pharmaceutical granulation in fixed bowl mixer-granulators, Int. J. Pharm. 133 (1996) 127–131.
[29] M. Landin, P. York, M.J. Cliff, R.C. Rowe, Scale-up of a pharmaceutical granulation in planetary mixers, Pharm. Dev. Technol. 4 (2) (1999) 145–150.
[30] A. Faure, I.M. Grimsey, R.C. Rowe, P. York, M.J. Cliff, Applicability of a scale-up methodology for wet granulation processes in Collette Gral high shear mixer-granulators, Eur. J. Pharm. Sci. 8 (1999) 85–93.
[31] A. Faure, I.M. Grimsey, R.C. Rowe, P. York, M.J. Cliff, Process control in a high shear mixer-granulator using wet mass consistency: the effect of formulation variables, J. Pharm. Sci. 88 (1999) 191–195.
[32] G.J.B. Horsthuis, J.A.H. van Laarhoven, R.C.B.M. van Rooij, H. Vromans, Studies on upscaling parameters of the Gral high shear granulation process, Int. J. Pharm. 92 (1993) 143–150.
[33] G. Singh Rekhi, R.B. Caricofe, D.M. Parikh, L.L. Augsburger, A new approach to scale-up of high-shear granulation process, Pharm. Technol. Yearbook (1996) 58–67.
[34] S. Watano, K. Terashita, K. Miyanami, Frequency analysis of power consumption in agitation granulation of powder materials with sparingly soluble acetaminophen, Chem. Pharm. Bull. 40 (1992) 269–271.
[35] K. Terashita, M. Kato, A. Ohike, K. Miyanami, Analysis of end-point with power consumption in high speed mixer, Chem. Pharm. Bull. 38 (1990) 1977–1982.

[36] J.N. Staniforth, S.M. Quincey, Granulation monitoring in a planetary mixer using a probe vibration analysis technique, Int. J. Pharm. 32 (1986) 177–185.
[37] A. Ohike, K. Ashihara, R. Ibuki, Granulation monitoring by Fast Fourier Transform technique, Chem. Pharm. Bull. 47 (1999) 1734–1739.
[38] M.S. Spring, The conductivity of the damp mass during the wet massing stage of the granulation process, Drug Dev. Ind. Pharm. 9 (1983) 1507–1512.
[39] W.C. Fry, W.C. Stagner, K.C. Wichman, Computer-interfaced capacitive sensor for monitoring the granulation process, J. Pharm. Sci. 73 (1984) 420–421.
[40] W.C. Fry, W.C. Stagner, K.C. Wichman, N.R. Anderson, Computer-interfaced capacitive sensor for monitoring the granulation process II: system response to process variables, Pharm. Technol. October (1987) 30–42.
[41] P. Wehrlé, P. Nobelis, A. Cuine, A. Stamm, Scaling-up of wet granulation. A statistical methodology, Drug Dev. Ind. Pharm. 19 (1993) 1983–1997.
[42] S. Ogawa, T. Kamijima, Y. Miyamoto, M. Miyajima, H. Sato, K. Takayama, T. Nagai, A new attempt to solve the scale-up problem for granulation using response surface methodology, J. Pharm. Sci. 83 (1994) 439–443.
[43] D. Vojnovic, M. Moneghini, F. Rubessa, Experimental design for a granulation process with "a priori" criteria, Drug Dev. Ind. Pharm. 21 (1995) 823–831.
[44] D. Vojnovic, M. Moneghini, D. Chicco, Nonclassical experimental design applied in the optimization of a placebo granulate formulation in high-shear mixer, Drug Dev. Ind. Pharm. 22 (1996) 997–1004.
[45] Y. Miyamoto, S. Ogawa, M. Miyajima, M. Matsui, H. Sato, K. Takayama, T. Nagai, An application of the computer optimization technique to wet granulation process involving explosive growth of particles, Int. J. Pharm. 149 (1997) 25–36.
[46] Y. Miyamoto, A. Ryu, S. Sugawara, M. Miyajima, M. Matsui, K. Takayama, T. Nagai, Optimization of the granulation process for designing tablets, Chem. Pharm. Bull. 46 (1998) 1432–1437.
[47] B.J. Ennis, G. Tardos, R. Pfeffer, A microlevel-based characterization of granulation phenomena, Powder Technol. 65 (1991) 257–272.
[48] S.M. Iveson, J.D. Litster, Growth regime map for liquid-bound granules, AIChE J. 44 (1998) 1510–1518.
[49] S.A. Cryer, Modeling agglomeration processes in fluid-bed granulation, AIChE J. 45 (1999) 2069–2078.
[50] J.D. Litster, D.J. Smit, M.J. Hounslow, Adjustable discretized population balance for growth and aggregation, AIChE J. 41 (1995) 591–603.
[51] A.A. Adetayo, J.D. Litster, S.E. Pratsinis, B.J. Ennis, Population balance modelling of drum granulation of materials with wide size distribution, Powder Technol. 82 (1995) 37–49.
[52] A.A. Adetayo, B.J. Ennis, Unifying approach to modeling granule coalescence mechanisms, AIChE J. 43 (1997) 927–935.
[53] A.A. Adetayo, B.J. Ennis, A new approach to modeling granulation processes for simulation and control purposes, Powder Technol. 108 (2000) 202–209.
[54] P.C. Knight, T. Instone, J.M.K. Pearson, M.J. Housnlow, An investigation into the kinetics of liquid distribution and growth in high shear mixer agglomeration, Powder Technol. 97 (1998) 246–257.
[55] T. Schaefer, O. Wørts, Control of fluidized bed granulation. IV. Effects of binder solution and atomization on granule size and size distribution, Arch. Pharm. Sci. Ed. 6 (1978) 14–25.
[56] S.H. Schaafsma, P. Vonk, P. Segers, W.F. Kossen, Description of agglomerate growth, Powder Technol. 97 (1998) 183–190.
[57] S.H. Schaafsma, Down-scaling of a fluidised bed agglomeration process, Chapters 5 and 6, PhD thesis, University of Groningen, Groningen, 2000.
[58] T. Schaefer, O. Wørts, Control of fluidized bed granulation. II. Estimation of droplet size of atomized binder solutions, Arch. Pharm. Sci. Ed. 5 (1977) 178–193.
[59] L. Juslin, O. Antikainen, P. Merkku, J. Yliruusi, Droplet size measurement. I. Effect of three independent variables on droplet size distribution and spray angle from a pneumatic nozzle, Int. J. Pharm. 125 (1995) 247–256.
[60] S. Watano, Y. Sato, K. Miyanami, T. Murakami, Y. Ito, T. Kamata, N. Oda, Scale-up of agitation fluidized bed granulation I. Preliminary experimental approach for optimization of process variables, Chem. Pharm. Bull. 43 (1995) 1212–1216.
[61] T. Schaefer, O. Wørts, Control of fluidized bed granulation. I. Effect of spray angle, nozzle height and starting materials on granule size and size distribution, Arch. Pharm. Sci. Ed. 5 (1977) 51–60.
[62] J.D. Litster, S.M. Iveson, K.P. Hapgood, Predicting and controlling granule properties in granulation processes, in: s s (Ed.), Proceedings from the World Congress on Particle Technology, article number 92, III, The Institution of Chemical Engineers, Brighton, 1998.
[63] T. Schaefer, O. Wørts, Control of fluidized bed granulation. V. Factors affecting granule growth, Arch. Pharm. Sci. Ed. 6 (1978) 69–82.
[64] S. Watano, Y. Sato, K. Miyanami, Control of granule growth in fluidized bed granulation by an image processing system, Chem. Pharm. Bull. 44 (1996) 1556–1560.
[65] P. Frake, D. Greenhalgh, S.M. Grierson, J.M. Hempenstall, D.R. Rudd, Process control and end-point determination of a fluid bed granulation by application of near infra-red spectroscopy, Int. J. Pharm. 151 (1997) 75–80.
[66] S. Watano, M. Uchigami, K. Miyanami, T. Yasutomo, 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. 44 (1996) 1267–1269.
[67] J. Rantanen, S. Lehtola, P. Rämet, J.-P. Mannermaa, J. Yliruusi, On-line monitoring of moisture content in an instrumented fluidized bed granulator with a multi-channel NIR moisture sensor, Powder Technol. 99 (1998) 163–170.
[68] A. Menon, N. Dhodi, W. Mandella, S. Chakrabarti, Identifying fluid-bed parameters affecting product variability, Int. J. Pharm. 140 (1996) 207–218.
[69] S. Watano, H. Takashima, K. Miyanami, Scale-up of agitation fluidizes bed granulation by neural network, Chem. Pharm. Bull. 45 (1997) 1193–1197.
[70] S. Watano, Y. Sato, K. Miyanami, T. Murakami, Y. Ito, T. Kamata, N. Oda, Scale-up of agitation fluidized bed granulation III. Effects of powder feed weight and blade angle on granule size, density and shape, Chem. Pharm. Bull. 43 (1995) 1224–1226.
[71] S. Watano, Y. Sato, K. Miyanami, Scale-up of agitation fluidized bed granulation IV. Scale-up theory based on the kinetic energy similarity, Chem. Pharm. Bull. 43 (1995) 1227–1230.
[72] J.T. Rantanen, S.J. Laine, O.K. Antikainen, J.-P. Mannermaa, J.K. Yliruusi, Visualization of fluid bed granulation with self-organizing maps, J. Pharm. Biomed. Anal. (2001) in press.