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DRUGS AND THE PHARMACEUTICAL SCIENCES

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Scale-Up Considerations in Granulation

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1. INTRODUCTION

Scale-up of any engineering process is a great technical and economic challenge. Scale-up of granulation processes, in particular, is difficult and often problematic due to the inherently heterogenous nature of the materials used. However, recent improved understanding of the rate processes that control granulation improves our ability to do rational scale-up.

There are two situations where process scale-up is needed: (1) commercialization of newly developed processes and products and (2) expansion of production capacities in response to increased market demand.

For pharmaceutical applications, the challenge is almost always associated with new product development. Scale-up in the pharmaceutical industry is unique in that experiments at laboratory and pilot scale are also required to produce product of the desired specification for different stages of clinical trials. This gives additional constraints and challenges to engineers and technologists during scale-up.

A change in scale invariably impacts on process conditions and, consequently, on the product quality. For pharmaceutical industries, the Food and Drug Administration (FDA) ranks the impacts on the drug product arising from changes of process conditions including production scales into three levels as shown in Table 1 (1). Level 1 is reserved for changes that are unlikely to have any detectable impact on the formulation quality and performance (2). For all practical purposes, scale-up should aim to achieve an impact equivalent to or less than Level 1.

In this chapter, we will first consider general scale-up approaches from a chemical engineering perspective. We will then look specifically at understanding pharmaceutical granulation scale-up through considering granulation as a combination of rate processes. Each rate process is affected by changes in process during scaling, as well as by formulation decisions. Finally, we will present suggestions for scaling of fluid-bed and high-shear mixer granulation that follow from this approach.

Table 1 Scale-Up and Postapproval Changes Level Component or Composition Change Levels

	% Excipient (w/w of total dosage unit)		
Excipient	Level 1	Level 2	Level 3
Filler	±5	±10	>10
Disintegrant			
Starch	±3	±6	>6
Other	±0.5	±1	>1
Binder	±0.5	±1	>1
Lubricant			
Ca or Mg Stearate	±0.25	±0.5	>0.5
Other	±1	±2	>2
Glidant			
Talc	±1	±2	>2
Other	±0.1	±0.2	>0.2
Film coat	±1	±2	>2
Total drug recipient change (%)	5	10	N/a

Source: Adapted from Ref. 2.

2. GENERAL CONSIDERATIONS IN PROCESS SCALE-UP: DIMENSIONAL ANALYSIS AND THE PRINCIPLE OF SIMILARITY

It is important to recognize that designing a commercial scale operation via several stages of scale-up is, in one sense, an admission of failure. If we have a strong understanding of our processes, then full-scale design can be performed using appropriate mathematical models, given feed formulation properties and clear required product specifications. Mature chemical engineering processes, such as distillation, are designed this way.

However, most solids processing technology do not have this level of maturity yet. In this case, scale-up studies reduce uncertainties in the design and operation of the scaled unit most economically. On this basis, the starting point in scale-up must really be the commercial unit. In theory, once sufficient information for the commercial unit is known, scale-up can be done by applying the similarity principles from data collected on a smaller unit. The similarity principle states (3): Two processes can be considered similar if they take place in similar geometric space and all dimensionless groups required to describe the processes have the same numerical values.

To establish the necessary dimensionless groups, a systematic dimensional analysis needs to be carried out where Buckingham Π theorem is used to reduce the number of dimensionless groups (4). Assuming that a process can be described by k variables, we can express one variable as a function of the other $k-1$ variables, i.e.,

$$x_1 = f(x_2, x_3, \mathrm{K}, x_{k-1}) \tag{2.1}$$

To conform to the dimensional homogeneity, the dimensions of the variable on the left-hand side of the equation must be equal to those on the right-hand side. With some simple mathematical rearrangements, Eq. 2.1 can be transformed into an

equation of dimensionless groups (Π terms), i.e.,

$$\Pi_1 = \phi(\Pi_2, \Pi_3, \mathrm{K}, \Pi_{k-r}) \tag{2.2}$$

Eq. 2.2 is a relationship among $k-r$ independent dimensionless products, where r is the minimum number of reference dimensions required to describe the variables. While the Buckingham Π theorem itself is straightforward, development of a dimensionless expression for a process or a phenomenon requires a systematic dimensional analysis [Ref. 4 for more details]. For most engineering problems, variables can be divided into three groups: (1) geometric variables, (2) material property variables, and (3) process variables. The reference dimensions are normally the basic dimensions such as mass (M), length (L), and time (T).

It is important to note that a systematic dimensional analysis can only be applied to processes where a clear understanding of the processes is established. Omission of any important variables of the process will lead to an erroneous outcome of the dimensional analysis, inevitably causing major problems in scale-up. Zlokarnik et al. (3) divided the application of dimensional analysis to five general cases with different levels of understanding in each case:

1. The science of the basic phenomenon is unknown—dimensional analysis cannot be applied;
2. Enough is known about the science of the basic phenomenon to compile a tentative draft list—the resulting Π set is unreliable;
3. All the relevant variables for the description of the problems are known—application of dimensional analysis is straight forward;
4. The problem can be described by a mathematical equation—mathematical functions are better than Π relationships, which may help reducing the number of dimensionless groups.
5. A mathematical solution of the problem exists—application of dimensional analysis is unnecessary.

Clearly, the more we understand a process or phenomenon, the better we can scale it up with confidence.

Full application of the similarity principle requires all the relevant Π groups to be measured at the small scale and kept constant during scale-up. Unfortunately, most industrial processes are very complex with many physical and chemical phenomena occurring. This leads to a large set of dimensionless groups required to fully characterize the process. This is particularly the case with processes involving particulate materials such as granulation. Maintaining all the dimensionless groups constant on the two scales is very difficult, if not impossible, due to constraints on the degrees of freedom in variables that can be changed on scale-up. In this case, scale-up can only be done on the basis of "partial similarity." That is, not all dimensionless numbers can be maintained the same on the two scales.

To scale up on the basis of partial similarity, experiments are carried out on a succession of equipment at different scales and results extrapolated to the final scale. That is, the scale-up ratio is kept low. With conflicting requirements on the dimensionless groups during scale-up, a common approach is to maintain one dimensionless group constant and check the effect of other dimensionless groups on the dependent variable by varying these dimensionless groups during experimentation. Once determined, only the dominant dimensionless number will be kept constant on scale-up. This partial similarity approach is often applied to granulation.

3. ANALYSIS OF GRANULATION RATE PROCESSES AND IMPLICATIONS FOR SCALE-UP

Many of the required granule product attributes are directly related to the size, size distribution, and density of the granule product. These granule properties develop as a result of three classes of rate process in the granulator (Fig. 1):

1. Wetting and nucleation
2. Growth and consolidation
3. Breakage and attrition.

Each of these processes is analyzed in depth in Litster and Ennis (5). In this section, we will summarize each rate process in turn, particularly highlighting the main formulation properties and process variables. Wherever possible, we will define dimensionless groups that can be used in scale-up.

3.1. Wetting and Nucleation

The first step in granulation is the addition of a liquid binder to the powder to form nuclei granules. Within the granulator, the key region for wetting and nucleation is the spray zone where liquid binder droplets contact the moving powder surface. The nucleation process is considered to consist of four stages (Fig. 2):

1. Droplet formation
2. Droplet overlap and coalescence at the bed surface

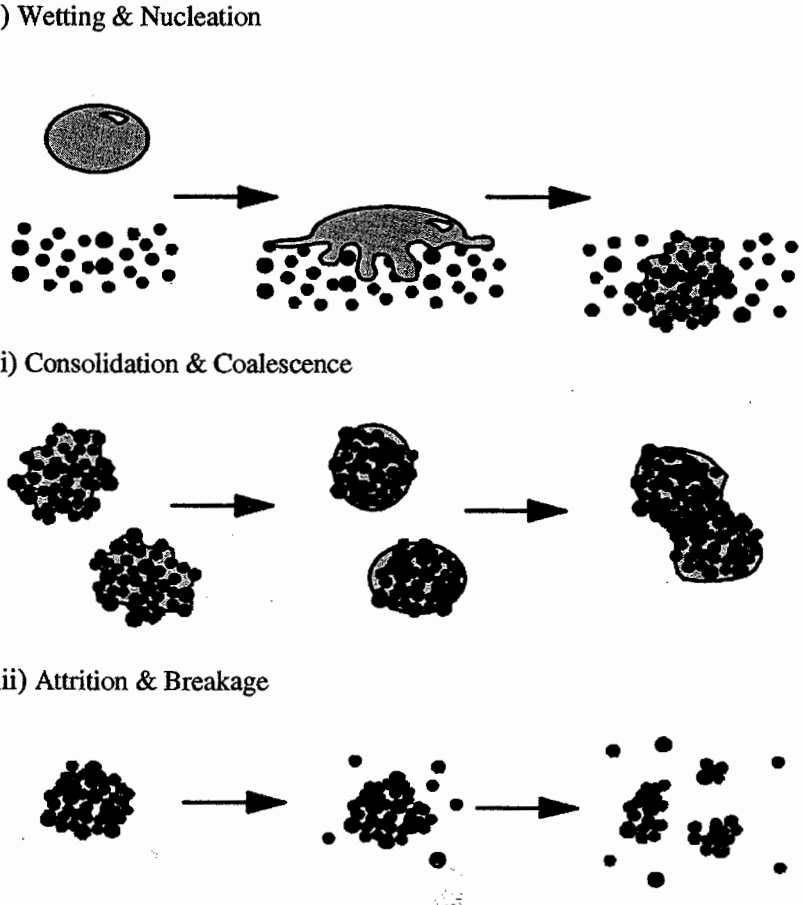


Figure 1 A classification of granulation rate processes. (From Ref. 5.)

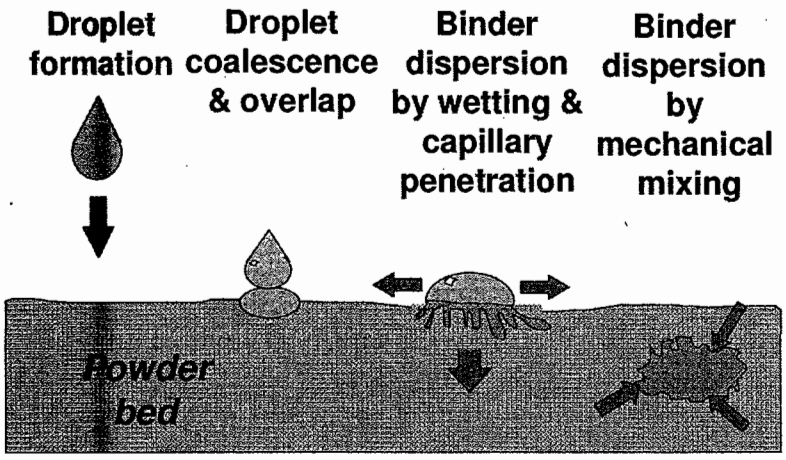


Figure 2 Wetting and nuclei formation in the spray zone of a granulator.

3. Drop penetration into the bed by capillary action
4. Mechanical dispersion of large clumps within the powder bed (only applicable to mixer granulators).

Poor wetting and nucleation lead to broad granule size distributions and poor distribution of the liquid binder, which increases substantially the chances of poor drug distribution. Despite the action of other rate processes, the broad size distributions and poor liquid distribution often persist throughout the granulation.

For ideal nucleation, the granulator should operate in the drop-controlled regime. Here, each drop which hits the powder bed penetrates into the bed to form a single nucleus granule. There is (almost) no drop overlap at the bed surface and mechanical dispersion of large, wet powder clumps is unnecessary.

To predict the required conditions for drop-controlled nucleation we must understand

1. The thermodynamics and kinetics of drop penetration, largely controlled by formulation properties
2. The flux of drops onto the bed surface, largely controlled by process parameters.

The drop penetration time t_p can be estimated using a model, which considers the rate at which liquid flows into the pores in the powder surface under capillary action (6):

$$t_p = 1.35 \frac{V_0^{2/3}}{\varepsilon_{eff}^2 R_{eff}} \frac{\mu}{\gamma_{LV} \cos\theta} \tag{3.1}$$

where V_0 is the drop volume, μ is the liquid viscosity, and $\gamma_{LV} \cos\theta$ is the adhesive tension between the liquid and the powder. The effective pore size R_{eff} and porosity ε_{eff} of the powder bed are given by

$$R_{eff} = \frac{\phi d_{32}}{3} \frac{\varepsilon_{eff}}{(1 - \varepsilon_{eff})} \tag{3.2}$$

$$\varepsilon_{eff} = \varepsilon_{tap}(1 - \varepsilon + \varepsilon_{tap}) \tag{3.3}$$

where φ is the particle sphericity, d_{32} is the specific surface mean particle size, ε is the loose packed bed porosity, and ε_{tap} is the tapped bed porosity.

For drop-controlled nucleation, the drop penetration time must be small compared to the bed circulation time t_c before that section of powder passes again through the spray zone, i.e., the dimensionless penetration time should be small:

$$\tau_p = \frac{t_p}{t_c} < 0.1 \tag{3.4}$$

To avoid drop overlap on the bed surface and caking of the powder, the dimensionless spray flux ψ must also be kept small. ψ_a is the ratio of the rate of production of drop projected area by the nozzle to the rate at which powder surface area passed through the spray zone and is defined as

$$\psi_a = \frac{3V}{2Ad_d} \tag{3.5}$$

Figure 3 shows how the nuclei granule size distribution broadens as the spray flux increases. For drop-controlled nucleation, the dimensionless spray flux should be kept < 0.2. For $\psi_a > 0.7$ the surface of the powder bed in the spray zone is effectively caked.

We can represent the nucleation behavior in a regime map (Fig. 4). Drop-controlled nucleation is achieved only when both ψ_a and τ_p are low. Figure 5 shows an example of full granulation data from a 25 L fielder mixer granulator on this type of regime map. The granule size distribution is much narrower when nucleation is kept in the drop-controlled regime (lower left-hand corner). This illustrates that poor nucleation usually results in broad final granule size distributions despite the impact of other processes occurring in the granulator.

3.2. Growth and Consolidation

Granule growth is very complex. The key question in establishing growth behavior is: Will two granules which collide in a granulator stick together (coalesce) or

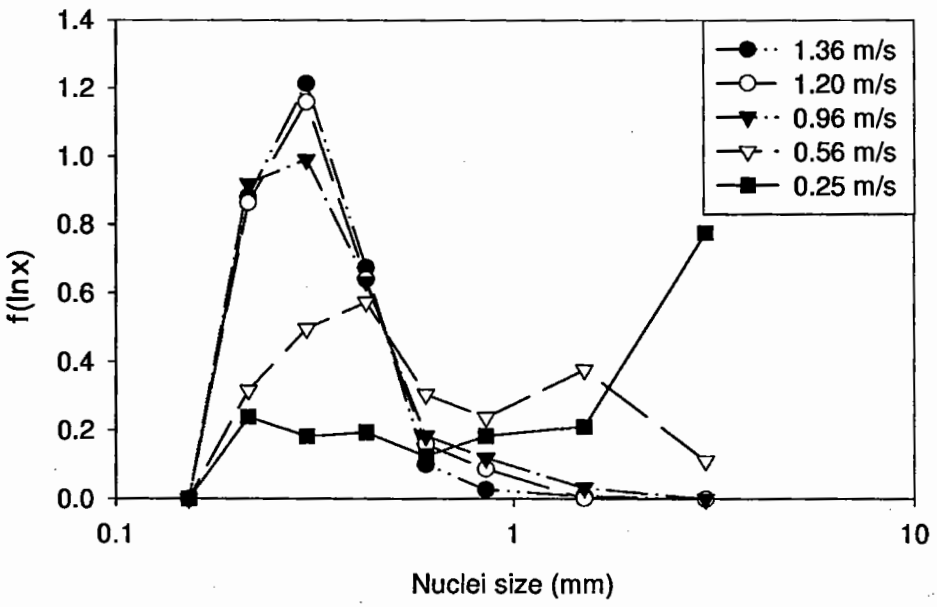


Figure 3 Effect of powder velocity on nuclei size distribution for lactose with water at 310 kPa. (From Ref. 6.)

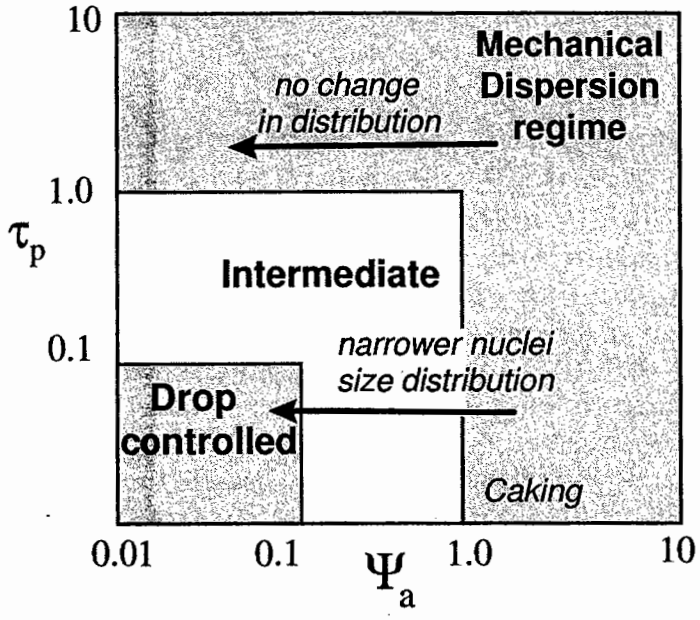


Figure 4 Nucleation regime map. For ideal nucleation in the drop-controlled regime, it must have (1) low ψ_a and (2) low t_p. In the mechanical dispersion regime, one or both of these conditions are not met, and good binder dispersion requires good mechanical mixing.

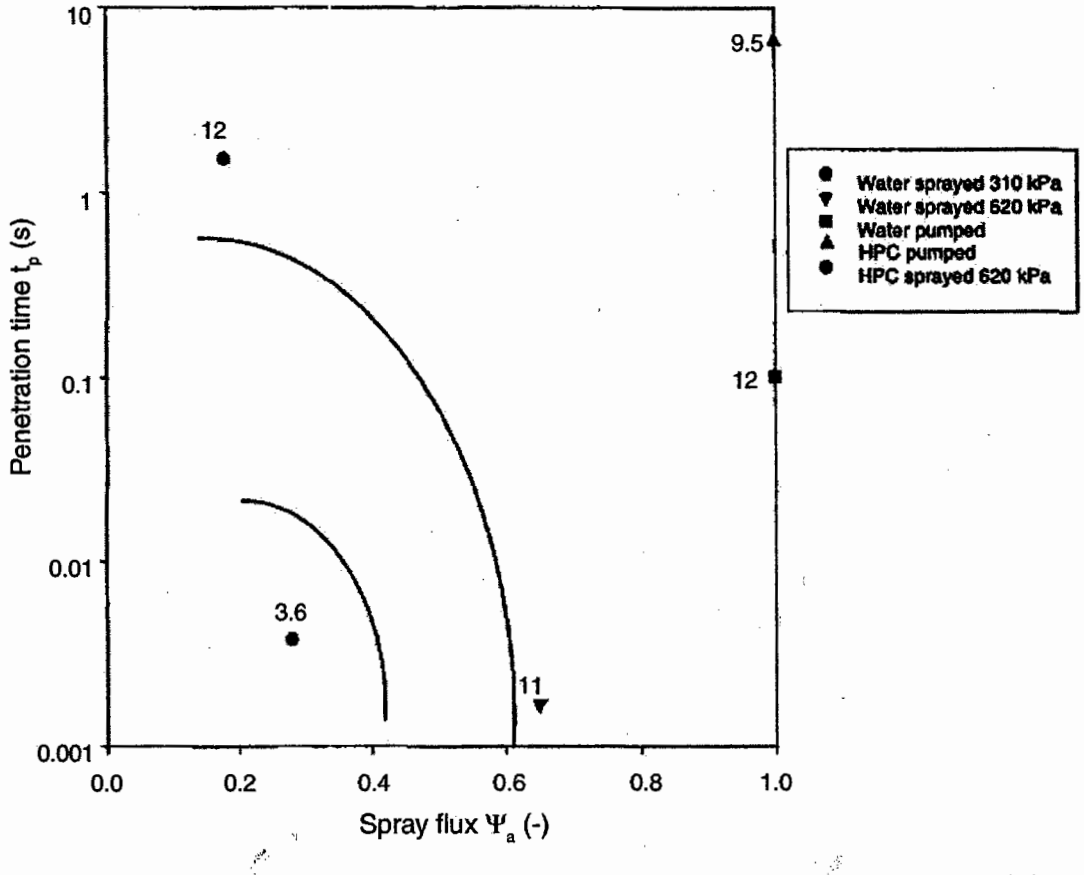


Figure 5 Nucleation regime map in 25 L Fielder mixer at 15% liquid content. Merck lactose with water and HPC as liquid binders. (From Ref. 6.)

rebound? To answer this question it is useful to look at two extreme cases, which cover most applications:

Deformable porous granules: These granules are typically formed by a nucleation process described earlier with the drop size of the same order, or larger, than the powder size. Most of the liquid in the granule is contained in the pores between particles in the granule and held there by capillary action. For successful coalescence, this liquid must be made available at the contact point between colliding granules. This model is often suitable for drum mixer granulation.

Near-elastic granules: Here, the wetted granule is considered as a nearly elastic sphere with a liquid layer on the surface. This is a good model for cases where the drop size is much smaller than the granule size and the granulator has simultaneous drying. This model is often suitable for fluid-bed granulation.

The different growth modes for deformable porous granules can be represented on a regime map (Fig. 6). For growth to occur by coalescence, the liquid content needs to be large enough to provide 85–105% saturation of the pores in the granule. Granules that are weak, i.e., form large contact areas on collision, fall into the steady growth regime. When two granules collide, a large contact area is formed and liquid is squeezed into the contact area, allowing successful coalescence. In this regime, granules grow steadily and the growth rate is very sensitive to moisture content (Fig. 7A).

Strong granules do not deform much on collision and granules rebound, rather than coalesce. However, as granules consolidate slowly, eventually liquid is squeezed into the granule surface and this liquid layer causes successful coalescence. This is the

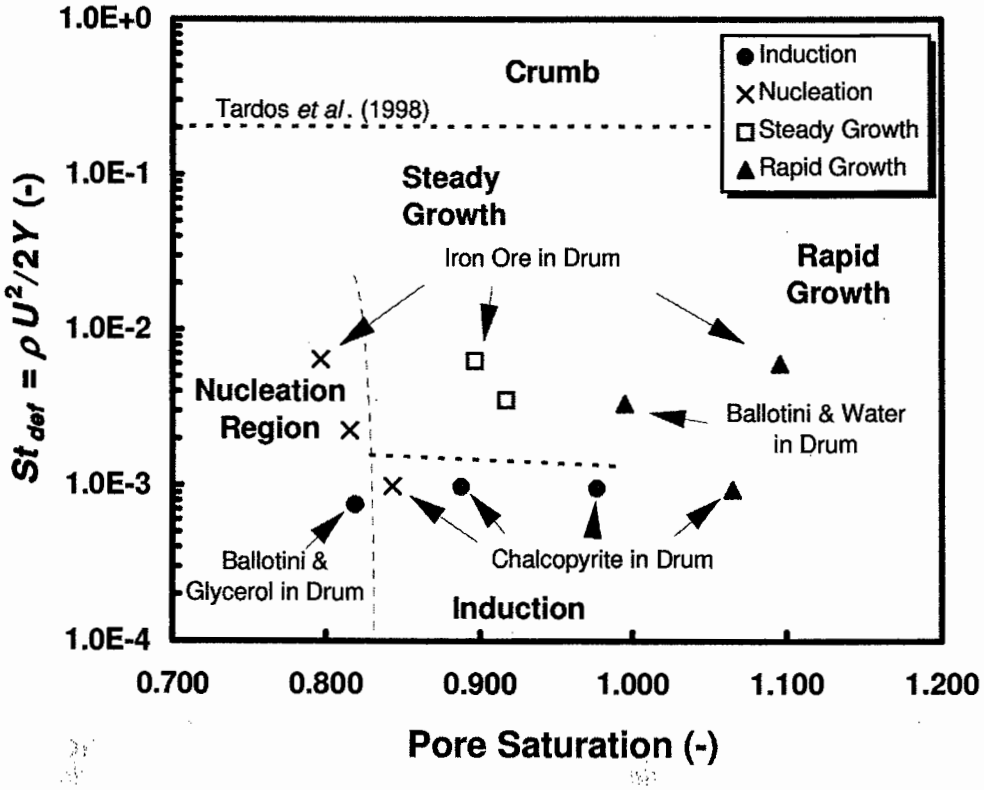


Figure 6 Granule growth regime map. (From Ref. 7.)

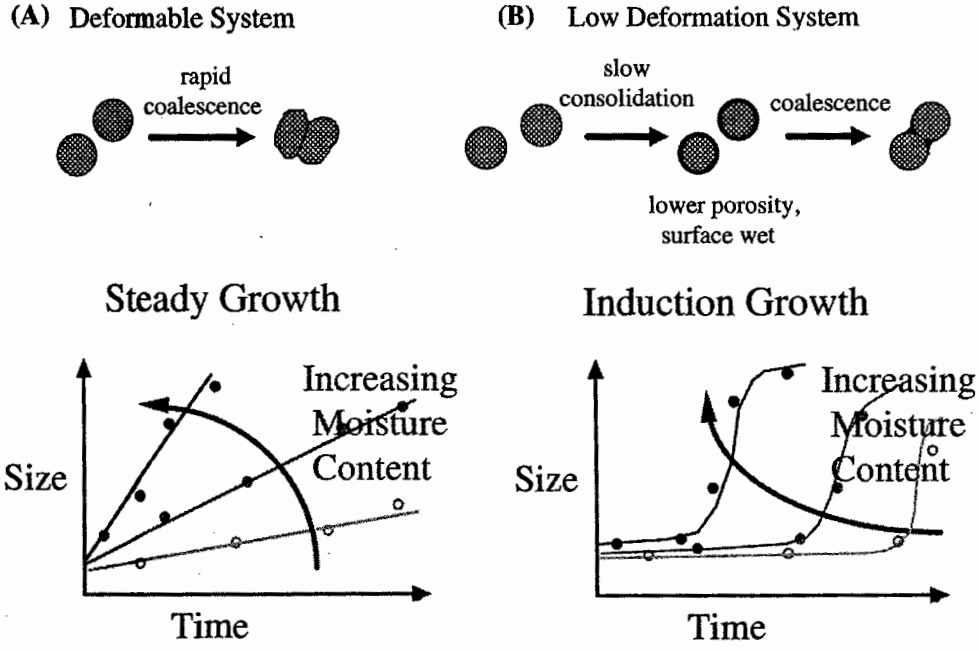


Figure 7 Coalescence growth modes for deformable granules.

induction growth regime (Fig. 7B). At lower moisture contents, nuclei granules form and consolidate. Some growth by layering may occur, but there is insufficient liquid for growth by coalescence. This is the nucleation regime. Very weak granules simply fall apart and cannot sustain growth. This is the crumb regime.

There are two dimensionless groups that dictate the growth behavior, the Stokes deformation number St_{def} and the maximum pore saturation s_{max}, which are defined as

$$St_{def} = \frac{\rho_g U_c^2}{2Y} \tag{3.6}$$

$$S_{max} = \frac{w\rho_s(1-\varepsilon_{min})}{\rho_l \varepsilon_{min}} \tag{3.7}$$

where ρ_g, ρ_s, and ρ_l, are the granule, particle, and liquid densities, respectively; U_c is the effective granule collision velocity; Y is the granule yield strength; w is the liquid content (kg liquid/kg dry powder); and ε_{min} is the minimum granule porosity after complete consolidation.

Understanding where your system sits on the growth regime map is important for troubleshooting and scale-up. Granules that grow in the induction regime are easy to scale with respect to granule size, provided that the induction time is not exceeded. However, granule density often changes with scale because consolidation kinetics are important and these kinetics can change with scale. On the other hand, in the steady growth region it is difficult to control granule size, but granule density quickly settles to a minimum value and varies little with process parameters.

To make effective use of the granulation regime map we need reasonable estimates of the effective collision velocity U_c (controlled by process conditions) and dynamic yield stress Y (a function of formulation properties). Table 2 gives estimates of the average and maximum collision velocities for different process equipment. In

Table 2 Estimates of U_c for Different Granulation Processes

Type of granulator	Average U_c	Maximum U_c
Fluidized beds	$(6U_b d_p)/d_b$	$(6U_b d_p)/d_b\delta^2$
Tumbling granulators	ωd_p	ωD_{drum}
Mixer granulators	$\omega_i d_p$, $\omega_c d_p$	$\omega_i D$, $\omega_c D_c$

Source: From Ref. 5.

high-shear mixers, the difference between the average and maximum collision velocities can be very large.

The dynamic yield stress of the granule matrix is a function of strain rate due to the contribution of viscous dissipation to the granule strength. Therefore, it is dangerous to use static strength measurements to predict performance in the granulator. Iveson et al. (8) show how dynamic yield stress can be estimated from peak flow stress measurements in a high-speed load frame. They were able to correlate data for different formulations and strain rates in a single line when plotted as the dimensionless peak flow stress (Str^*) vs. the capillary number (Ca) (Fig. 8). This line can be fitted by a simple empirical equation of the form

$$Str^* = k_1 + k_2 Ca^n \tag{3.8}$$

where $Str^* = \sigma_{pk} d_p/\gamma \cos\theta$ is the dimensionless peak flow stress, $Ca = \mu\dot{\varepsilon} d_p/\gamma \cos\theta$ is the ratio of viscous to capillary forces, σ_{pk} is peak flow stress, $\dot{\varepsilon}$ is the bulk strain rate, and θ is the solid–liquid contact angle. k_1 gives the static strength of the pellets. k_2 determines the transition between strain-rate independent and strain-rate dependent behavior. n is an exponent which gives the power law dependency of the flow stress on viscosity and strain rate. The best-fit value of n was found to be 0.58 ± 0.04 and the transition between strain-rate independent and dependent flow stress occurred at $Ca \sim 10^{-4}$.

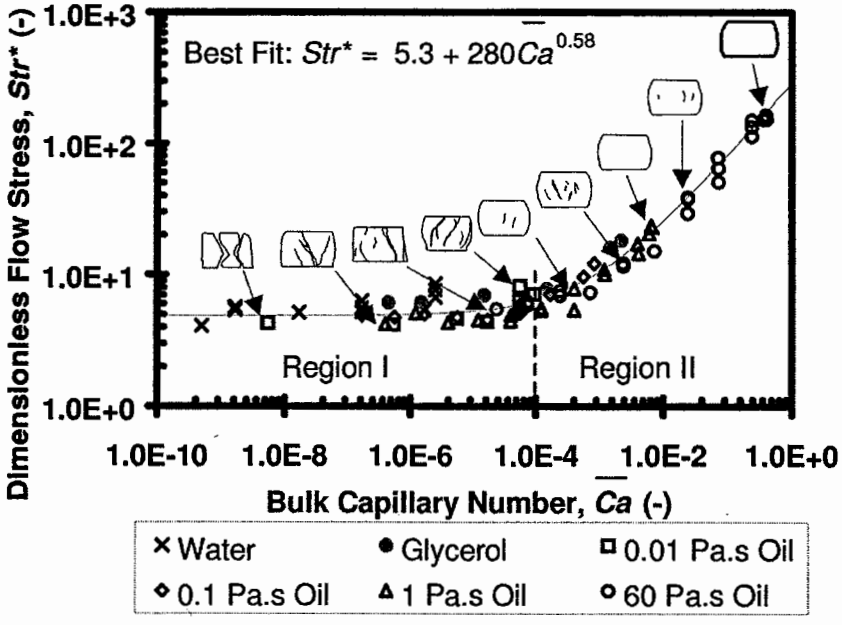


Figure 8 Dimensionless flow stress vs. capillary number for widely sized 35 μm glass ballotini with six different binders.

The rate of consolidation of granules can also be correlated with St_{def} in the form

$$k_c = \beta_c \exp(a \times St_{def}) \tag{3.9}$$

where β_c and α are constant, k_c is the consolidation rate constant for a first-order consolidation equation of the form

$$\frac{\varepsilon - \varepsilon_{min}}{\varepsilon_0 - \varepsilon_{min}} = \exp(-k_c t) \tag{3.10}$$

For near-elastic granules the conceptual model originally developed by Ennis et al. (9) considers the collision between two near-elastic granules each coated with a layer of liquid (Fig. 9). In this case the key dimensionless group is the viscous Stokes number St_v

$$St_v = \frac{4\rho_g U_c d_p}{9\mu} \tag{3.11}$$

St_v is the ratio of the kinetic energy of the collision to the viscous dissipation in the liquid layer. Successful coalescence will occur if St_v exceeds some critical value St^* and we can define three growth regimes as follows:

Noninertial growth ($St_{v,max} < St^*$): The viscous Stokes number for all collisions in the granulator is less than the critical Stokes number. All collisions lead to sticking and growth by coalescence. In this regime, changes to process parameters will have little or no effect on the probability of coalescence.

Inertial growth ($(St_{v,av} \approx St^*$): Some collisions cause coalescence while the others lead to rebound. There will be steady granule growth by coalescence. The extent and the rate of growth will be sensitive to process parameters which will determine the proportion of collisions that lead to coalescence. Varying process parameters and formulation properties can push the system into either the noninertial or the coating regimes.

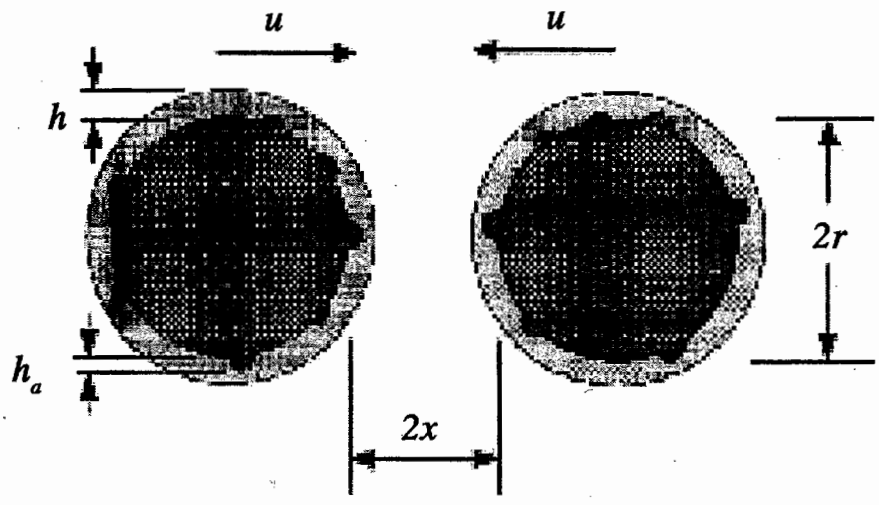


Figure 9 Two near-elastic granules colliding—the basis for the coalescence/rebound criteria. (From Ref. 9.)

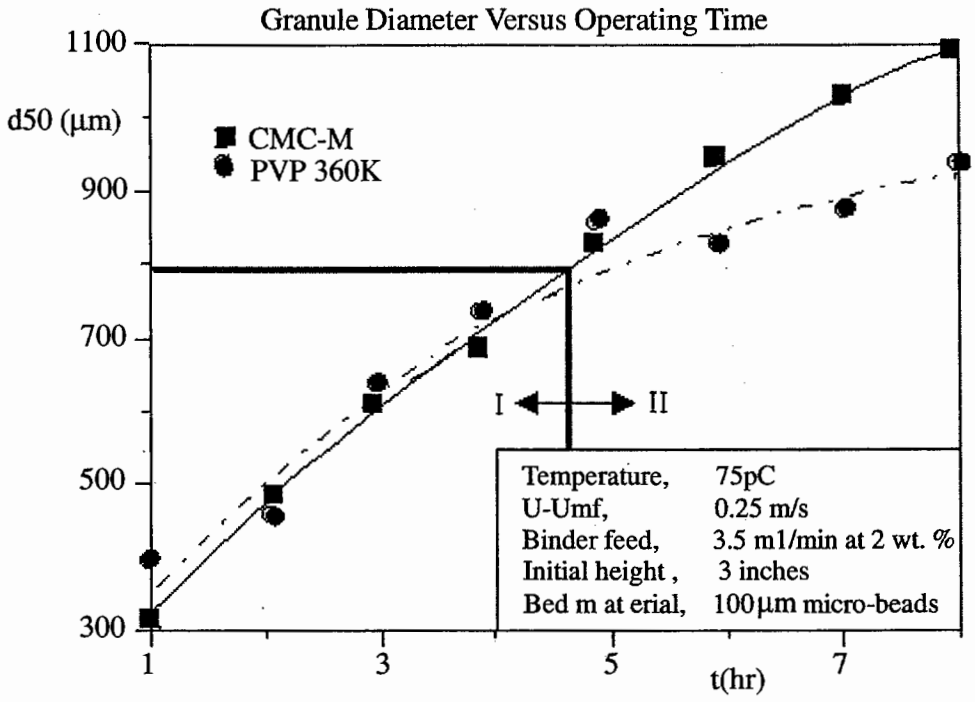


Figure 10 Growth of glass ballotini granules in a fluidized bed with binders of different viscosity. (From Ref. 9.)

Coating regime ($St_{v,min} > St^*$): The kinetic energy in most or all collisions exceeds viscous dissipation in the liquid layer. There is no coalescence. Granule growth will only occur by the successive layering of new material in the liquid phase (melt, solution, or slurry) onto the granule.

Figure 10 shows an example of granule growth in a fluidized bed where the growth regime changes as the granules grow. Glass ballotini is grown with two liquid binders of different viscosity. Initially, both systems grow steadily at the same rate (noninertial regime). When the granule size reaches ≈800 μm, the PVP bound granule growth begins to slow down indicating a transition to the inertial growth regime (only some collisions are successful). Finally, the PVP granules level off at a maximum size of ≈900 μm showing transition to the coating regime, where no granule collisions are successful. In contrast, the more viscous CMC-M granules grow steadily throughout the 8 hr experiment, i.e., they remain in the noninertial regime for the whole experiment.

3.3. Breakage and Attrition

Breakage and attrition really cover two separate phenomena:

1. Breakage of wet granules in the granulator
2. Attrition or fracture of dried granules in the granulator, drier, or in subsequent handling.

Breakage of wet granules will influence and may control the final granule size distribution. It is only an important phenomenon for high-shear granulators. Wet granule breakage is much less studied than nucleation and growth. There is very little

quantitative theory or modeling available to predict conditions for breakage, or the effect of formulation properties on wet granule breakage.

Tardos et al. (10) considered that a granule breaks if the applied kinetic energy during an impact exceeds the energy required for breakage. This analysis leads to a Stokes deformation number criteria for breakage:

$$St_{\text{def}} > St^*_{\text{def}} \tag{3.12}$$

where St^*_{def} is the critical value of Stokes number that must be exceeded for breakage to occur. However, this model is probably an oversimplification. Figure 8 shows schematics of the failure mode of different formulations in dynamic yield strength measurements. Failure behavior varies widely from semibrittle behavior at low capillary numbers to plastic failure at high capillary numbers. We expect a purely plastic granule to smear rather than break when its yield stress is exceeded. At high impeller speeds such materials will coat the granulator wall or form a paste. Semibrittle granules will break at high-impact velocity giving a maximum stable granule size or a weak crumb. Nevertheless, Eq. 3.12 provides a good starting point for quantifying wet granule breakage.

Dry granule attrition is important where drying and granulation occur simultaneously (e.g., in fluidized beds) and in subsequent processing and handling of the granular product. We can consider dry granule breakage as brittle or semibrittle phenomena. The key granule properties that control the breakage are the granule fracture toughness K_c and the flaw or crack size c in the granule. K_c is set by formulation properties, while c is closely related to granule porosity controlled by the consolidation process in the granulator.

Dry granule breakage usually results in production of fines by wear, erosion, or attrition brought about by diffuse microcracking. Within a fluid bed there are a large number of low-velocity collisions between particles as they shear past each other. This process is analogous to abrasive wear. For abrasive wear of agglomerates, the volumetric wear rate V is given by (11)

$$V = \frac{d_i^{1/2}}{A^{1/4} K_c^{3/4} H^{1/2}} P^{5/4} l \tag{3.13}$$

where d_i is indentor diameter, P is applied load, H is the hardness of the particles, l is wear displacement of the indentor, and A is the apparent area of contact of the indentor with the surface. The number and relative velocity of the collisions depend on the number of bubbles in the bed and hence the excess gas velocity $(u - u_{\text{mf}})$. The applied pressure in a fluid bed depends on bed depth. Thus, the attrition rate B_w in a fluidized bed granulator is

$$B_w = \frac{d_0^{1/2}}{K_c^{3/4} H^{1/2}} L^{5/4} (u - u_{\text{mf}}) \tag{3.14}$$

where d_0 is the distributor hole orifice size and L is the fluidized bed height. Figure 11 shows the attrition rates of several formulations in a fluidized bed with a direct correlation between attrition rate and the material properties grouping in Eq. 3.13 and (3.14).

Note that Eq. 3.13 and (3.14) only hold for breakage via a wear mechanism. For attrition during impact or compaction, there are different dependencies of the attrition rate on the materials properties [Ref. 5 for more details].

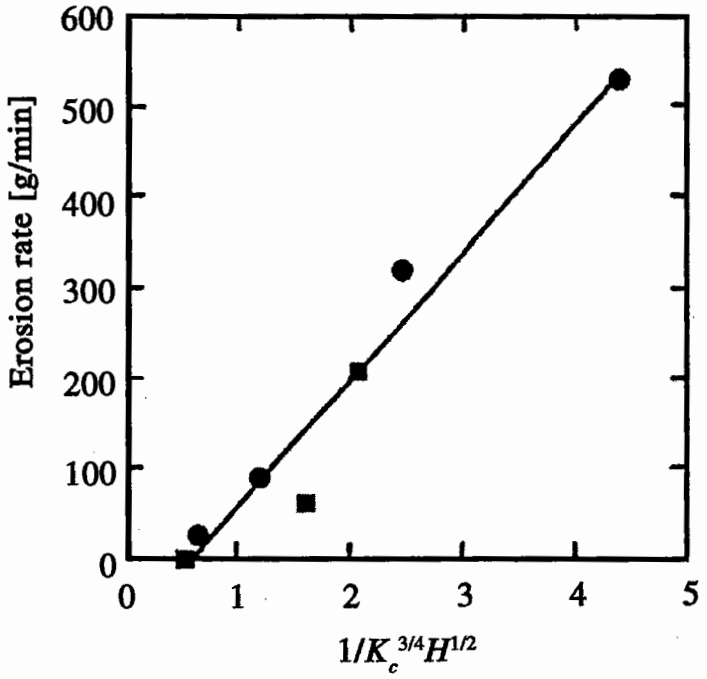


Figure 11 Erosion rates of agglomerate materials during attrition of granules in a fluidized bed. (From Ref. 12.)

3.4. Implications for Scale-Up

Table 3 summarizes the key controlling dimensionless groups for the rate processes described earlier and the main process parameters and formulation properties that impact on these groups.

In addition to these groups, there are dimensionless groups to describe: (1) the geometry of the equipment and (2) the flow of the powder and granules in the granulator. Both these classes of controlling groups are very equipment dependent.

For scale-up using full dimensional similarity, all these dimensionless groups need to be held constant. This is normally impossible due to the small number of

Table 3 Summary of Controlling Groups for Granulation Rate Processes

Rate process	Controlling groups	Key formulation properties	Key process parameters
Wetting and nucleation	Dimensionless spray flux ψ, dimensionless penetration time τ_p	t_p, μ, $\gamma \cos\theta$, d_p, ε, ε_{tap}	$V^{\&}$, $A^{\&}$(influenced by nozzle design and position, no. of nozzles, and powder flow patterns)
Growth and consolidation	Stokes deformation number St_{def}, viscous Stokes number St_v, liquid saturation S	Y, ρ_g, μ, $\gamma \cos\theta$, d_p, ε_{tap}	U_c (influenced by powder flow patterns; see Table 2)
Attrition and breakage	Stokes deformation number St_{def}	K_c, H, Y, ρ_g, μ, $\gamma \cos\theta$, d_p, ε_{tap}	U_c, L, $u - u_{mf}$

degrees of freedom and the large number of constraints. In particular, for regulatory reasons it is usually not possible to change formulation properties during scale-up except during the very early stages of process development. This leaves only a relatively small number of process parameters as degrees of freedom.

Therefore, a partial similarity approach for scale-up is recommended. The general steps are

1. Maintain similar geometry throughout the scale-up process. For most of the pharmaceutical granulation equipment, this can be achieved from either 10 or 25 L nominal batch size to full scale. Be wary, however, in some cases key geometric parameters do vary with scale on a particular design, e.g., relative chopper size, relative fill height. Manufacturers should be lobbied hard to provide geometrically similar designs at all scales.
2. Set key dimensionless groups to maintain similar powder flow during scale-up. In particular, avoid changes of flow regime during scale-up that make maintaining granule attributes during scale-up impossible.
3. Use your experience and an understanding of your process to decide which product attributes are the most important, and which granulation rate process is most dominant in controlling these attributes. This is difficult to do a priori, but with good characterization of your formulation and process, the regime map approaches described earlier are very useful.
4. Use your remaining degrees of freedom in the choice of process parameter values to keep the most important one or two rate process dimensionless groups constant.

This approach is most easily demonstrated on a particular type of equipment (Section 5 for fluidized beds and Section 6 for high-shear mixers).

4. SCALE-DOWN, FORMULATION CHARACTERIZATION, AND FORMULATION DESIGN IN PHARMACEUTICAL GRANULATION

In the development of a new pharmaceutical product, important decisions about the manufacturing process are made with a few grams or tens of grams of formulation. To provide, the drug product for clinical trials and the final design at large scale, granulations are often conducted at several laboratory-and pilot scales as well. Typical nominal batch sizes are 1, 10, 25, and 65 L scaling to commercial operation at 300 or 600 L.

Small-scale granulations up to 1 L are often done by hand, and certainly performed in equipment that is very different from the equipment that will be used for scales from 10 L and larger. At this level, the general scale-up approach described in Section 3.4 does not hold. How do we scale down to make the best use of data from granulation of these small amounts?

The key is to consider granulation as a particle design process (Fig. 12). During scaling up from 10 L, formulation properties cannot be varied. Only process parameters can be used to keep key granule attributes in the target range. Therefore, very small-scale-experiments should target major formulation design decisions and attempts to mimic completely different geometries at larger scale should be avoided.

Table 3 summarizes key formulation properties that should be measured. Most of these require relatively small amounts of material and can be measured at this

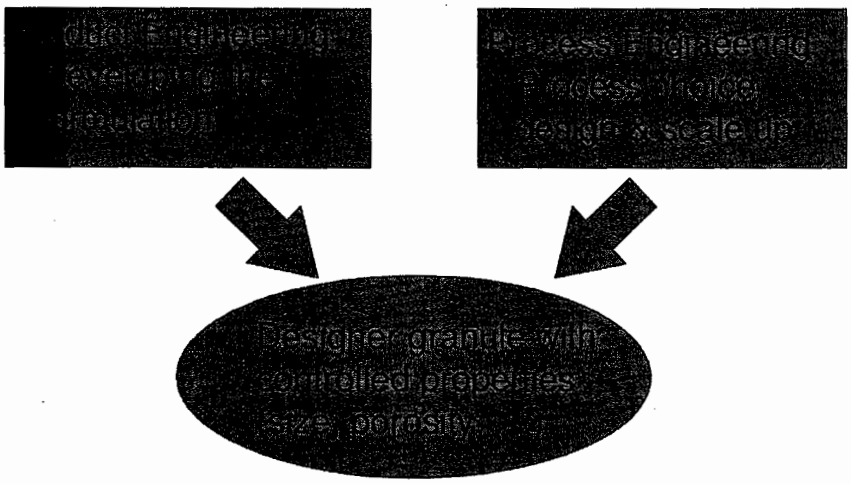


Figure 12 Granulation as an example of particle design. Both formulation properties and process parameters influence granule attributes.

level. By using these data to help estimate key controlling groups for the granulation rate processes in the larger-scale equipment, appropriate changes to the formulation can be made. This avoids major headaches at a later stage. Good communication between the technologists who design the formulations and the process engineers who scale the process and transfer the product to manufacturing is an essential part of this paradigm.

Some of the questions that can be addressed at this stage of formulation development and scale-up include:

1. Wetting and nucleation
   - Contact angle: Are the active and all the excipients easily wetted by the liquid binder?
   - Drop penetration time: Is the liquid phase too viscous, or the particle size too small to achieve fast drop penetration?
2. Growth and consolidation
   - What is the dynamic yield stress of the formulation?
   - How much liquid binder is required for granule growth?
   - What is the likely growth regime?
   - What range of granule density is likely?
3. Attrition and breakage
   - Will extensive granule breakage occur in the granulator?
   - What are dry granule strength (fracture toughness) and porosity?
   - Are attrition and dust formation during handling likely?
4. Downstream processing issues
   - Does the formulation compress well for tableting?
   - Can the desired dissolution profiles be met?

Details of how to measure key formulation properties are described in more detail in Litster and Ennis (5).

5. SCALE-UP OF FLUIDIZED BED GRANULATORS

There are many different variations of fluidized bed granulators including bubbling fluidized bed, draft tube fluidized beds, and spouted beds (5). However, in this section, we limit ourselves only to the scale-up of the most commonly used fluidized bed granulator, i.e., bubbling fluidized bed granulator. In particular, as most fluidized bed granulators used in the pharmaceutical industry are operated in batch mode, we will concentrate on the scale-up of batch bubbling fluidized bed granulators.

5.1. Bed Hydrodynamics and Scale-Up

Particle growth in a fluidized bed is closely related to the particle mixing and the flow pattern in the bed. This dictates that the hydrodynamics of the scaled bed should be the same as the small unit, i.e., hydrodynamic similarity. Basic fluidized bed hydrodynamics are described in Chapter 9.

In bubbling fluidized beds, bed expansion, solids mixing, particle entrainment, granule growth, and attrition are intimately related to the motion of bubbles in the bed (Fig. 13). The volume flow rate of bubbles in the bed Q_b, the bubble size d_b, and the bubble rise velocity u_b are the key parameters that characterize the bubbly flow. There are numerous correlations relating these bubble parameters to process conditions [see, for example, Kunii and Levenspiel (13) and Sanderson and Rhodes (14)]. In general, Q_b is a strong function of the excess gas velocity $u - u_{mf}$. Growing granules are usually Geldart type B powders, or perhaps type A powders at the start of the batch. For group B powders, d_b increases with bed height and is a function of

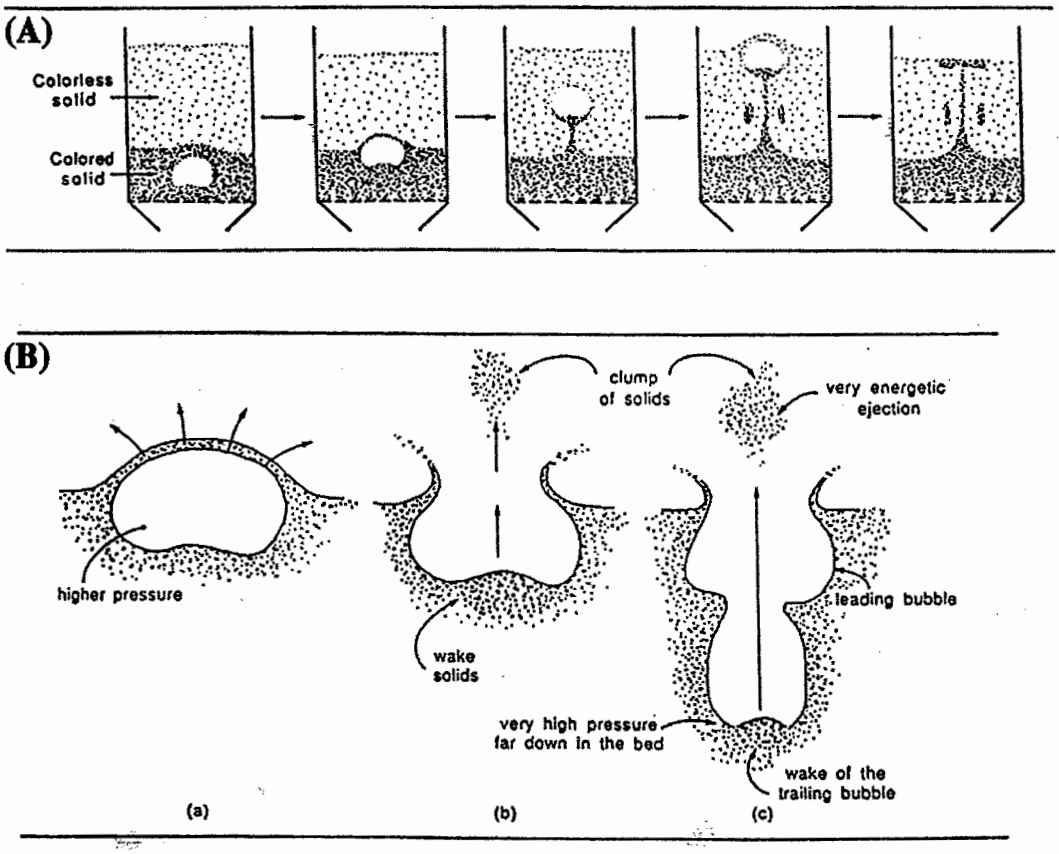


Figure 13 Effect of bubbles on (A) solids mixing and (B) solids entrainment. (From Ref. 13.)

excess gas velocity. The bubble-rise velocity is directly related to d_b. For the simplest models for group B powders we can write

$$Q_b = (u - u_{mf})\pi D_F^2 \tag{5.1}$$

$$u_b = 0.71\sqrt{gd_b} \tag{5.2}$$

$$d_b \propto (u - u_{mf})^{0.4} L^{0.8} \tag{5.3}$$

Thus, the excess gas velocity $u - u_{mf}$ and the bed height L are the key process parameters that control bubbling behavior in the bed.

Several rules exist for scaling up a bubbling fluidized bed under the condition of hydrodynamic similarity. Fitzgerald and Crane (15) proposed that the following dimensionless numbers be kept constant during scale-up:

- Particle Reynolds number based on gas density $(d_p u \rho_G)/\mu$
- Spolid particle to gas density ratio ρ_s/ρ_G
- Particle Froude number $u/(gd_p)^{0.5}$
- Geometric similarity of distributor, bed, and particle L/d_p

where d_p is the particle diameter, u is the fluidization velocity (superficial gas velocity), μ is the viscosity of fluidizing gas, ρ_G is the density of fluidizing gas, g is the gravitational acceleration, and L is the fluidized bed height.

In this approach, experiments on the smaller scale are performed with model materials, i.e., model gas (different from the larger-scale one) and model solid particles (different particle density, size, and size distribution). For readers interested in following Fitzgerald's scale-up rules, a detailed calculation procedure can be found in Kunii and Levenspiel's book (13), illustrated with an example.

In a series of publications, Glicksman et al. (16–18) divided the scale-up into two regimes, namely, inertia-dominated and viscous-dominated flow regimes. In viscous-dominated flow regime, where particle Reynolds number based on fluid density is ≤ 4, i.e., when, the $(d_p u \rho_G/\mu \leq 4$, dimensionless numbers that need to be kept constant are

$$\frac{u}{(gd_p)^{0.5}}, \frac{d_p u \rho_s}{\mu}, \frac{L}{d_p}, \frac{D_F}{d_p}, \phi, \text{ particle size distribution, bed geometry} \tag{5.4}$$

where D_F is the fluidized bed diameter.

In contrast, in inertia-dominated flow regime, $(d_p u \rho_G)/\mu \geq 400$, scale-up of the process demands that the following dimensionless numbers are kept constant:

$$\frac{u}{(gd_p)^{0.5}}, \frac{\rho_G}{\rho_s}, \frac{d_p u \rho_s}{\mu}, \frac{L}{d_p}, \frac{D_F}{d_p}, \phi, \text{particle size distribution, bed geometry} \tag{5.5}$$

In the intermediate region, where $4 \leq (d_p u \rho_G)/\mu \leq 400$, both the viscous and the inertial forces are important to the fluid dynamics, and all the dimensionless numbers for the two regions mentioned earlier will need to be kept constant during scale-up, i.e.,

$$\frac{\rho_s \rho_G d_p^3 g}{\mu^2}, \frac{u}{(gd_p)^{0.5}}, \frac{\rho_G}{\rho_s}, \frac{L}{d_p}, \frac{D_F}{d_p}, \phi, \text{particle size distribution, bed geometry} \tag{5.6}$$

Experimenting with only ambient air and particles made of the same material but different sizes, Horio et al. (19,20) developed what has been lately defined as the simplified scaling law. They demonstrated that, with similar bed geometry (ratio of bed height to diameter), using particles of different mean sizes but the same distribution characteristics, and operating the bed in proportional superficial gas velocities would ensure that the hydrodynamic conditions of the two beds remain similar. Expressed in mathematical terms

$$\begin{aligned} &u_2 - u_{\mathrm{mf},2} = \sqrt{\mathrm{m}}(u_1 - u_{\mathrm{mf},1}) \\ &u_{\mathrm{mf},2} = \sqrt{m}u_{\mathrm{mf},1} \\ &m = \frac{L_2}{L_1} \\ &\text{bed geometry} \end{aligned} \tag{5.7}$$

where 1 and 2 refer to the small-scale and large-scale beds, respectively.

Experimental results from Roy and Davidson (21) suggest that when $(d_{\mathrm{p}}\mathrm{u}\rho_{\mathrm{G}})/\mu < 30$, the criteria of Horio et al. (19,20) are sufficient to give similarity in behavior. However, when $(d_{\mathrm{p}}\mathrm{u}\rho_{\mathrm{G}})/\mu > 30$, the more restrictive approach of Fitzgerald and Crane has to be used.

Unfortunately, few of the previously mentioned scaling rules for bubbling fluidized beds have been strictly followed for the scaling up of fluidized bed granulators. This is largely because the scaling rules require model materials to be used at the smaller scale, whereas in pharmaceutical granulation, the formulation is unchanged during scale-up. However, the simplified rules presented by Horio combined with our understanding of granulation rate processes do provide some guide.

5.2. Granulation Rate Processes in Fluidized Beds

Figure 14 shows the rate processes occurring during fluidized granulation. Wetting, nucleation, and layered growth occur in the spray zone of the fluidized bed. Most consolidation and coalescence also occur in or near the spray zone because fluidized bed granulators are also driers. The drying process "freezes" the granule structure and prevents further growth. Thus, good design of the spray zone is very important and liquid flow rate is a critical process parameter. Beds should be designed to keep dimensionless spray flux low (drop-controlled regime). If this is not done, the formation of large clumps leads to rapid wet quenching and defluidization with likely loss of the batch. Figure 15 shows how the product granule size distribution is closely related to the design of the spray zone. The x-axis variable (spray surface area per mass in granulator) is closely related to our definition of dimensionless spray flux.

Due to the simultaneous drying, our consolidation and growth models for near-elastic granules is usually appropriate and the viscous Stokes number is a key controlling group [Eq. (3.11)]. This model predicts that in batch granulation, granules will grow toward a maximum size corresponding to the critical Stokes number and transition to the coating regimes (e.g., Fig. 10). The average and maximum granule collision velocities are set by the flow of bubbles in the fluid bed and are a function of bubble velocity and size (Table 3).

Fluidized beds produce porous granules because the consolidation time is limited to granule drying time, which is of the order of seconds, rather than minutes.

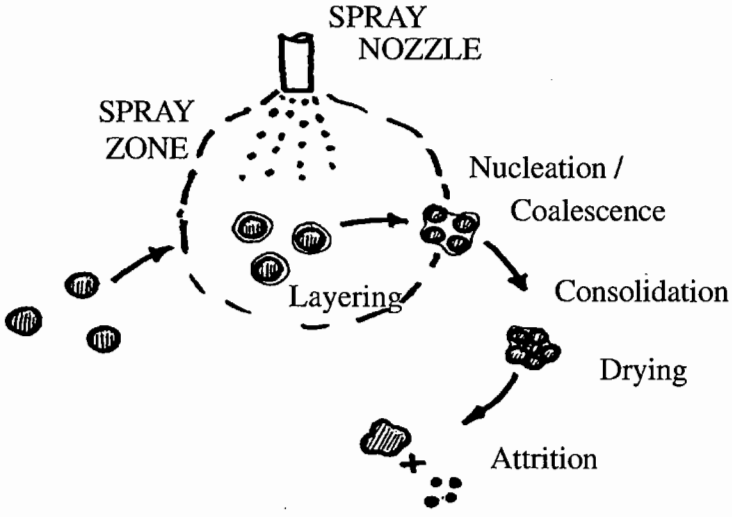
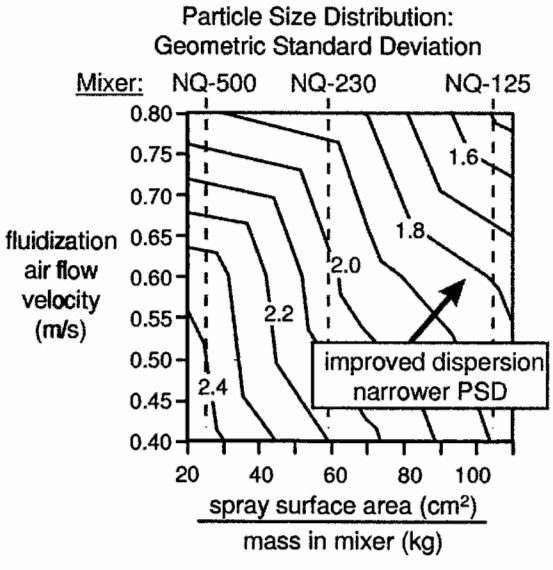


Figure 14 Important granulation processes in the fluidized bed. (From Ref. 5.)

Thus, process changes that reduce drying time (higher bed temperature, lower liquid flow rate, and smaller drop size) will decrease granule density (increase granule porosity). Increasing the liquid binder viscosity decreases granule voidage by increasing the resistance of the granule to deformation.

Dry granule attrition in the fluid bed is an important source of fines. Eq. 3.14 quantifies the attrition rate in terms of granule properties and process conditions (Fig. 11). Increasing fluid bed height increases both consolidation and attrition for two reasons: (1) it increases the effective "fluid" pressure on granules in the bed and (2) it increases the average bubble size in the bed, leading to more vigorous mixing and higher-velocity granule collisions.



Agglomeration in an Agitated Fluidized Bed

	Mixer Type		
	NQ-125	NQ-230	NQ-500
Powder feed (kg)	0.36	2.23	22.9
Spray area (cm²)	38.5	132.7	594
Spray area / Feed	107	60	26

Figure 15 Geometric standard deviation of granule size in an agitated fluid-bed granulator as a function of gas fluidization velocity and binder dispersion measured using spray surface area to mass in mixer. (From Ref. 10.)

5.3. Suggested Scaling Rules for Fluid Bed Granulators

Given this understanding of fluidized bed hydrodynamics and granulation rate process, we suggest the following guidelines for scaling fluidized bed granulators:

1. Maintain the fluidized bed height constant. Granule density and attrition rate increase with the operating bed height

$$L_2 = L_1 \tag{5.8}$$

2. If L is kept constant, then batch size scales with the bed cross-sectional area:

$$\frac{M_2}{M_1} = \frac{D_{F,2}^2}{D_{F,1}^2} \tag{5.9}$$

3. Maintain superficial gas velocity constant to keep excess gas velocity, and therefore bubbling and mixing conditions similar:

$$\frac{Q_2}{Q_1} = \frac{u_2}{u_1} = \frac{D_{F,2}^2}{D_{F,1}^2} \tag{5.10}$$

Note that the scaling rules defined by Eqs. 5.8–5.10 are consistent with Horio's simplified scaling rules (Eq. 5.7).

4. Keep dimensionless spray flux constant on scale-up. This is most easily achieved by increasing the area of bed surface under spray (usually by increasing the number of nozzles). By doing this, the liquid flow rate can be increased in proportion to batch size without changing critical spray zone conditions. Thus, batch times at small and large scale should be similar:

$$V_2^{\&} = V_1^{\&} \tag{5.11}$$

$$\frac{A_{spray,2}}{A_{spray,1}} = \frac{D_{F,2}^2}{D_{F,1}^2} \tag{5.12}$$

5. Keep viscous Stokes number constant. By adhering to the scaling rules described earlier, St_v should automatically be similar at small and large scale leading to similar consolidation and growth behavior.

There are also some cautionary notes relating to the minimum scale for the laboratory scale studies. Slug flow, a phenomenon where single gas bubbles as large as the bed diameter form in regular patterns in the bed, significantly reduces solid mixing. It occurs in tall and narrow beds. Stewart (22) proposed a criterion for the onset of slugging

$$\frac{u - u_{mf}}{0.35\sqrt{gD_F}} = 0.2 \tag{5.13}$$

To ensure that the bed is operating in bubbling mode without risking slugging, the ratio in Eq. 5.13 must be kept below 0.2. In addition, both the bed height to bed diameter and the particle diameter to bed diameter ratios should be kept low. For pilot fluidized bed, the diameter should be > 0.3 m.

To avoid the gas entry effect from the distributor (gas jet), there is also a requirement on minimum fluidized bed height. The jet length depends on the gas velocity and the size of the opening on the distributor. For the same opening size,

jet length increases with gas velocity through the hole; for a given gas velocity through the hole, small holes give shorter jets but are accompanied by a larger pressure drop across the distributor. Even at a superficial gas velocity as low as 0.2 m/sec with a hole size of 9.5 mm diameter, jet length as long as 0.6 m has been reported (23).

The amount of fluidization gas required to maintain constant fluidization velocity changes linearly with the cross-section area of the bed. However, for large fluidized beds, one of the major concerns is the even distribution of the fluidization gas across the whole area of the bed. In addition to the use of a plenum chamber and an even distribution of flow channels across the distributor, the distributor should be designed in such a way that the pressure drop across it is at least 20% of the total.

If these scaling rules are applied, there is a good chance to keep granule properties within the desired range on scaling. If fine tuning is needed at the large scale, minor adjustments to the liquid spray rate can be used to adjust granule properties, as all the granulation rate processes in fluidized beds are very sensitive to this parameter.

6. SCALE-UP OF HIGH-SHEAR MIXER GRANULATORS

Effective scale-up of mixer granulators is more difficult than in fluidized beds. There are several reasons for this:

- The geometric and mechanical design of mixer granulators varies enormously, as do the powder flow patterns in the mixer. There is no such thing as a generic high-shear mixer and caution is needed when transferring scaling rules from one design to another.
- Even with the same series from the same manufacturer, geometric similarity is not always maintained between different scales, e.g., impeller size in relation to bowl size.
- Powder flow in high-shear mixers is not fluidized and powder flow patterns are much harder to predict than in a fluidized bed.
- All three rate processes, i.e., wetting and nucleation, growth and consolidation, and breakage and attrition, are taking place simultaneously in the mixer granulator of all scales. However, the relative dominance of each of the rate processes can vary significantly on different scales of the same series, let alone in granulators of different series.

In this section, we will focus mainly on vertical shaft mixer, e.g., Fielder, Diosna designs. Some of the suggested approaches may be used with caution for other mixer designs.

6.1. Geometric Scaling Issue

For a simple vertical mixer design, the key dimensions are the impeller diameter D, which is usually equal to the bowl diameter, the chopper diameter D_c, and the fill height H_m. The dimensionless groups that need to be held constant for geometric similarity are

$$\frac{D_c}{D}, \frac{H_m}{D}$$

In addition, the shape and positioning of the impeller and chopper should be the same on scale-up. Unfortunately, manufacturers do not always adhere to these

rules. It is common for the absolute size of the chopper to be invariant, meaning its relative influence is much larger in the small-scale granulator.

Relative fill height is also often varied with scale. This often reflects the small-size batches required for early-stage clinical trials and the desire to maximize production rate (by maximizing batch size) at full scale. Varying relative fill height is very dangerous, as it can have a major impact on powder flow patterns.

6.2. Powder Flow Patterns and Scaling Issues

There are two flow regimes observed in a vertical shaft mixer granulator, namely, bumping and roping regimes (24). At low impeller speeds in the bumping regime, the powder is displaced only vertically as the blade passes underneath leading to a slow, bumpy powder motion in the tangential direction. There is almost no vertical turnover of the powder bed, as shown in Figure 16A.

At a higher impeller speed in the roping regime, material from the bottom of the bed is forced up the vessel wall and tumbles down at an angle of the bed surface toward the center of the bowl. There is both good rotation of the bed and good vertical turnover (Fig. 16B).

The transition from bumping to roping is due to a change in the balance between centrifugal force and gravity. The centrifugal force, which is caused by the rotational movement of the powder from the spinning of the blades, pushes the powder outward toward the wall of the bowl, while gravity keeps the powder tumbling back toward the center of the bowl from the buildup at the wall region. This balance between rotational inertia and gravity is given by the Froude number:

$$Fr = \frac{DN^2}{g} \tag{6.1}$$

where N is the impeller speed and g is the gravitational acceleration.

When the Froude number exceeds a critical value, transition from bumping to roping takes place:

$$Fr > Fr_c \tag{6.2}$$

Fr_c will be a function of relative fill height (H_m/D), impeller design (size and geometry), and powder flow properties.

Roping flow is more difficult to achieve as relative fill height increases because the centrifugal force is only imparted to powder in the impeller region. This region becomes a smaller fraction of the total powder mass as fill height increases. Schaefer (25) also showed that impeller design had a significant effect on both Fr_c and bed turnover rate.

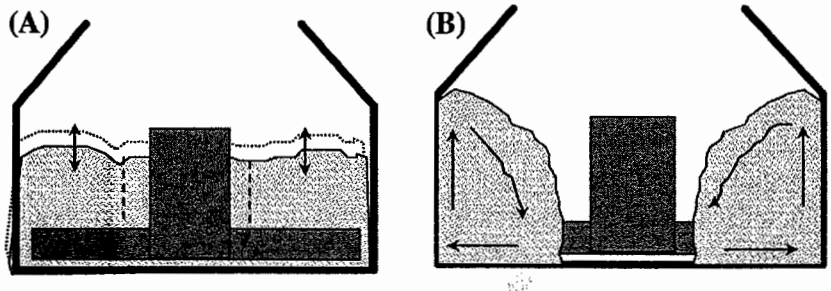


Figure 16 Powder flow regimes in Fielder mixer granulators: (A) bumping and (B) roping.

Cohesive powders transfer to roping at lower values of Fr because momentum from the spinning impeller is more effectively transferred into the powder mass. Note that powder flow properties generally change with the addition of the liquid binder and, therefore, flow patterns will probably change significantly during a batch granulation.

Figure 17 shows dry lactose powder surface velocity data in a 25 L fielder granulator (24). In the bumping flow regime, the powder surface velocity increases in proportion to the impeller speed. In the roping regime, the surface velocity stabilizes and is less sensitive to impeller speed. In all cases, the surface velocity of the powder is only of order of 10% of the impeller tip speed. Knight et al. (26) showed that dimensionless torque T is a direct function of Froude number and effective blade height h_{eff}:

$$T = T_0 + kFr^{0.5} \qquad \text{where } k = \beta\left(\frac{2h_{\text{eff}}}{D}\right)^{a} \tag{6.3}$$

Thus, to maintain a similar powder flow pattern during scale-up, the Froude number should be kept constant, i.e.,

$$\frac{N_2}{N_1} = \sqrt{\frac{D_1}{D_2}} \tag{6.4}$$

In addition, the dimensionless bed height should also be kept constant, i.e., the same fraction of the bowl is filled at all scales:

$$\frac{H_{m,2}}{H_{m,1}} = \frac{D_2}{D_1} \tag{6.5}$$

Historically, mixer granulators have been more commonly scaled up using constant tip speed or constant relative swept volume (25,27). Maintaining constant

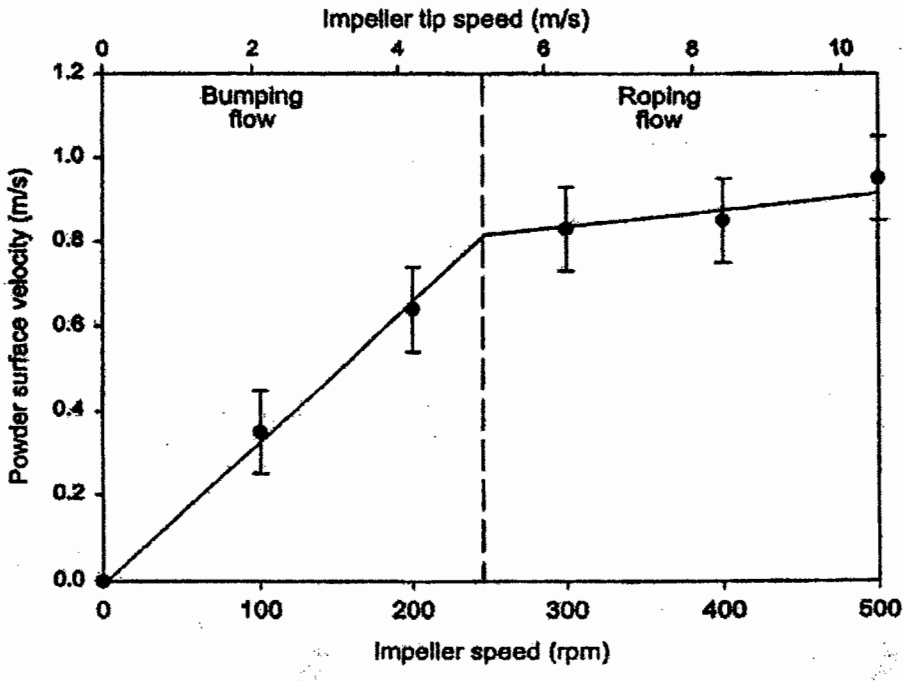


Figure 17 Powder surface velocities as a function of impeller tip speed. (From Ref. 24.)

impeller tip speeds leads to the scaling rule:

$$\frac{N_2}{N_1} = \frac{D_1}{D_2} \tag{6.6}$$

This scale-up rule leads to *Fr* decreasing, as scale increases. Combined with the common practice of overfilling full-scale granulators, this approach to scaling can often lead to a change in operating regime from roping to bumping on scale-up.

The constant swept volume approach to scale-up was introduced partly to account for variations in geometry on scale-up. The relative swept volume is defined as

$$V_{\mathrm{R}}^{\&} = \frac{V_{\mathrm{imp}}^{\&}}{V_{\mathrm{mixer}}} \tag{6.7}$$

where $V_{\mathrm{R}}^{\&}$ is the relative swept volume, $V_{\mathrm{imp}}^{\&}$ is the rate of swept volume of impeller, and V_{mixer} is the mixer volume.

On scale-up,

$$V_{\mathrm{R},1}^{\&} = V_{\mathrm{R},2}^{\&} \tag{6.8}$$

This approach is useful for comparing granulators where geometry changes with scale. For geometrically similar granulators, Eq. 6.8 is equivalent to scale-up with constant tip speed (Eq. 6.6).

6.3. Granulation Rate Processes and Related Scaling Issues

In high-shear mixer granulation, all three classes of rate process can have a significant effect on the granule size distribution. Section 3.1 describes conditions for good nucleation in the drop-controlled regime and uses examples from mixer granulation. For good nucleation, the granulator should be operated in the roping regime for good bed turnover and the dimensionless spray flux ψ_{a} should be kept low. This implies careful choice of the liquid flow rate, nozzle design, and positioning in the granulator.

To maintain similar nucleation behavior and equivalent liquid distribution, the dimensionless spray flux ψ_{a} should be kept constant on scale-up. If drop size from the full-scale nozzle is similar to the small scale, this implies

$$\frac{V_2^{\&}}{A_2^{\&}} = \frac{V_1^{\&}}{A_1^{\&}} \Rightarrow \frac{V_2^{\&}}{V_1^{\&}} = \frac{A_2^{\&}}{A_1^{\&}} \tag{6.9}$$

A common scale-up approach is to keep the same total spray time and still use a single nozzle at large scale. Thus, $V^{\&}$ is proportional to D^3. Despite the fact that the powder area flux will increase slightly with scale, this approach generally leads to a substantial increase in dimensionless spray flux. To keep dimensionless spray flux constant, multiple spray nozzles or longer spray times should be used at a large scale.

It should be noted that consolidation, growth, and breakage processes are controlled by St_{def}. This can lead to quite complicated growth behavior in mixer granulators. Figure 18 illustrates some of this complex behavior (27). Both decreasing liquid viscosity and increasing impeller speed increase the rate of granule growth but decrease the final equilibrium granule size. Both these effects increase St_{def}. In the early stage of granulation, this increases the probability of successful coalescence. However, as the granules grow, the critical value of Stokes number for breakage may be exceeded—at least near the impeller blade leading to a balance of breakage and growth and an equilibrium granule size. This example also highlights that most

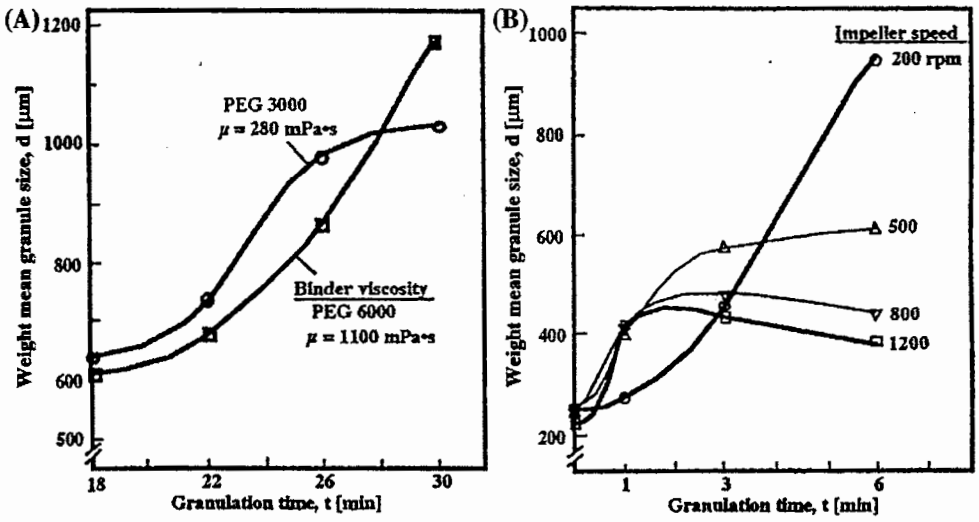


Figure 18 Variations in granule growth rate and extent of growth in a mixer granulator with changes to (A) binder viscosity and (B) impeller speed. (From Ref. 27.)

high-shear mixers have a very wide range of collision velocities in different parts of the bed. Granule coalescence will occur in regions of low collision velocity, while breakage and consolidation are more likely near the impeller. To properly quantify and predict this behavior, we need more sophisticated models that divide the granulator into at least two regions and incorporate better understanding of powder flow than we currently have.

Nevertheless, we can make some intelligent comments with regard to scale-up. In a mixer granulator, the maximum collision velocity for a granule will be of the order of the impeller tip speed. To maintain constant St_{def}, the impeller tip speed should be kept constant, i.e., Eq. 6.6. If a constant Fr rule is used (Eq. 6.4),

$$\frac{St_{def,2}}{St_{def,1}} = \frac{U_{c,2}^2}{U_{c,1}^2} = \frac{N_2^2 D_2^2}{N_1^2 D_1^2} = \frac{D_2}{D_1} \tag{6.10}$$

Thus, St_{def} increases with scale. This will lead to an increase in the maximum achievable granule density and a decrease in the maximum achievable particle size. The actual granule density and size may also depend on the kinetics of consolidation and growth and are difficult to predict without more sophisticated quantitative modeling. As such, the variation in St_{def} with scale potentially leads to changes in granule attributes that are difficult to predict.

The liquid saturation s (Eq. 3.7) should be kept constant on scaling. This implies a similar liquid content on a kilogram per kilogram dry powder basis provided the granule density does not change with scale. For operation in the steady growth regime, this is a reasonable assumption. However, for operation in the induction growth regime the change in density with scale is harder to predict.

6.4. Recommended Scaling Rules and a Case Study Example

The complexity of powder flow and granulation rate processes makes it impossible to recommend a single definitive set of scaling rules. It is important to know which granule attribute is of most importance during scaling and the main granulation rate process that controls this attribute.

Overall, we recommend the following approach:

1. Keep granulators geometrically similar during scale-up where manufacturer's designs permit. In particular, keep dimensionless fill height constant during scale-up (Eq. 6.5).
2. To ensure similar powder mixing, keep Froude number constant during scale-up by adjusting the impeller speed according to (Eq. 6.4). At the very least, make sure $Fr > Fr_c$ at all scales.
3. To achieve good binder distribution, ψ_a should be kept constant on scale-up. This is likely to mean multiple spray nozzles at the large scale to give sufficient spray zone area (Eq. 6.9).
4. To keep St_{def} constant for consolidation, breakage, and growth, constant impeller tip speed should be maintained. This is in conflict with scaling rule 2 mentioned earlier. Scale-up with constant tip speed is possible, provided that at large scale $Fr > Fr_c$.
5. Spray time during the batch and total batch time scaling rules require a sound understanding of how the kinetics of growth and consolidation vary with scale. We do not know these rules yet, and they are likely to be different for operation at different growth regimes. As a starting point, keeping batch times constant during scaling is probably reasonable provided this does not conflict with other scaling rules (especially rule 3 mentioned previously).

Conflicting scale-up goals lead us to consider more sophisticated operating strategies at a large scale including programming impeller speed to change during the batch operation. For example, begin the granulation with high impeller speed (constant *Fr*) to induce good dry powder turn over. This helps ensure good wetting and nucleation at the beginning of the batch when it is most important. Later, reduce the impeller speed to give a similar tip speed to smaller-scale operation to control granule density or size. As the powder mass is now wet, it will be more cohesive and operation above the critical Froude number for rolling flow will be easier to maintain. and Ennis (5) give a case study for scale-up of a lactose granulation that is useful for illustrating these scaling rules and conflicts. It is represented in the next section.

6.4.1. *Scale-Up of a Lactose Granulation from 25 to 300 L*

A lactose-based granulation in a 25 L granulator has given granules with acceptable properties. The operating conditions for the 25 L granulator are summarized as follows:

Parameter	Value
Nominal volume (L)	25
Powder charge (kg)	5
Impeller speed (rpm)	330
Spray time (min)	8
Drop size (μm)	100
ε_{min}	0.3
W	0.15
$V^{\&}$ (m^3/sec)	1.6×10^{-6}
Spray width W (m)	0.13
Powder surface velocity (m/sec)	0.85
ψ_a	0.22

The dimensionless spray flux ψ_a was calculated by

$$\psi_a = \frac{3V_2^{\&}}{2A_2^{\&}d_d} \tag{6.11}$$

This granulation is to be scaled to 300 L using the following rules and heuristics:

- Keep *Fr* constant
- Keep spray time constant
- Spray from a single nozzle at large scale.

How do ψ_a and St_{def} change on scale-up? What are the implications from granulation rate processes at full scale?

Scaling to 300 L granulation:

Assuming geometric similarity,

$$D_2/D_1 = 12^{1/3}$$

Keeping *Fr* constant,

$$N_2 = (D_1/D_2)^{0.5} N_1 = 218\,\text{rpm}$$

Assuming spray width scales with impeller diameter,

$$W_2 = (D_2/D_1)W_1 = 0.3\,\text{m}$$

powder surface velocity scales with tip speed,

$$v_2 = (D_2N_2/D_1N_1)v_1 = 1.28\,\text{m/sec}$$

Keeping spray time constant with one nozzle,

$$V_2^{\&} = 12V_1^{\&}$$

Thus, the dimensionless spray flux at 300 L is

$$\psi_{a,2} = \frac{3V_2^{\&}}{2W_2v_2d} = \frac{3(12V_1^{\&})}{2(12^{1/3}W_1)12^{1/6}v_1d} = 3.41\psi_{a,1} = 0.75$$

There has been a substantial increase in ψ_a on scale-up taking the granulation from nearly drop controlled into the mechanical dispersion regime. This could result in a much broader granule size distribution at a large scale. A similar spray flux could be achieved by using an array of four nozzles spaced at 90° intervals around the granulator (all positioned so the spray fan is at right angles to the direction of powder flow).

We cannot calculate the value of St_{def} because the dynamic yield stress Y for the lactose/binder system is not given. However, if we neglect changes in Y due to the larger strain rate, then St_{def} will increase as

$$St_{def,2} = \frac{U_{c,2}^2}{U_{c,2}^1} St_{def,1} = \frac{(D_2N_2)^2}{(D_1N_1)^2} St_{def,1} = 2.3St_{def,1}$$

There is a significant increase in St_{def} with scale-up that could impact on the granule density and maximum size. It is not possible to scale with constant

St_{def} while simultaneously maintaining constant Fr. Scale-up summary data are given in the following table:

Parameter	25 L	300 L
Nominal volume (L)	25	300
Powder charge (kg)	5	60
Impeller speed (rpm)	330	218
Spray time (min)	8	8
Drop size (μm)	100	100
ε_{min}	0.3	0.3
W	0.15	0.15
$V^{\&}$ (m^3/sec)	1.6×10^{-6}	19.2×10^{-6}
Spray width W (m)	0.13	0.3
Powder surface velocity (m/sec)	0.85	1.28
ψ_a	0.22	0.75
$St_{def}/St_{def,\ 25\ L}$	1	2.3

7. CONCLUDING REMARKS

Scaling of granulators using the traditional chemical engineering dimensional analysis approach of complete similarity is not possible due to the complexity of the process and the constraints on formulation changes during scaling pharmaceutical processes. Nevertheless, scale-up using partial similarity that strives to keep some key dimensionless groups invariant is possible. It is very important to understand the powder flow phenomena in the granulator of choice and to maintain the same flow regime during scaling (bubbling vs. slugging, bumping vs. roping).

The second important requirement is to maintain constant key dimensionless groups that control the important granulation rate process of most interest during scale. This is somewhat easier to do in fluidized beds than in high-shear mixers.

Very small-scale tests, which have no geometric similarity to pilot-and full-scale tests should be used to focus on formulation design and measurement of key formulation properties that influence the granulation rate processes.

Insightful understanding of the granulation processes is essential for the identification of key variables and parameters for the dimensional analysis and scale-up considerations. While development of definitive mathematical models for the granulation processes is incomplete, the scaling approaches recommended in this chapter help reduce uncertainty during new product development and transfer to industrial sites.

NOMENCLATURE

$A^{\&}$	area flux of powder through the spray zone
d_d	liquid drop size (diameter)
d_i	indentor diameter
d_p	particle or granule size
d_b	bubble size
D_{drum}	drum granulator diameter
D	impeller diameter of mixer granulators
D_c	chopper diameter of mixer granulators
D_F	Fluidized bed diameter

Fr	Froude number
g	gravitational acceleration
H	hardness of granules
H_m	fill height of mixer granulators
L	characteristic length of a fluidized bed
K_c	fracture toughness of granules
M_1, M_2	mass of particles in the fluidized bed
m	scaling ratio
N	impeller speed
St_{def}	Stokes deformation number
S_{max}	granule pore saturation
t_p	drop penetration time
u	superficial fluidization velocity
u_1	fluidization velocity on the smaller bed
u_2	fluidization velocity on the larger bed
$u_{mf,1}$	minimum fluidization velocity on the smaller bed
$u_{mf,2}$	minimum fluidization velocity on the scaled bed
u_b	bubble rise velocity
U_c	particle collision velocity
$V_R^{\&}$	relative swept volume
$V_{imp}^{\&}$	rate of swept volume of impeller
V_{mixer}	mixer volume
$V^{\&}$	volumetric spray rate
w	liquid to solid mass ratio
W	spray zone width
Y	dynamic yield stress of granules
μ	viscosity of binder
ρ_g	granule density
ρ_G	density of fluidizing gas
ρ_s	particle density
ρ_l	binder liquid density
θ	solid liquid contact angle
γ_{LV}	liquid surface tension
δ	dimensionless bubble space, defined as the ratio of bubble space over bubble radius
ω	drum peripheral speed
ω_i	impeller peripheral speed
ω_c	chopper peripheral speed
ψ_a	dimensionless spray flux
ε_{min}	minimum porosity of granule
ε_{tap}	granule bed tap density

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