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Steady states in granulation of pharmaceutical powders with application to scale-up

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ABSTRACT

Theoretical and experimental evidence is given to show that steady states can be reached during agglomerate growth and break-up in high-shear granulation of fine powders. An earlier theoretical model [G.I. Tardos, I.M. Khan and P.R. Mort, Critical parameters and limiting conditions in binder granulation of fine powders, *Powder Technology*, 94, 245–258 (1997).], based on simple energy-dissipation considerations hinted at the existence of these states at the point where growth is counterbalanced by breakage. Further theoretical evidence is obtained from molecular dynamic simulations of wet and dry particles situated in a constant shear field [I. Talu, G.I. Tardos and M.I. Khan, Computer simulation of wet granulation, *Powder Technology*, 110, 59–75 (2000).], where the size distribution of initially identical particles, shifts in time to reach a dynamic steady state. Under the conditions of this steady state, the number of breaking agglomerates approximately equals the number of forming ones to yield a time independent final-size distribution.

Experimental evidence to support the theoretical findings is obtained during the present research by measuring particle size distributions *at line* at crucial points during granulation of a typical pharmaceutical powder in a high-shear mixer. In order to reach a steady state, binder addition has to be slow enough and wet massing has to be long enough so that neither has an influence on the final properties of the granules. We show experimentally that if binder is spread properly and homogeneously in the powder and continuous shearing of the wet mass ensures homogeneous, equal growth of the granules, the steady state will only be a function of the total amount of fluid added provided that the shear forces in the machine are maintained constant.

These findings are important in that they show that under carefully controlled conditions of binder addition and shear in the mixer, the granulation process is robust and controllable and can, in principle, be scaled up with ease once the powder ingredients and the total amount of binder are fixed.

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1. Introduction

Batch wet granulation of fine powders in the pharmaceutical industry is presently considered a mostly “black box” process. Usually only a few process variables can be measured and control of the equipment is reduced to end-point control, i.e., stopping the process at an appropriate time to achieve granules of desired properties such as size distribution, density and homogeneity. Scale-up of high-shear granulation processes usually starts at the 100–200 g scale (i.e., 1–2 L granulator capacity) and typically ends at a granulation mass size of 200 to 400 kg (600–1200 L granulator capacity). Scale-up proceeds in a stepwise fashion, using “geometrically similar” granulators of increasing working volume. It is not unusual to move through six different granulator volumes in the process. In each step, process variables are adjusted using a variety of often conflicting heuristics;

some of the more common scaling rules are listed in [Table 1](#). In practice, the process variables are adjusted at each scale to match dry granule and/or final dosage form functional properties. Thus, in reality, scale-up is mostly an empirical exercise.

Batch wet granulation usually contains two main periods, binder introduction and wet massing. During *binder introduction*, water or another appropriate liquid (binder) is poured, sprayed or dripped into the moving powder mix. The expectation is that, due to the movement of the powder and the wetting properties of the liquid, the binder is distributed on most powder surfaces rendering them sticky enough to allow particle–particle coalescence upon mutual collisions. *Wet massing* is the subsequent process by which, due to relative movement of different particles in the mixer and to the presence of the sticky surfaces, granules grow and consolidate. Unfortunately, the two processes can be separated neither spatially nor temporally unless the processes are performed in different vessels [1], and the net result is that growth occurs both during binder introduction and also during wet massing. Since the process is extremely complicated and many

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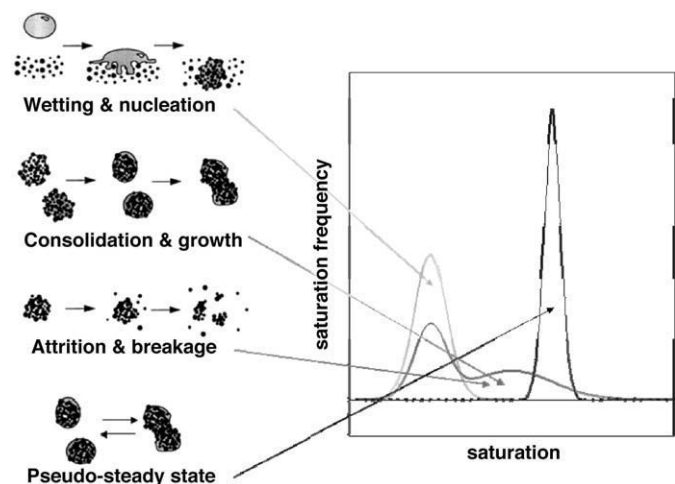
Table 1
Common scale-up heuristics for high-shear granulators

Variable	Rule
Fluid level	Adjust to match mean granule size at each scale
Main impeller speed	Constant tip speed; constant Froude number
Spray rate	Constant spray time; constant spray flux
Mixing time	Constant mixing time; constant swept volume

processes occur simultaneously, *granule growth and consolidation are path and position dependent* and stopping the process at a given point usually does not yield consistently similar granule properties. This becomes even more problematic when the process is transferred from one machine to another during, for example, scale-up or changing the starting ingredients from one supplier to another.

There have been numerous approaches to rationalizing granulation scale-up, which are reviewed elsewhere [2,3]. While these have yielded more physically-based scaling relationships for key process variables, for example, the dimensionless spray flux [4] and constant shear stress [3], the inherent complexity of high-shear granulation has prevented the development of a robust, physically-based, quantitative scaling methodology. In large part, this complexity stems from the way the pharmaceutical industry typically operates high-shear granulators: fast (short granulation times) and wet (large binder excess). Under these conditions, the elementary granulation processes, nucleation, consolidation and growth, and breakage, all occur simultaneously. The processes are transient, coupled, and their rates vary non-linearly with key process variables such as fluid level and impeller speed. By itself, this coupling of dynamic, non-linear processes would make scale-up challenging. In addition, the high rate at which liquid is typically added to a granulator results in macroscopic inhomogeneities which further complicate the dynamics. This makes granulation sensitive to the details of mixing patterns in a granulator, which themselves vary with granulator scale and geometry. No simple scaling rule, physically-based or purely heuristic, can account for all of these complexities.

The complexity of granulation scale-up can be understood by considering how granulating fluid is distributed among granules as granulation proceeds. The fluid distribution is critical, as granules are bound by capillary and viscous forces created by liquid bridges between primary particles [5,6]. When liquid droplets are imbibed into the dry mix at the beginning of granulation, they form granule nuclei, which typically have relatively low saturations [7]. As

**Fig. 1.** Elementary granulation processes [2,13] and evolution of the saturation distribution (schematic).**Table 2**
Composition of dry powder mix

Ingredient	%
Lactose monohydrate	73
Microcrystalline cellulose	20
Hydroxypropyl cellulose	3
Croscarmellose Na	3
API	1
Citric acid	1 (added with granulating fluid)
Magnesium stearate	0.5-1

granulation proceeds, more nuclei are formed while existing nuclei begin to collide with each other, leading to growth and consolidation. The liquid saturation of the daughter granules is higher than that of the nuclei. Thus, a liquid saturation distribution develops in the wet mass as shown schematically in Fig. 1. Granule breakage also occurs in parallel. This does not necessarily change granule saturation, but it does produce smaller granules with relatively high saturation, and in this way affects the saturation distribution. In general, the saturation distribution evolves in time as shown in Fig. 1, where different saturation profiles are shown as a function of the main granulation process taking place in the mixer. At sufficiently long times, the system evolves to a state where the binder distribution narrows and most granules contain about the same amount of binder. The specific path depends on the spray rate and amount of granulating fluid. Perhaps most importantly, it depends on the shear stress in the agitated wet mass, since this is the fundamental variable that controls granule growth and breakage rates. The shear stress depends on the impeller speed, impeller and bowl geometry, and the wet mass "rheology", which in turn is a function of the granule size distribution and liquid saturation [8]. Thus, all of the primary process variables that control the granule size distribution are coupled through the saturation distribution.

A significant simplification occurs if granulating fluid addition is stopped at a well-established value and the wet mass is agitated for an extended time. This will significantly reduce and/or totally eliminate any macroscopic inhomogeneity in the distribution of granulating fluid as mentioned above. On a particle micro-scale, granules continue to grow, and as they do, the breakage rate increases [9]. As this occurs, the saturation distribution narrows. Ultimately, it becomes single-valued as the granules reach a critical size that is determined by their dynamic yield stress and the maximum shear stress in the granulator. This implicitly assumes that granules are agitated for a sufficiently long time so that all of them pass, on average, with the same frequency through regions of highest shear stress in the granulator. The steady-

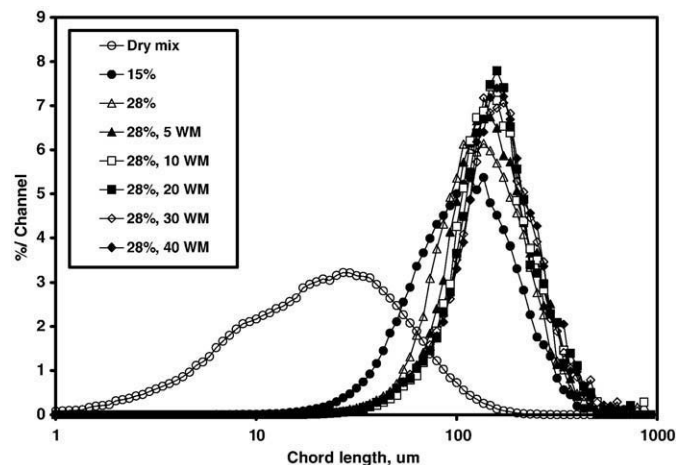
**Fig. 2.** Evolution of chord-length distribution, 2-L granulator, 28% fluid level, impeller speed 800 RPM, temperature 22 °C.

Table 3

Evolution of chord-length distribution statistics, 2-L granulator, impeller speed 800 RPM, temperature 22 °C

Fluid level, %	Wet massing time (min)	Chord length (μm)		
		C ₁₀	C ₅₀	C ₉₀
0	0	5	25	70
15	0	52	115	230
28	0	75	138	257
28	5	83	150	273
28	10	89	157	290
28	20	87	160	289
28	30	85	163	291
28	40	87	165	289

state granule size and saturation are then *scale-independent* and will grow and consolidate to the same extent regardless of the volume (scale) of the granulator. Putting this in terms of controllable variables, the granulating fluid level (ratio of fluid to dry ingredients) is scale-independent, and for a given fluid level, granule growth is determined by the main impeller speed alone that, in turn, limits the maximum stresses in the machine.

Thus, by allowing sufficient mixing time for granule growth and breakage to achieve a steady state, the granule size and porosity become independent of mixing time and fluid addition rate. The granulating fluid level is scale-independent and the only process variable that requires change with scale is the main impeller speed, which must be adjusted to generate the same maximum shear stress. This modest change in operating practice reduces granulator scale-up to a *one-dimensional* problem.

The existence of a steady-state condition in granulation is consistent with the energy-dissipation granulation model proposed earlier by Ennis et al. [5] and Tardos and co-workers [10,14]. This model assumes that sufficient liquid is present in the granulator following the binder addition phase to promote granule growth and that the liquid is homogeneously spread on all granular surfaces. It is also assumed that particles have only one characteristic dimension denoted by the length scale a .

The model characterizes granule growth in terms of two Stokes numbers, one for particle coalescence and the other for granule deformation. Each of these dimensionless groups is a ratio of particle kinetic energy to energy dissipation, either by viscous dissipation in liquid bridges (for coalescence) or by plastic deformation (for granule deformation). The analysis shows that two critical length scales exist: a_{cr}^{coal} , the particle size below which particles coalesce and above which they rebound; and a_{cr}^{def} , the granule size below which granules are stable and above which they deform and ultimately break.

The model shows that particles will grow by nucleation and coalescence until they reach the coalescence limit, a_{cr}^{coal} . Since this limit accounts only equal size granules or particles, larger particles can still grow by layering with smaller particles to yield granules somewhat larger than a_{cr}^{coal} . Granules that grow beyond, a_{cr}^{def} , become unstable, deform and eventually break. The process will stabilize at some point between the two critical sizes and will be characterized by a size distribution that will shift slowly toward larger sized granules. It will reach, after a long enough time, the limit, a_{cr}^{def} that in this case will be a theoretical *steady-state condition*.

It is clear from the simple theory presented above that steady states of granule growth can take place and are in fact predicted by simple considerations of energy conservation. Molecular dynamic simulations (MDS) of dry and wet particles situated in a shear field support this conclusion further [11]. Starting with monodisperse particles, the simulations show that as time progresses, larger agglomerates form and the size distribution widens. The increase in size slows as time progresses and, a steady-state distribution is reached. This appears to be a true dynamic steady state when agglomerates form, grow to the

critical size, break and reform and grow again resulting in an almost constant particle size distribution.

The research described in this paper was conceived to demonstrate experimentally the existence of steady states in granulation. Furthermore, the concept of “one-dimensional” batch granulator scale-up was demonstrated in a series of granulation experiments with a conventional pharmaceutical formulation conducted in vertical-axis high-shear granulators of 2, 25, and 300 L volumes, respectively. The granulators have similar bowl and main impeller geometries and based on this and previous scaling work [3] are expected to produce similar mixing patterns and shear-stress distributions.

2. Experimental

Experiments consisted of a series of “conventional” and “steady-state” granulations performed at three scales as mentioned above. The so-called “conventional” experiments were carried out according to the protocol routinely used in pharmaceutical production with short binder introduction and wet massing times. “Steady-state” runs, on the other hand, were performed with slower binder addition rates and extended wet massing. We describe below the equipment and instrumentation used to perform the granulations and characterize the wet and dry granules.

2.1. Composition of initial powder mix

A typical lactose-microcrystalline cellulose formulation was chosen for this experiment, and the composition is shown in Table 2. A hydrophobic, low solubility drug substance (API) was added as a tracer to characterize the dissolution behavior of the granules, while 1% citric acid was added to the granulating fluid (USP water) as a tracer to indicate how the binder was distributed in the granules following agglomeration in the high-shear mixer. This is accomplished by performing a citric acid assay using HPLC of final granules in different sieve fractions. Magnesium stearate was added into the granulated dry mix as die lubricant for tableting.

2.2. Granulation in the 2-L granulator

Initial small-scale, “steady state” granulation experiments were conducted in a 2 L Fukae Powtec granulator (LFD-GS2J) equipped with a horizontal impeller (about 15 cm in diameter) located at the bottom of the cylindrical vessel and a “chopper” mounted on the side-walls. The batch size was 400 g on a dry basis. In most experiments, the granulating fluid was added to the granulator at a rate of 8 g/min (2%/min) with a

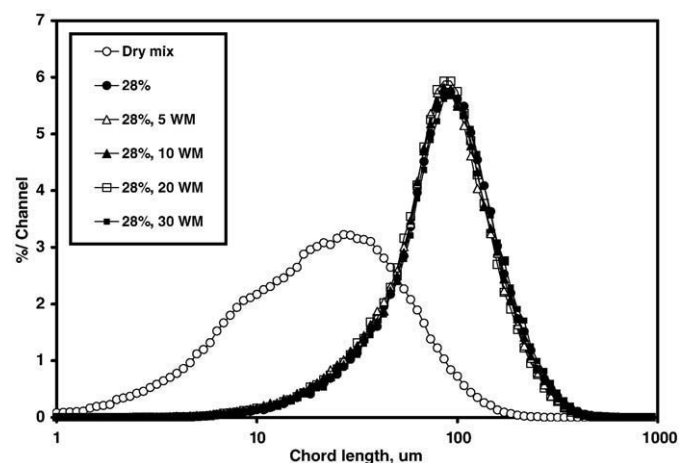


Fig. 3. Evolution of chord-length distribution. Identical conditions as in Fig. 2. Experiment performed at 45 °C.

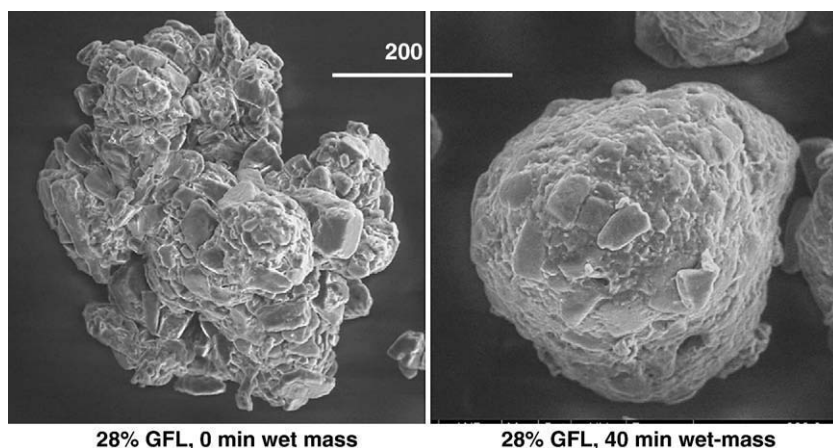


Fig. 4. Granule morphology changes during wet massing.

peristaltic pump in the form of drops. Since the chopper only has a secondary role to break-up large agglomerates that may form, it was set at 2000 RPM in all experiments. The granulator bowl was outfitted with a cooling jacket and was cooled with running tap water ($\sim 22^\circ\text{C}$) to maintain a constant bed temperature and to avoid evaporation of the granulating fluid during the relatively extended liquid addition and wet massing period.

In a typical experiment, powders were loaded into the granulator and dry mixed for 90 s. A sample of the dry mix was taken from the granulator and the particle size was measured at-line with a Lasentec FBRM system (see description of instrument, below). At the end of the liquid (binder) addition phase, the granulator was stopped and another sample was taken and its particle size measured with the Lasentec system. The batch was then wet massed and the particle size distribution was measured in the same manner after 5, 10, 20, 30, and 40 min of wet massing.

2.3. Granulation in the 25-L granulator

The 25-L scale-up exercise was conducted in a 25-L Fielder granulator (PMA 25) with a standard main impeller blade. This machine is geometrically similar to the 2 L mixer and a 5-kg batch size was chosen to match the fill ratio of the smaller machine. The chopper was set at 3000 RPM. Granulating fluid was delivered with a peristaltic pump at 100 g/min (2%/min). A Spraying Systems equipped with a flat

fan spray nozzle (650033) was employed for liquid delivery. The granulator bowl temperature was controlled by flowing chilled water ($\sim 15^\circ\text{C}$) through its cooling jacket, and the bed temperature was maintained below 30°C (measured manually during sampling) at all times during the process.

2.4. Granulation in the 300-L granulator

The 300 L scale-up exercise was performed in a 300-L Fielder granulator (PMA 300), with a 70 kg batch size. Again special attention was given to select a geometrically similar unit to the two smaller machines and the fill ratio was chosen to match the characteristics of the small-scale machines. The chopper was set at 1000 RPM. Liquid was delivered at 1.4 kg/min (2%/min) with a pressure pot and a hollow cone spray nozzle (Spray Systems, 1/4 TTSS-D7-25-SS). An M8 blade with swept back angled blades was used to generate comparable mixing intensity to that in the smaller granulators. The granulator bowl temperature was controlled by flowing chilled water ($\sim 15^\circ\text{C}$) through its cooling jacket, and the bed temperature was maintained at or below 30°C as measured using the internal temperature probe of the machine.

2.5. Drying, lubricating, compressing

Characteristic samples were withdrawn from all granulators at specific times and tray-dried at 40°C for 24 h. The final granules

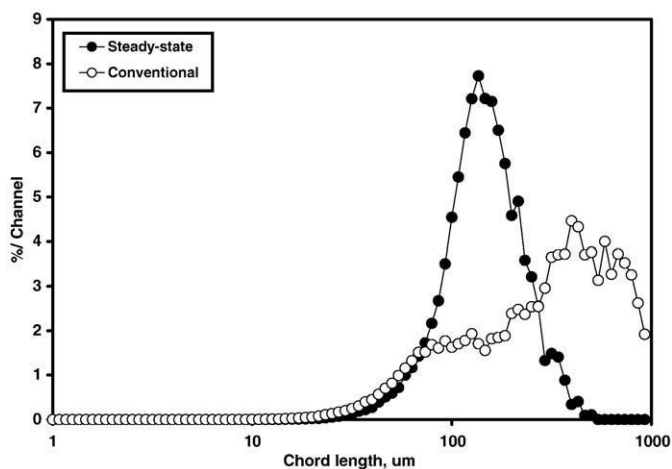


Fig. 5. Chord-length distributions of wet granules, 2-L scale: filled circles, steady-state granulation (28% GFL, 40 min wet massing time); open circles, conventional granulation (40% GFL, 5 minute mixing time, no wet massing).

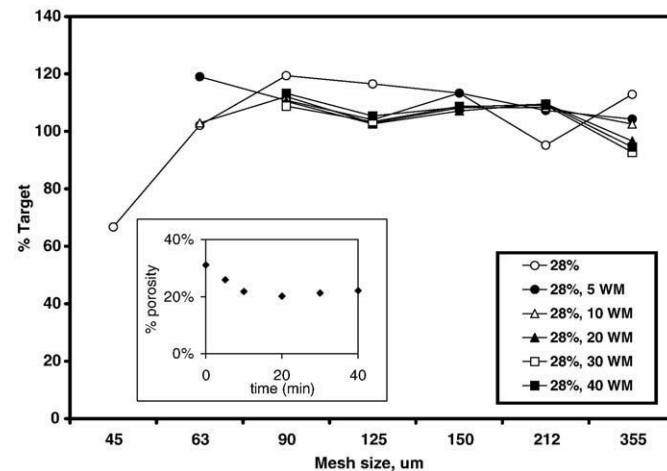


Fig. 6. Time evolution of citric acid sieve assay profiles, 25-L granulator, 28% fluid level, impeller speed of 380 RPM. Inset: porosity vs. wet massing time, 850–1750 mm sieve fraction, 25-L granulator, 32% fluid level, impeller speed of 380 RPM.

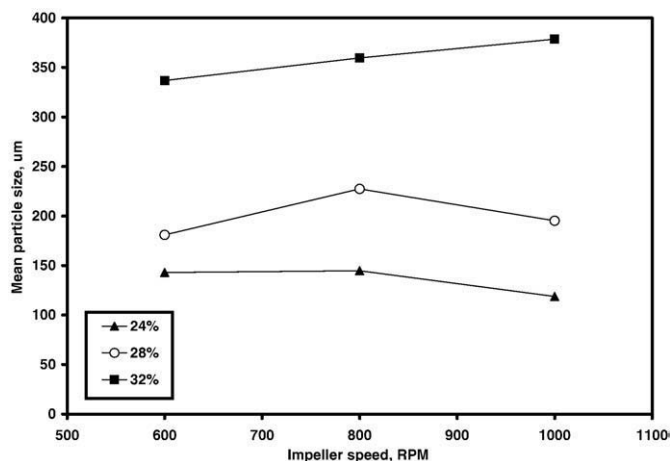


Fig. 7. Mean granule size of steady-state granulations, 2-L granulator.

produced in the 300-L experiments were dried in a Fluid Air 150 fluid-bed dryer at a process air flow rate of 1300 scfm and a maximum inlet temperature of 85 °C. The drying time was approximately 50 min. Dry samples were lubricated with 0.1, 0.3, and 0.5% magnesium stearate, respectively, by a Turbula mixer for 10 min and then compressed into tablets in an "Auto" Series Carver hydraulic press (model 3888.1010A00), using 8/32", round, flat-face tooling. The weight of the tablets was approximately 100 mg and the tablets were compressed at three compression levels (4, 7, and 11 kN).

2.6. Granule and tablet characterization

Particle size and size distribution of wet granules were measured at-line with a Lasentec D600L FBRM (Focused Beam Reflectance Monitor). During a typical experiment, a sample of the wet mass (approximately 2–3 g) was placed into a 250 ml beaker filled with about 70 ml of acetone (HPLC grade, Fisher). The Lasentec probe was then submerged into the beaker and the attached mixer was used to disperse the granules. The working parameters for the Lasentec were: scanning rate 4 m/s, 2 s scan time, "coarse" hardware setting, mixer speed of 400 RPM. Square-weighted chord-length distributions were plotted. When dry-mixes were measured, a "fine" rather than a "coarse" hardware setting was used.

The particle size of the unmilled, tray-dried granules was measured with a Coulter LS100 laser-diffraction particle size analyzer equipped with a dry powder feed system. The parameters for the

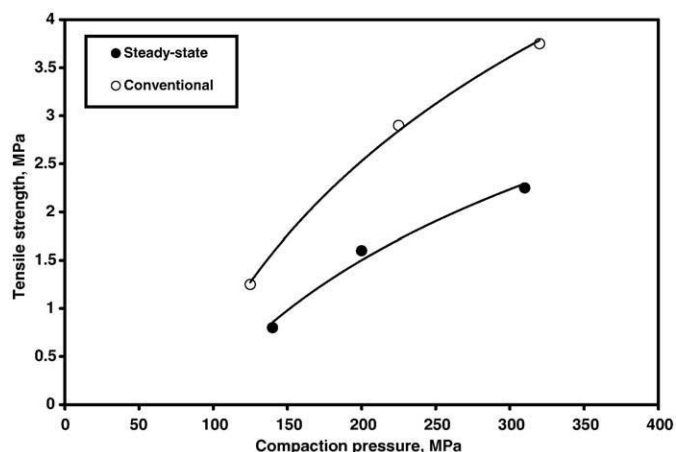


Fig. 8. Compaction profiles of granules obtained from steady-state and conventional granulation. (Data courtesy of Steve Galen).

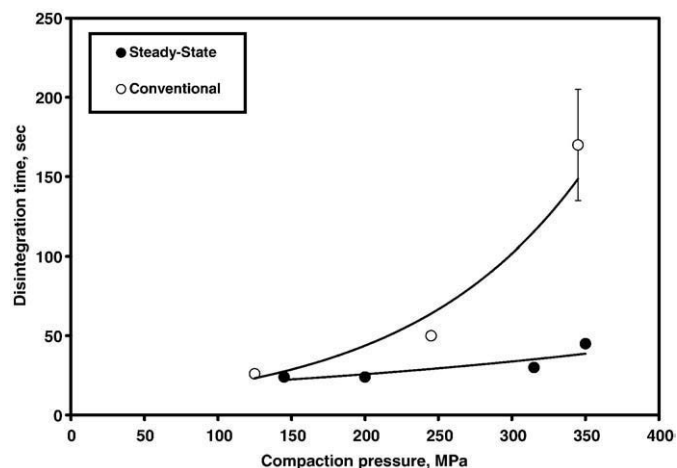


Fig. 9. Disintegration times of tablets compressed from steady-state and conventional granulation. (Data courtesy of Yu Cheng and Ashkan Kamali).

Coulter were: Fraunhofer optical model, 20 s run length and the reported data is an average of 3 consecutive runs. Since the Lasentec and the Coulter analyzers have an upper size limit of 1 mm and 850 µm, respectively, particles larger than these sizes escape detection and introduce some error when larger granules are present. Since this rarely happened during the results described below, we neglected these errors in the results presented in the paper except where specifically mentioned.

Granule porosity was measured by mercury intrusion with a Micromeritics Poremaster-60 mercury porosimeter. The granules were subjected to the "low" and "high" pressure methods. After initial introduction to mercury, the sample was scanned from contact +0.5 psi to 50 psi in the low pressure unit. The sample was then transferred to the high pressure chamber, and the sample was scanned from 30 to 30,000 psi. The results from the two methods are then merged to form a single pore size distribution, from which the intrusion volume was obtained. This, combined with the true density measured with the Micromeritics Accupyc 1330 Helium Pycnometer, yielded the porosity.

Compaction profiles were generated with an ESH compaction simulator. Tablets were compressed at high speed (960 mm/s) with 12/32" flat, circular punches, and an instrumented die.

Dissolution profiles of granules and tablets were measured with a Distek dissolution apparatus using direct UV detection of the API with

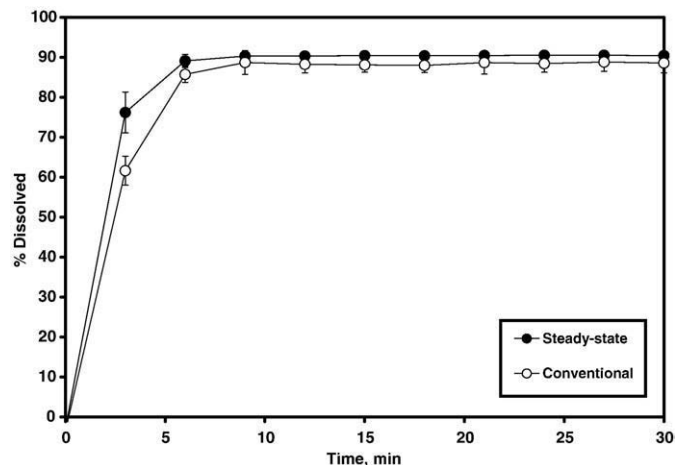


Fig. 10. Dissolution profiles of tablets compressed from steady-state and conventional granulation.

a Hewlett-Packard model 8453 diode array spectrometer. Sample analysis was automated using a Hewlett-Packard model 8902A multi-channel peristaltic pump. When running the automated method, Distek 10 μm nylon filters were placed in the sampling probes to prevent particles in the dissolution vessels from flowing into the UV cuvettes. After the samples were pulled, the pump and flow was reversed for 1 s to flush any particles from the filters back into the vessels.

Tablet disintegration times were measured with a Vankel VK100 disintegration tester. USP water at 37 °C was used as the media.

3. Small-scale experiments to steady state

3.1. The existence of steady states in granulation

Preliminary experiments were performed at the 2 L scale to test whether the granulation achieves a steady state during extended wet massing. Most of these experiments were performed with a fluid level of 28% and a main impeller speed of 800 RPM. This impeller speed was chosen to assure good “roping” flow of the dry ingredients [12].

Fig. 2 shows the chord-length distributions (CLDs) of samples taken at various times during granulation. The corresponding chord-length statistics are listed in Table 3. The distribution denoted “dry mix” was obtained immediately after the mixing of dry ingredients, i.e., with no binder present in the machine. Two samples were taken during binder addition: after about 15% liquid introduced and at the end of the binder addition phase. As seen, during addition of the granulating fluid, the mode of the distribution increases by approximately a factor of two. Five samples were analyzed during wet massing, and, as seen, the mode of the distribution stabilizes and the distribution narrows significantly. This narrowing is consistent with growth of smaller granules and simultaneous breakage of larger ones. Samples taken after the binder-introduction phase (28% binder) and after 5 min of wet massing, contained a few larger (about 1 mm in diameter) granules that were above the detection limit of the Lasentec FBRM. As a consequence, some profiles in Fig. 2 do not contain this information and are therefore skewed slightly towards smaller sizes, and the actual values of c_{90} are larger than those shown in Table 3. Since the number of these larger particles was in general small (about 3–5 in a typical sample) and was absent in samples taken at later times, i.e., after longer wet massing, we neglected their influence in the two samples when they were present. As seen in the figure, within approximately 20 min, the distributions stabilized completely, and there is no significant change in the distribution with an additional 20 min of agitation. This suggests that in 20 min of wet massing or less, “steady state” has been achieved due to the equilibrium of granule growth and breakage.

Fig. 3 shows results from an identical experiment as described above only the temperature of the granulating powder mix was kept at constant but much higher value: 45 °C, as compared to 22 °C for the experiment described in Fig. 2. As seen, the overall granule growth is somewhat reduced and, at the same time, the steady state is reached earlier in that the size distribution achieved immediately after binder introduction does not change significantly upon further wet massing. This behavior is partially due to binder evaporation but perhaps more importantly it is due to better binder spreading (over thinner layers)

Table 4
Main impeller speeds used in scale-up experiments

Shear rate	Impeller speed, RPM		
	2-L Fukae	25-L Fielder	300-L Fielder
Low (L)	600	296	146
Middle (M)	800	395	194
High (H)	1000	494	242

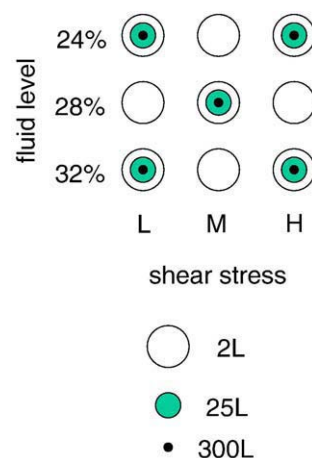


Fig. 11. Granulation scale-up experimental design.

and a reduction in granule surface yield strength caused by the higher temperature. This, in turn, yields faster deformation and the establishment of final-size granules, earlier in the process.

Fig. 4 shows SEM pictures of typical steady-state granules at the end of the liquid delivery stage (0 min wet massing time) and the final sample (taken at 40 min of wet massing). There is considerable change in surface morphology and granule sphericity that is complete after about 40 min. We believe that the “roping” motion of the powder and the shear forces generated within act to round and spheronize the deformable wet granules during wet massing.

The ultimate particle size distribution shown in Figs. 2 and 3 proved not to be as single-valued as the idealized theoretical models discussed earlier would suggest. Fig. 5 shows two cord-size distribution of wet granules produced, respectively, by a steady state with 28% binder and 40 min of wet massing and a “conventional” granulation process using 40% binder¹ delivered over 5 min with no additional wet massing time. As seen in the figure, the distribution is significantly narrower for the “steady state” as compared to the “conventional” granulation. The particle size distribution of the tray-dried steady-state granules obtained from this run proved to be sufficiently narrow that it did not require milling prior to lubrication and tableting. The size was also well within the typical final particle size range of 200–500 μm that is targeted for a granulation prior to compaction. This appears to be an important advantage of the steady-state approach that in effect eliminates a processing step in the production of pharmaceutical tablets.

Fig. 6 shows the citric acid distribution in different cut sizes of a steady-state granulation performed with 28% binder at different wet massing times between zero (immediately after binder introduction) up to 40 min, in the 25-L machine. As seen in the figure, the citric acid assay results show a wide distribution immediately after binder introduction especially at the small granule (initial particle) sizes probably due to the presence of dry powder in the mixer. After about 10–20 min of wet massing the distribution of citric acid across the steady-state granule size fractions becomes quite uniform. This indicates that the liquid saturation becomes uniform across the size classes and is consistent with narrowing of the saturation distribution. Consistent with this and the granule size results, the granule porosity becomes constant after approximately 20 min of wet massing. Together, these results show that a steady-state condition is achieved during extended wet massing.

¹ The fluid level of the conventional granulation was chosen to produce dried granules with approximately the same mean particle size as the steady-state granulation.

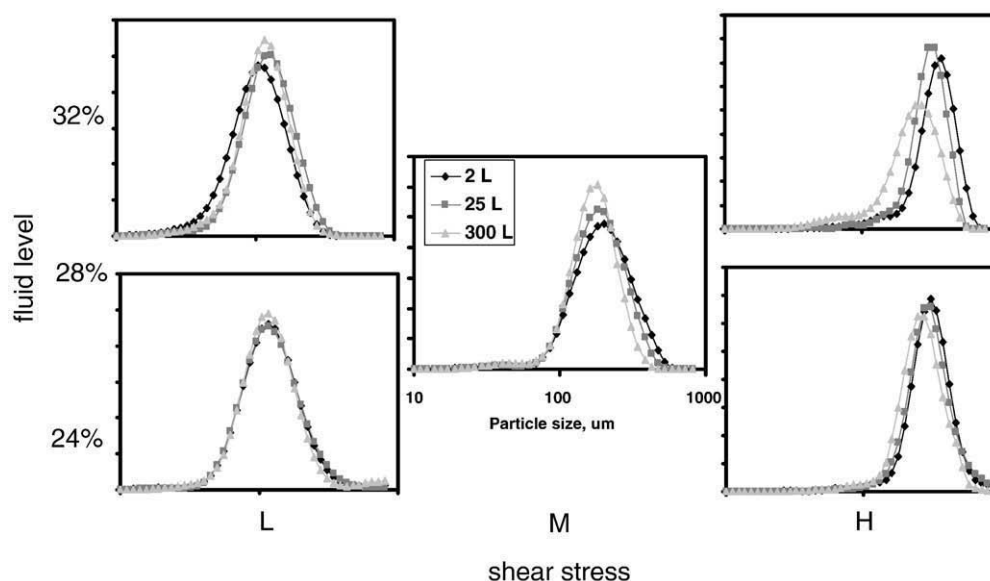


Fig. 12. Particle size distributions of dried, unmilled granules from scale-up experiments.

A series of granulations were produced to map out the dependence of the granule size distribution on granulating fluid level (GFL) between 24 and 32% and main impeller speed between 600 and 1000 RPM. These conditions were chosen to generate a response surface with the 28% GFL, 800 RPM granulation at its midpoint; this surface was the base case for scale-up experiments described below. All granulations were produced by spraying granulating fluid at 2%/min and wet massing for 40 minutes. At all conditions, the particle size distributions of tray-dried, unmilled granules were unimodal and narrow. The mean particle size is plotted in Fig. 7. As expected, the granule size increased sharply with granulating fluid level at all impeller speeds. However, the shear-rate dependence changed qualitatively with fluid level. At 24%, the mean particle size decreased slightly at the highest impeller speed. At 28%, it passed through a maximum at 800 RPM, and at 32%, it increased monotonically. This behavior reflects a smooth change in the balance between granule growth and breakage rates, with breakage being more dominant at low fluid levels and growth being more dominant at higher levels over the range of shear rate investigated. It exemplifies the coupling between the effects of fluid level and shear stress during granulation.

3.2. Functional properties of granules produced by steady-state granulation

A major concern at the beginning of this study was that the extended mixing times required to achieve a steady-state granule size distribution would produce over-consolidated granules that could not be compressed and/or would not dissolve. While we did not conduct an exhaustive study of compactability or tablet performance, we executed a small set of experiments to probe the downstream processability of the steady-state granulation.

Compaction profiles of lubricated steady-state granules are compared to the compaction profile of milled, lubricated conventional granules in Fig. 8. Although the tensile strength of tablets obtained from granules produced by the steady-state procedure is not as high as, that of tablets produced from granules of a conventional granulation, it is not prohibitively low. We believe that the low compactability can be addressed by modifying the lubrication system and/or adding extragranular MCC.

Fig. 9 shows a comparison of disintegration times of tablets compressed from lubricated granules as a function of tablet compaction pressure. Disintegration of the tablets produced from granules

generated by the steady-state approach was very fast and practically independent of the compression force. In comparison, while still acceptable, the disintegration times of the conventional tablets were longer and they increased significantly with increasing compaction force.

The porosity of granules made by steady-state granulation was measured by mercury porosimetry and found to be quite low: 16%, compared to typical porosity values of 40–50% for granules produced via a conventional granulation process. Although granule porosity is not directly linked to tablet porosity and dissolution performance, over-granulation is well-known to cause depressed dissolution. Fig. 10 shows dissolution results of tablets made from granules produced by steady-state and conventional granulation as characterized by API release profiles. The rates of dissolution of the two types of tablets were found to be comparable, indicating that granule consolidation during extended wet massing did not compromise the dissolution rate of the granules.² This result was somewhat unexpected given the low porosity and dense appearance of the granules produced by steady-state granulation.

4. Steady-state granulation scale-up

A series of experiments was conducted in 25-L and 300-L granulators to test the accuracy of “one-dimensional” scaling of steady-state granulation by adjusting the main impeller speed to match the maximum shear stress at each scale. The impeller-speed scaling used a correlation established independently from indirect shear-stress measurements using test particles with well-defined yield stress, $\tau \sim \omega D^{-0.8}$ [3]. We used this correlation to match the three impeller speeds that were used in the 2-L experiments, denoted low (L), medium (M), and high (H) below. The respective impeller speeds are listed in Table 4.

Since experimentation with the larger machines is expensive and time consuming, a statistically-designed experiment was used as shown schematically in Fig. 11. The design consisted of three fluid and three shear-stress levels; the operating points represent the corners and midpoint of the granulation response surface generated at the 2-L scale. This five-point design was executed at both 25-L and 300-L

² The apparent incomplete recovery of all API in both tablets is likely due to the precision of the procedure given the very small amount of API (1 mg) present in the tablets.

scales. In all experiments, granulating fluid was added at 2%/min and wet massing was continued until steady state was reached (approximately 30–40 min in each case).

Results of the statistical-designed experiments are summarized in Fig. 12 and Table 5 where the mean granule sizes and the deviation from the results obtained at the 2-L scale are listed. As seen in the figure, at all but the highest stress and fluid level, there is a good match between the granule size distributions at all three scales. The best agreement is evident at the lowest binder level (GFL) and shear stress, where the mean granule sizes at all three scales agree within 1%. The poorest agreement is seen at the highest fluid level and shear stress, particularly at 300-L scale, which differs in mean particle size by 31% from the result at the 2 L scale. The scale-up accuracy in the mean particle size of the remaining experiments was 18% or better. In general, scale-up accuracy appears to be better at lower shear stresses, although one needs to note that such good agreement, even at our worst match of 31% difference, represents a significant step forward in granulation scale-up. This is especially significant since these comparisons are of *unmilled* granules. Furthermore, the impeller-speed scaling was based on independent shear-stress measurements, and no adjustment was made to match particle size. Thus, this was an a priori scaling exercise, based on first principles. In this context, the scaling accuracy is excellent.

A closer look reveals some systematic differences in granulation performance at each scale. At 300-L scale, the mean granule size decreased with increasing impeller speed at all fluid levels. In contrast, the particle size at 25 L was insensitive to impeller speed, and at 2 L it showed opposite dependence at low and high fluid level. Also, there is a systematic narrowing of the granule size distribution with increasing scale at all but the high GFL/high-shear-stress condition. These qualitative differences most likely are caused by differences in the mixing patterns (shear-stress distribution) in the granulators and indicate the limitation in the assumption of “geometric similarity” between granulators, i.e. the difficulty in holding all relevant dimensionless groups constant across all scales.

4.1. Role of the chopper

Our scaling rule to achieve equal stresses at different granulator scales assumes that shear stresses in the powder are created by the main impeller and it ignores the action of the chopper. In order to assess the impact of the chopper, one experiment was run at 25-L scale with the chopper removed (28% GFL). The granule size distribution was largely unaffected by chopper removal as shown in Fig. 13. This indicates that the chopper plays no direct role in granulation under pseudo-steady conditions. However, a small number of very large granules, ca. 1–2 cm in diameter and spherical in shape, were found buried in a ring around the main impeller shaft approximately in the middle of the wet mass. We speculate that these were trapped in the axis of the toroidal flow of the agitated wet mass. This is a region of very low shear stress, akin to the “eye of a storm” where larger particles can segregate and grow by layering without deformation or breakage. With the chopper in place, the toroidal flow is disrupted, and particles near the rotational axis are ejected into the

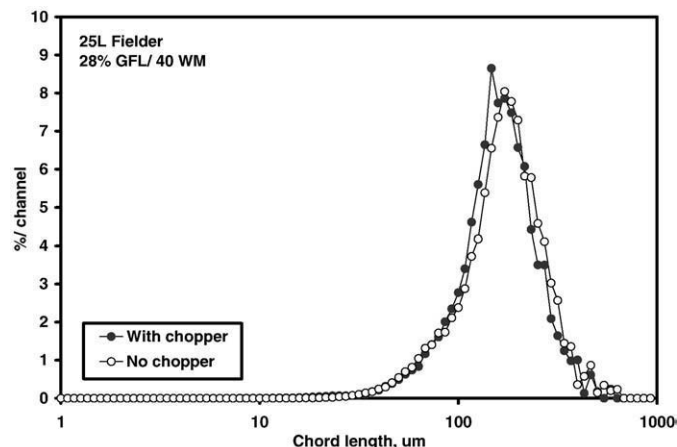


Fig. 13. Chord-length distributions of unmilled 25-L granules, with and without the use of the chopper.

active flow region. Thus, at least under pseudo-steady granulation conditions, the chopper appears to act only as a stationary baffle with the role to disrupt the symmetry of the flow.

5. Conclusions

This work has proven that steady or pseudo-steady state conditions can be achieved in batch granulation in high-shear mixers. The approach used here – slow addition of granulating fluid followed by long wet massing times coupled with a stable roping flow pattern throughout the granulation process – was successful at producing granules with uniform morphology and very narrow size distribution. The functional properties were equivalent to the performance of conventional granules, despite marked differences in porosity and morphology. Dissolution performance was excellent, and tensile strength at the same magnesium stearate concentration was comparable although the steady-state granules showed symptoms of over-lubrication. In the future, lower levels of magnesium stearate will be required due to the reduced surface area of the granules, thereby avoiding the drop in tensile strength seen in this work.

We also showed that the steady-state approach can be successfully applied to scale-up. The approach dramatically simplified the complexity of the scale-up process and improved the accuracy. Overall, the scale-up accuracy is excellent, especially considering that scale-up was done on an a priori basis, e.g. the impeller-speed scaling was not adjusted to match granule size distributions. This is significant because it allows the possibility of skipping several intermediate scales during traditional scale-up, and jumping directly up or down to any scale without additional engineering or development work at scale. For example, most formulation and process development could be performed at small-scale (e.g. 2 L), and scale-up to commercial scale could be achieved directly.

There is still room for improvement in scaling accuracy, although we believe that significant changes in granulator and/or blade design and operation would be required to make further headway. Specifically, the homogeneity of shear stress (mixing intensity) needs to be improved. Pragmatically, a better match in granule size distribution between the scales can be achieved by adjusting the main impeller speed; this more empirical scaling methodology will be necessary when moving between granulators that are not geometrically similar and for which the shear-stress scaling is not known. In this case, additional experiments may be necessary to locate the optimal operating point at each scale. However, since only one variable needs adjustment, the scale-up effort for steady-state granulation is still markedly reduced in comparison to scaling of conventional granulations.

Table 5

Mean particle size of granules obtained from scale-up experiments and their deviation from values at the 2-L scale

GFL	Shear rate	2-L Target, MPS, μm	% Deviation (MPS, μm)	
			25 L	300 L
24%	Low	146	0/(146)	-1/(145)
	High	119	+18/(140)	+9 (130)
28%	Mid	223	-7/(207)	-16/(187)
	Low	337	-1/(333)	-13/(293)
32%	High	379	-11/(337)	-31/(262)

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References

- [1] P.R. Mort, S.W. Capeci, J.W. Holder, Control of agglomerate attributes in a continuous binder-agglomeration process, *Powder Technology* 117 (2001) 173–176.
- [2] S.M. Iveson, J.D. Litster, K. Hapgood, B.J. Ennis, Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review, *Powder Technology* 117 (2001) 3–39.
- [3] G.I. Tardos, K.P. Hapgood, O.O. Ipadeola, J.N. Michaels, Stress measurements in high shear granulators using calibrated test particles: application to scale-up, *Powder Technology* 140 (2003) 217–227.
- [4] K.P. Hapgood, J.D. Litster, R. Smith, Nucleation regime map for liquid bound granules, *AIChE Journal* 49 (2) (2003) 350–361.
- [5] B.J. Ennis, G.I. Tardos, R. Pfeffer, A microlevel-based characterization of granulation phenomena, *Powder Technology* 65 (1991) 257–272.
- [6] S.J.R. Simons, R.J. Fairbrother, Direct observations of liquid binder–particle interactions: the role of wetting behaviour in agglomerate growth, *Powder Technology* 110 (2000) 44–58.
- [7] K.P. Hapgood, J.D. Litster, E.T. White, P.R. Mort, D.G. Jones, Dimensional spray flux in wet granulation: Monte-Carlo simulations and experimental validation, *Powder Technology* 141 (1–2) (2004) 20–30.
- [8] S.M. Iveson, N.W. Page, J.D. Litster, The importance of wet-powder dynamic mechanical properties in understanding granulation, *Powder Technology* 130 (2003) 97–101.
- [9] L. Vogel, W. Peukert, Characterisation of grinding-relevant particle properties by inverting a population balance model, *Particle & Particle Systems Characterization* 19 (2002) 149–157.
- [10] G.I. Tardos, I.M. Khan, P.R. Mort, Critical parameters and Limiting conditions in binder granulation of fine powders, *Powder Technology* 94 (1997) 245–258.
- [11] I. Talu, G.I. Tardos, M.I. Khan, Computer simulation of wet granulation, *Powder Technology* 110 (2000) 59–75.
- [12] J.D. Litster, K.P. Hapgood, J.N. Michaels, A. Sims, M. Roberts, S.K. Kameneni, Scale-up of mixer granulators for effective liquid distribution, *Powder Technology* 124 (2002) 272–280.
- [13] P. Vonk, C.P.F. Guillaume, J.S. Ramaker, Growth mechanisms of high-shear pelletization, *International Journal of Pharmaceutics* 117 (1) (1997) 93–102.
- [14] M.I. Khan, G.I. Tardos, Stability of wet agglomerates in granular shear flows, *Journal of Fluid Mechanics* 347 (1997) 347–368.