

Scale Up of Powder-Blending Operations

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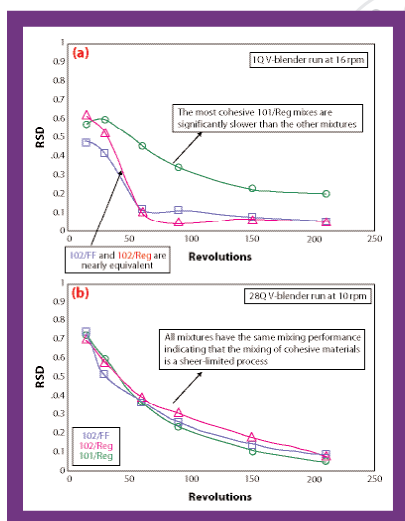


Figure 1: (a) Relative standard deviation (RSD) for axially segregated blends of varying cohesion in a 1-qt V-blender. (b) RSD for axially segregated blends of varying cohesion in a 28-qt V-blender.

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In the manufacture of many pharmaceutical products, dry-particle blending is a critical step that directly affects content uniformity. Tumbling blenders—a common way to mix granular constituents—are hollow containers attached to a rotating shaft; the vessel is partially loaded with materials and rotated. Their main advantages are large capacities, low-shear stresses, flexibility, containment, and easy cleaning. The blenders come in a variety of geometries and sizes (ranging from a minimum of <16 qt to a maximum >500 ft³).

The convective blender is another common mixer, in which flow is created by impellers rotating within a fixed shell. The blender can impart high shear, reduce ingredient segregation, and be used for wet granulation. Although the blenders are available in several sizes, the largest capacity is often an inverse function of the maximum shear rate.

Currently, no rigorous techniques can predict blending scale-up criteria for either type of blender without prior experimental work. Typically, blending studies start with a small-scale, try-it-and-see approach, during which the following questions usually arise:

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- What rotation rates should be used?
- Should filling levels be the same?
- How long should the blender be operated?
- Are variations to the blender geometry between scales acceptable?

To further complicate this issue, rotation rates for typical equipment are often fixed, obviating questions that suggest true dynamic or kinematic scale-up may not be possible under such conditions.

Regarding scale-up requirements, mixing processes can be classified into two fundamentally different groups: free-flowing and cohesive materials. Their mixing requirements vary.

Free-flowing materials

Free-flowing materials are powders and granulations in which interparticle cohesive forces are small enough for particles to move individually. Particles are $>100\ \mu\text{m}$ and interparticle attraction forces are similar to or smaller than the particle weight. The materials do not require substantial shear to be mixed, and tumbling blenders are often preferred. The main process risks are caused by segregation either within the blender or after blender discharge.

To understand scale-up requirements, one must first recognize that most tumbling blenders are symmetrical, which can be the greatest impediment to achieving a homogeneous mixture. The mixing rate is often limited by the amount of material that crosses from one side of the symmetry plane to the other (1–5). Some

blender types have been built asymmetrically and have greater mixing proficiency. By rocking the vessel as it rotates, the mixing rate can dramatically increase (6). Asymmetry can be induced by strategically placing baffles; this approach has been successfully tested on small-scale equipment (4, 7–9) and used in the design of some commercial equipment.

When these methods to induce asymmetry are unavailable, careful attention must be paid to the loading procedure because it can severely affect the mixing rate. Nonsystematic loading of multiple ingredients will dramatically affect the mixing rate if dispersion is the critical blending mechanism. For instance, in a V-blender, it is preferable to load the vessel either through the exit valve or with equal volume into each shell. This approach ensures that near-equal amounts of all constituents will be present in each shell of the blender. Care must be taken when loading a minor ($\sim 1\%$) component into the blender. Adding a small amount early in the loading process could send most of the material into one shell and substantially slow the mixing process. Smaller blenders entail shorter dispersal distances for complete homogeneity and thus may not be as affected by highly asymmetric loading. As a final caution, the order in which constituents are added can significantly affect the degree of final homogeneity, especially if ordered mixing (bonding of one component to another) can occur (10).

For example, in a V-blender, inter-shell flow is the slowest step because it

is dispersive in nature. Both inter- and intra-shell mixing processes can be described by similar equations such as:

$$\sigma^2 = Ae^{-kN} \quad [1]$$

in which σ^2 is the mixture variance, N is the number of revolutions, A is an unspecified constant, and k is the rate constant (3, 11). The rate constants for convective mixing, however, are several orders of magnitude greater than for dispersive mixing. Thus, unequal loading across the symmetry plane emphasizes dispersive mixing and leads to slower mixing than top-to-bottom loading, which favors convective mixing.

One must consider whether the rotation rate should change with variations in size. Previous studies of laboratory-scale V-blenders and double cones have shown that, when far from the blender's critical speed (*i.e.*, the speed at which tangential acceleration caused by rotation matches the acceleration), the rotation rate does not strongly affect the mixing rate (3, 4). In addition, the number of revolutions was the most important parameter governing final homogeneity. Equation 1 was derived by assuming that the mixture went through a specific incremental mixedness increase with each revolution (either by dispersion or convection). Although this approach is successful at modeling increasing mixture homogeneity, no scaling rules have been determined for the rate constants that govern this equation.

Given a geometrically similar blender and the same mixture composition, the fill level also should be kept

constant with changes in scale.

An increase in vessel size at the same fill level may correspond to a significant decrease in the relative volume of particles in the cascading layer compared with the bulk (this effect could accompany a large decrease in mixing rate). It has been shown in 1-pt V-blenders that running at 40% fill leads to a mixing rate that is nearly three times faster than at 60% fill (3). Thus, although fill level should be kept constant for geometric similarity, it may be impossible to match the mixing rate per revolution across changes in scale if the depth of the flowing layer is a critical parameter.

The Froude number ($Fr = [\Omega^2 R]/g$, in which Ω is the rotation rate, R is the vessel radius, and g is the acceleration from gravity) is often suggested for tumbling blender scale-up (12–15). This relationship balances gravitational and inertial forces and can be derived from the general equations of motion for a general “fluid”. Unfortunately, no experimental data support this approach's validity. Continuum mechanics may offer other dimensionless groups, if a powder flow–powder stress relationship can be determined. Fr is derived from equations based on continuum mechanics, but the scale of the physical system for granular materials blending is approximately the mean free path of individual particles, which may invalidate the continuum hypothesis. A less commonly recommended scaling strategy is to match the blender's tangential (wall) speed. This hypothesis also has no been tested.

Consider scaling a 5-ft³ to a 25-ft³

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blender using Fr as the scaling parameter. The requisites are to ensure geometric similarity (*i.e.*, all angles and ratios of lengths are kept constant) and to keep the total number of revolutions constant. With geometric similarity, the 25-ft³ blender must look like a photocopy enlargement of the 5-ft³ blender. In this case, the linear increase is 71%. For geometric similarity, the fill level must stay the same. To maintain the same Froude number, the rpm Ω must be reduced by a factor of $1.71^{-1/2} = 0.76$, corresponding to 11.5 rpm. In practice, because most free-flowing blends are not particularly sensitive to blend speed and blenders available are often fixed speed, the speed closest to 11.5 rpm would be selected. If the initial blend time was 15 min at 15 rpm, 225 revolutions must be maintained with the 25-ft³ scale. If 11.5 rpm was selected, the blend time would be 19.5 min. Though this approach is convenient and used often, it is empirical.

Common violations of this approach that can immediately cause problems include attempting to scale from one geometry to another, changing fill level without concern to its effect, and keeping blending time constant while changing blender speed.

Cohesive powders

A substantially dissimilar scenario arises for cohesive powders. The effect of cohesion on powder flow and scale-up, in particular for mixing operations, is an open problem, and only a brief discussion is provided here. In simple terms, a cohesive powder can be defined as a material in which the

adhesive forces between particles exceed the particle weight by at least an order of magnitude. In such systems, particles no longer flow independently; rather, they move in “chunks” in which characteristic size depends on the intensity of the cohesive stresses. Two main effects are often observed for cohesive blends: The overall mixture is sufficiently cohesive to affect the flow of the material in the blender, and a specific ingredient (often the active substance) is cohesive enough to display formation of agglomerates.

Cohesive-flow effects. The magnitude of cohesive-flow effects depends primarily on the intensity and nature of the cohesive forces (*e.g.*, electrostatic, van der Waals, capillary moisture) and the packing density of the material, which determines the number of interparticle contacts per unit area. This dependence on density is complex: Cohesive materials often display highly variable densities that strongly depend on the immediate material’s processing history.

A few guidelines can be asserted within a fixed operational scale:

- Slightly cohesive powders mix faster than free-flowing materials.
- Strongly cohesive powders mix much more slowly.
- Strongly cohesive powders often require externally applied shear.
- Baffles attached to vessels do not increase shear substantially.

Because there is no systematic way to measure cohesive forces under practical conditions, cohesion’s effects on scale-up have been studied rarely. The most important observation is that cohesive effects are much stronger

in smaller vessels and tend to disappear in larger vessels. The reason is simple: Although cohesive forces are surface effects, the gravitational and convective forces that drive flow in powder blenders grow proportionally to the vessel volume. Thus, as the blender's scale increases, gravitational and convective forces increase, thereby overwhelming cohesive forces. The characteristic "chunk" size of a cohesive powder flow is a property of the material, and thus to a first approximation it is independent of the blender size. As the blender size increases, the chunk-to-blender size ratio shrinks.

Both arguments can be mathematically expressed in terms of a dimensionless cohesion number Π_c ,

$$\Pi_c = \sigma / \rho g R = (\sigma / \rho g) / R = S / R$$

in which σ is the effective (surface averaged) cohesive stress (under actual flow conditions), ρ is the powder density under flow conditions, g is the acceleration of gravity, and R is the vessel volume. The group $S = (\sigma / \rho g)$ is the chunk size, which can be defined as the internal length scale of the flow driven by material properties.

Thus, as R increases, Π_c decreases. Figure 1 shows the evolution of the relative standard deviation (RSD) of a blending experiment in a small V-blender for three mixtures of various cohesion. Three systems were studied: a low-cohesion system composed of 50% Fast-Flo lactose and 50% Avicel 102; a medium cohesion system composed of 50% regular lactose and 50% Avicel 102, and a high cohesion sys-

tem composed of 50% regular lactose and 50% Avicel 101. In all cases, an aliquot of the system was laced with 6% micronized acetaminophen, which was used as a tracer to determine the axial mixing rate in V-blenders of different capacities (1, 8, and 28 qt).

Core sampling was used to gather 35–70 samples per experimental time-point from three cores across each half of the blender. Samples were quantified using near-infrared spectroscopy. A simple model was used to determine mixing rates for top–bottom and left–right loaded experiments. Variance measurements were split into axial and radial components to gain more insight into mixing mechanisms and the separate effects of cohesion and vessel size on these mechanisms.

Convective mixing rates for radially segregated (top–bottom) loading were nearly constant regardless of changes in vessel size or mixture cohesion. Measured variances at short mixing times (e.g., 5 revolutions) were highly variable. These variations were attributed to unpredictable cohesive flow patterns during the first few rotations of the blender. Scale-up of radial mixing processes could be obtained by simply allowing for a few (<10) extra revolutions to cancel this variability. As long as the shear limit was reached, the mixing rates were the same for all mixtures and vessel sizes, thus indicating that required mixing times were needed to ensure the process outcome could be kept constant regardless of mixture cohesion or mixer size.

For axially segregated (left–right) loading, the scale-up factors depended

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on cohesion, indicating that scale-up is a mixture-dependent problem. As Figure 1 shows, the most cohesive system mixed much slower in the smaller (1 qt) blender. *However, all three systems mixed at nearly the same rate in the larger (28 qt) vessel.*

The conclusion from these results is that laboratory-scale experiments for cohesive powders are of questionable validity for predicting full-scale behavior. Behavior at small scales is likely to be strongly affected by cohesive effects that are of much less intensity in the large scale. Moreover, the powder's density, and therefore the intensity of cohesive effects, might also depend on vessel size and speed.

Cohesive effects in agglomeration.

This effect, which is familiar to the experienced formulator, occurs when a specific ingredient, typically the API, shows a tendency to agglomerate. As particles become smaller, cohesive effects grow larger. At some point, agglomeration tendencies become very significant. The critical factor in achieving homogeneity becomes the shear rate, which is dependent on both scale and speed. This problem is common in direct compression applications, but has been rarely identified primarily because of the small number of samples typically used to characterize blends. Two situations should be distinguished: agglomerates that do not reform once destroyed can be eliminated simply by implementing adequate delumping methods, preferably when loading ingredients to the blender; and agglomerates that form within the blender and pose a much more significant challenge.

Several mechanisms drive the dynamic formation of agglomerates in a blender:

- electrostatic charging, in which dielectric materials develop polarization leading to aggregation,
- moisture transfer, in which hygroscopic materials can sequester moisture from other ingredients and develop solid or capillary bridges with each other,
- softening of low-melting point ingredients (*e.g.*, MgSt), which act as a glue to create lumps of nonpolar ingredients.

A full discussion of these effects is beyond the scope of this article. Our comments are limited to three main observations:

- This type of problem can be managed by careful application of shear within the blender (*i.e.*, use of an intensified bar [I-bar]) or at the discharge (passage through a mill) immediately before compression or encapsulation.
- The most common scale-up criterion for the application of shear *via* impellers and I-bars is to match the linear speed of the moving element. It must be clearly understood that though the method is intuitively appealing, the criterion is not scientifically tested.
- Even when shear is used, dynamic agglomeration might resurface. Thus, monitoring dynamic agglomeration is important. The combination of stratified sampling and multi-batch statistical analysis seeking to identify the presence of non-Gaussian superpotent tails in the composition distribution is a

powerful method for monitoring the presence of agglomerates.

Conclusion

A systematic, generalized approach for the scale-up of granular mixing devices is still far from attainable. Clearly, more research is required to test current hypotheses and to generate new approaches to the problem. Still, we can offer some simple guidelines that can help the practitioner wade through the scale-up process:

- Make sure that changes in scale have not changed the dominant mixing mechanism in the blender (e.g., convective to dispersive). This can often happen by introducing asymmetry in the loading conditions.
- For free-flowing powders, the number of revolutions is a key parameter but rotation rates are largely unimportant.
- For cohesive powders, mixing depends on shear rate. Rotation rates are very important.
- When performing scale-up tests, take enough samples to provide an accurate description of the mixture state in the vessel. Furthermore, be wary of how you interpret your samples. Know what the mixing index means and what your confidence levels are.
- A simple way to increase the mixing rate is to decrease the fill level. Though this effect may be undesirable from a throughput point of view, a decreased fill level reduces the chance that dead-zones will form.

- Adding asymmetry to the vessel, either by design or with baffles, can tremendously affect the mixing rate. However, not all baffles accomplish significant cross-flow and contrary to oft-repeated claims, baffles *do not* increase shear significantly.

Until rigorous scale-up rules are determined, these cautionary rules are the state-of-the-art for now. The best advice is to be cautious: understand the physics behind the problem and that statistics of the data collected. Remember that a fundamental understanding of the issues is still limited and luck is unlikely to be on your side. Unfortunately, a frustrating trial-and-error method still must be used.

References

1. J.T. Carstensen and M.R. Patel, "Blending of Irregularly Shaped Particles," *Powder Technol.* **17** (3), 273–282 (1977).
2. J. Adams and A. Baker, "An Assessment of Dry Blending Equipment," *Trans. Inst. Chem. Eng.* **34**, 91–107 (1956).
3. D. Brone, A. Alexander, and F.J. Muzzio, "Quantitative Characterization of Mixing of Dry Powders in V-blenders," *AIChE J.* **44** (2), 271–278 (1998).
4. D. Brone and F. Muzzio, "Enhanced Mixing in Double-Cone Blenders," *Powder Technol.* **110** (3), 179–189 (2000).
5. S.S. Wiedenbaum, "Mixing of Solids in a Twin Shell Blender," *Ceram. Age*, August, 39–43 (1963).
6. C. Wightman and F.J. Muzzio, "Mixing of Granular Material in a Drum Mixer Undergoing Rotational and Rocking Motions, Part I: Uniform Particles," *Powder Technol.* **98** (2), 113–124 (1998).
7. K.W. Carley-Macaulay and M.B. Donald, "The Mixing of Solids in Tumbling Mixers-I," *Chem. Eng. Sci.* **17** (7), 493–506 (1962).
8. K.W. Carley-Macaulay and M.B. Donald, "The Mixing of Solids in Tumbling Mix-

BLENDING AND MIXING

- ers-II," *Chem. Eng. Sci.* **19** (3), 191–199 (1964).
9. K.J. Sethuraman and G.S. Davies, "Studies on Solids Mixing in a Double-Cone Blender," *Powder Technol.* **5** (2), 115–118 (1971).
 10. P.M.C. Lacey, "Developments in the Theory of Particulate Mixing," *J. Appl. Chem.* **4**, 257–268 (1954).
 11. O. Sudah, D. Coffin-Beach, and F.J. Muzzio, "Quantitative Characterization of Mixing of Free-Flowing Granular Materials in Tote(Bin)-Blenders," *Powder Technol.* **126** (2), 191–200 (2002).
 12. R.H. Wang and L.T. Fan, "Methods for Scaling-Up Tumbling Mixers," *Chem. Eng.* **81** (11), 88–94 (1974).
 13. P.J. Lloyd, P.C.M. Yeung, and D.C. Freshwater, "The Mixing and Blending of Powders," *J. Soc. Cosmetic Chem.* **21**, 205–220 (1970).
 14. B. Roseman and M.B. Donald, "Mixing and Demixing of Solid Particles, Part 2: Effect of Varying the Operating Conditions of a Horizontal Drum Mixer" *Br. Chem. Eng.* **7** (1), 823 (1962).
 15. S.S. Wiedenbaum, "Mixing of Solids," in *Advances in Chemical Engineering*, T.B. Drew and J.W. Hoopes, Eds. (Academic Press, New York, NY, 1958) pp. 209–324.

Supplemental information: Defining mixedness

The final objective of any granular mixing process is to produce a homogeneous blend. Determining mixture composition throughout the blend is difficult for granular systems. To date, few reliable techniques for on-line measuring of composition have been developed; granular mixtures are almost always quantified by removing samples from the mixture. To determine blending behavior over time, the blender is stopped at fixed intervals for repeated sampling; a process that

may change the blend state. Once samples are collected, the mean value and sample variance is determined and used in a mixing index (1–2). In general, the pharmaceutical industry has relied on the RSD, and the usual specification is that the measured RSD should be smaller than a given value (6% and 5% are the two most commonly cited values). This approach contains the intrinsic assumptions that the blend is a random structure with a Gaussian (normal) distribution of compositions, and that a small number of samples can sufficiently characterize variability throughout the blend. Unfortunately, in many instances in which blends segregate, agglomerate, and/or achieve incomplete mixing, distributions deviate substantially from normality, and a simple measure of breadth such as the RSD does not predict the frequency of extreme values.

Furthermore, sample size can have a large impact on apparent variability. Samples that are too small can show exaggerated variation and magnify sampling error, while too large a sample can blur concentration gradients. Hence it is paramount that a sufficient number of samples is taken that represents a large cross-section of the blender volume.

Another concern is thinking that standard sampling techniques retrieve samples that are truly representative of local concentration at a given location. Thief probes remain the most commonly used instrument for data gathering. These in-

struments sometimes induce large sampling errors from poor flow into the thief cavity or sample contamination (carry over from other zones of the blender) during thief insertion (2). A method to assess blend uniformity and blend sampling error is given in a PDA report (3).

Finally, the degree of mixedness at the end of a blending step is not always a good indicator of the homogeneity to be expected in the final product. Many granular mixtures can spontaneously segregate into regions of unlike composition when perturbed by factors such as flow, vibration, shear. Once a good blend is achieved, the mixture must be handled carefully to avoid demixing.

Mixing mechanisms

Current thinking describes the blending process as taking place by three essentially independent mechanisms: convection, dispersion, and shear. Convection causes large groups of particles to move in the direction of flow (orthogonal to the axis of rotation), the result of vessel rotation or impeller motion. Dispersion is the random motion of particles as a result of collisions or interparticle motion, usually orthogonal to the direction of flow. Shear separates particles that have joined because of agglomeration or cohesion and requires high forces. Although these definitions are helpful from a conceptual standpoint, blending does not take place as merely three independent, scaleable mechanisms. Rather, the mechanisms act simultaneously and exhibit different scale

dependence, making scale up a difficult task at best.

Powder mixing in tumbling blenders takes place as the result of particle motions in a thin cascading layer at the surface of the material, while the remainder of the material below rotates with the vessel as a rigid body. All the mixing (and all the segregation) in a tumbling blender occurs in the cascading region. Tumbling blenders impart very little shear, unless an intensifier bar (I-bar) or chopper blade is used. In some cases, high shear is detrimental to the active ingredient and is avoided. Without an I-bar, the little shear that is present occurs at the powder cascade, concurrently with tensile normal stresses, which tend to separate adjacent particles. Compressive normal stresses are static and are due entirely to the weight of the powder loaded to the vessel.

In convective mixers, homogenization is driven by the flow field created by the motion of the impeller. Typically, the entire powder mass experiences a certain amount of shear at all times. Shear levels are controlled entirely by the speed of the impeller that drives the flow. Shear always results in tensile stresses. Though different from tumbling mixers, convective mixers also apply compressive normal stresses that can be much larger than those caused by the powder weight (hence their use as granulators).

In general, regarding scale-up requirements, mixing processes can be classified into two fundamentally different groups, free-flowing and

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cohesive materials, having various mixing requirements.

References

1. M. Poux *et al.*, "Powder Mixing: Some Practical Rules Applied to Agitated Systems," *Powder Technol.* **68** (3): 213–234 1991.
2. F.J.Muzzio *et al.*, "Sampling Practices in Powder Blending," *Int. J. Pharm.* **155** (2): 153–178 (1997).
3. PDA, Technical Report No. 25, "Blend Uniformity Analysis: Validation and In-Process Testing," *J. Pharm. Sci. Technol.* **51**(S3) 1997.**PT**



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