

Scale Up of Liquid and Semisolid Manufacturing Processes

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The author points out some major obstacles to effective scale-up and describes methods available to pharmaceutical scientists for addressing scalability issues.

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Process scale-up is an increase in batch size or production capacity, usually in response to increased product demand, concerns about high production costs, or an increased need for clinical research supplies. Conversely, *scale-down* is a decrease in batch size or productivity, usually in response to decreased product demand. Pharmaceutical manufacturing scales range from the laboratory to the pilot plant to full production. The transition from one scale to another, however, is fraught with problems.

These problems include but are not limited to dissimilar processing equipment between one scale and another; various requirements for process control at different production scales; insufficient data about equipment performance at different production scales; the complexity of pharmaceutical processing, which may involve several very different unit operations and equipment; and variations in macroscopic and microscopic properties of formulation components and products at different production scales. Additional

complications arise from a reliance on trial-and-error methodology to resolve scale-up problems. Commentary about the paucity of published data relating to the scalability of pharmaceutical manufacturing processes is presented elsewhere (1).

This lack of information continues to be a problem and fosters a reliance on empiricism. Yet, changes in processing equipment, analytical instrumentation, process analytical technology, and computer software have contributed to a research environment that facilitates scalability, particularly in the past 10 years. On the other hand, in an industry in which competitive advantages may be gained by an easier approach to scale-up, publishing one's achievements in scalability would not necessarily be in a manufacturer's best interests.

Process variations resulting from a change in scale

Scale-up success often is thought to be more likely if geometrically similar processing equipment is used at each manufacturing scale. *Geometric similarity* means that equipment shape and dimensions are proportional from one production scale to another. It would seem, then, that geometric similarity would ensure results that are independent of scale. Equipment manufacturers often tout the scalability of their equipment, specifically referring to the geometric similarity of various equipment sizes.

Unfortunately, this claim is not necessarily true. Although a system's

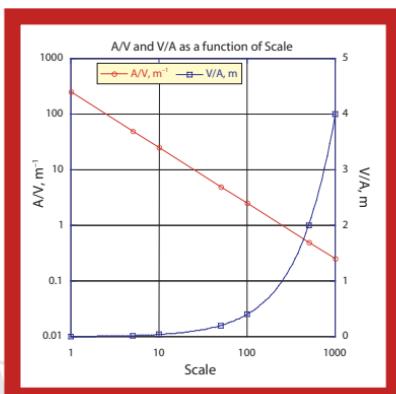


Figure 1: The ratio of area to volume (A:V) and volume to area (V:A) as a function of scale.

chemical kinetics and thermodynamic properties are not affected by changes in scale, many other system properties are affected. Geometric similarity does not ensure mechanical, thermal, or chemical similarity in scaled systems. Pharmaceutical processes can vary with scale—even when the equipment uses the same operating principle (e.g., a low-shear mixer) and the same design characteristic (e.g., a planetary mixer) and maintains geometric similarity—thus resulting in different outcomes for what appears to be the same process.

Processes may be characterized as dependent on volume, area, or length. For a given linear change in scale (L), the effect on area (L^2) or volume (L^3) is very different. Thus, a 10-fold change in linear scale results in a change in volume of three orders of magnitude and a change in area of two orders of magnitude. Figure 1 shows the dependence of the area:volume (A:V) ratio and of

the V:A ratio on the linear scale. At small production scales, area is more prominent than volume. At larger production scales, volume is far more prominent than area. As a result, process outcomes are often dependent on scale. Interfacially controlled processes such as heat transfer, particle dispersion, or surfactant adsorption at interfaces during emulsification are area-dependent processes. As scale increases, the area relative to the volume decreases and the overall efficiency of the process can decline considerably.

Volume-dependent processes such as droplet coalescence in an emulsion system or the amount of heat generated in a system tend to dominate system behavior at larger scales. Heat-exchange provisions (e.g., jacketed equipment) that are adequate at a small scale may be grossly inadequate at a larger scale and necessitate a major change in equipment design. Thus, a problematic aspect of scaling up or down is the potential for a change in the predominant mechanism of a unit operation (e.g., mixing or dissolution) with a change in scale.

When pharmaceutical manufacturing operations are based almost exclusively on geometric similarity, attempts to scale up or scale down the process often fail because of the effect of changes in scale on the controlling mechanism(s) in a pharmaceutical process. As Tatterson points out, “It is unwise to scale a process without knowing the controlling mechanisms. It is required that the controlling mechanism[s] be the same between

the two different scales. If there is a mechanism change, then a regime change has occurred” (2).

The importance of mixing in pharmaceutical manufacturing. Mixing may be the primary unit operation in a given process; it is involved in the manufacture of virtually all liquid and semisolid pharmaceuticals. Paul *et al.* estimate that mixing problems related to pharmaceutical process scale-up and process development cost the pharmaceutical industry more than \$500 million per year (3).

Given the centrality of mixing to the processing of pharmaceutical liquids and semisolids, the nature and design of the mixing equipment are of the utmost importance to the manufacturing operation and product replicability from batch to batch.

Flow regimes (hydraulic conditions) in a pharmaceutical system undergoing mixing—whether driven by dynamic or static mixers—can range from laminar to turbulent in various regions of the system at the same time.

A transitional-flow regime, in which flow is neither laminar nor turbulent but is somewhere in between, may also be present. The flow regime in the vicinity of an impeller is often turbulent, while the flow regime elsewhere in the system can be laminar or transitional. A further indication of the importance of the flow regime is evident from the input power needed per unit volume for the scale-up of geometrically similar impeller-agitated tank systems: for a turbulent-flow regime, power is $\rho N^3 D^2$ (in which ρ is den-

sity, and N and D are the rotational speed of the impeller and the diameter of the impeller, respectively); for a laminar flow regime, power is ηN^2 (in which η is the viscosity) (4).

Scale up of solutions. Insofar as the scale-up of solutions is concerned, Gorsky advocates three methods: application of a power law, use of dimensionless numbers, and the scale-of-agitation approach (5).

The power law approach uses the following relationship (5):

$$N_2 = N_1(1 \div R)^n \quad [1]$$

in which n is the power law exponent and N_1 and N_2 are the rotational speeds of the impeller at scales 1 and 2, respectively. R is a geometric scaling factor such as $D_1 T_1$ or $D_2 T_2$, in which D is the impeller diameter and T is the mixing tank diameter, or $Z_1 T_1$ or $Z_2 T_2$, in which Z is the height of liquid in the mixing tank. Depending on the scaling objective, commonly encountered values encompass the range $0 \leq n \leq 1$. For example, for equal blend times, $n = 0$; for equal mass transfer rates, $n = \frac{1}{2}$; and for equal solids suspension, $n = \frac{3}{4}$.

The dimensionless numbers method such as the Reynolds number (*i.e.*, the ratio of inertial to viscous forces in a flow),

$$Re = (D^2 \rho N \div \eta)$$

or the Froude number (*i.e.*, the ratio of inertial stress to the gravitational force per unit area in a liquid),

$$Fr = (DN^2 \div g)$$

are used as a means of correlating

process characteristics at various production scales. D , N , and η in these dimensionless numbers are the same as previously defined, whereas ρ and g are density and gravitational acceleration, respectively.

The scale-of-agitation approach—developed in the mid- to late-1970s (6, 7)—uses the power law relationship [1] in conjunction with dimensionless numbers and an empirical scale-of-agitation (*i.e.*, bulk-fluid velocity) to facilitate scale-up under conditions of geometric similarity. Gorsky provides a detailed review and application of the scale-of-agitation approach (5).

These methods tend to be problematic once the systems deviate from Newtonian flow behavior and geometric similarity. Nonetheless, Zlokarnik provides a rational basis for the scaling of such systems by using a rheologically appropriate dimensionless term to compensate for the non-Newtonian behavior of more-complex systems (8). The rheological behavior of shear-thinning (pseudoplastic) systems may be described by the Ostwald–de Waele equation between the shear rate extremes corresponding to the zero shear viscosity, η_0 , and to the infinite shear viscosity, η_∞ :

$$\tau = K\dot{\gamma}^a \quad [2]$$

in which τ is the shear stress, $\dot{\gamma}$ is the rate of shear, and K and a are constants. The ratio $\eta:\eta_0$ corresponding to the ratio $\tau:\tau_0$ would then be used to facilitate scaling.

Particularly difficult scale-up problems arise with the scaling of disperse

systems because multiple, mechanistically different phenomena are involved (*e.g.*, coalescence, dispersion, and maintenance of particle suspension). Leng and Calabrese note the difficulties inherent in scaling up an emulsion system in which differences in scale result in various proportions of the system behaving in both a turbulent and a laminar manner (9). Droplet dispersion is more apt to occur in a turbulent-flow regime such as in a small vessel, but droplet coalescence is more apt to occur in a laminar-flow regime (*e.g.*, in a large vessel). Not surprisingly, identical outcomes at two different manufacturing scales are not readily achieved.

Improving the likelihood of scalability

As Louis Pasteur is reputed to have said, "Chance favors only the mind that is prepared." The pharmaceutical technologist confronted with a scaling problem could prepare his or her mind to increase the likelihood of successful scaling of formulation components and the product by:

- identifying the physical and chemical phenomena involved in the pharmaceutical manufacturing process;
 - understanding whether and how these phenomena are affected by a change in scale (*i.e.*, Are they dependent on volume, area, or length?);
 - identifying the predominant or controlling process mechanism;
 - identifying the critical process variables that affect scalability;
 - identifying or determining the physicochemical properties (*e.g.*, density, particle size, viscosity) of the formulation components and the products relevant to scalability;
 - using dimensional analysis to reduce the number of variables required to characterize a process as the manufacturing scale changes;
 - using software that enables the estimation of equipment performance and material characteristics.
- Dimensional analysis is a powerful approach to scale-up that deserves serious consideration as a principal method of affecting equivalent results at various production scales (10, 11). Dimensional analysis goes beyond the mere computation of dimensionless numbers by requiring the analysis of a physical process and the conditions under which the process behaves similarly from one scale to another. This analysis is necessary if the relevant physical variables are to be described in terms of the basic dimensions of mass, length, time, and temperature.
- Aside from preparing one's mind to tackle a scale-up problem, experimental and computational methods can have a substantial effect on the resolution of a scaling problem. Experimental methods range from laboratory-scale to pilot-plant to full-scale production studies. Again, geometrically similar, proportionately scaled equipment can facilitate data analysis. Economies of scale are lost, of course, in a full-scale production facility. Such studies are often prohibitively expensive.
- On the other hand, there may be an advantage to conducting pilot-

plant or full-scale studies using model systems (*i.e.*, “mock up” studies) that behave similarly to the pharmaceutical system that will be scaled. Mock-up studies can provide valuable insight into size- or scale-related system behavior without the investigator incurring the expenses associated with the actual formulation. Zlokarnik has used aqueous solutions of various hydrocolloids to simulate conditions in biotechnology studies (8).

Today, the Internet abounds with numerous Web sites devoted to manufacturing process simulations, particularly those based on mixing (12, 13). Current literature has begun to reflect the increasing availability of simulation software of various types and of the increasing importance of pharmaceutical engineering (14, 15).

It should no longer be necessary for a pharmaceutical scientist to resort to empiricism to resolve a scale-up problem. The likelihood of scale-up success is greater than ever before because of the continued development and refinement of software for simulating and computing fluid dynamics in the processing of solutions and disperse systems over a wide range of rheological conditions. Today, scale-up should be considered a challenge, not a problem.

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