

ation is the narrowest possible droplet size distribution. It is normally characterized by the ‘‘Sauter mean diameter’’ d_{32} [14] or by the median d_{50} of the size distribution. d_{32} or d_{50} , respectively, therefore has to be regarded as the target quantity of this operation.

The characteristic length of the dispersion chamber, e.g., the slot width between rotor and stator in dispersion mills or the nozzle diameter in high-pressure homogenizers (utilizing high-speed fluid shear), will be denoted as d .

As material parameters, the densities and the viscosities of both phases as well as the interfacial tension σ must be listed. We incorporate the material parameters of the disperse phase ρ_d and μ_d in the relevance list and note separately the material numbers ρ/ρ_d and μ/μ_d . Additional material parameters are the (dimensionless) volume ratio of both phases φ and the mass portion c_i of the emulsifier (surfactant) (e.g., given in ppm).

The process parameters have to be formulated as intensive quantities. In appliances where liquid throughput q and power input P are separated from each other as two freely adjustable process parameters, the volume-related power input P/V and the period of its duration ($\tau = V/q$) must be considered:

$$(P/V) \tau = E/V [M L^{-1} T^{-2}] \quad (43)$$

In appliances with only one degree of freedom (e.g., high-pressure homogenizers), the power is being introduced by the liquid throughput. Here, the relevant intensively formulated power P is therefore power per liquid throughput, P/q . In nozzles, $P \propto \Delta p q$, which results in

$$P/q = (\Delta p q)/q = \Delta p [M L^{-1} T^{-2}] \quad (44)$$

Therefore, the volume-related energy input E/V and the throughput-related power input P/q ($\triangleq \Delta p$) represent homologous quantities of the same dimension. For the sake of simplicity Δp will be introduced in the relevance list.

Now, this six-parameter relevance list of the dimensional parameters (the dimensionless parameters ρ/ρ_d , μ/μ_d , φ , c_i are excluded) reads

$$\{d_{32}; d; \rho_d, \mu_d, \sigma; \Delta p\} \quad (45)$$

The corresponding dimensional matrix

	ρ_d	d	σ	Δp	μ_d	d_{32}
M	1	0	1	1	1	0
L	-3	1	0	-1	-1	0
T	0	0	-2	-2	-1	0
M + T/2	1	0	0	0	1	0
3M + L + 3T/2	0	1	0	3	2	1
-T/2	0	0	1	1	1	2

delivers the remaining three dimensionless numbers:

$$\Pi_1 \equiv \frac{\Delta p d}{\sigma} \quad \equiv \text{Eu We} \quad \equiv \text{La (Laplace number)}$$

$$\Pi_2 \equiv \frac{\mu_d}{(\rho_d d \sigma)^{\frac{1}{2}}} \quad \equiv \frac{\text{We}^{\frac{1}{2}}}{\text{Re}} \quad \equiv \text{Oh (Ohnesorge number)}$$

$$\Pi_3 \equiv d_{32}/d$$

The complete pi set is given as

$$\{d_{32}/d, \text{La}, \text{Oh}, \rho/\rho_d, \mu/\mu_d, \varphi, c_i\} \quad (46)$$

Assuming a quasi-uniform power distribution in the throughput or in the volume, a characteristic length of the dispersion space becomes irrelevant. In the relevance list, Eq. (45), the parameter d must be cancelled. The target number $\Pi_3 \equiv d_{32}/d$ has to be dropped and the dimensionless numbers La^* and Oh^* have to be built by d_{32} instead of d . At given and constant material conditions ($\rho/\rho_d, \mu/\mu_d, \varphi, c_i = \text{const}$) the process characteristics will be represented in the following pi space:

$$\text{Oh}^{*-2} = f(\text{La}^* \text{Oh}^{*2}) \quad \rightarrow \quad d_{32} \left(\frac{\rho_d \sigma}{\mu_d^2} \right) = f \left\{ \Delta p \left(\frac{\mu_d^2}{\rho_d \sigma^2} \right) \right\} \quad (47)$$

This dependency has been confirmed on two colloid mills in the scale 1:2.2 [15]; see Fig. 12. For a material system of vegetable oil/water and $\varphi = 0.5$, the following correlation is found:

$$d_{32} = 4.64 \times 10^5 \Delta p^{-\frac{2}{3}} \quad d_{32}[\mu\text{m}]; \quad \Delta p[\text{M}/(\text{L T}^2)] \quad (48)$$

Similar results have been presented for other two-parameter appliances [16].

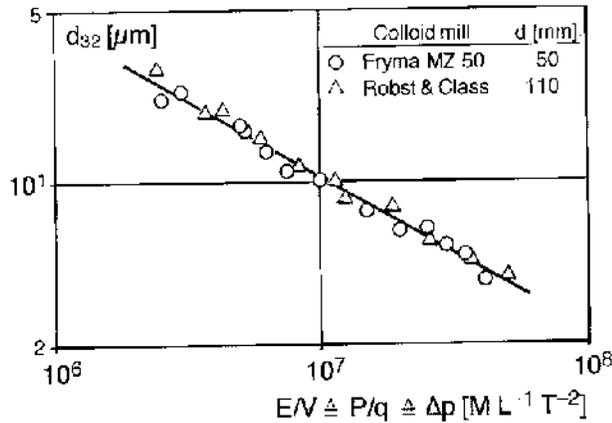


Figure 12 The relationship $d_{32} = f(\Delta p)$ for two colloid mills of different size. Material system: vegetable oil/water and $\varphi = 0.5$. (From Ref. 15.)

It should be pointed out that the dimensional representations in the form of Eq. (48) as $d_{32} = f(\Delta p)$ present a serious disadvantage as compared to the dimensionless one: Eq. (48) is valid only for the investigated material system and tells nothing about the influence of the physical parameters!

Example 7: Fine Grinding of Solids in Stirred-Ball Mills. The fine grinding of solids in mills of different shape and mode of operation is used to produce finest particles with a narrow particle size distribution. Therefore—as in the previous example—the target quantity is the median value d_{50} of the particle size distribution.

The characteristic length of a given mill type is d . The physical properties are given by the particle density ρ_p , the specific energy of the fissure area β , and the tensile strength σ_Z of the material. Should there be additional material parameters of relevance, they can easily be converted to material numbers by the aforementioned ones.

As process parameter, the mass-related energy input $E/\rho V$ must be taken into account. The relevance list reads

$$\{d_{50}; d; \rho_p, \beta, \sigma_Z; E/\rho V\} \tag{49}$$

	ρ_p	d	β	$E/\rho V$	σ_Z	d_{50}
M	1	0	1	0	1	0
L	-3	1	0	2	-1	1
T	0	0	-2	-2	-2	0
M + T/2	1	0	0	-1	0	0
3M + L + 3T/2	0	1	0	-1	-1	1
-T/2	0	0	1	1	1	0

From this dimensional matrix the following pi set arises:

$$\{d_{50}/d, (E/\rho V)\rho d/\beta, \sigma_Z d/\beta\} \tag{50}$$

Assuming a quasi-uniform energy input in the mill chamber, its characteristic diameter d will be irrelevant. Then the pi set is reduced to

$$\{(E/\rho V)\rho d_{50}/\beta, \sigma_Z d_{50}/\beta\} \rightarrow d_{50}(\sigma_Z/\beta) = f\{(E/\rho V)(\rho/\sigma_Z)\} \tag{51}$$

In the case of unknown physical properties, σ_Z and β , Eq. (51) is reduced to $d_{50} = f(E/\rho V)$, which is then used for the scale-up of a given type of mill and a given grinding material.

For fine-grinding of, e.g., limestone for paper and pottery manufacturing, bead mills are widely used. The beads of steel, glass, or ceramic have a diameter of 0.2–0.3 mm and occupy up to 90% of the total mill volume ($\phi \leq 0.9$). They are

kept in motion by perforated stirrer discs while the liquid/solid suspension is pumped through the mill chamber. Mill types frequently in use are stirred disc mill, centrifugal fluidized-bed mill, ring gap mill.

H. Karbstein et al. [17] pursued the question of the smallest size of the laboratory bead mill that would still deliver reliable data for scale-up. In different-size rigs ($V = 0.25\text{--}25$ liters) a sludge consisting of limestone ($d_{50} = 16 \mu\text{m}$) and 10% aqueous Luviscol solution (mass portion of solids $\varphi = 0.2$) was treated. It was found that the minimum size of the mill chamber should be $V = 1$ liter. A further, unexpected but dramatic result was that the validity of the process characteristics

$$d_{50} \propto (E/\rho V)^{-0.43} \quad E/\rho V \leq 10^4 \quad (52)$$

expires at $E/\rho V \cong 10^4$ and the finest particle diameter cannot fall below $d_{50} \cong 1 \mu\text{m}$.

These facts and the scattering of the results made a systematic investigation of the grinding process necessary [18]. The grinding process in bead mills is determined by the frequency and the intensity of the collision between beads and grinding medium. According to this assumption, the grinding result will remain constant if both these quantities are kept constant. The intensity of the collision is essentially given by the kinetic energy of the beads:

$$E_{\text{kin}} \propto m_M u^2 \propto V_M \rho_M u^2 \propto d_M^3 \rho_M u^2 \quad (53)$$

(d_M, ρ_M = diameter and density of the mill beads, u = tip velocity of the stirrer). On the other hand, the frequency depends on the size of the mill chamber and therefore on the overall mass-related energy input. To achieve the same grinding result in different-size bead mills, E_{kin} as well as $E/\rho V$ have to be kept idem. The input of the mechanical energy can be measured from the torque and the rotational speed of the perforated discs, and the kinetic energy can be calculated from Eq. (53).

The preceding assumption was examined with the same material system and the same grinding media (beads). Three different-size bead mills were used (V [liters] = 0.73; 5.54; 12.9). Figure 13 shows the results. To achieve a satisfactory correlation, the size of the mill chamber d will have to be introduced in the relevance list. A further finding is that under the same conditions a smaller mill delivers a coarser product. This had already been found in the previously cited paper [17].

As to the course of the function $d_{50} = f(E_{\text{kin}})$ at $E/\rho V = 10^3 \text{ kJ/kg} = \text{const}$, the following explanation is given in Ref. 18. With E_{kin} increasing, the particle size first diminishes but later increases. This is plausible if the introduced specific energy is viewed as a product of the frequency and the intensity of the collision. At $E/\rho V = \text{const}$ and increasing the intensity of the collision, the frequency has to diminish, resulting in a coarser product.

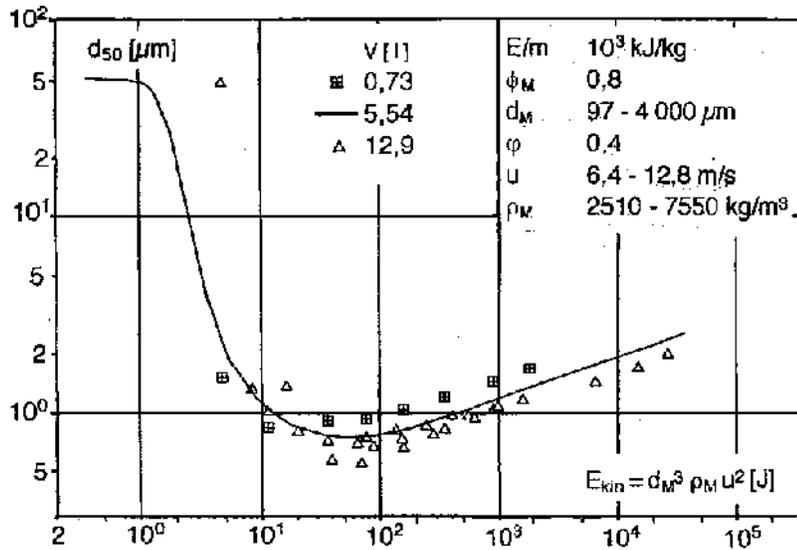


Figure 13 The relationship $d_{50} = f(E_{kin})$ for three colloid mills of the same type but different size. Identical material system and constant $E/\rho V = 10^3$ kJ/kg. (From Ref. 18.)

IX. NOMENCLATURE

a	thermal diffusivity ($\equiv \lambda/\rho C_p$)
A	surface
c_f	concentration of foamer and flocculant, resp.
C_p	heat capacity at constant pressure
d	stirrer diameter
d_p	particle or droplet diameter
D	vessel diameter
D	diffusivity
F	force
g	gravitational acceleration
G	gravitational constant
l, L	characteristic length
m	mass
M	dimension of mass
n	rotational speed
$p, \Delta p$	pressure, pressure difference
P	power
q	volumetric throughput

R	universal gas constant
t	(running) time
T	dimension of time
v	velocity
v_s	velocity of sound
V	liquid volume

A. Greek Characters

β	temperature coefficient of density; specific energy of the fissure area in grinding
ϕ	degree of filling
γ	temperature coefficient of dynamic viscosity
$\dot{\gamma}$	shear rate
ν	kinematic viscosity
μ	dynamic viscosity; scale-up factor ($\mu = l_T/l_M$)
φ	volume or mass portion
λ	thermal conductivity
Π	dimensionless product
$\rho, \Delta\rho$	density, density difference
σ	(interfacial) surface tension
σ_Z	tensile strength
θ	period of time
$T, \Delta T$	temperature, temperature difference
Θ	dimension of temperature
τ	residence time; shear stress

B. Subscripts

G	gas
L	liquid
S	solid
M	model, laboratory scale
T	technological, industrial scale

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2

Parenteral Drug Scale-Up

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I. INTRODUCTION

The term *parenteral* is applied to preparations administered by injection through one or more layers of skin tissue. The word, derived from the Greek words *para* and *etheron*, meaning “outside of the intestine,” is used for those dosage forms administered by routes other than the oral route. Because the administration of injectables, by definition, requires circumventing the highly protective barriers of the human body, the skin, and the mucous membranes, the dosage form must achieve an exceptional purity. This is generally accomplished by strict adherence to good manufacturing practices.

The basic principles employed in the preparation of parenteral products do not vary from those widely used in other sterile and nonsterile liquid preparations. However, it is imperative that all calculations be accurate and precise. Therefore, the issue of parenteral solution scale-up essentially becomes a liquid scale-up task, which requires a high degree of accuracy. A practical yet scientifically sound means of performing this scale-up analysis of liquid parenteral systems is presented in this chapter. The approach is based on the scale-of-agitation method. For single-phase liquid systems, the primary scale-up criterion is equal liquid motion when comparing pilot-size batches to a larger, production-size batches.

One of the most important processes involved in the scale-up of liquid parenteral preparations is mixing [1]. For liquids, mixing can be defined as a transport process that occurs simultaneously in three different scales, during which one substance (*solute*) achieves a uniform concentration in another substance (*solvent*). On a large, visible scale, mixing occurs by *bulk diffusion*, in which the elements are blended by the pumping action of the mixer’s impeller. On the microscopic scale, elements that are in proximity are blended by eddy currents, and they

create drag, where local velocity and shear-stress differences act on the fluid. On the smallest scale, final blending occurs via molecular diffusion, whose rate is unaffected by the mechanical mixing action. Therefore, large-scale mixing depends primarily on flow within the vessel, whereas small-scale mixing is dependent mostly on shear. This approach focuses on large-scale mixing using three viable approaches, specifically concentrating on the scale-of-agitation method.

II. GEOMETRIC SIMILARITY

There are several methods to achieve appropriate scale-up of mixing. The first involves geometric similarity. This technique employs proportional scale-up of geometric parameters of the vessel. The scaled-up parameters may include such geometric ratios as D/T , where D is the diameter of the impeller and T is the diameter of the tank, and Z/T , where Z is the height of the liquid in the vessel. Similar ratios are compared for both small-scale equipment (D_1T_1) and the larger-scale equipment (D_2T_2). For example,

$$R = D_1T_1 = D_2T_2 \quad (1)$$

where R is the geometric scaling factor.

After R has been determined, other required parameters, such as the rotational speed of the larger equipment, can then be calculated by power law relationships. In the preceding example, the required rotational speed, N , can be calculated as

$$N_2 = N_1 \left(\frac{1}{R} \right)^n \quad (2)$$

Rotational speeds may be expressed either in terms of rpm or in terms of sec^{-1} . The power law exponent, n , has a definite physical significance. The value of n and its corresponding significance are determined either empirically or through theoretical means. Table 1 lists the most common values assigned to n .

The scale-up can be completed by using predicted values of N_2 to determine the horsepower requirements of the large-scale system. In most designs, D/T will be in the following range:

$$0.15 \leq \frac{D}{T} \leq 0.6 \quad (3)$$

and Z/T will be in the range

$$0.3 \leq \frac{Z}{T} \leq 1.5 \quad (4)$$

These values, in conjunction with N and the horsepower requirements, completely define the major parameters of the systems.

Table 1 Common Values Assigned to the Power Law Exponent, n , When Comparing Large- to Small-Scale Equipment

n	Physical interpretation
0	Equal blend time
$\frac{1}{2}$	Equal surface motion
$\frac{2}{3}$	Equal mass transfer rates
$\frac{3}{4}$	Equal solids suspension
1	Equal liquid motion (equal average fluid velocity)

III. DIMENSIONLESS NUMBERS METHOD

The second method for achieving appropriate scale-up of mixing uses dimensionless numbers to predict scale-up parameters. The use of dimensionless numbers simplifies design calculations by reducing the number of variables to consider. The dimensionless-number approach has been used with good success in heat transfer calculations and to some extent in gas dispersion (mass transfer) for mixer scale-up. Usually, the primary independent variable in a dimensionless-number correlation is the Reynolds number:

$$N_{\text{Re}} = \frac{D^2 \rho N}{\mu} \quad (5)$$

where

N = shaft speed (sec^{-1})

D = propeller blade diameter (cm)

ρ = density of solution dispersion (g/cm^3)

μ = viscosity of solution dispersion ($\text{g}/[\text{cm}/\text{sec}]$).

Other dimensionless numbers are used widely for various scale-up applications. One example is the Froude number:

$$N_{\text{Fr}} = \frac{DN^2}{g} \quad (6)$$

where g is acceleration due to gravity in $\text{cm}/\text{sec}^{-1}$. The Froude number compares inertial forces to gravitational forces inside the system.

Another example is the power number, which is a function of the Reynolds number and the Froude number:

$$N_P = \frac{Pg_c}{\rho N^3 D^5} \quad (7)$$

where P is power and g_c is a gravitational conversion factor. This number relates density, viscosity, rotational speed, and the diameter of the impeller. The power number correlation has been used successfully for impeller geometric scale-up. Approximately half a dozen other dimensionless numbers are involved in the various aspects of mixing, heat and mass transfer, etc.

Both of the preceding methods belong to a traditional fluid mechanical approach known as *dimensional analysis* [2]. Unfortunately, these methods cannot always achieve results in certain manufacturing environments. Therefore, a third method is introduced, which can be applied easily to the various research and production situations. This method actually is a combination of the first two methods.

IV. SCALE-OF-AGITATION APPROACH

The basis of the scale-of-agitation approach is a geometric scale-up with the power law exponent, $n = 1$ (see Table 1). This provides for equal fluid velocities in both large- and small-scale equipment. Furthermore, several dimensionless groups are used to relate the fluid properties to the physical properties of the equipment being considered. In particular, bulk-fluid velocity comparisons are made around the largest blade in the system. This method is best suited to turbulent flow agitation in which tanks are assumed to be vertical cylinders.

Although good success may be achieved in applying this technique to marine-type propeller systems, the original development was based on low-rpm, axial, or radial impeller arrangements. Because the most intensive mixing occurs in the volume immediately around the impeller, this discussion focuses on this particular region of mixing. Table 2 describes the nomenclature used to develop the theory behind the approach.

The analysis proceeds as follows. First, determine the D/T ratio of the tank, based on the largest impeller, in which the original (usually R&D) batches had

Table 2 Nomenclature

Q	Effective pumping capacity or volumetric pumping flow, in cm^3/sec
N	Shaft speed, in sec^{-1}
N_{Re}	Impeller Reynolds number, dimensionless
N_Q	Pumping number, dimensionless
D	Diameter of the largest mixer blade, in cm
ρ	Density of the fluid, in g/cm^3
μ	Viscosity of the fluid, in $\text{g}/[\text{cm}/\text{sec}]$
v_b	Bulk fluid velocity, in cm
T	Diameter of the tank, in cm
A	Cross-sectional area of the tank, in cm^2

been compounded. It is also necessary to know the rotational speed and the horsepower of the mixer used.

The only two product physical properties needed are density and viscosity. Generally, parenterals, like most solution-type products, will follow Newtonian fluid behavior and may also be considered incompressible. Therefore, point densities and viscosities can be used satisfactorily.

The next step in the analysis is to calculate the impeller Reynolds number achieved during this original compounding using Eq. (5). The impeller Reynolds number must be greater than 2000 to proceed with the analysis [3]. Mixing achieved in the initial R&D processing must be in the turbulent range. If the impeller Reynolds number is less than 2000, then mixing in the pilot tank was either inadequate or represented some other special case, such as moderately viscous fluids. In these situations, another D/T ratio curve must be used.

Proceeding further, obtain the value of the terminal pumping number in the R&D pilot process by using the following formula:

$$N_Q = 1.1283 - 1.07118 \left(\frac{D}{T} \right) \quad (8)$$

Equation (8) is an empirical relationship obtained by the linear regression between D/T and the terminal pumping numbers [4]. It is important to note that a family of curves exists for each D/T ratio when N_Q (pumping number) is plotted against the impeller Reynolds number [5]. In the turbulent range ($N_{Re} > 2000$), the N_Q curves flatten out and thus are independent of the Reynolds number. The terminal pumping number, $N_{Q/Re>2000}$, plotted against the D/T ratio results in Eq. (8). The cross-sectional area of the pilot-size tank is determined by using Eq. (9):

$$A = \frac{\pi T^2}{4} \text{ cm}^2 \quad (9)$$

Then the value of the effective pumping capacity for the pilot-size mixer is calculated using Eq. (10):

$$Q = N_Q N D^3 \text{ cm}^3/\text{sec} \quad (10)$$

Finally, by inserting the values derived in Eqs. (9) and (10) into Eq. (11), the value for bulk-fluid velocity around the largest impeller of the system is obtained:

$$v_b = \frac{Q}{A} \text{ cm/sec} \quad (11)$$

The bulk-fluid velocity can be inserted into Table 3 to determine the level of agitation achieved in the original R&D pilot batch. The larger-size production tank and mixer are then designed so that the scale of agitation produced in the larger vessel matches that required for the pilot-size batches. The scale-of-agitation approach was first developed in the mid-1970s by engineers at Chemineer,

Table 3 Process Requirements: The Set Degree of Agitation for Blending and Motion

Scale of agitation	Bulk-fluid velocity (cm/sec)	Description of mixing
1	3	Agitation levels 1 and 2 are characteristic of applications requiring minimum fluid velocities to achieve the product result
2	6	Agitators capable of level 2 will: <ol style="list-style-type: none"> a. Blend miscible fluids to uniformity if specific gravity differences are less than 0.1 and if the viscosity of the most viscous is less than 100 times that of the other b. Establish complete fluid-batch control c. Produce a flat but moving fluid-batch surface
3	9	Agitation levels 3–6 are characteristic of fluid velocities in most chemical (including pharmaceutical) industries agitated batches
4	12	Same as 3
5	15	Same as 3 and 4
6	18	Agitators capable of level 6 will: <ol style="list-style-type: none"> a. Blend miscible fluids to uniformity if specific gravity differences are less than 0.6 and if the viscosity of the most viscous is less than 10,000 times that of the other b. Suspend trace solids (<2%) with settling rates of 2–4 ft/min c. Produce surface rippling at lower viscosities
7	21	Agitation levels 7–10 are characteristic of applications requiring high fluid velocities for process result, such as mixing of the high-viscosity suspension preparations
8	24	Same as 7
9	27	Same as 7 and 8
10	30	Agitators capable of level 10 will: <ol style="list-style-type: none"> a. Blend miscible fluids to uniformity if specific gravity differences are less than 1.0 and if the viscosity of the most viscous is less than 100,000 times that of the other b. Suspend trace solids (<2%) with settling rates of 4–6 ft/min c. Provide surging surface at low viscosities

Inc. [6]. Table 3 summarizes the scale-of-agitation parameters and gives a qualitative description of the type of mixing associated with the various levels. According to this approach, mixing is a similar process if the calculated bulk-fluid velocities for the production-size vessels lie within ± 1 unit level of the scale of agitation required from an analysis of the R&D pilot batches. It is quite easy to match the required scale of agitation by simply adjusting the rpm when working

with variable-speed equipment. Thus, a given tank equipped with a variable-speed mixer will generally be capable of several agitation levels.

V. SCALE-OF-AGITATION APPROACH EXAMPLE

To illustrate the actual application of the scale-of-agitation approach to scale-up, the method was applied to the scale-up of typical injectables solution from a 378 liter pilot batch to a 3780 liter production-size batch. The example product is a Newtonian fluid with density of 1.018 g/cm³ and a viscosity of 0.0588 g/(cm/sec)(5.88 cps). The tank used in the manufacturing of the pilot batch had the following parameters:

$$T = \text{diameter of the tank} = 74.6 \text{ cm}$$

$$A = \text{cross-sectional area} = 4371 \text{ cm}^2$$

The agitation was accomplished with a turbine-type mixer, and the largest axial impeller was 40.64 cm. The pilot batch was mixed at 90 rpm (1.5 sec⁻¹). From the initial known data the D/T ratio was determined:

$$\frac{D_{378L}}{T_{378L}} = \frac{40.64 \text{ cm}}{74.60 \text{ cm}} = 0.54 \quad (12)$$

Then the value of the impeller Reynolds number was obtained by plugging known values into Eq. (5):

$$\begin{aligned} N_{\text{Re}(3785L)} &= \frac{D_{378L}^2 \rho N_{378L}}{\mu} \\ &= \frac{(40.64 \text{ cm})^2 (1.018 \text{ g/cm}^3)(1.5 \text{ sec}^{-1})}{0.0588 \text{ g/(cm/sec)}} = 44449 \end{aligned} \quad (13)$$

Because the value of the Reynolds number is greater than 2000, Eq. (8) is used to obtain the pumping number. The pumping number is inserted into Eq. (10) to obtain the effective pumping capacity:

$$\begin{aligned} Q_{378L} &= (N_{Q(378L)})(N_{378L})(D_{378L}^3) = (0.55)(1.5 \text{ sec}^{-1})(40.64 \text{ cm})^3 \\ &= 55375 \text{ cm}^3/\text{sec} \end{aligned} \quad (14)$$

Knowing the effective pumping capacity of agitation and the cross-sectional area of the pilot-batch tank, bulk-fluid velocity is obtained by using Eq. (11):

$$v_{b(378L)} = \frac{Q_{378L}}{A_{378L}} = \frac{55,375 \text{ cm}^3/\text{sec}}{4371 \text{ cm}^2} = 12.6 \text{ cm/sec} \quad (15)$$

Inserting this bulk-fluid velocity into Table 3, one can calculate the level of agitation used in the pilot batch of indictable solution as 4, which is described as

characteristic of fluid velocities in most chemical process industries' agitated batches.

Now the appropriate shaft speed for scaled-up production equipment can be calculated. The tank used for production batches has a capacity of 3780 L. It is equipped with a turbine-type agitator, which has a shaft speed range of 20–58 rpm. The diameter of this tank is 167 cm. The diameter of the largest axial impeller is 87 cm. Given the diameter of the production tank, the cross-sectional area can be determined as

$$A_{3780L} = \frac{\pi T_{3780L}^2}{4} = \frac{\pi(167 \text{ cm})^2}{4} = 21,904 \text{ cm}^2 \quad (16)$$

The next step is solving Eq. (10) for effective pumping capacity in the larger vessel:

$$Q_{3780L} = (v_{b(378L)})(A_{3780L}) = (12.6 \text{ cm/sec})(21,904 \text{ cm}^2) = 275,990 \text{ cm}^3/\text{sec} \quad (17)$$

Earlier, the analysis established that the mixing of this product occurs in the turbulent flow regime because the Reynolds number obtained far exceeds the minimally required 2000. Therefore, the pumping number can be calculated for the 3780-L tank by using Eq. (8) to obtain

$$N_{Q(3780L)} = 1.1283 - \left[(1.07118) \left(\frac{87 \text{ cm}}{167 \text{ cm}} \right) \right] = 0.57 \quad (18)$$

Finally, Eq. (10) is rearranged to solve for the appropriate shaft speed to be used in a 3780-L batch:

$$N_{3780L} = \frac{Q_{3780L}}{N_{Q(3780L)} D_{3780L}^3} = \frac{275,990 \text{ cm}^3/\text{sec}}{(0.57)(87 \text{ cm})^3} = 0.73 \text{ sec}^{-1} = 44 \text{ rpm} \quad (19)$$

The shaft speed value obtained is well within the rpm range of the 3780-L tank agitator. To determine the rpm range for production batches, start with level-3 agitation at the low rpm end and level-5 agitation at the high rpm end. Table 3 provides bulk velocities for levels 3 and 5. In turn, these are used to calculate the respective pumping capacities, defined via Eq. (11). The low and high speeds are then calculated, as described earlier, by rearranging Eq. (10).

This method can easily be used to show the logic behind the scale-up from original R&D batches to production-scale batches. Although scale-of agitation analysis has its limitations, especially in the mixing of suspension, non-Newtonian fluids and gas dispersions, similar analysis could be applied to these systems, provided that pertinent system variables were used. These variables may include superficial gas velocity, dimensionless aeration numbers for gas systems, and terminal settling velocity for suspensions.

VI. LATEST REVISIONS OF THE APPROACH

As was discussed earlier, the scale-of-agitation approach has been successfully used in the scale-up of various liquid systems, including parenteral drugs. However, in the late 1990s, it was revised slightly to ensure even more accurate results [7]. We have already determined that the mixing in the agitated tank must be in the turbulent state in order for Eq. (8) to work properly. Therefore, an assumption is made that the full turbulence is achieved at N_{Re} above 2000. However, one should be aware that this assumption may result in an error of 12% in the N_Q calculation. One may come to the conclusion that some inadequacies may be encountered in the areas of mixing close to $N_{Re} = 2000$. This later revision of the approach thrived on the fact that because this scale-up process was based on the use of existing equipment, it may not be possible to build in as much of a safety factor as possible when engineering a new facility. Therefore, it would be important to determine N_Q very accurately. Trying to achieve an even more accurate N_Q determination, the relationship between the D/T ratio on the N_{Re} vs. N_Q grid was re-examined. Upon replotting Figure 1 using linear coordinates, the following trend was observed (see Fig. 2). The curves rise sharply at first, which somewhat resembles the dissolution profile for a solid dosage form. Lagenbucher's equation for dissolution profile curves is:

$$Y = 1 - \exp\left[\frac{-(X)^a}{b}\right] \tag{20}$$

Similarly, an equation for curves in Figure 2 may be expressed as follows:

$$N_Q = 1 - \exp\left[\frac{-(N_{Re})^a}{b}\right] \tag{21}$$

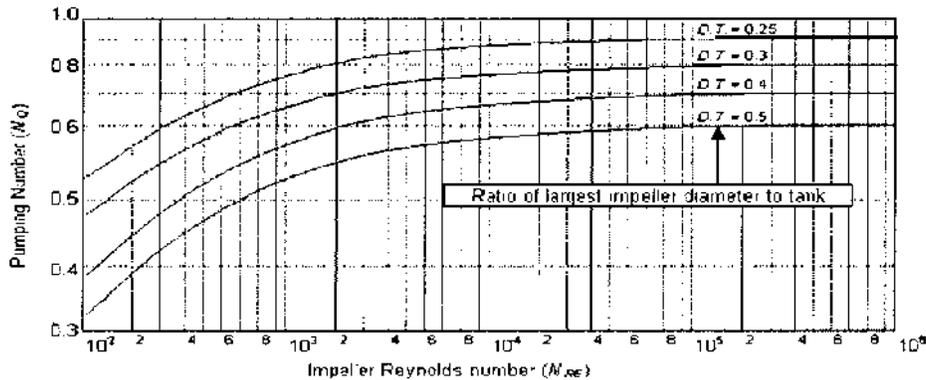


Figure 1 Pumping number versus impeller Reynolds number for turbine- and marine-type propeller agitators.

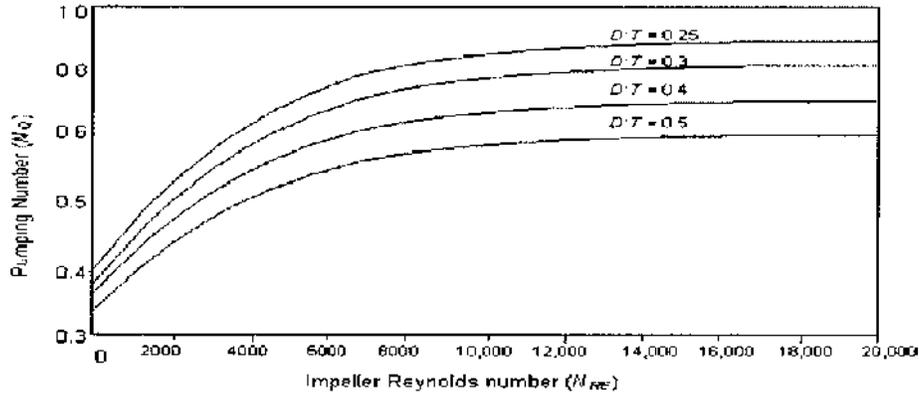


Figure 2 Pumping number versus impeller Reynolds number for turbine- and marine-type propeller agitators on linear coordinates.

where a and b are constants. Further, the equation for constant a was determined by

$$a = -0.272\left(\frac{D}{T}\right) + 0.39 \quad (22)$$

The constant b was found to be independent of the D/T ratio and had a value of 7.7.

However, Eq. (21) covered applications only where N_{Re} were below 1000. Another equation [8] to determine N_Q in the systems where N_{Re} is higher than 1000 is

$$N_Q = \frac{AN_{Re}}{N_{Re} + B} \quad (23)$$

where both A and B are functions of the D/T ratio and were determined to be

$$A = -1.08\left(\frac{D}{T}\right) + 1.12 \quad (24)$$

$$B = 578 - 1912\left(\frac{D}{T}\right) + 1980\left(\frac{D}{T}\right)^2 \quad (25)$$

These equations yield an approximate 5% maximum error, as compared to an approximate 10% error in Eq. (8).

However, it is also necessary to mention that the strength of the analysis is in its ability to mathematically transfer the mixing environment from the bench scale to the maximum compounding vessel, as close to the original pilot batch as possible. In our experience, the maximum rpm ranges empirically achieved dur-

ing compounding equal 6–20 rpm, which are well within the maximum 10% error that one may encounter via Eq. 8 in the marginal cases, where N_{Re} is close to 2000. Therefore, it is safe to conclude that the method outlined in Eq. (8) through (11) is the most efficient for finding mixing parameters of the scaled-up system. Yet Eq. (25) and (23) show the way for a closer N_Q determination, which may be more useful for the systems with higher viscosities and thus with lower N_{Re} .

VII. SCALE-OF-AGITATION APPROACH FOR SUSPENSIONS

In order to reduce the problem of adequately dispersing the insoluble drug during the formulation of sterile aqueous suspensions, the micronized material, i.e., material with a particle size of 10–30 μm , is used. Uniform distribution of the drug is required to ensure an adequate dose at the concentration per unit volume indicated on the label. Improper formulation or scale-up can result in caking of the insoluble material at the bottom of the container, making it difficult to disperse, to take up in a syringe, and thus to administer. To avoid caking, various flocculating agents are added to the product. Proper scale-up, however, is essential for adequate mixing conditions, which affect the caking process. During scale-up of a suspension product, along with the parameters, already discussed, the settling rate should be considered. The presence of a two-phase, solid–liquid system classifies an agitation problem as a solid–suspension one. In such problems, the suspension of solid particles having a settling velocity greater than 0.5 ft/min (0.25 cm/sec) within a continuous liquid phase is the purpose of the proper agitation and scale-up. The estimated terminal settling velocity, u_t , of spherical particles of a 10- to 30 μ size in low-viscosity 1- to 300-cps suspensions is empirically determined as 1. For ease of analysis, the particle shape is assumed to be a sphere, since most of the studies for settling velocities are conducted on spherical beads. A different particle geometry (cylinders, disks, crushed solids, many crystalline forms) would not compromise the integrity of the analysis, due to the usage of micronized materials. First, one must determine the design settling velocity u_d , which is a product of the terminal settling velocity u_t and a correction factor f_w , from Table 4.

$$u_d = u_t f_w \quad (26)$$

Upon determination of the design settling velocity, one must choose the scale of agitation required, using Table 5 [9], which serves as a suspension products equivalent of Table 3. The chosen scale of agitation is then plugged into the chart of Figure 3 to find the value of constant ϕ . Rearranging Eq. (27) for constant ϕ , we get

$$\phi = \frac{N^{3.75} D^{2.81}}{u_d} \quad (27)$$

Table 4 % Solids vs. Correct Factor f_w in Suspensions

Solids, %	Factor, f_w
2	0.8
5	0.84
10	0.91
15	1.0
20	1.10
25	1.20
30	1.30
35	1.42
40	1.55

Table 5 Process Requirements Set the Degree of Agitation for Solids Suspension

Scale of agitation	Description of mixing
1–2	Agitation levels 1 and 2 are characteristic of applications requiring minimal solids-suspension levels to achieve the process result. Agitators capable of scale levels of 1 and 2 will: <ol style="list-style-type: none"> a. Produce motion of all of the solids of the design settling velocity in the vessel b. Permit moving fillets of solids on the tank bottom, which are periodically suspended.
3–5	Agitation levels 3–5 are characteristic of most chemical process industry solids-suspension applications and are typically used for dissolving solids. Agitators capable of scale levels of 3–5 will: <ol style="list-style-type: none"> a. Suspend all the solids of design settling velocity completely off the vessel bottom b. Provide slurry uniformity to at least 1/3 of fluid-batch height c. Be suitable for slurry drawoff at low exit-nozzle elevations
6–8	Agitation levels 6–8 characterize applications where the solids-suspension levels approach uniformity. Agitators capable of scale levels of 6–8 will: <ol style="list-style-type: none"> a. Provide concentration uniformity of solids to 95% of the fluid-batch height. b. Be suitable for slurry drawoff up to 80% of fluid-batch height
9–10	Agitation levels 9 and 10 characterize applications where the solid-suspension uniformity is the maximum practical. Agitators capable of scale levels of 9 and 10 will: <ol style="list-style-type: none"> a. Provide slurry uniformity of solids to 98% of the fluid-batch height b. Be suitable for slurry drawoff by means of overflow

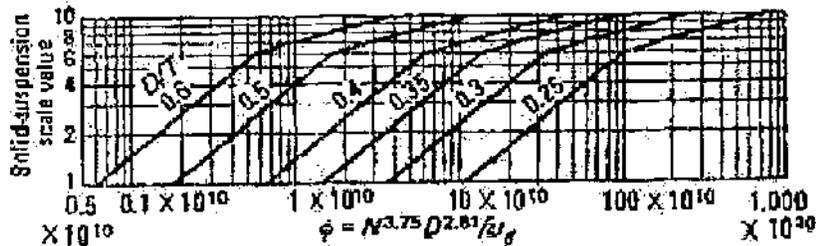


Figure 3 Solid-suspension scale value vs. ϕ

Plugging this into Eq. (28) for mixer speed we easily find the agitation rpm:

$$N = \frac{1}{3.75} \sqrt[3]{\frac{\phi u_d}{D^{2.81}}} \quad (28)$$

VIII. CONCLUSIONS

The foregoing scale-up approach for liquid parenteral solutions provides a precise transfer of the compounding mixing equipment environment to the production scale. Due to the unsurpassed importance of proper agitation during the preparation of injectables, the lion's share of this chapter was devoted to the scale-up of agitating equipment. Other pieces of equipment used during the manufacture of parenteral drugs, such as sterilization equipment, filtration systems, various pumps, and packaging equipment, are geometrically scalable and are easily selected from the wide variety available.

One must also stress the importance of quality considerations during compounding and full adherence to current Good Manufacturing Practices while producing parenteral products. Personnel responsible for the process design and scale-up of the equipment must ensure proper documentation of the scale-up with tractability of all the preparatory work from the pilot batch(es) to the manufacture of the marketed products. Spreadsheet programs are useful for documenting equipment parameters and for the subsequent calculations required for proper scale-up.

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3

Nonparenteral Liquids and Semisolids

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I. INTRODUCTION

A manufacturer's decision to scale up (or scale down) a process is ultimately rooted in the economics of the production process, i.e., in the cost of matériel, personnel, and equipment associated with the process and its control. While process scale-up often reduces the unit cost of production and is therefore economically advantageous per se, there are additional economic advantages conferred on the manufacturer by scaling up a process. Thus, process scale-up may allow for faster entry of a manufacturer into the marketplace or improved product distribution or response to market demands and correspondingly greater market-share retention.¹ Given the potential advantages of process scale-up in the pharmaceutical industry, one would expect the scale-up task to be the focus of major efforts on the part of pharmaceutical manufacturers. However, the paucity of published studies or data on scale-up—particularly for nonparenteral liquids and semisolids—suggests otherwise. On the other hand, one could argue that the paucity of published studies or data is nothing more than a reflection of the need to maintain a competitive advantage through secrecy.

One could also argue that this deficiency in the literature attests to the complexity of the unit operations involved in pharmaceutical processing. If pharma-

¹ On the other hand, the manufacturer may determine that the advantages of process scale-up are compromised by the increased cost of production on a larger scale and/or the potential loss of interest or investment income. R. G. Griskey [1] addresses the economics of scale-up in some detail in his chapter on engineering economics and process design, but his examples are taken from the chemical industry. For a more extensive discussion of process economics, see Holland and Wilkinson [2].

chemical technologists view scale-up as little more than a ratio problem, whereby

$$\text{scale-up ratio} = \frac{\text{large-scale production rate}}{\text{small-scale production rate}} \quad (1)$$

then the successful resolution of a scale-up problem will remain an empirical, trial-and-error task, rather than a scientific one. In 1998, in a monograph on the scale-up of disperse systems, Block [3] noted that due to the complexity of the manufacturing process that involves more than one type of unit operation² (e.g., mixing, transferring), process scale-up from the bench or pilot plant level to commercial production is not a simple extrapolation:

The successful linkage of one unit operation to another defines the functionality of the overall manufacturing process. Each unit operation per se may be scalable, in accordance with a specific ratio, but the composite manufacturing process may not be, as the effective scale-up ratios may be different from one unit operation to another. Unexpected problems in scale-up are often a reflection of the dichotomy between *unit operation* scale-up and *process* scale-up. Furthermore, commercial production introduces problems that are not a major issue on a small scale: e.g., storage and materials handling may become problematic only when large quantities are involved; heat generated in the course of pilot plant or production scale processing may overwhelm the system's capacity for dissipation to an extent not anticipated based on prior laboratory-scale experience [3].

Furthermore, unit operations may function in a rate-limiting manner as the scale of operation increases. When Astarita [4] decried the fact, in the mid-1980s, that “there is no scale-up algorithm which permits us to rigorously predict the behavior of a large-scale process based upon the behavior of a small-scale process,” it was presumably as a consequence of all of these problematic aspects of scale-up.

A clue to the resolution of the scale-up problem for liquids and semisolids resides in the recognition that their processing invariably involves the unit operation of mixing. Closer examination of this core unit operation reveals that flow conditions and viscosities during processing can vary by several orders of magnitude, depending upon the scale of scrutiny employed, i.e., whether on a *microscopic* (e.g., molecular) or a *macroscopic* (e.g., bulk) scale. Therefore, the key to effective processing scale-up is the appreciation and understanding of microscale and macroscale transport phenomena, i.e., diffusion and bulk flow, respectively. Transport by diffusion involves the flow of a property (e.g., mass, heat, momentum, electromagnetic energy) from a region of high concentration to a region of

² The term *unit operations*, coined by Arthur D. Little in 1915, is generally used to refer to distinct *physical* changes or unit actions (e.g., pulverizing, mixing, drying), while unit operations involving *chemical* changes are sometimes referred to as *unit processes*. The physical changes comprising unit operations involve primarily contact, transfer of a physical property, and separation between phases or streams.

low concentration as a result of the microscopic motion of electrons, atoms, molecules, etc. Bulk flow, whether convection or advection, however, involves the flow of a property as a result of macroscopic or bulk motion induced artificially (e.g., by mechanical agitation) or naturally (e.g., by density variations) [5].

II. TRANSPORT PHENOMENA IN LIQUIDS AND SEMISOLIDS AND THEIR RELATIONSHIP TO UNIT OPERATIONS AND SCALE-UP

Over the last four decades or so, transport phenomena research has benefitted from the substantial efforts made to replace empiricism by fundamental knowledge based on computer simulations and theoretical modeling of transport phenomena. These efforts were spurred on by the publication in 1960 by Bird, Stewart, and Lightfoot [6] of their quintessential monograph on the interrelationships among three fundamental types of transport phenomena: mass transport, energy transport, and momentum transport. All transport phenomena follow the same pattern in accordance with the generalized diffusion equation, or GDE. The unidimensional *flux*, or overall transport rate per unit area in one direction, is expressed as a system property multiplied by a gradient [5]:

$$\left. \frac{\partial \Gamma}{\partial t} \right|_x = \delta \left(\frac{\partial^2 \Gamma}{\partial x^2} \right) = \delta \left(\frac{\partial \Gamma}{\partial x} \right) = \delta \left(\frac{\partial E}{\partial x} \right) \quad (2)$$

The letter Γ represents the concentration of a property Q (e.g., mass, heat, electrical energy) per unit volume, i.e., $\Gamma = Q/V$, t is time, x is the distance measured in the direction of transport, δ is the generalized diffusion coefficient, and E is the gradient or driving force for transport.

Mass and heat transfer can be described in terms of their respective concentrations Q/V . While the concentration of mass, m , can be specified directly, the concentration of heat is given by

$$\frac{mC_p T}{V} = \rho C_p T \quad (3)$$

where C_p is the specific heat capacity and T is temperature. Thus, the specification of $\rho C_p T$ in any form of the generalized diffusion equation will result in the elimination of ρC_p , assuming it to be a constant, thereby allowing the use of temperature as a measure of heat concentration [5]. In an analogous manner, momentum transfer can be specified in terms of the concentration of momentum u when its substantial derivative is used instead of its partial derivative with respect to time:

$$\frac{Du}{Dt} = \nu \nabla^2 u \quad (4)$$

where ν is the kinematic viscosity. If pressure and gravitational effects are introduced, one arrives at the Navier–Stokes relationships that govern Newtonian fluid dynamics.

When the flux of Γ is evaluated three-dimensionally, it can be represented by [5]:

$$\frac{d\Gamma}{dt} = \frac{\partial\Gamma}{\partial t} + \frac{\partial\Gamma}{\partial x} \frac{dx}{\partial t} + \frac{\partial\Gamma}{\partial y} \frac{dy}{\partial t} + \frac{\partial\Gamma}{\partial z} \frac{dz}{\partial t} \quad (5)$$

At the simplest level, as Griskey [1] notes, Fick’s law of diffusion for mass transfer and Fourier’s law of heat conduction characterize mass and heat transfer, respectively, as vectors; i.e., they have magnitude and direction in the three coordinates x , y , and z . Momentum or flow, however, is a tensor, which is defined by nine components rather than three. Hence, its more complex characterization at the simplest level, in accordance with Newton’s law,

$$\tau_{yx} = -\eta \left(\frac{dv_x}{dy} \right) \quad (6)$$

where τ_{yx} is the shear stress in the x -direction, dv_x/dy is the rate of shear, and η is the coefficient of Newtonian viscosity. The solution of Eq. (2), the generalized diffusion equation,

$$\Gamma = f(t,x,y,z) \quad (7)$$

will take the form of a parabolic partial differential equation [5]. However, the more complex the phenomenon—e.g., with convective transport a part of the model—the more difficult it is to achieve an analytic solution to the GDE. Numerical solutions, however, where the differential equation is transformed to an algebraic one, may be somewhat more readily achieved.

A. Transport Phenomena and Their Relationship to Mixing as a Unit Operation³

As noted earlier, virtually all liquid and semisolid products involve the unit of operation of mixing.⁴ In fact, in many instances, it is the primary unit operation.

³ Reprinted in part, with revisions and updates, by courtesy of Marcel Dekker, Inc., from L. H. Block, “Scale-up of disperse systems: theoretical and practical aspects,” in *Pharmaceutical Dosage Forms: Disperse Systems* (H. A. Lieberman, M. M. Rieger, and G. S. Banker, eds.), 2nd ed., vol. 3, Marcel Dekker, New York, 1998, pp. 366–378.

⁴ *Mixing*, or *blending*, refers to the random distribution of two or more initially separate phases into and through one another, while *agitation* refers only to the induced motion of a material in some sort of container. Agitation does not necessarily result in an intermingling of two or more separate components of a system to form a more or less uniform product. Some authors reserve the term *blending* for the intermingling of miscible phases, while *mixing* is employed for materials that may or may not be miscible.

Even its indirect effects, e.g., on heat transfer, may be the basis for its inclusion in a process. Yet mechanistic and quantitative descriptions of the mixing process remain incomplete [7–9]. Nonetheless, enough fundamental and empirical data are available to allow some reasonable predictions to be made.

The diversity of dynamic mixing devices is unsettling: Their dynamic, or moving, component's blades may be impellers in the form of propellers, turbines, paddles, helical ribbons, Z-blades, or screws. In addition, one can vary the number of impellers, the number of blades per impeller, the pitch of the impeller blades, and the location of the impeller and thereby affect mixer performance to an appreciable extent. Furthermore, while dispersators or rotor/stator configurations may be used rather than impellers to effect mixing, mixing may also be accomplished by jet mixing or static mixing devices. The bewildering array of mixing equipment choices alone would appear to make the likelihood of effective scale-up an impossibility. However, as diverse as mixing equipment may be, evaluations of the rate and extent of mixing and of flow regimes⁵ make it possible to find a common basis for comparison.

In low-viscosity systems, miscible liquid blending is achieved through the transport of unmixed material, via flow currents (i.e., bulk or convective flow), to a mixing zone (i.e., a region of high shear or intensive mixing). In other words, mass transport during mixing depends on *streamline* or *laminar* flow, involving well-defined paths, and *turbulent* flow, involving innumerable, variously sized, eddies or swirling motions. Most of the highly turbulent mixing takes place in the region of the impeller, fluid motion elsewhere serving primarily to bring fresh fluid into this region. Thus, the characterization of mixing processes is often based on the flow regimes encountered in mixing equipment. Reynolds' classic research on flow in pipes demonstrated that flow changes from laminar to irregular, or turbulent, once a critical value of a dimensionless ratio of variables has been exceeded [10,11]. This ratio, universally referred to as the Reynolds number, N_{Re} , is defined by Eqs. (8a) and (8b),

$$N_{Re} = \frac{Lv\rho}{\eta} \quad (8a)$$

$$N_{Re} = \frac{D^2N\rho}{\eta} \quad (8b)$$

where ρ is density, v is velocity, L is a characteristic length, and η is the Newtonian viscosity; Eq. (8b) is referred to as the *impeller* Reynolds number, since D is the impeller diameter and N is the rotational speed of the impeller. N_{Re} represents the ratio of the inertia forces to the viscous forces in a flow. High values of N_{Re}

⁵ The term *flow regime* is used to characterize the hydraulic conditions (i.e., volume, velocity, and direction of flow) within a vessel.

correspond to flow dominated by motion, while low values of N_{Re} correspond to flow dominated by viscosity. Thus, the transition from laminar to turbulent flow is governed by the density and viscosity of the fluid, its average velocity, and the dimensions of the region in which flow occurs (e.g., the diameter of the pipe or conduit, the diameter of a settling particle). For a straight circular pipe, laminar flow occurs when $N_{Re} < 2,100$; turbulent flow is evident when $N_{Re} > 4,000$. For $2,100 \leq N_{Re} \leq 4,000$, flow is in transition from a laminar to a turbulent regime. Other factors, such as surface roughness, shape, and cross-sectional area of the affected region, have a substantial effect on the critical value of N_{Re} . Thus, for particle sedimentation, the critical value of N_{Re} is 1; for some mechanical mixing processes, N_{Re} is 10–20 [12]. The erratic, relatively unpredictable nature of turbulent eddy flow is further influenced, in part, by the size distribution of the eddies, which are dependent on the size of the apparatus and the amount of energy introduced into the system [10]. These factors are indirectly addressed by N_{Re} . Further insight into the nature of N_{Re} can be gained by viewing it as inversely proportional to eddy advection time, i.e., the time required for eddies or vortices to form.

In turbulent flow, eddies move rapidly, with an appreciable component of their velocity in the direction perpendicular to a reference point, e.g., a surface past which the fluid is flowing [13]. Because of the rapid eddy motion, mass transfer in the turbulent region is much more rapid than that resulting from molecular diffusion in the laminar region, with the result that the concentration gradients existing in the turbulent region will be smaller than those in the laminar region [13]. Thus mixing is much more efficient under turbulent flow conditions. Nonetheless, the technologist should bear in mind potentially compromising aspects of turbulent flow, e.g., increased vortex formation [14] and a concomitant incorporation of air, increased shear and a corresponding shift in the particle size distribution of the disperse phase.

Although continuous-flow mixing operations are employed to a limited extent in the pharmaceutical industry, the processing of liquids and semisolids most often involves batch processing in some kind of tank or vessel. Thus, in the general treatment of mixing that follows, the focus will be on batch operations⁶ in which mixing is accomplished primarily by the use of dynamic mechanical mixers with impellers, although jet mixing [17,18] and static mixing devices [19]—long used in the chemical process industries—are gaining advocates in the pharmaceutical and cosmetic industries.

Mixers share a common functionality with pumps. The power imparted by the mixer, via the impeller, to the system is akin to a pumping effect and is characterized in terms of the shear and flow produced:

⁶ The reader interested in continuous-flow mixing operations is directed to references that deal specifically with that aspect of mixing, such as the monographs by Oldshue [15] and Tattersson [16].

$$\left. \begin{array}{l} P \propto Q\rho H \\ \text{or} \\ H \propto \frac{P}{Q\rho} \end{array} \right\} \quad (9)$$

where P is the power imparted by the impeller, Q is the flow rate (or pumping capacity) of material through the mixing device, ρ is the density of the material, and H is the velocity head, or shear. Thus, for a given P , there is an inverse relationship between shear and volume throughput.

The power input in mechanical agitation is calculated using the *power number*, N_P ,

$$N_P = \frac{Pg_c}{\rho N^3 D^5} \quad (10)$$

where g_c is the force conversion factor

$$g_c = \frac{kg \cdot m \cdot \text{sec}^{-2}}{\text{newton}} = \frac{g \cdot \text{cm} \cdot \text{sec}^{-2}}{\text{dyne}}$$

N is the impeller rotational speed (sec^{-1}), and D is the diameter of the impeller. For a given impeller/mixing tank configuration, one can define a specific relationship between the Reynolds number [Eq. (8)]⁷ and the power number [Eq. (10)] in which three zones (corresponding to the laminar, transitional, and turbulent regimes) are generally discernible. Tatterson [20] notes that for mechanical agitation in laminar flow, most *laminar* power correlations reduce to $N_P N_{Re} = B$, where B is a complex function of the geometry of the system,⁸ and that this is equivalent to $P \propto \eta \cdot N^2 D^3$; “if power correlations do not reduce to this form for laminar mixing, then they are wrong and should not be used.” Turbulent correlations are much simpler: for systems employing baffles,⁹ $N_P = B$; this is equivalent to $P \propto \rho \cdot N^3 D^5$. Based on this function, slight changes in D can result in substantial changes in power.

Valuable insights into the mixing operation can be gained from a consideration of system behavior as a function of the Reynolds number, N_{Re} [21]. This is shown schematically in Figure 1 in which various dimensionless parameters (dimensionless velocity, v/ND ; pumping number, Q/ND^3 ; power number, $N_P = Pg_c/\rho N^3 D^5$; and dimensionless mixing time, $t_m N$) are represented as a log-log function of N_{Re} . Although density, viscosity, mixing vessel diameter, and impeller rotational speed are often viewed by formulators as independent variables, their

⁷ Here, the Reynolds number for mixing is defined in SI-derived units as $N_{Re} = (1.667 \times 10^{-5} ND^2 \rho)/\eta$, where D , impeller diameter, is in millimeters, η is in Pa·sec, N is impeller speed, in r.p.m., and ρ is density.

⁸ An average value of B is 300, but B can vary between 20 and 4000 [20].

⁹ Baffles are obstructions placed in mixing tanks to redirect flow and minimize vortex formation.

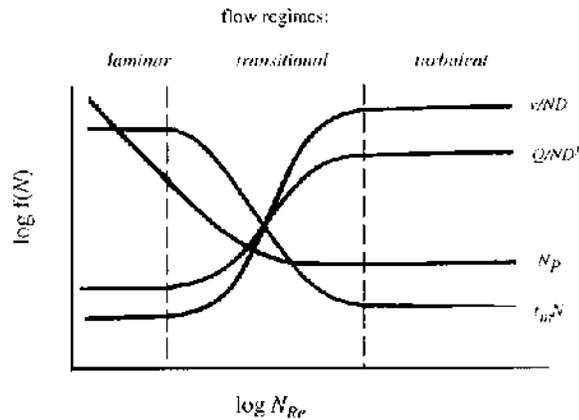


Figure 1 Various dimensionless parameters (dimensionless velocity, $v^* = v/ND$; pumping number, $N_Q = Q/ND^3$; power number, $N_p = P g_c \lambda \rho N^3 D^5$; and dimensionless mixing time, $t^* = t_m N$) as a function of the Reynolds number for the analysis of turbine-agitator systems. (Adapted from Ref. 21.)

interdependency, when incorporated in the dimensionless Reynolds number, is quite evident. Thus, the schematic relationships embodied in Figure 1 are not surprising.¹⁰

Mixing time is the time required to produce a mixture of predetermined quality; the rate of mixing is the rate at which mixing proceeds toward the final state. For a given formulation and equipment configuration, mixing time, t_m , will depend upon material properties and operation variables. For geometrically similar systems, if the geometrical dimensions of the system are transformed to ratios, mixing time can be expressed in terms of a dimensionless number, i.e., the dimensionless mixing time, θ_m or $t_m N$:

$$t_m N = \theta_m = f(N_{Re}, N_{Fr}) \Rightarrow f(N_{Re}) \quad (11)$$

The Froude number, $N_{Fr} = v/\sqrt{Lg}$, is similar to N_{Re} ; it is a measure of the inertial stress to the gravitational force per unit area acting on a fluid. Its inclusion in Eq. (11) is justified when density differences are encountered; in the absence of substantive differences in density, e.g., for emulsions more so than for suspensions, the Froude term can be neglected. Dimensionless mixing time is independent of the Reynolds number for both laminar and turbulent flow regimes, as in-

¹⁰ The interrelationships are embodied in variations of the Navier–Stokes equations, which describe mass and momentum balances in fluid systems [22].

licated by the plateaus in Figure 1. Nonetheless, because there are conflicting data in the literature regarding the sensitivity of θ_m to the rheological properties of the formulation and to equipment geometry, Eq. (11) must be regarded as an oversimplification of the mixing operation. Considerable care must be exercised in applying the general relationship to specific situations.

Empirical correlations for *turbulent* mechanical mixing have been reported in terms of the following dimensionless mixing time relationship [23]:

$$\theta_m = t_m N = K \left(\frac{T}{D} \right)^a \quad (12)$$

where K and a are constants, T is tank diameter, N is impeller rotational speed, and D is impeller diameter. Under *laminar* flow conditions, Eq. (12) reduces to

$$\theta_m = H_0 \quad (13)$$

where H_0 is referred to as the *mixing number* or *homogenization number*. In the *transitional* flow regime,

$$H_0 = C(N_{Re})^a \quad (14)$$

where C and a are constants, with a varying between 0 and -1 .

Flow patterns in agitated vessels may be characterized as radial, axial, or tangential relative to the impeller but are more correctly defined by the direction and magnitude of the velocity vectors throughout the system, particularly in a transitional flow regime: While the dimensionless velocity, v^* , or v/ND , is essentially constant in the laminar and turbulent flow zones, it is highly dependent on N_{Re} in the transitional flow zone (Fig. 1). Initiation of tangential or circular flow patterns, with minimal radial or axial movement, is associated with vortex formation, minimal mixing, and, in some multiphase systems, particulate separation and classification. Vortices can be minimized or eliminated altogether by redirecting flow in the system through the use of baffles¹¹ or by positioning the impeller so that its entry into the mixing tank is off-center. For a given formulation, large tanks are more apt to exhibit vortex formation than small tanks. Thus, full-scale production tanks are more likely to require baffles, even when smaller (laboratory- or pilot-plant scale) tanks are unbaffled.

Mixing processes involved in the manufacture of disperse systems, whether suspensions or emulsions, are far more problematic than those employed in the blending of low-viscosity miscible liquids, due to the multiphase character of the

¹¹ The usefulness of baffles in mixing operations is offset by increased cleanup problems (due to particulate entrapment by the baffles or congealing of product adjacent to the baffles). Furthermore, "overbaffling"—excessive use of baffles—reduces mass flow and localizes mixing, which may be counterproductive.

systems and deviations from Newtonian flow behavior. It is not uncommon for both laminar and turbulent flow to occur simultaneously in different regions of the system. In some regions, the flow regime may be in transition, i.e., neither laminar nor turbulent but somewhere in between. The implications of these flow regime variations for scale-up are considerable. Nonetheless, it should be noted that the mixing process is only completed when Brownian motion occurs to a sufficient extent that uniformity is achieved on a molecular scale.

B. Viscous and Non-Newtonian Materials

Mixing in high-viscosity materials ($\eta > \sim 10^4$ cPs) is relatively slow and inefficient. Conventional mixing tanks and conventional impellers (e.g., turbine or propeller impellers) are generally inadequate. In general, due to the high viscosity, N_{Re} may well be below 100. Thus, laminar flow is apt to occur rather than turbulent flow. As a result, the inertial forces imparted to a system during the mixing process tend to dissipate quickly. Eddy formation and diffusion are virtually absent. Thus, efficient mixing necessitates substantial convective flow, which is usually achieved by high velocity gradients in the mixing zone. Fluid elements in the mixing zone, subjected to both shear and elongation, undergo deformation and stretching, ultimately resulting in the size reduction of the fluid elements and an increase in their overall interfacial area. The repetitive cutting and folding of fluid elements also result in decreasing inhomogeneity and increased mixing. The role of molecular diffusion in reducing inhomogeneities in high-viscosity systems is relatively unimportant until these fluid elements have become small and their interfacial areas have become relatively large [24]. In highly viscous systems, rotary motion is more than compensated for by viscous shear, so baffles are generally less necessary [25].

Mixing equipment for highly viscous materials often involves specialized impellers and configurations that minimize high shear zones and heat dissipation. Accordingly, propeller-type impellers are not generally effective in viscous systems. Instead, turbines, paddles, anchors, helical ribbons, screws, and kneading mixers are resorted to, successively, as system viscosity increases. Multiple impellers or specialized impellers (e.g., sigma-blades, Z-blades) are often necessary, along with the maintenance of narrow clearances, or gaps, between impeller blades and between impeller blades and tank (mixing chamber) walls in order to attain optimal mixing efficiency [24,25]. However, narrow clearances pose their own problems. Studies of the power input to anchor impellers used to agitate Newtonian and shear-thinning fluids showed that the clearance between the impeller blades and the vessel wall was the most important geometrical factor: N_p at constant N_{Re} was proportional to the fourth power of the clearance divided by tank diameter [26]. Furthermore, although mixing is promoted by these specialized impellers in the vicinity of the walls of the mixing vessel, stagnation is often encountered in regions adjacent to the impeller shaft. Finally, complications (wall effects) may arise from the formation of a thin, particulate-free, fluid layer adja-

cent to the wall of the tank or vessel that has a lower viscosity than the bulk material and allows slippage (i.e., nonzero velocity) to occur, unless the mixing tank is further modified to provide for wall-scraping.

Rheologically, the flow of many non-Newtonian materials can be characterized by a time-independent power law function (sometimes referred to as the Ostwald–deWaele equation):

$$\tau = K\dot{\gamma}^a \quad \text{or} \quad \log \tau = K' + a(\log \dot{\gamma}) \quad (15)$$

where τ is the shear stress, $\log \tau = K' + a(\log \dot{\gamma})$ is the rate of shear, K' is the logarithmically transformed proportionality constant K with dimensions dependent upon a , the so-called flow behavior index. For pseudoplastic or shear-thinning materials, $a < 1$; for dilatant or shear-thickening materials, $a > 1$; for Newtonian fluids, $a = 1$. For a power law fluid, the average apparent viscosity, η_{avg} , can be related to the average shear rate by the following equation:

$$\eta_{\text{avg}} = K' \left(\frac{dv}{dy} \right)_{\text{avg}}^{n'-1} \quad (16)$$

Based on this relationship, a Reynolds number can be derived and estimated for non-Newtonian fluids from

$$\left[N_{\text{Re}} = \frac{Lv\rho}{\eta} \right] \Rightarrow \left[N_{\text{Re,nonN}} = \frac{ND_i^2\rho}{K'(dv/dy)_{\text{avg}}^{n'-1}} \right] \quad (17)$$

Dispersions that behave, rheologically, as Bingham plastics require a minimum shear stress (the yield value) in order for flow to occur. Shear stress variations in a system can result in local differences wherein the yield stress point is not exceeded. As a result, flow may be impeded or absent in some regions compared to others, resulting in channeling or cavity formation and a loss of mixing efficiency. Only if the yield value is exceeded *throughout* the system will flow and mixing be relatively unimpeded. Helical ribbon and screw impellers would be preferable for the mixing of Bingham fluids, in contrast to conventional propeller or turbine impellers, given their more even distribution of power input [27]. From a practical vantage point, monitoring power input to mixing units could facilitate process control and help to identify problematic behavior. Etchells et al. [28] analyzed the performance of industrial mixer configurations for Bingham plastics. Their studies indicate that the logical scale-up path from laboratory to pilot plant to production, for geometrically similar equipment, involves the maintenance of constant impeller tip speed, which is proportional to $N \cdot D$, the product of rotational speed of the impeller (N) and the diameter of the impeller (D).

Oldshue [25] provides a detailed procedure for selecting mixing times and optimizing mixer and impeller configurations for viscous and shear-thinning materials that can be adapted for other rheologically challenging systems.

Gate and anchor impellers, long used advantageously for the mixing of viscous and non-Newtonian fluids, induce complex flow patterns in mixing tanks: both

primary and secondary flows may be evident. *Primary* flow or circulation results from the direct rotational movement of the impeller blade in the fluid; *secondary* flow is normal to the horizontal planes about the impeller axis (i.e., parallel to the impeller axis) and is responsible for the interchange of material between different levels of the tank [29]. In this context, rotating viscoelastic systems, with their normal forces, establish stable secondary flow patterns more readily than Newtonian systems. In fact, the presence of normal stresses in viscoelastic fluids subjected to high rates of shear ($\sim 10^4 \text{ sec}^{-1}$) may be substantially greater than shearing stresses, as demonstrated by Metzner et al. [30]. These observations, among others, moved Fredrickson [31] to note that “neglect of normal stress effects is likely to lead to large errors in theoretical calculations for flow in complex geometries.” However, the effect of these secondary flows on the efficiency of mixing, particularly in viscoelastic systems, is equivocal. On the one hand, vertical velocity near the impeller blade in a Newtonian system might be 2–5% of the horizontal velocity, whereas in a non-Newtonian system, vertical velocity can be 20–40% of the horizontal. Thus, the overall circulation can improve considerably. On the other hand, the relatively small, stable toroidal vortices that tend to form in viscoelastic systems may result in substantially incomplete mixing. Smith [29] advocates the asymmetric placement of small deflector blades on a standard anchor arm as a means of achieving a dramatic improvement in mixing efficiency of viscoelastic fluids without resorting to expensive alternatives, such as pitched blade anchors or helical ribbons.

Side-wall clearance, i.e., the gap between the vessel wall and the rotating impeller, was shown by Cheng et al. [32] to be a significant factor in the mixing performance of helical ribbon mixers not only for viscous and viscoelastic fluids but also for Newtonian systems. Bottom clearance, i.e., the space between the base of the impeller and the bottom of the tank, however, had a negligible, relatively insignificant effect on power consumption and on the effective shear rate in inelastic fluids. Thus, mixing efficiency in nonviscoelastic fluids would not be affected by variations in bottom clearance. For viscoelastic fluids, on the other hand, bottom clearance effects were negligible only at lower rotational speeds (≤ 60 rpm); substantial power consumption increases were evident at higher rotational speeds.

The scale-up implications of *mixing*-related issues, such as impeller design and placement, mixing tank characteristics, new equipment design, and the mixing of particulate solids, are beyond the scope of this chapter. However, extensive monographs are available in the chemical engineering literature (many of which have been cited herein¹²) and will prove to be invaluable to the formulator and technologist.

¹² The reader is directed to previously referenced monographs by Oldshue and by Tatterson as well as to standard textbooks in chemical engineering, including the multivolume series authored by McCabe et al., and the encyclopedic *Perry's Chemical Engineers' Handbook*.