How to Scale Up Scientifically

Michael Levin

COMSTOCK

The author reviews dimensional analysis as a straight-forward approach to scale up.

Michael Levin is president and CEO of Metropolitan Computing Corporation, tel. 973.887.7800, fax 973.887.8447, michael.levin@mcc-online.com.

A rational approach to scale-up has been used in the physical sciences for quite some time. This approach, called *dimensional analysis,* is a proven method of developing functional relationships that describe any given process in a dimensionless form to facilitate modeling and scale-up or scale-down. This short article reviews and demonstrates the dimensional analysis method as applied to pharmaceutical processes and includes references to works that have become classics in the field of granulation scale-up.

What is dimensional analysis?

Dimensional analysis is a method for producing dimensionless numbers and deriving functional relationships among them that completely characterize the process. The analysis can be applied even when the equations governing the process are not known.

Imagine a dimensionless space in which you have no mass, no length, and no time. It is obvious that in such a space, there are no scale-up problems because there is no scale.

Dimensional analytical procedure was first systematically applied to fluid flow 90 years ago by Lord Rayleigh (1), on the basis of the principle of similitude referred to by Newton in one of his early works.

Dimensionless numbers

Physical quantities such as force or speed have the basic dimensional qualities of length (L), mass (M), time (T), and so forth. For example, speed has dimensions of L/T, and force has a dimensional composition of ML/T^2.

Unlike the regular physical quantities, dimensionless numbers have no dimensions. Such numbers are frequently used to describe the ratios of various physical quantities. Most relevant to the forthcoming discussion are Newton (*Ne,* power), Froude (*Fr*), and Reynolds (*Re*) numbers, which, respectively, are expressed as

$$Ne = P/(\rho n^3 d^5)$$
$$Fr = n^2 d/g$$
$$Re = d^2 n\rho/\eta$$

in which P is the power consumption (ML^2/T^3), ρ is the specific density of particles (M/L^3), n is the impeller speed (T^{-1}), d is the impeller diameter (L), g is the gravitational constant (L/T^2), and η is the dynamic viscosity (M/LT).

The Newton (power) number, which relates the drag force acting on a unit area of the impeller and the inertial stress, is a measure of the power required to overcome friction in fluid flow in a stirred reactor. In mixer-granulation applications, this number can be calculated from the power consumption of the impeller.

The Froude number, first introduced to quantify the resistance of ships (2), has been described for powder blending (3) and was suggested as a criterion for dynamic similarity as well as a scale-up parameter in wet granulation (4). The mechanics of the phenomenon was described as an interplay of the centrifugal force (pushing the particles against the mixer wall) and the centripetal force produced by the wall, thereby creating a "compaction zone."

The Reynolds number, which relates the inertial force to the viscous force, is frequently used to describe mixing processes (5), especially in chemical engineering, for example, for problems of water–air mixing in vessels equipped with turbine stirrers where scale-up can range from 2.5 to 906 L, which is a scale-up factor of 1:71 (see, for example, Reference 6).

Theory of models

Scale-up, then, is simple: Express the process using a complete set of dimensionless numbers and try to match them at various scales. This dimensionless space in which the measurements are presented or measured will make the process scale invariant.

According to the modeling theory, two processes are considered similar if there is a geometrical, kinematic, and dynamic similarity (7). Two systems are called *geometrically similar* if they have the same ratio of characteristic linear dimensions. For example, two cylindrical mixing vessels are geometrically similar if they have the same ration of height to diameter. Two geometrically similar systems are called *kinematically similar* if they have the same ratio of velocities between corresponding points. Two kinematically similar systems are *dynamically similar* when they have the same ratio of forces between corresponding points. For any two dynamically similar systems, all the dimensionless numbers necessary to describe the process have the same numerical value (8).

Lack of geometrical similarity is often the main obstacle when applying dimensional analysis to solve scale-up problems. It has been shown, for example, that Collette Gral 10, 75, and 300 are not geometrically similar (4). In such cases, a proper correction to the resulting equations is required.

Buckingham's Π theorem

The fundamental theorem of the dimensional analysis, the Π theorem, states: Every physical relationship between n dimensional variables and constants can be reduced to a relationship between $m = n - r$ mutually independent dimensionless groups, in which r is the number of dimensions; that is, fundamental dimensional units (rank of the dimensional matrix). The theorem is universally ascribed to Buckingham, who introduced the term and popularized it in the United States (9), although it was proven earlier by others.

It starts with a relevance list

Dimensional analysis starts with a *relevance list,* which is a list of all variables thought to be crucial for the process being analyzed. To set up a relevance list for a process, one needs to compile a complete set of all dimensional relevant and mutually independent variables and constants that affect the process. The word *complete* is crucial. All entries in the list can be further subdivided as geometric, physical, or operational. Each relevance list should include only one target (*i.e.,* dependent "response") variable.

Pitfalls of dimensional analysis often relate to selecting the reference list, target variable, or measurement errors (*e.g.,* friction losses of the same order of magnitude as the power consumption of a motor). The larger the scale-up factor, the more precise the measurements of the small scale must be (8).

Dimensional matrix

Dimensional analysis can be simplified by arranging all relevant variables from the relevance list into a matrix, with a subsequent transformation yielding the required dimensionless numbers. The dimensional matrix consists of a square *core matrix* and a *residual matrix*. The rows of the matrix consist of the basic dimensions, whereas the columns represent the physical quantities from the relevance list. The most important physical properties and process-related parameters, as well as the target variable (*i.e.,* the one we would like to predict on the basis of other variables) are placed in one of the columns of the residual matrix.

The core matrix is linearly transformed into a matrix of unity in which the main diagonal consists only of ones and the remaining elements are all zero. The dimensionless numbers are then created as a ratio of columns in the residual matrix and the core matrix, with the exponents indicated in the residual matrix. The following examples illustrate this rather simple process.

Case study I

Hans Leuenberger *et al.* proposed a theory of granulation end point determination and scale up using dimensional analysis, starting with the relevance list in Table I (7, 10, 11). The list reflects certain assumptions that are used to simplify the model; namely, that there are short range interactions only and no viscosity factor (and therefore, no Reynolds number).

Table I: Variables used in dimensional analysis.

Quantity	Symbol	Units	Dimensions
Power consumption	P	Watt	ML^2/T^3
Specific density	ρ	kg/m^3	M/L^3
Blade diameter	d	m	L
Blade speed	n	rev/s	T^{-1}
Binder amount	m	kg	M
Bowl volume	V_b	m^3	L^3
Gravitational constant	g	m/s^2	L/T^2
Bowl height	h	m	L

Why is the gravitational constant included? Well, imagine the same process to be done on the moon. Would you expect any difference?

One target variable (power consumption) and seven process variables or constants thus represent the number $n = 8$ of the Π theorem, and there are three basic dimensions (r); namely, M, L, and T. According to the theorem, the process can be reduced to a relationship between $m = n - r = 8 - 3 = 5$ mutually independent dimensionless groups.

To find these groups, or numbers, form the dimensional matrix shown in Figure 1. One transformation changes the -3 in the L-row, ρ-column to 0. Subsequent multiplication of the T-row by -1 transfers the -1 of the n-column to $+1$ (see Figure 2). Five dimensionless groups are formed from the five columns of the residual matrix by dividing each element of the residual matrix by the column headers of the unity matrix, with the exponents shown in the residual matrix.

	Core matrix			Residual matrix				
	ρ	d	n	P	m	V_b	g	h
Mass *M*	1	0	0	1	1	0	0	0
Length *L*	–3	1	0	2	0	3	1	1
Time *T*	0	0	–1	–3	0	0	–2	0

Figure 1: Initial dimensional matrix for case study I.

	Unity matrix			Residual matrix				
	ρ	d	n	P	m	V_b	g	h
M	1	0	0	1	1	0	0	0
3M + *L*	0	1	0	5	3	3	1	1
−*T*	0	0	1	3	0	0	2	0

Figure 2: Initial dimensional matrix after one linear transformation.

The residual matrix contains five columns, therefore five dimensionless Π groups (numbers) are formed (see Table II).

The end result of the dimensional analysis is an expression of the form

$$\Pi_0 = f(\Pi_1, \Pi_2, \Pi_3, \Pi_4)$$

Assuming that the groups Π_2, Π_3, and Π_4 are "essentially" constant, the Π-space can be reduced to a simple re-

Table II: Dimensionless Π groups for case study I.

Π group	Expression	Definition
Π_0	$P/(\rho^1 d^5 n^3) = Ne$	Newton (power) number
Π_1	$q/(\rho^1 d^3 n^0) = qt/(V_p \rho)$	Specific amount of liquid V_p is volume of particles, q is the binder addition rate, and t is the binder addition time
Π_2	$t/(\rho^0 d^3 n^0) = (V_p/V_b)^{-1}$	Fractional particle volume
Π_3	$g/(\rho^0 d^1 n^2) = Fr^{-1}$	Froude number
Π_4	$h/(\rho^0 d^1 n^0) = h/d$	Ratio of lengths

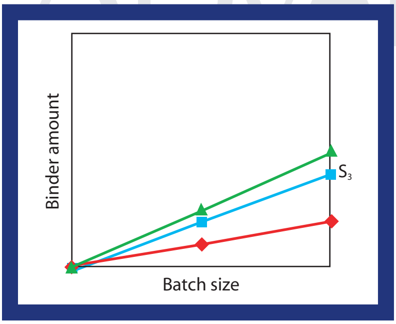

Figure 3: Binder amount versus batch size. Adapted from Reference 11.

lationship $\Pi_0 = f(\Pi_1)$; that is, the value of Newton number *Ne* at any point in the process is a function of the specific amount of granulating liquid.

Up to this point, all considerations were rather theoretical. From the theory of modeling, we know that the above dimensional groups are functionally related. The form of this functional relationship *f*, however, can be established only through experiments.

Leuenberger and his group empirically established that the amount of binder required to reach a desired endpoint (as expressed by the absolute value of *Ne*) is essentially proportional to the batch size (see Figure 3), thus specifying the functional dependence *f* and establishing a rational basis for granulation scale-up.

According to Leuenberger, the correct amount of granulating liquid per batch is a scale-up invariable, provided that the binder is mixed in as a dry powder and then water is added at a constant rate. This functionality was shown for nonviscous binders.

The ratio of quantity of granulating liquid to batch size at the inflection point S_3 of power versus time curve is constant, irrespective of batch size and type of machine. Moreover, for a constant rate of low viscosity binder addition proportional to the batch size, the rate of change (slope or time derivative) of the torque or power consumption curve is linearly related to the batch size for a wide spectrum of high-shear and planetary mixers. In other words, the process end point, as determined in a certain region of the curve, is a practically proven scale-up parameter for moving the product from laboratory to production mixers of various sizes and manufacturers.

Different vessel and blade geometries will contribute to differences in absolute values of the signals, but the signal profile of a given granulate composition in a high-shear mixer is very similar to one obtained in a planetary mixer.

To calculate *Ne*, the power of the load on the impeller rather than the mixer motor should be used. Before attempting to use dimensional analysis, one must measure or estimate power losses for empty-bowl mixing. This baseline, however, does not stay constant; it changes significantly with load, mixer condition, or motor efficiency, which may present inherent difficulties in using power meters instead of torque. Torque, of course, is directly proportional to the power drawn by the impeller so that the power number can be calculated from the torque and speed measurements.

Case study II

Scale-up in fixed-bowl mixer granulators has been studied using the classical dimensionless numbers of Newton (power), Reynolds, and Froude to predict end-points in geometrically similar, high-shear Fielder PMA 25-, 100-, and 600-L machines (12).

The relevance list included power consumption of the impeller (as a response) and six factor quantities: specific density, impeller diameter, impeller speed, gravitational constant, vessel height (all with units and dimensions shown in Table I), and viscosity of the wet mass (η, units of Pa-s, dimensions *M*/*LT*). Dynamic viscosity has replaced the binder amount and bowl volume of Leuenberger's relevance list, thus making it applicable to viscous binders.

	Core matrix			Residual matrix			
	ρ	d	n	P	η	g	h
Mass *M*	1	0	0	1	1	0	0
Length *L*	–3	1	0	2	–1	1	1
Time *T*	0	0	–1	–3	–1	–2	0

Figure 4: Dimensional matrix for case study II.

	Unity matrix			Residual matrix			
	ρ	d	n	P	η	g	h
M	1	0	0	1	1	0	0
3*M* + *L*	0	1	0	5	2	1	1
–*T*	0	0	1	3	1	2	0

Figure 5: Matrix for case study II after linear transformation.

The dimensional matrix and the matrix after the already familiar linear transformation are shown in Figures 4 and 5, respectively. The residual matrix contains four columns, therefore four dimensionless Π groups (numbers) are formed in accordance with the Π-theorem (see Table IV). Under the assumed condition of dynamic similarity, therefore, $Ne = f(Re, Fr, h/d)$.

When corrections for gross vortexing, geometric dissimilarities, and powder-bed height variation are made, data correlations from all mixers allow predictions of optimum end-point conditions. The linear regression of the Newton number (power) on the adjusted Reynolds number (in log/log domain) yields $Ne = 7.96 \times 10^{2}\,(Re\ Fr\ h/d)^{-0.732}$ (see Figure 6).

The 0.7854 correlation coefficient for the final curve-fitting effort, however, indicates the presence of many unexplained outlier points. To main-

Table IV: Dimensionless Π groups for Case study II.

Π group	Expression	Definition
Π_0	$P/(\rho^1 d^5 n^3) = Ne$	Newton (power) number
Π_1	$\eta/(\rho^1 d^2 n^1) = Re^{-1}$	Reynolds number
Π_2	$g/(\rho^0 d^1 n^2) = Fr^{-1}$	Froude number
Π_3	$h/(\rho^0 d^1 n^0) = h/d$	Ratio of lengths

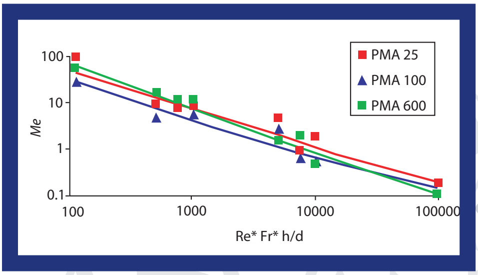

Figure 6: Power number versus dimensionless processing factors. Adapted from Reference (12).

tain the geometric similarity between mixers, it is important to keep the batch size in proportion to the overall shape of the mixer and especially its bowl height. A special consideration is required when using torque values from mixer torque rheometers for the viscosity of wet granulation, because these values are proportional to kinematic viscosity $\nu = \eta/\rho$ rather than dynamic viscosity η required to calculate the Reynolds numbers.

Case study III

Fraure *et al.* applied this same approach to a planetary Hobart AE240 mixer with two interchangeable bowls (13). The relevance list, assuming the absence of chemical reaction and heat transfer, included power consumption, specific density, blade diameter, blade speed, dynamic viscosity, gravitational constant, and wet powder bed height (h, units of m, dimensions of L). As a measure of power consumption, net impeller power consumption ΔP (motor power consumption minus the dry blending baseline level was used. Dimensional analysis and application of the Buckingham theorem indicated that *Ne, Re, Fr,* and h/d (proportional to the fill ratio) adequately described the process. A relationship $Ne = k[ReFr\ (h/d)]^{-r}$ was postulated and the constants k and r were found empirically with a good correlation (>0.92) between the observed and predicted numbers.

Once the process similarity is established or the appropriate corrections are made, scale-up problems can be greatly reduced or even completely eliminated, because the same equation predicts the power number of the granulation process regardless of the batch size.

References

1. Lord Rayleigh, "The Principle of Similitude," *Nature* **95**, 66–68 (18 March 1915).
2. C.W. Merrifield "The Experiments Recently Proposed on the Resistance of Ships," *Trans. Inst. Naval Arch.* (London) **11,** 80–93 (1870).
3. J.Y. Oldshue, "Mixing Processes," in *Scale-Up of Chemical Processes: Conversion from Laboratory-Scale Tests to Successful Commercial-Size Design,* A. Bisio and R.L. Kabel, Eds. (Wiley, New York, NY, 1985).

4. G.J.B. Horsthuis *et al.*, "Studies on Upscaling Parameters of the Gral High-Shear Granulation Process," *Int. J. Pharm.* **92** (143), (1993).
5. O. Reynolds, "An Experimental Investigation of the Circumstances which Determine Whether the Motion of Water Shall Be Direct or Sinusous and of the Law of Resistance in Parallel Channels," *Philos Trans. R. Soc. London* **174,** 935–982 (1883).
6. M. Zlokarnik, "Problems in the Application of Dimensional Analysis and Scale-Up of Mixing Operations," *Chem. Eng. Sci.* **53** (17), 3023–3030 (1998).
7. H. Leuenberger, "Scale-Up of Granulation Processes with Reference to Process Monitoring," *Acta Pharm. Technol.* **29** (4), 274–280 (1983).
8. M. Zlokarnik, *Dimensional Analysis and Scale-Up in Chemical Engineering* (Springer-Verlag, 1991).
9. E. Buckingham, "On Physically Similar Systems; Illustrations of the Use of Dimensional Equations," *Phys. Rev. NY* **4,** 345–376 (1914).
10. H. Leuenberger, H.P. Bier, and H.B. Sucker, "Theory of the Granulating-Liquid Requirement in the Conventional Granulation Process," *Pharm. Technol.* **6,** 61–68 (1979).
11. H.P. Bier, H. Leuenberger, and H. Sucker, "Determination of the Uncritical Quantity of Granulating Liquid by Power Measurements on Planetary Mixers," *Pharm. Ind.* **4,** 375–380 (1979).
12. M. Landin *et al.*, "Scale-Up of a Pharmaceutical Granulation in Fixed Bowl Mixer–Granulators," *Int. J. Pharm.* **133,** 127–131 (1996).
13. A. Faure *et al.*, "A Methodology for the Optimization of Wet Granulation in a Model Planetary Mixer," *Pharm. Dev. Technol.* **3** (3), 413–422 (1998). **PT**