Wet Granulation: End-Point Scale-Up

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Scale-Up Basics

Once you determine an acceptable end-point of granulation in terms of process and product parameters, the task of its scale-up should include:

- Understanding and application of the principles of Dimensional Analysis
- Instrumentation to measure critical process parameters
- Procedures to measure / calculate dimensional numbers describing your process
- Creating a prediction equation that will calculate the required Newton Power Number Np
- Implementation of a computerized monitoring and control of your process that will stop the process when the desired Np is reached

Follow the examples and case studies presented below to scale-up your end-point scientifically.

Dimensional Analysis

A rational approach to scale-up using dimensional analysis has been in use in chemical engineering for quite some time. This approach, based on the use of process similarities between different scales, was being applied to pharmaceutical granulation since the early work of Hans Leuenberger in 1979 (40).

Dimensional analysis is a method for producing dimensionless numbers that completely describe the process. The analysis should be carried out before the measurements are made because dimensionless numbers essentially condense the frame in which the measurements are performed and evaluated. The method can be applied even when the equations governing the process are not known. Dimensional analytical procedure was first proposed by Lord Rayleigh in 1915 (94).

Principle of Similitude

Imagine that you have successfully scaled up from a 10 liter batch to 300 liter batch. What exactly happened? You may say: “I got lucky”. Apart from luck, there had to be similarity in the processing and the end-point conditions of the wet mass of the two batches.

According to the modeling theory, two processes may be considered similar if there is a geometrical, kinematic and dynamic similarity (95).

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 ratio of height to diameter.

Two geometrically similar systems are called kinematically similar if they have the same ratio of velocities between corresponding system points. Two kinematically similar systems are dynamically similar when they have the same ratio of forces between corresponding points. Dynamic similitude for wet granulation would imply that the wet mass flow patterns in the bowl are similar.

The gist of dimensionless analysis is as follows: For any two dynamically similar systems, all the dimensionless numbers necessary to describe the process have the same numerical value (96). Once a process is expressed in terms of dimensionless variables, we are magically transferred in a world where there is no space and no time. Therefore, there is no scale and, consequently, there are no scale-up problems. The process is characterized solely by numerical values of the dimensionless variables (numbers). In other words, dimensionless representation of the process is scale-invariant.

Lack of geometrical similarity often is the main obstacle in applying the Dimensional Analysis to solving the scale-up problems. It was shown, for example, that Collette Gral 10, 75 and 300 are not geometrically similar (29). In such cases, a proper correction to the resulting equations is required.

Dimensionless Numbers

Dimensionless numbers most commonly used to describe wet granulation process are Newton, Froude and Reynolds:

$N_p = \Delta P / (\rho n^3 d^5)$ Newton (power)

$Fr = n^2 d / g$ Froude

$Re = d^2 n \rho / \eta$ Reynolds

(for list of symbols, notation and dimensions, see Appendix).

Newton (power) number, which relates the drag force acting on a unit area of the impeller and the inertial stress, represents a measure of power requirement 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 or estimated from the power consumption of the motor.

Froude Number (96) has been described for powder blending and was suggested as a criterion for dynamic similarity and a scale-up parameter in wet granulation (29).

The mechanics of the phenomenon was described as interplay of the centrifugal force (pushing the particles against the mixer wall) and the centripetal force produced by the wall, creating a “compaction zone”.

Reynolds numbers relate the inertial force to the viscous force (97). They are frequently used to describe mixing processes and viscous flow, especially in chemical engineering (98).

We have seen that there exists sort of a “principle of equifinality” that states: “An end-point is an end-point is and end-point, no matter how it was obtained”. Different processing pathways can lead to different end-points, each with its own set of granulation properties. However, once an end-point is reached, it is characterized by certain numerical values of the dimensionless variables describing the process, and these values will be independent of scale.

At the same end-point, no matter how defined, the rheological and dimensional properties of the granules are similar. As we will see from the examples described below, that means that the density and dynamic viscosity of the wet mass are constant, and the only variables that are left are the process variables, namely batch mass, impeller diameter and speed, and the geometry of the vessel.

Comparison of attainable Froude Numbers

Horsthuis et al. (29) showed that an end-point can be reproduced and scaled up in Gral mixers by keeping the Froude numbers constant. For the same end-point, in dynamically similar mixers (same geometrical ratios, same flow patterns), all dimensionless numbers describing the system should have the same numerical value, but Froude numbers for any mixer are easiest to compute.

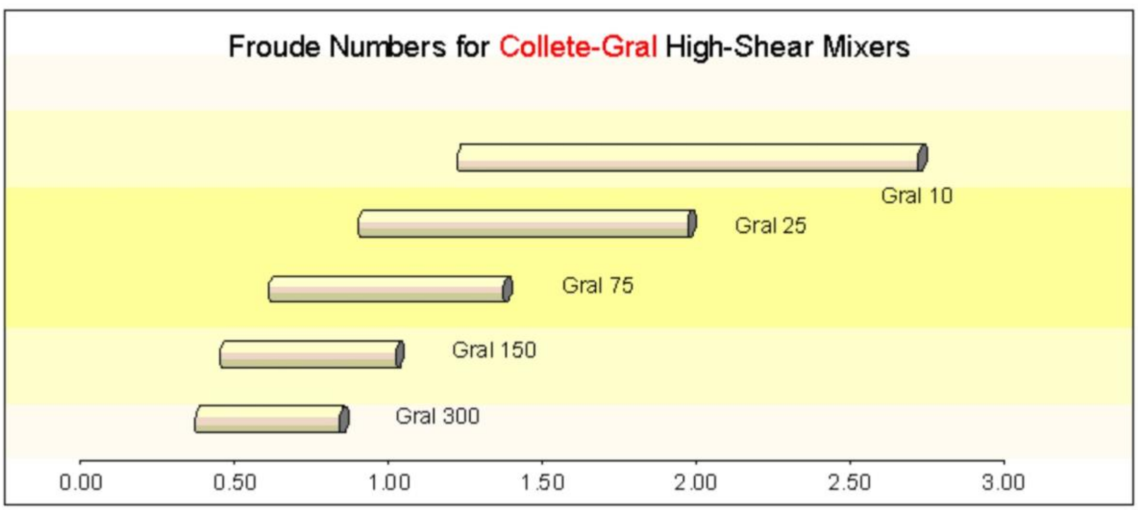

Fig. 1. The range of Froude numbers for Collette Gral high-shear mixers.

Each mixer has a range of attainable Froude numbers, and an end-point transfer between mixers can only be achieved when such ranges overlap. Fig. 1 represents such a range for Collette Gral mixers. It can be seen that Gral 10 and Gral 150 has no overlap of Froude number ranges, and therefore a direct scale-up is not possible (in addition, Gral mixers are not exactly similar geometrically, as was stated elsewhere).

The range of Froude numbers for Fielder PMA series mixers is shown on Fig. 2. The 10 liter laboratory scale mixer at its lowest speed settings can reach the Froude numbers of all other mixers, except one. These considerations can be useful for planning a scale-up or technology transfer operation.

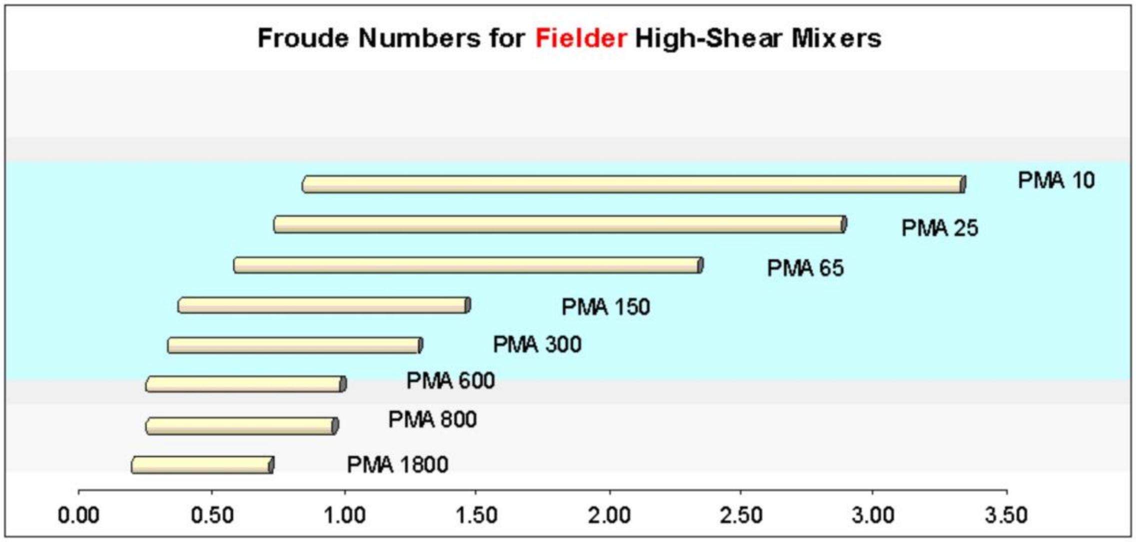

Fig. 2. The range of Froude numbers for Fielder PMA high-shear mixers.

Π-theorem (Buckingham)

The so-called π-theorem or Buckingham theorem (99) states:

Every physical relationship between n dimensional variables and constants

$$f(x0, x1, x2, \dots , xn) = 0$$

can be reduced to a relationship

$$f(\Pi 0, \Pi 1, \dots , \Pi m) = 0$$

between m = n - r mutually independent dimensionless groups,

where r = number of dimensional units, i.e. fundamental units (rank of the dimensional matrix).

Scientific scale-up procedure:

1. Describe the process using a complete set of dimensionless numbers, and

2. Match these numbers at different scales.

The dimensionless space in which the measurements are presented or measured will make the process “scale invariant”.

Relevance List

The dimensional analysis starts with a list of all variables thought to be important for the process being analyzed (the so-called “relevance list”).

To set up a relevance list for any process, one needs to compile a complete set of all relevant and mutually independent variables and constants that affect the process. The word “complete” is crucial here. All entries in the list can be subdivided into geometric, physical and operational. Each relevance list should include only one target (dependent “response”) variable.

Many pitfalls of dimensional analysis are associated with the selection of the reference list, target variable, or measurement errors (e.g. when friction losses are of the same order of magnitude as the power consumption of the motor). The larger the scale-up factor, the more precise the measurements of the smaller scale have to be (96).

Dimensional Matrix

Dimensional analysis can be simplified by arranging all relevant variables from the relevance list in a matrix form, with a subsequent transformation yielding the required dimensionless numbers. The dimensional matrix consists of a square core matrix and a residual matrix (you will see examples in the Case Studies below).

The rows of the matrix consist of the basic dimensions, while 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 (that is, 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 then linearly transformed into a matrix of unity where the main diagonal consists only of ones and the remaining elements are all zero. The dimensionless numbers are then created as a ratio of the residual matrix and the core matrix with the exponents indicated in the residual matrix. This rather simple process will be illustrated below in the examples.

Case Study I: Leuenberger (1979,1983)

This example is based on the ground-breaking studies conducted by Hans Leuenberger at the University of Basel and Sandoz AG (40, 100-103).

Table I. The Relevance List used by Leuenberger [1983]

	Quantity	Symbol	Units	Dimensions

1	Power consumption	P	Watt	$M L^2 T^{-3}$
2	Specific density	ρ	kg / m^3	$M L^{-3}$
3	Blade diameter	d	m	L
4	Blade velocity	n	rev / s	T^{-1}
5	Binder amount	s	kg	M
6	Bowl volume	V_b	m^3	L^3
7	Gravitational constant	g	m / s^2	$L T^{-2}$
8	Bowl height	H	m	L

The Relevance List in Table I reflects certain assumptions used to simplify the model, namely, that there are short range interactions only and no viscosity factor (and therefore, no Reynolds number).

Why do we have to consider the gravitational constant? Well, imagine the same process to be done on the moon - would you expect any difference?

One target variable (Power consumption) and 7 process variables / constants thus represent the number n=8 of the Π-theorem. The number of basic dimensions r = 3 (M, L, and T). According to the theorem, the process can be reduced to relationship between m = n - r = 8 – 3 = 5 mutually independent dimensionless groups.

Table II. The Dimensional Matrix for Case Study I

	Core matrix			Residual Matrix				
	ρ	d	n	P	s	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

The Dimensional Matrix in Table II was constructed as described above, with the rows listing the basic dimensions and the columns indicating the physical quantities from the relevance list.

Table III. The Transformed Dimensional Matrix for Case Study I

	Unity matrix			Residual Matrix				
	ρ	d	n	P	s	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

Transformation of the Dimensional Matrix (Table III) into a unity matrix is straightforward. To transform -3 in L-row / ρ -column into zero, one linear transformation is required. The subsequent multiplication of the T-row by –1 transfers the -1 of the n-column to +1.

The 5 dimensionless groups are formed from the 5 columns of the residual matrix by dividing each element of the residual matrix by the column headers of the unity matrix, with the exponents indicated in the residual matrix.

The residual matrix contains five columns; therefore five dimensionless Π groups (numbers) will be formed (Table IV).

Table IV: Dimensionless Π groups formed from the matrix in Table III.

Π group	Expression		Definition
Π_0 =	$P / (\rho^1 * d^5 * n^3)$	$= N_p$	Newton (Power) number
Π_1 =	$s / (\rho^1 * d^3 * n^0)$	$\sim q\, t / (\rho V_p)$	Specific Amount of Liquid $V_p \equiv$ Volume of particles q = binder addition rate t = binder addition time
Π_2 =	$V_b / (\rho^0 * d^3 * n^0)$	$\sim (V_p / V_b)^{-1}$	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

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, Π_4 are “essentially constant”, the Π-space can be reduced to a simple relationship $\Pi_0 = f\,(\Pi_1)$, that is, the value of Newton number N_p at any point in the process is a function of the specific amount of granulating liquid.

Up to this point, all the 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 have empirically established that the characteristic (that is, relative to the batch size) amount of binder liquid required to reach a desired end-point (as expressed by the absolute value of N_p and, by proxy, in terms of Net Power Consumption ΔP) is “scale-up invariable”, that is, independent of the batch size (Fig. 3), thus specifying the functional dependence *f* and establishing rational basis for granulation scale-up.

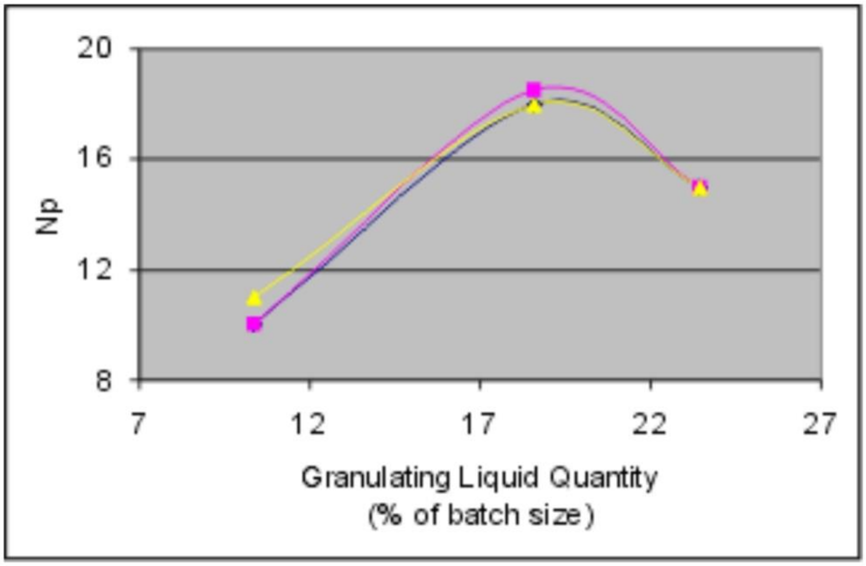

Fig. 3. Newton Power Number as a function of the Characteristic Liquid Quantity (adapted from Bier, Leuenberger and Sucker, 1979, ref. 40).

Experiments with 5 different planetary mixers with batch sizes ranging from 3.75 kg up to 60 kg showed that, if the binder is mixed in as a dry powder and then liquid is added at a constant rate proportional to the batch size, the ratio of granulation liquid quantity to a batch size is constant. This was shown for non-viscous binders.

The ratio of quantity of granulating liquid to batch size at the inflection point of power vs. 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 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 different sizes and manufacturers.

As we have indicated before, for any desired end-point, the power consumption will be proportional to the Newton power number, at a constant mixer speed.

The Leuenberger's ideas relating to the use of power consumption for wet granulation end-point determination were tested and implemented by numerous researchers [e.g., (9, 20, 34, 39, 40).

In 2001, Holm, Schaefer and Larsen (74) have applied the Leuenberger method to study various processing factors and their effect on the correlation between power consumption and granule growth. They have found that such a correlation did indeed exist but was dependent, as expected, on the impeller design, the impeller speed, and the type of binder. The conclusion was that it was possible to control the liquid addition by the level detection method whereby the liquid addition is stopped at a predetermined level of power consumption. An alternative approach involves an inflection point (peak of signal derivative with respect to time).

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

For accuracy, in power number N_p calculations, the power of the load on the impeller rather than the mixer motor should be used. Before attempting to use dimensional analysis, one has to measure / estimate power losses for empty bowl or dry stage mixing. Unlike power consumption of the impeller (based on torque measurements), the baseline for motor power consumption does not stay constant and changes significantly with load on the impeller, mixer condition or motor efficiency. This may present inherent difficulties in using power meters instead of torque. Torque, of course, is directly proportional to power drawn by the impeller (the power number can be determined from the torque and speed measurements) and has a relatively constant baseline.

Case Study II: Landin et al. (1996)

Scale-up in fixed bowl mixer-granulators has been studied by Ray Rowe and Mike Cliff's group (42) using the classical dimensionless numbers of Newton (Power), Reynolds and Froude to predict end-point in geometrically similar high-shear Fielder PMA 25, 100, and 600 liter machines.

Table V. Relevance List for Case Study II (Landin et al., 1996)

	Quantity	Symbol	Units	Dimensions
1	Power consumption	P	Watt	$M L^2 T^{-3}$
2	Specific density	ρ	kg / m^3	$M L^{-3}$
3	Blade diameter	D	m	L
4	Blade speed	n	rev / s	T^{-1}
5	Dynamic viscosity	η	Pa * s	$M L^{-1} T^{-1}$
6	Gravitational constant	g	m / s^2	$L T^{-2}$
7	Bowl height	H	m	L

The relevance list (Table V) included power consumption of the impeller (as a response) and six factor quantities: impeller diameter, impeller speed, vessel height, specific density and dynamic viscosity of the wet mass, and the gravitational constant.

Note that dynamic viscosity has replaced the binder amount and bowl volume of the Leuenberger's relevance list, thus making it applicable to viscous binders and allowing long range particle interactions responsible for friction.

Table VI. The Dimensional Matrix for Case Study II

	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

The dimensional matrix for Case Study II (Table VI) is different from Table II: the columns for mass [M] and bowl volume [L^3] are replaced by a viscosity [$ML^{-1}T^{-1}$] column. Evidently, it was assumed that the mass and volume can be adequately represented in the Relevance List by the density and powder height in a semi-cylindrical vessel of a known diameter.

	Unity matrix			Residual Matrix			
	ρ	d	n	P	η	g	H
M	1	0	0	1	1	0	0
3M + L	0	1	0	5	2	1	1
-T	0	0	1	3	1	2	0

Table VII. The Transformed Dimensional Matrix for Case Study II.

The residual matrix (Table VII) contains four columns, therefore four dimensionless Π groups (numbers) will be formed, in accordance with the Π-theorem (7 variables – 3 dimensions = 4 dimensionless groups).

Table VIII: Dimensionless Π groups formed from the matrix in Table VII

Π group	Expression		Definition
Π_0 =	$P / (\rho^1 * d^5 * n^3)$	= N_p	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 =	$H / (\rho^0 * d^1 * n^0)$	$= H / d$	Geometric number (Ratio of Characteristic Lengths)

Table VIII lists the resulting groups; they correspond to Newton power, Reynolds, and Froude numbers, and the ratio of characteristic lengths.

Under the assumed condition of dynamic similarity, from the dimensional analysis theory, it follows that $\Pi_0 = f(\Pi_1, \Pi_2, \Pi_3,)$, and, therefore, $N_p = f(Re, Fr, H/d)$.

When corrections for gross vortexing, geometric dissimilarities, and powder bed height variation were made, data from all mixers (Fielder PMA 25, 100 and 600 Liter) correlated to the extent that allows predictions of optimum end-point conditions. The linear regression of Newton Number (power) on the product of adjusted Reynolds Number, Froude Number and the Geometric number (in log/log domain) yields [Fig. 4] an equation of the form:

$$\mathrm{Log}_{10} N_p = a \cdot \log_{10} (Re \cdot Fr \cdot H / d) + b$$

where b = 796 and a = - 0.732.

Theoretically, in such a representation of the granulation process, a slope a= -1 would signify a true laminar flow whereby a slope significantly less than -1 or approaching 0 would indicate turbulence. Thus, one would expect planetary mixers to have a slope closer to -1 compared to that of high shear granulators. However, the results described here and in subsequent studies do not show a clear difference between slopes of regression for planetary and high shear mixers.

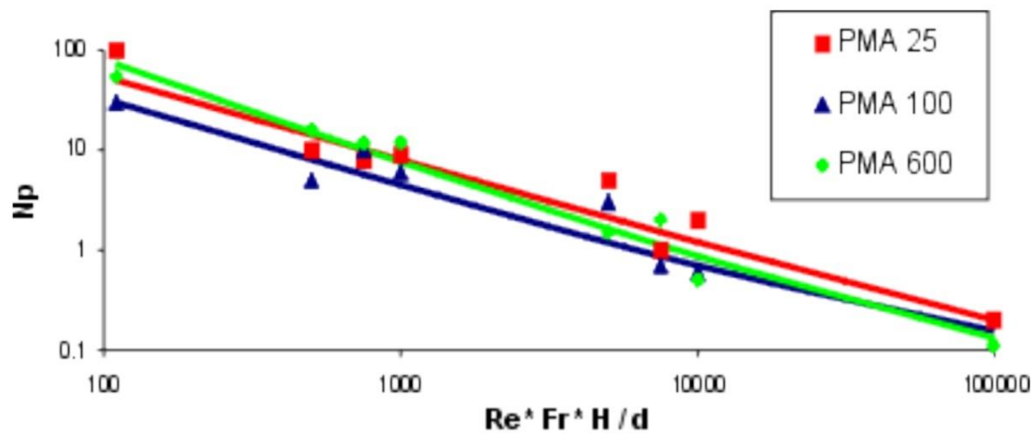

Fig. 4. Regression lines of the Newton Power Number on the product of Reynolds number, Froude Number, and the length ratio for 3 different Fielder mixers (from Landin et al., 1996, ref. 42).*

However, the correlation coefficient of 0.7854 for the final curve fitting effort indicates the presence of many unexplained outlier points. One of the possible concerns was an inherent error in measuring the height of the powder bed from the wet mass density.

In a subsequent communication (43) it was shown that, in order to maintain geometric similarity, it is important to keep the batch size proportional to the bowl shape.

Another concern is interpretation of data from mixer torque rheometer that was used to assess the viscosity of wet granulation. The torque values obtained from the rheometer were labeled *"wet mass consistency"* and were used instead of dynamic viscosity to calculate Reynolds numbers. It was shown (41, 62) that such torque values are proportional to kinematic viscosity $\nu = \eta / \rho$ rather than dynamic viscosity η required to compute Reynolds numbers. The degree of proportionality between ν and η was found to be formulation dependent.

Consequently, it was prudent to acknowledge that the above regression equation is not dimensionless because for all practical purposes, the Reynolds number Re was replaced by ΨRe, what the authors called a *"pseudo Reynolds number"* with the dimensions $[L^{-3}\ T]$. This predicament did not deter a plethora of other studies in the same line of reasoning to be published in recent years. Note that this pseudo

Reynolds number has a physical meaning: it is a reciprocal of volumetric flow rate.

Case Study III: Faure et al. (1998)

The same approach was applied to planetary Hobart AE240 mixer with two interchangeable bowls, 5 and 8.5 liters (45). Assuming the absence of chemical reaction and heat transfer, the following relevance list for the wet granulation process was suggested (Table VIII):

Table IX. Relevance List for Case Study III (Faure et al., 1998)

	Quantity	Symbol	Units	Dimensions
1	Net Power	ΔP	Watt	$M L^2 T^{-3}$
2	Wet mass bulk or specific density	ρ	kg / m^3	$M L^{-3}$
3	Impeller radius (or diameter)	d	m	L
4	Impeller speed	n	rev / s	T^{-1}
5	Granulation dynamic viscosity	η	Pa * s	$M L^{-1} T^{-1}$
6	Gravitational constant	g	m / s^2	$L T^{-2}$
7	Height of granulation bed in the bowl	h	m	L

One difference from Table V of the previous study is the use of Net Power ΔP that was defined as motor power consumption under load minus the dry blending baseline level.

An assumption was made that a motor drive speed is proportional to the impeller blade speed. Another consideration was that the ratio of characteristic lengths h/d is proportional to (and, therefore, can be replaced by) a fill ratio V_m / V_b, which was, in turn, shown to be proportional to (and therefore could be replaced in the final equation by) the quantity $m / (\rho d^3)$. This is a preferred method of representing a fill ratio because the wet mass m is easier to measure than the height of the granulation bed in the bowl.

Dimensional analysis and application of the Buckingham theorem lead to four dimensionless quantities that adequately describe the process: Ne, ΨRe, Fr, and h/d As before, a relationship of the form

$$N_p = 10^b (\Psi Re \cdot Fr \cdot \rho R_b^3 / m)^a, \quad \text{or}$$

$$Log_{10} N_p = a \cdot \log_{10} (\Psi Re \cdot Fr \cdot \rho R_b^3 / m) + b$$

was postulated and the constants a and b (slope and intercept in a log-log domain) were found empirically (b = 2.46 and a = - 0.872) with a good correlation (>0.92) between the observed and predicted numbers (Fig. 5). Radius of the bowl R_b cubed was used to represent the bowl volume V_b. The graph indicates a collection of end-points produces with different mixers and different processing factors.

It was noted that the above equation can be interpreted to indicate that

$$\Delta P \sim \eta \cdot d^2 \cdot V_m / V_b,$$

that is, that the net power consumption of the impeller varies directly with the fill ratio, wet mass viscosity and the surface swept by the blades ($\sim d^2$).

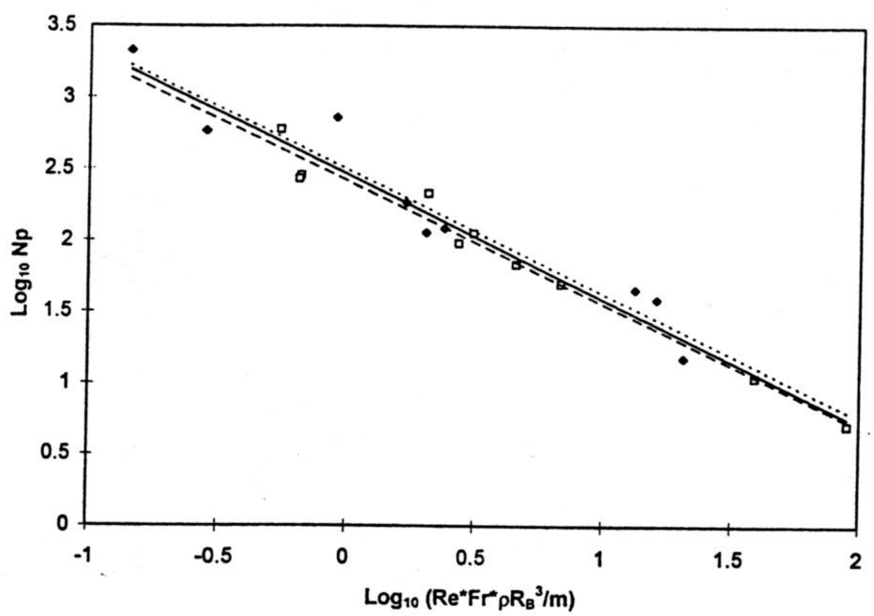

Fig. 5. Regression graph of Case Study III. The Reynolds Number Re was, in fact, a dimensional "pseudo Reynolds number" ΨRe. Data from a dual bowl Hobart AE240 planetary mixer (ref. 45).

Reproduced from Faure A, Grimsey IM, Rowe RC, York P, Cliff MJ. A methodology for the optimization of wet granulation in a model planetary mixer. Pharm Dev Tech 3(3):413-422, 1998

Wet masses produced at the same end-point (regardless of bowl and batch size, impeller speed, and moisture content) have been consistently shown to result in the same final dry granule size distribution, bulk density, flow and mechanical strength.

Case Study IV: Landin et al. (1999)

Following the methodology developed in the previous Case Study using the same assumptions, this study was also performed on planetary mixers Collette MP20, MP90, and MPH 200 (44). The relevance list and dimensional matrix were the same as before, and torque measurements from torque rheometer were again used to represent kinematic viscosity (instead of dynamic viscosity) in Reynold numbers.

Fig. 6 represents the resulting regression line

$$\text{Log}_{10} N_p = a \cdot \log_{10} (\Psi\text{Re} \cdot \text{Fr} \cdot \rho R_b{}^3 / m) + b$$

for the combined results from three mixers with bowl sizes 20, 90, and 200 liters showed a pretty good fit to data ($r^2 > 0.95$). The values for the slope and intercept were found to be: a = - 0.68, b = 1280. Data from two other mixers with bowl sizes 5 and 40 liter produces lines that were significantly different from the first set of mixers. The authors explained this difference by an assumption of "different flow patterns" in the two groups of mixers.

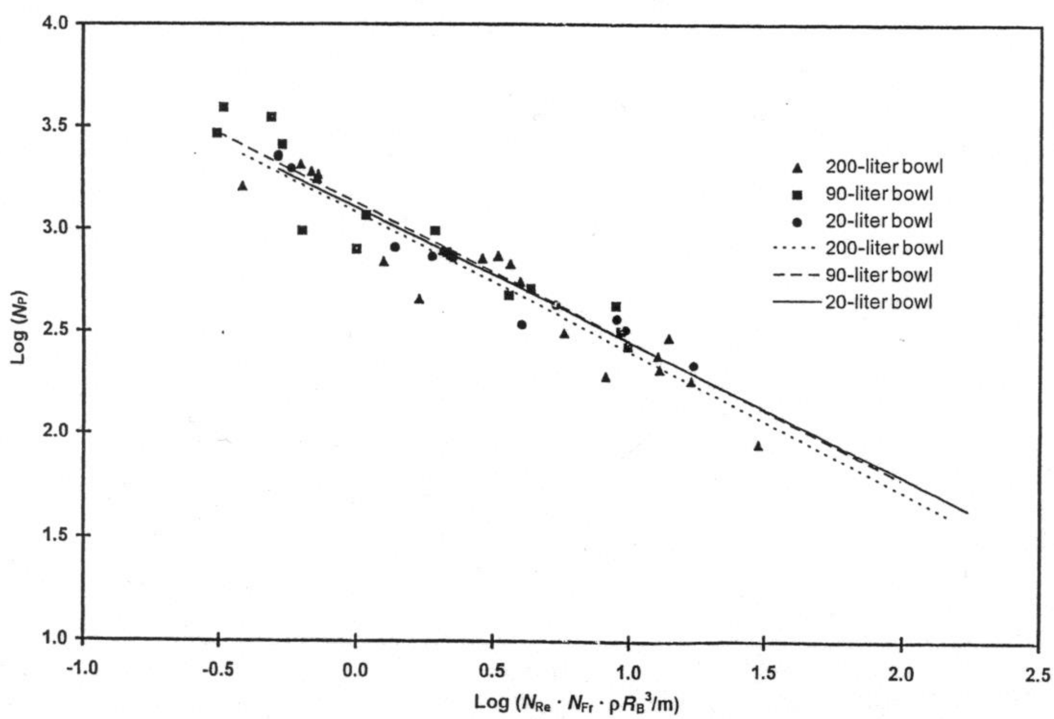

Fig. 6. Regression graph of Case Study IV. The Reynolds Number Re was, in fact, a dimensional "pseudo Reynolds" number ΨRe.* Data from Collette MP20, MP90, and MPH 200 planetary mixers (ref. 44).

*Reproduced from Landin M, York P, Cliff MJ, Rowe RC. Scaleup of a pharmaceutical granulation in planetary mixers. Pharm Dev Technol, 4(2):145-150, 1999

Case Study V: Faure et al. (1999)

This study was done on Collette Gral Mixers (8, 25, 75 and 600 Liter) and followed the accepted – and by now, standard - methodology developed earlier (48). The problem with the scale-up in the Gral mixers was the lack of geometric similitude: there was significant "distortion factor" between the bowl geometries at different scales. In addition, the researchers had to take into account the lack of dynamic similitude due to different wall adhesion and lid interference that was partially relieved by using a PolyTetraFluoroEthylene (PTFE) lining.

The end result of the dimensional analysis and experimental work was, again, a regression equation (Fig. 7) of the form

$$Log_{10} N_p = a \cdot \log_{10} (\Psi Re \cdot Fr \cdot \rho R_b{}^3 / m) + b$$

The regression coefficient was $r^2 > 0.88$ using the data from the 8, 25 and 75 liter bowls with PTFE lining, and the 600 liter bowl that did not require the lining. The slope was found to be a = -0.926, and the intercept b = 3.758.

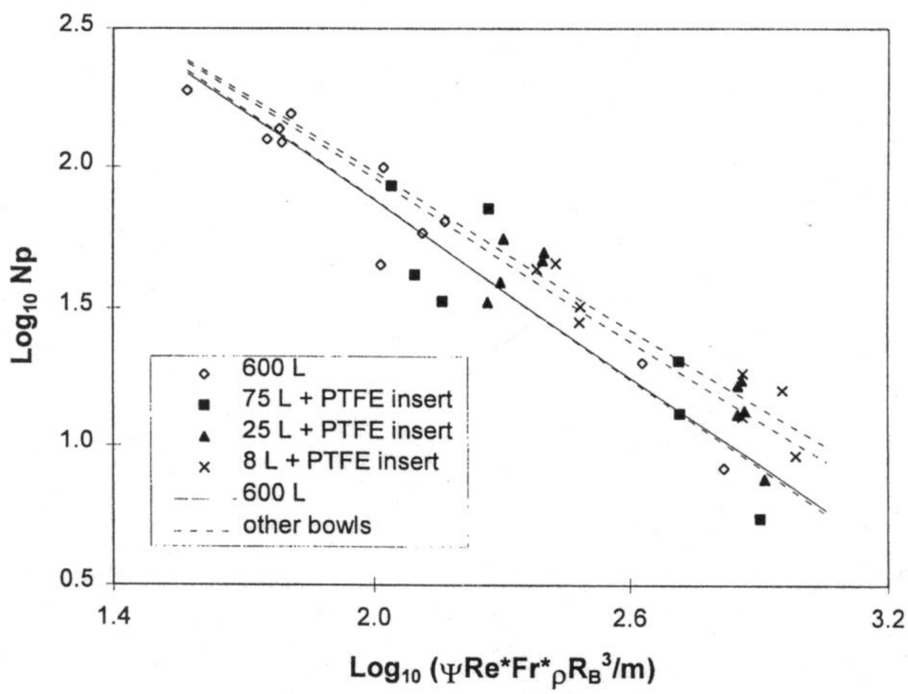

Fig. 7. Regression graph of Case Study V.* Data from Collette Gral 8, 25, 75 and 600 liter mixer-granulators (ref.48).

Case Study VI: Hutin et al. (2004)

In this study, the foregoing methodology of dimensional analysis was applied to a kneading process of drug - cyclodextrin complexation (104). Aoustin kneader with dual Z blades was instrumented for torque measurements and multiple runs were made at 2 scales (2.5 and 5 Liter).

The Relevance List for this study (Table IX) differs from those discussed previously by addition of blade length as one of the crucial factors affecting the process.

Table IX. Relevance list for Hutin et al. (2004)

	Quantity	Symbol	Units	Dimensions
1	Power consumption	P	Watt	$M L^2 T^{-3}$
2	Specific density	ρ	kg / m^3	$M L^{-3}$
3	Blade radius	d	M	L
4	Blade speed	n	rev / s	T^{-1}
5	Dynamic viscosity	η	Pa * s	$M L^{-1} T^{-1}$
6	Gravitational constant	g	m / s^2	$L T^{-2}$
7	Powder bed height	h	M	L
8	Blade length	l	M	L

Introduction of the blade length, after the proper operations with the dimensional matrix, creates another dimensionless quantity, namely, d / l, so that the resulting regression equation has the form of

$$N_p = b (\Psi Re * Fr * h / d * d / l))^{-a}$$

Experiments showed that the model fits data remarkably well ($r^2 > 0.99$).

Unfortunately, the Pharmaceutical Technology journal does not grant permissions to reproduce individual graphs; therefore an interested reader is referred to the source article to see the regression lines from this study.

Practical Considerations for End-Point Scale-Up

Once the desired end-point is determined, it can be reproduced by stopping the batch at the same level of net power consumption ΔP (for the same mixer, formulation, speed, batch size and amount/rate of granulating liquid). To account for changes in any of these variables, you have to compute the Newton power number N_p for the desired end-point:

$$N_p = \Delta P / (\rho\, n^3\, d^5)$$

In other words, if you have established an end-point in terms of some Net Impeller or Motor Power ΔP and would like to reproduce this end-point on the same mixer at a different speed or wet mass density, calculate Newton Power Number N_p from the given Net Impeller Power ΔP, impeller speed n, blade radius d, and wet mass density ρ (assuming the same batch size), and then recalculate the target ΔP with the changed values of speed n or wet mass density ρ.

Wet mass viscosity η can be calculated from Net Impeller Power ΔP, blade radius d and impeller speed n, using the following equations:

$$\Delta P = 2\pi\, \Delta\tau * n$$

$$\eta = \varphi * \Delta\tau / (n * d^3)$$

where $\Delta\tau$ is the net torque required to move wet mass, n is the speed of the impeller, d is the blade radius or diameter, and φ is mixer specific “viscosity factor” relating torque and dynamic viscosity (note: the correlation coefficient φ can be established empirically by mixing a material with a known dynamic viscosity, e.g. water). Alternatively, you can use impeller torque τ as a measure of kinematic viscosity and use it to obtain a non-dimensionless “pseudo-Reynolds” number, based on the so-called “mix consistency” measure, that is, the end-point torque, as described in the case studies.

Fill Ratio h/d can be calculated from a powder weight, granulating liquid density (1000 kg/m^3 for water), rate of liquid addition, time interval for liquid addition, and bowl volume V_b. The calculations are performed using the idea that the fill ratio h/d (wet mass height to blade diameter) is proportional to V/V_b, and wet mass volume V can be computed as

$$V = m / \rho,$$

where m is the mass (weight) of the wet mass and ρ is the wet mass density.

Now, the weight of the wet mass is computed as the weight of powder plus the weight of added granulating liquid. The latter, of course, is calculated from the rate and duration of liquid addition and the liquid density.

Finally, following the examples discussed in the case studies, you can combine the results obtained at different end-points of the test batch or from different batches or mixer scales (assuming geometrical similarity).

Given wet mass density ρ, wet mass viscosity η, fill ratio $h/d \sim m\, V_b / \rho$, setup speed n, and blade radius or diameter d, you can calculate the Reynolds number Re (or the "pseudo-Reynolds" number) and the Froude number Fr. Then you can estimate the slope "a" and intercept "b" of the regression equation

$$N_p = b \cdot (Re \cdot Fr \cdot h/d)^a$$

or

$$\log N_p = \log b + a \cdot \log (Re \cdot Fr \cdot h/d)$$

And, inversely, once the regression line is established, you can calculate Newton Power number N_p (which is the target quantity for scale up) and Net Power ΔP (which can be observed in real time as a true indicator of the target end-point) for any point on the line.

List of Symbols and Dimensions

a, b	Slope and intercept of a regression equation
d	Impeller (blade) diameter or radius (m); dimensional units [L]
g	Gravitational constant (m / s^2); dimensional units [LT^{-2}]
h	Height of granulation bed in the bowl (m); dimensional units [L]
H	Bowl height (m); dimensional units [L]
l	Blade length (m); dimensional units [L]
n	Impeller speed (revolutions / s); dimensional units [T^{-1}]
P	Power required by the impeller or motor (W = J / s); dimensional units [ML^2T^{-5}]
R_b	Radius of the bowl (m); dimensional units [L]
q	Binder liquid addition rate
s	Amount of granulating liquid added per unit time (kg); dimensional units [M]
t	Binder addition time (s); dimensional units [T]
V_p	Particle volume (m^3); dimensional units [L^3]
V_m	Wet mass volume (m^3); dimensional units [L^3]
V_b	Bowl volume (m^3); dimensional units [L^3]
w	Wet mass; dimensional units [M]
ρ	Specific density of particles (kg / m^3); dimensional units [$M L^{-3}$]
$\nu = \eta / \rho$	Kinematic viscosity (m^2 / s); dimensional units [L^2T^{-1}]
η	Dynamic viscosity (Pa*s); dimensional units [$M L^{-1} T^{-1}$]
τ	Torque (N-m); dimensional units [$M L^2 T^{-2}$]. End point torque values were described as "wet mass consistency" numbers. Note: torque has the same dimensions as work or energy.
$\varphi = \eta \cdot n \cdot d^3 / \Delta\tau$	Dimensionless "viscosity factor" relating net torque $\Delta\tau$ and dynamic viscosity η
$Fr = n^2 d / g$	Froude number. It relates the inertial stress to the gravitational force per unit area acting on the material. It is a ratio of the centrifugal force to the gravitational force.
$N_p = P / (\rho n^3 d^5)$	Newton (power) number. It relates the drag force acting on a unit area of the impeller and the inertial stress.
$Re = d^2 n \rho / \eta$	Reynolds number. It relates the inertial force to the viscous force.
$\Psi Re = d^2 n \rho / \tau$	"Pseudo Reynolds number" (m^3/s); dimensional units [L^{-3} T]. Note: this variable physically is a reciprocal of volume flow rate.
$Ga = Re^2 / Fr$	Galileo number

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