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Wet Granulation: End-Point Determination and Scale-Up

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INTRODUCTION

Wet granulation is used mainly to improve flow and compressibility of powders, and to prevent segregation of the blend components. Particle size of the granulate is affected by the quantity and feeding rate of the granulating liquid.

Wet massing in a high shear mixing is frequently compared to the fluid bed mixing and to the roller compaction technique,[1] and the results seem to be formulation dependent. Compared to high shear granulation, low shear or fluid bed process requires less fluid binder, not only resulting in a shorter drying time, but also in a less cohesive material.[2–4]

For excellent classical review of the wet granulation process, equipment and variables, and measurement instruments available in the field, see papers by Holm et al.[5–12] These papers have become a standard reference for numerous subsequent publications.

Because of rapid densification and agglomeration that are caused by the shearing and compressing action of the impeller in a high shear single pot system, mixing, granulation, and wet massing can be done relatively quickly and efficiently. The dangers lie in the possibility of overgranulation because of excessive wetting and producing low porosity granules, thus affecting the mechanical properties of the tablets. As the liquid bridges between the particles are formed, granules are subjected to coalescence alongside with some breakage of the bonds.

It stands to reason that mean granule size is strongly dependent on the specific surface area of the excipients, as well as the moisture content and liquid saturation of the agglomerate. During the wet massing stage, granules may increase in size to a certain degree while the intragranular porosity goes down. However, some heating and evaporation may also take place leading to a subsequent decrease in the mean granule size, especially in small-scale mixers.

Load on the main impeller is indicative of granule apparent viscosity and wet mass consistency. It can be seen as an interplay of acceleration (direct impact of the impeller), centrifugal, centripetal, and friction forces that act on the particles.

According to Cliff,[13,14] binder addition rate controls granule density, while impeller and chopper speed control the granule size and granulation rate. The endpoint controls the mix consistencen and reproducibility. Other factors that affect the granule quality include spray position and spray nozzle type, and of course, the product composition. Such variables as mixing time and bowl or product temperature are not independent factors in the process but rather are responses of the primary factors listed above.

WHAT IS AN END-POINT?

End-point can be defined by the formulator as a target particle size mean or distribution. Alternatively, the end-point can be defined in rheological terms. It has been shown[15] that once you have reached the desired end-point, the granule properties and the subsequent tablet properties are very similar regardless of the granulation processing factors, such as impeller or chopper speed or binder addition rate. I would call this “the principle of equifinality."

The ultimate goal of any measurement in a granulation process is to estimate the viscosity and density of the granules, and, perhaps, to obtain an indication of the particle size mean and distribution. One of the ways to obtain this information is by measuring the load on the main impeller.

Mixer instrumentation, in general, has numerous benefits. In addition to a possible end-point determination, it can be used to troubleshoot the machine performance (for example, help detect worn-out gears and pulleys or identify mixing and binder irregularities). Instrumentation can serve as a tool for formulation fingerprinting, assure batch reproducibility, aid in raw material evaluation, process optimization, and scale-up.

WHAT CAN BE MEASURED ON A MIXER-GRANULATOR?

Current

Current in direct current (DC) motors can be used as some indication of the load on the main impeller because impeller torque is proportional to current in
some intervals\textsuperscript{[13]} and therefore, a current meter (ammeter) can be used for small scale DC motors. However, for alternating current motors (most often used in modern mixers), there may be no significant change in the current as motor load varies up to 50\% of full scale. At larger loads, the current draw may increase but this increase is not linearly related to load, and, consequently, the current is completely ineffective as a measurement of load. Moreover, the current baseline may shift with time.

**Voltage**

Voltage measurement generally has no relation to load.

**Capacitance**

Capacitive sensor responds to the moisture distribution and granule formation.\textsuperscript{[16–19]} It provided similar end-points (based on the total voltage change) under varying rates of agitation and liquid addition. Capacitive sensor can be threaded into an existing thermocouple port for in-process monitoring.

**Conductivity**

Conductivity of the damp mass\textsuperscript{[20]} makes it possible to quantify uniformity of liquid distribution and packing density during wet massing time.

**Probe Vibration**

Probe vibration analysis\textsuperscript{[21,22]} requires a specially constructed probe that includes a target plate attached to an accelerometer (for in-process monitoring). This measurement is based on the theory that increasing granule size results in the increase of the acceleration of agglomerates striking the probe target. The method has a potential for granulation monitoring and endpoint control.

**Boots Diosna Probe**

This probe\textsuperscript{[23]} measured the densification and increase in size of the granules (changes in momentum of granules moving with constant velocity because of a mass change of the granules). The method did not gain popularity because of its invasive nature.

**Chopper Speed**

Chopper speed has no significant effect on the mean granule size.\textsuperscript{[5,6]}

**Impeller or Motor Shaft Speed**

Rate of impeller rotation could be used as some indication of the work being done on the material.\textsuperscript{[24]} As the motor or impeller power consumption is proportional to the product of torque and speed, the latter is an important factor in evaluating the corresponding load.

**Motor Slip and Motor Load Analyzer**

Motor slip is the difference between the rotational speed of an idle motor and the motor under load.\textsuperscript{[25,26]} Motor slip measurements, although relatively inexpensive, do not offer advantages over the power consumption measurements. The method did not gain popularity, probably because the slip is not linearly related to the load\textsuperscript{[27]} despite some claims to the contrary.

**Impeller Tip Speed**

Impeller tip speed corresponds to the shear rate and has been used as a scale-up parameter in fluid mixing.\textsuperscript{[28]} For processing of lactose granulations in Gral mixers, however, it was shown by Horsthuis et al.\textsuperscript{[29]} that the same tip speed did not result in the same end-point [in terms of particle size distribution (PSD)]. These findings were contradicted by other studies with Fielder mixers indicating that for a constant tip speed, successful scale-up is possible when liquid volume is proportional to the batch size and wet massing time is related to the ratio of impeller speeds.\textsuperscript{[30]}

**Relative Swept Volume**

Relative swept volume, that is, the volume swept by the impeller (and chopper) per unit time, divided by the mixer volume, has been suggested as a scale-up factor.\textsuperscript{[11,12,31]} This parameter is related to work done on the material and was studied extensively at various blade angles.\textsuperscript{[32]} Higher swept volume leads to higher temperature and denser granules. However, it was shown by Horsthuis et al.\textsuperscript{[29]} that the same relative swept volume did not result in the same end-point (in terms of PSD).

**Temperature**

Product and jacket temperature are usually measured by thermocouples. These response variables are controlled by a variety of factors, notably, the speed of the main impeller and the rate of the binder addition.
**Binder Addition Rate**

There are conflicting reports on the preferred method of adding the binder. For example, Holm[32] does not generally recommend adding dry binder to the mix (as commonly done in order to avoid preparation of a binder solution) because homogeneity of binder distribution cannot be assured. Others recommend just the opposite.[34–36]

Slow continuous addition of water (in case the water-soluble binder is dry mixed) or a binder solution to the mix is a granulation method of choice.[5,6,10–12,37–44] The granulating fluid should be added at a slow rate to avoid local overwetting.[33]

If the binder solution is added continuously, then the method of addition (pneumatic or binary nozzle, atomization by pressure nozzle) should be considered in any end-point determination and scale-up.

An alternative to a continuous binder liquid addition method is to add binder liquid all at once[29] to assure the ease of processing and reproducibility, reduce processing time, and to avoid wet mass densification that may occur during the liquid addition. This latter phenomenon may obscure the scale-up effect of any parameter under investigation.

**Power Consumption**

One of the most popular and relatively inexpensive measurements is the power consumption of the main mixer motor. It is measured by a watt transducer or a power cell utilizing Hall effect (a measurable transversive voltage between the two radial sides of a current conductor in a magnetic field, an effect discovered by E.H. Hall in 1879).

Power consumption of the mixer motor for end-point determination and scale-up is widely used (Leuenberger[43] and subsequent work, Holm[5] and subsequent work, Landin et al.[45–48], Faure et al.[49–53], and many others[16,33,37–44,54,55]) because the measurement is economical, does not require extensive mixer modifications, and is well correlated with the granule growth.

Power consumption correlates with the mean granule size of a granulation,[8] although the correlation is not always linear in the entire range. Intrgranular porosity also shows some correlation with power consumption.[56] Normalized work of granulation (power profile integrated over time) can accurately determine end-points and is correlated well with properties of the granulates.[57]

The main problem with the power consumption measurements is that this variable reflects load on the motor rather than load on the impeller. It relates to the overall mixer performance, depends on the motor efficiency, and can change with time regardless of the load.

Motor power consumption is a product of current, voltage, and the so-called power factor. In the range of interest, motor power consumption is generally proportional to load on the motor and, to some degree, can reflect the load on the impeller (Fig. 1).

However, up to 30% of the power consumption of a motor can be attributed to no-load losses because of windage (by cooling fan and air drag), friction in the bearings, and core losses that comprise hysteresis and eddy current losses in the motor magnetic circuit. Load losses include stator and rotor losses (resistance of materials used in the stator, rotor bars, magnetic steel circuit) and stray load losses such as current losses in the windings.[58]

Attempts to use a no-load (empty bowl, or dry mix) value as a baseline may be confounded by a possible nonlinearity of friction losses with respect to the load.[59] As the load increases, so does the current draw of the motor. This results in heat generation that further impacts the power consumption.[27] A simple test might be to run an empty mixer for several hours and see if there is any shift in the baseline. Also, as the motor efficiency drops with age, the baseline most definitely shifts over time.

Motor power consumption is non-linearly related to the power transmitted to the shaft[60] and the degree of this non-linearity could only be “guestimated.”

**Impeller Torque**

In a mixing process, changes in torque on the blades and power consumption of the impeller occur as a result of
change in the cohesive force or the tensile strength of the agglomerates in the moistened powder bed.

Direct torque measurement requires installation of strain gages on the impeller shaft or on the coupling between the motor and impeller shaft (Fig. 2). As the shaft is rotating, a device called slip ring is used to transmit the signal to the stationary data acquisition system.

Planetary mixer instrumentation for direct torque measurement does not substantially differ from that of a high shear mixer. Engineering design should only take into account the planetary motion in addition to shaft rotation.[61]

Impeller torque is an excellent in-line PAT measurement of the load on the main impeller.[39,62]

**Torque Rheometer**

A torque rheometer is a device that provides an off-line measurement of torque required to rotate the blades of the device and this torque can be used to assess rheological properties of the granulation. It has been extensively used for end-point determination.[45,63–65] The torque values thus obtained were termed as “measure of wet mass consistency.”[50,51,66]

One of the main concerns is that using the torque value that the unit is reporting instead of the dynamic viscosity for calculation of Reynolds numbers renders the latter to become dimensional. Therefore, the Reynolds number calculated from torque rheometer data is referred to as “pseudo-Reynolds” dimensional number. Because of the fact that torque was shown to be proportional to a kinematic (rather than dynamic) viscosity,[67] it can have a conditional use in the dimensional analysis of the process, as will be shown below.

**Reaction Torque**

By the third law of Newton, for every force there is a counterforce, collinear, equal and opposite in direction. As the impeller shaft rotates, the motor tries to rotate in the opposite direction, but it does not because it is bolted in place. The tensions in the stationary motor base can be measured by a reaction torque transducer.

Reaction torque is a less expensive alternative to direct impeller torque and is recommended for mixers that have the motor and impeller shafts axially aligned (in this case, the reaction torque is equal to direct torque and is opposite in sign).

**Other Possibilities**

When the agglomeration process is progressing very rapidly, neither power consumption nor torque on the impeller may be sensitive enough to adequately reflect changes in the material. Some investigators feel that other measurements, such as torque or force on the impeller blades may be better suited to monitor such events.

There are other ideas floating around, for example, use of neural network to describe and predict the behavior of the wet granulation[68] or control the end-point by rapid image processing system.[69]

A technique for measuring tensile strength of granules, in addition to power consumption measurement, to facilitate optimal end-point determination was recently described by Betz, Bürgin, and Leuenberger.[54]

Powder flow patterns in wet granulation can be studied using positron emission particle tracking.[70] Eventually, this and similar techniques can be used to validate various mathematical and statistical models of the process.

**Emerging Technology**

**Acoustic**

Applicability of piezoelectric acoustic emission sensors to end-point determination has been studied since the beginning of this century.[71] The technique is very promising, especially because it is non-invasive, sensitive, and relatively inexpensive. Granulation process signatures obtained with acoustic transducer can be used to monitor changes in particle size, flow, and compression properties.[72,73]
Near-infrared

Use of a refractive near-infrared (NIR) moisture sensor for end-point determination of wet granulation was described by several authors.\cite{74,75} There are technological challenges associated with this approach, as the sensor can only measure the amount of water at the powder surface.

NIR monitoring of the granulation process was attempted by researchers at many major pharmaceutical corporations with a modest success. In particular, yet unpublished work by David Rudd of GlaxoSmithKline in England should be mentioned as a part of the global effort in the field of Process Analytical Technology.

Focused beam reflectance measurement

Focused beam reflectance measurement (FBRM) is a particle size determination technique based on a laser beam focusing in the vicinity of a sapphire window of a probe. The beam follows a circular path at speeds of up to 6 m/sec. When it intersects with the edge of a particle passing by a window surface, an optical collector records a backscatter signal. The time interval of the signal multiplied by the beam speed represents a chord length between two points on the edge of a particle. The chord length distribution (CLD) can be recalculated to represent either a number or volume weighted PSD.

In many cases, where precision is more important than accuracy, CLD measurements are adequate to monitor dynamic changes in process parameters related to the particle size and shape, concentration, and rheology of fluid suspensions.

Several attempts were made to evaluate the use of FBRM particle size analyzer as a potential tool for granulation end-point determination.\cite{76} Dilworth et al.\cite{77} have compared power consumption, FBRM, and acoustic signals in a study of a wet granulation process in Fielder PMA 200 mixer. It was found that these techniques were complimentary, with FBRM probe capable to follow median granule size growth even when the power consumption curve showed a plateau.

A major disadvantage of the FBRM method is that the measured CLD does not directly represent a PSD. Conversion of CLD to PSD is not straightforward and requires sophisticated mathematical software that is not easy to validate. Moreover, CLD depends on optical properties and shape of the particles, as well as the focal point position. The total number of counts measured is a function both of solids concentration and probe location.

END-POINT DETERMINATION

End-point detection in wet granulation has become a major scientific and technological challenge.\cite{78} Monitoring granulation is most commonly achieved by collecting either power or torque signals, or both. In what follows, we will compare both methods.

Torque vs. Power

When we say, “power consumption,” we usually refer to the main motor. It reflects the load on the motor because of useful work, as well as the power needed to run the motor itself (losses because of eddy currents, friction in couplings, etc.).

It is quite possible (and, indeed, quite pertinent) to talk about the power consumption of the impeller, which is, obviously, quantitatively less than the power consumption of the motor and relates directly to the load on the impeller.

Power $\sim$ Torque $\times$ Speed

Impeller power consumption can be calculated as a product of the direct torque, rotational impeller speed, and a coefficient (usually equal to 2$\pi$ times a unit conversion factor, if required).

The power consumption of the mixer motor differs from that of the impeller by the variable amount of power draw imposed by various sources (mixer condition, transmission, gears, couplings, motor condition, etc.).

Compared to impeller torque, motor power consumption is easier to measure; wattmeters are inexpensive and can be installed with almost no downtime. However, motor power signal may not be sensitive enough for specific products or processing conditions. Wear and tear of mixer and motor may cause power fluctuations. Moreover, power baseline may shift with load.

Impeller torque, on the other hand, is closer to where the action is, and is directly related to the load on the impeller. Torque is not affected by mixer condition.

Although the motor power consumption is strongly correlated with the torque on the impeller,\cite{39} it is less sensitive to high frequency oscillations caused by direct impact of particles on the blades as evidenced by Fast Fourier Transform (FFT) technique.\cite{16}

Power consumption or torque fluctuations are influenced by granule properties (PSD, shape index, and apparent density) and the granulation time. Fluctuation of torque/power consumption and intensity of spectrum obtained by FFT analysis can be used for end-point determination.\cite{38}
It was observed that when the end-point region of a granulation is reached, the frequency distribution of a power consumption signal reaches a steady state.\[^9\] It should be repeated here that torque shows more sensitivity to high frequency oscillations.

**Torque and Power Profiles**

Fig. 3 illustrates the classical power and torque profiles that start with a dry mixing stage, rise steeply with binder solution addition, level off into a plateau, and then exhibit overgranulation stage. The power and torque signals have similar shape and are strongly correlated. The pattern shows a plateau region where power consumption or torque is relatively stable.

The peak of the derivative indicates the inflection point of the signal. Based on the theory by Leuenberger (1979 and subsequent work), usable granulates can be obtained in the region that starts from the peak of the signal derivative with respect to time and extends well into the plateau area.\[^44\] Prior to the inflection point, a continuous binder solution addition may require variable quantities of liquid. After that point, the process is well defined and the amount of binder solution required to reach a desired end-point may be more or less constant.

Torque or power consumption pattern of a mixer is a function of the viscosity of both the granulate and binder. With the increasing viscosity, the plateau is shortened and sometimes vanishes completely, thereby increasing the need to stop the mixer at the exact end-point.

At low impeller speeds or high liquid addition rates, the classic S-shape of the power consumption curve may become distorted with a steep rise leading into overgranulation.\[^9\]

The area under the torque-time curve is related to the energy of mixing and can be used as an end-point parameter. Area under power consumption curve divided by the load gives the specific energy consumed by the granulation process. This quantity is well correlated with the relative swept volume.\[^11,12,32\]

The consumed energy is completely converted into heat of the wet mass\[^5\] so that the temperature rise during mixing shows some correlation with relative swept volume and Froude number\[^29\] that relates the inertial stress to the gravitational force per unit area acting on the material.

Fig. 4 represents a record of a typical granulation batch done by an experienced operator on large Hobart mixer. You can see that the batch was stopped on the downslope of the derivative.

On a Fig. 5 you can see another batch made by the same operator. This time it is a power consumption trace, but again it extends beyond the peak of the derivative and the end-point thus can be deemed reproducible.

In the batch represented in Fig. 6, a novice operator trainee has stopped the batch well before the peak of the derivative. This required a major adjustment of the tableting operation (force and speed) to produce tablets in an acceptable range of material properties (hardness and friability).

In this batch (Fig. 7), the same novice operator has stopped the granulation process, opened the lid, took a sample, and decided to granulate for another 10 sec. You can see that there is no indication that the peak of the derivative was reached at the end-point.

Thus, it seems that the monitoring torque or power can fingerprint not only the product, but the process and the operators as well.

A number of publications relate to the practical experience of operators on the production floor.\[^33,80–82\]
Agglomeration of particles in wet granulation have been studied extensively.\cite{24,83} The optimal end-point can be thought of as the factor affecting a number of agglomerate properties (Fig. 8).

With so many variables involved in a granulation process, it is no wonder that more and more researchers throw in a number of factors together in an attempt to arrive at an optimum response.\cite{34,84–92}

The final goal of any granulation process is a solid dosage form, such as tablets. Therefore, when optimizing a granulation process, the list of factors affecting tablet properties may include both the granulation end-point and the tableting processing parameters, such as compression force or tablet press speed.

In one of the most interesting works based on the experimental design approach, an attempt was made to find a statistical relationship between the major factors affecting both granulation and compaction, namely, granulation end-point, press speed (dwell time), and compression force.\cite{93} The resulting equation allowed optimization of such standard response parameters as tablet hardness, friability, and disintegration time. This study has also investigated the possibility of adjusting the tableting parameters in order to account for an inherent variability of a wet granulation process.

Multivariate optimization of wet granulation may include hardness, disintegration, and ejection as response variables.\cite{94} Compressibility property of
granulations is extremely sensitive to various processing parameters of wet granulation.\(^{(93)}\)

Recently, the experimental design procedure was applied to low shear wet granulation\(^{(96)}\) with a factorial design used to evaluate the influence of such factors as binder strength and agitator speed.

**End-Point Reproducibility**

As will be shown in the following section, for every blend and a fixed set of values for processing factors (such as mixer geometry, blade speed, powder volume, amount, and method of addition of granulating liquid), a wet granulation process state (end-point) is completely characterized by rheological properties of the wet mass (density, viscosity), which are, in turn, a function of particle size, shape, and other properties. The process can be quantified with the help of dimensionless Newton Power Number \(N_p\) that will assume a certain numerical value for every state (condition) of the granulate. Under fixed processing conditions, \(N_p\) will be proportional to Net Power Consumption \(\Delta P\) for any end-point (defined, in part, by wet mass density). Thus, in order to reproduce an end-point, it is sometimes sufficient to monitor power of the impeller (or the motor) and stop when a predefined net level of the signal is reached. If, however, any of the processing variables or the rheological definition of the end-point has changed, a more sophisticated approach is required, as described below.

**END-POINT SCALE-UP**

**Scale-Up Attempts**

Numerous studies were undertaken in an attempt to determine empirically (and, lately, with a solid theoretical foundation) useful scale-up parameters of the wet granulation process.\(^{(50,91,97)}\)

In a seminal and elegant work published in 1993, Horsthuis et al. from Organon in The Netherlands have studied granulation process in Gral mixers of 10, 75, and 300 L size.\(^{(29)}\) Comparing relative swept volume, blade tip speed and Froude numbers with respect to end-point determination (as expressed by the time after which there is no detectable change in particle size), they have concluded that only constant Froude numbers result in a comparable end-point.

In another attempt to determine good scale-up parameters, the University of Maryland group under the direction of Dr. Larry Augsburger\(^{(30)}\) has applied the ideas of Leuenberger and Horsthuis to show that, for a specific material, end-point can be expressed in terms of wet massing time. For a constant ratio of a binder volume to a batch size, this factor was found to be inversely proportional to impeller speed when the impeller tip speed was held constant for all batches. However, this result was not corroborated by other studies or other materials.

Yet another example of semiempirical scale-up effort\(^{(97)}\) was based on the fact that normalized power profiles are very similar and allow for direct comparison of different size granulators, at least for the equipment and materials used in the study. Normalized power curve rose at a relatively constant rate in the region where the ratio of water to dry mass is 0.1–0.2 (“slope plateau”). Despite a rapid increase in the slope of the power curve, the desired end-point was still detectable at a moment when the slope of the power consumption signal exceeded the plateau level by a factor of 5 (empirical observation). Using this approach, an acceptable end-point (target particle size of 135\(\mu m\)) was first established on a 10-L Fielder and then scaled to 65-L Fielder and 250-L Diosna.

**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 Leuenberger in 1979.\(^{(43)}\)

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 Rayleigh in 1915.\(^{(98)}\)
Principle of Similitude

Imagine that you have successfully scaled up from a 10-L batch to 300-L 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.\[^{29}\]

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 the corresponding system points. Two kinematically similar systems are dynamically similar when they have the same ratio of forces between the 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.\[^{100}\] Once a process is expressed in terms of dimensionless variables, we are magically transferred to 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 the wet granulation process are Newton, Froude, and Reynolds:

\[
N_p = \frac{\Delta P}{(\rho \times n^3 \times d^5)} \quad \text{Newton (power)}
\]

\[
Fr = n^2 \times \frac{d}{g} \quad \text{Froude}
\]

\[
Re = d^2 \times n \times \frac{\rho}{\eta} \quad \text{Reynolds}
\]

(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\[^{101}\] 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.\[^{102}\] They are frequently used to describe mixing processes and viscous flow, especially in chemical engineering.\[^{103}\]

We have seen that there exists a sort of “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 could 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, and 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.

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. 9 represents such a range for Collette Gral mixers. It can be seen that Gral 10 and Gral 150 have 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. 10. The 10-L 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.

\textbf{II-theorem (Buckingham)}

The so-called II-theorem (or Buckingham theorem)\cite{104} states:

Every physical relationship between \( n \) dimensional variables and constants \( f(x_0, x_1, x_2, \ldots, x_n) = 0 \) can be reduced to a relationship \( f(P_0, P_1, \ldots, P_m) = 0 \) between \( m = n - r \) mutually independent dimensionless groups, where \( r \) = number of dimensional units, i.e., fundamental units (rank of the dimensional matrix).

\textbf{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.”

\textbf{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.\cite{100}

\textbf{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 groundbreaking studies conducted by Leuenberger at the University of Basel and Sandoz AG.

The Relevance List in Table 1 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?

Table 1  The relevance list used by Leuenberger (1983)

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Symbol</th>
<th>Units</th>
<th>Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power consumption</td>
<td>$P$</td>
<td>Watt</td>
<td>$M , L^2 , T^{-3}$</td>
</tr>
<tr>
<td>Specific density</td>
<td>$\rho$</td>
<td>kg/m$^3$</td>
<td>$M , L^{-3}$</td>
</tr>
<tr>
<td>Blade diameter</td>
<td>$d$</td>
<td>m</td>
<td>$L$</td>
</tr>
<tr>
<td>Blade velocity</td>
<td>$n$</td>
<td>rev/sec</td>
<td>$T^{-1}$</td>
</tr>
<tr>
<td>Binder amount</td>
<td>$s$</td>
<td>kg</td>
<td>$M$</td>
</tr>
<tr>
<td>Bowl volume</td>
<td>$V_b$</td>
<td>m$^3$</td>
<td>$L^3$</td>
</tr>
<tr>
<td>Gravitational constant</td>
<td>$g$</td>
<td>m/sec$^2$</td>
<td>$L , T^{-2}$</td>
</tr>
<tr>
<td>Bowl height</td>
<td>$H$</td>
<td>m</td>
<td>$L$</td>
</tr>
</tbody>
</table>

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

The Dimensional Matrix in Table 2 was constructed as described above, with the rows listing the basic dimensions and the columns indicating the physical quantities from the relevance list.

Transformation of the dimensional matrix (Table 3) into a unity matrix is straightforward. To transform-3 in L-row/$\rho$-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 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 indicated in the residual matrix.

The residual matrix contains five columns; therefore five dimensionless $\Pi$ groups (numbers) will be formed (Table 4).

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 $\Pi_2, \Pi_3, \Pi_4$ are “essentially constant,” the $\Pi$-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

Table 2  The dimensional matrix for case study I

<table>
<thead>
<tr>
<th>Core matrix</th>
<th>Residual matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$</td>
<td>$P$</td>
</tr>
<tr>
<td>$d$</td>
<td>$s$</td>
</tr>
<tr>
<td>$n$</td>
<td>$V_b$</td>
</tr>
<tr>
<td>$\text{Mass (M)}$</td>
<td>1</td>
</tr>
<tr>
<td>$\text{Length (L)}$</td>
<td>$-3$</td>
</tr>
<tr>
<td>$\text{Time (T)}$</td>
<td>0</td>
</tr>
</tbody>
</table>
consumption $\Delta P$) is “scale-up invariable,” that is, independent of the batch size (Fig. 11), thus specifying the functional dependence $f$ and establishing rational basis for granulation scale-up.

Experiments with five different planetary mixers with batch sizes ranging from 3.75 kg 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 the 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. In 2001, Holm, Schaefer, and Larsen 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 the 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 the 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

### Table 3 The transformed dimensional matrix for case study I

<table>
<thead>
<tr>
<th></th>
<th>Unity matrix</th>
<th>Residual matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$p$</td>
<td>$d$</td>
</tr>
<tr>
<td>$M$</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>$3M + L$</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>$-T$</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 4 Dimensionless $\Pi$ groups

<table>
<thead>
<tr>
<th>$\Pi$ group</th>
<th>Expression</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Pi_0$</td>
<td>$P/(\rho^1 \times d^5 \times n^3) = N_p$</td>
<td>Newton (Power) number</td>
</tr>
<tr>
<td>$\Pi_1$</td>
<td>$s/(\rho^3 \times d^3 \times n^0) \sim q/(\rho V_p)$</td>
<td>Specific amount of liquid $V_p \equiv$ volume of particles $q =$ binder addition rate $t = $ binder addition time</td>
</tr>
<tr>
<td>$\Pi_2$</td>
<td>$V_b/(\rho^0 \times d^3 \times n^0) \sim (V_p/V_b)^{-1}$</td>
<td>Fractional particle volume</td>
</tr>
<tr>
<td>$\Pi_3$</td>
<td>$g/(\rho^0 \times d^3 \times n^0) = Fr^{-1}$</td>
<td>Froude Number</td>
</tr>
<tr>
<td>$\Pi_4$</td>
<td>$H/(\rho^0 \times d^4 \times n^0) = H/d$</td>
<td>Ratio of lengths</td>
</tr>
</tbody>
</table>

Formed from the matrix in Table 3.
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 Rowe and Cliff’s group using the classical dimensionless numbers of Newton (power), Reynolds, and Froude to predict the end-point in geometrically similar high-shear Fielder PMA 25, 100, and 600 L machines.

The relevance list (Table 5) 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.

The dimensional matrix for Case Study II (Table 6) is different from Table 2: 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 could be adequately represented in the relevance list by the density and powder height in a semicylindrical vessel of a known diameter.

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

Table 8 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 L) correlated to the extent that allows predictions of the 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. 12) an equation of the form:

\[
\log_{10} N_p = a \log_{10}(Re \times Fr \times H/d) + b
\]

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 the slopes of regression for planetary and high-shear mixers.

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 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 the 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 that such torque values are proportional to kinematic
viscosity $\nu = \eta / \rho$ rather than dynamic viscosity $\eta$ required to compute Reynolds numbers. The degree of proportionality between $\nu$ and $\eta$ 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 $CRe$, 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 L. Assuming the absence of chemical reaction and heat transfer, the following relevance list for the wet granulation process was suggested (Table 9):

One difference from Table 5 of the previous study is the use of net power $\Delta P$ 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 $m/ (\rho \times d^3)$. 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: $Ne$, $\Psi Re$, $Fr$, and $h/d$. As before, a relationship of the form

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

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. 13). Radius of the bowl $R_b$ cubed was used to represent the bowl volume $V_b$. The graph indicates a collection of end-points produced with different mixers and different processing factors.

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

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

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

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,
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. 14 represents the resulting regression line

$$\log_{10} N_p = \frac{a}{C^2 \log_{10} \left( \frac{C \Re}{C^2 \Fr/m} \right) + b}$$

for the combined results from three mixers with bowl sizes 20, 90, and 200 L 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 L 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.

**Case Study V: Faure et al. (1999)**

This study was done on Collette Gral Mixers (8, 25, 75, and 600 L) and followed the accepted—and by now, standard—methodology developed earlier. 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 because of different wall adhesion and lid interference that was partially relieved by using a Polytetrafluoroethylene (PTFE) lining.

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

**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. Aoustin kneader with dual Z blades was instrumented for torque measurements and multiple runs were made at two scales (2.5 and 5 L).

The relevance list for this study (Table 10) differs from those discussed previously by addition of blade length as one of the crucial factors affecting the process.

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

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

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 DETERMINATION AND SCALE-UP

How to Determine an End-Point?

A wet granulation end-point should be defined empirically in terms of wet mass density and viscosity, PSD, flowability or tableting parameters (e.g., capping compression).

It is advisable to run a trial batch at a fixed speed and with a predetermined method of binder addition (for example, add water continuously at a fixed rate to a dry mix with a water-soluble binding agent).

Before adding the liquid, measure the baseline level of motor power consumption \( P_0 \) or impeller torque \( t_0 \) at the dry mix stage.

During the batch, stop the process frequently to take samples and, for each sample, note the end-point values of power consumption \( P_e \) or impeller torque \( t_e \). For each of these “end-points,” measure the resulting wet mass density \( \rho \). As a result, you will be able to obtain some data that will relate the “end-point parameters” listed above with the processing variables in terms of net motor power consumption \( \Delta P_m = (P_e - P_o) \) or net impeller power consumption \( \Delta P_i = 2\pi \times (t_e - t_o) \times n \), where \( n \) is the impeller speed [dimension \( \text{T}^{-1} \)].

Once the desired end-point is determined, it can be reproduced by stopping the batch at the same level of net power consumption \( \Delta P \) (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:

\[
N_p = \frac{\Delta P}{(\rho \times n^3 \times d^2)}
\]

In other words, if you have established an end-point in terms of some net impeller or motor power \( \Delta P \) 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 \( \Delta P \), impeller speed \( n \), blade radius \( d \), and wet mass density \( \rho \) (assuming the same batch size).

### Table 9

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Symbol</th>
<th>Units</th>
<th>Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net power</td>
<td>( \Delta P )</td>
<td>Watt</td>
<td>( \text{M L}^2 \text{T}^{-3} )</td>
</tr>
<tr>
<td>Wet mass bulk or specific density</td>
<td>( \rho )</td>
<td>kg/m(^3)</td>
<td>( \text{M L}^{-3} )</td>
</tr>
<tr>
<td>Impeller radius (or diameter)</td>
<td>( d )</td>
<td>m</td>
<td>L</td>
</tr>
<tr>
<td>Impeller speed</td>
<td>( n )</td>
<td>rev/sec</td>
<td>( \text{T}^{-1} )</td>
</tr>
<tr>
<td>Granulation dynamic viscosity</td>
<td>( \eta )</td>
<td>Pa sec</td>
<td>( \text{M L}^{-1} \text{T}^{-1} )</td>
</tr>
<tr>
<td>Gravitational constant</td>
<td>( g )</td>
<td>m/sec(^2)</td>
<td>L ( \text{T}^{-2} )</td>
</tr>
<tr>
<td>Height of granulation bed in the bowl</td>
<td>( h )</td>
<td>m</td>
<td>L</td>
</tr>
</tbody>
</table>

**Fig. 13** Regression graph of Case Study III. The Reynolds number \( \text{Re} \) was, in fact, a dimensional “pseudo Reynolds number” \( \Psi \text{Re} \). Data from a dual bowl Hobart AE240 planetary mixer. (Reproduced from Ref.[49].)
and then recalculate the target $\Delta P$ with the changed values of speed $n$ or wet mass density $\rho$.

Wet mass viscosity $\eta$ can be calculated from Net Impeller power $\Delta P$, blade radius $d$, and impeller speed $n$, using the following equations:

$$\Delta P = 2\pi \times \Delta \tau \times n$$
$$\eta = \phi \times \Delta \tau / (n \times d^3)$$

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 $\phi$ is mixer specific “viscosity factor” relating torque and dynamic viscosity (note: the correlation coefficient $\phi$ can be established empirically by mixing a material with a known dynamic viscosity, e.g., water). Alternatively, you can use impeller torque $\tau$ 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

$$V = m/\rho$$

**Table 10** Relevance list for Hutin et al. (2004)

<table>
<thead>
<tr>
<th>Quantity</th>
<th>Symbol</th>
<th>Units</th>
<th>Dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>$P$</td>
<td>Watt</td>
<td>M L$^2$ T$^{-3}$</td>
</tr>
<tr>
<td>Specific density</td>
<td>$r$</td>
<td>kg/m$^3$</td>
<td>M L$^{-3}$</td>
</tr>
<tr>
<td>Blade radius</td>
<td>$d$</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Blade speed</td>
<td>$n$</td>
<td>rev/sec</td>
<td>T$^{-1}$</td>
</tr>
<tr>
<td>Dynamic viscosity</td>
<td>$\eta$</td>
<td>Pa sec</td>
<td>M L$^{-1}$ T$^{-1}$</td>
</tr>
<tr>
<td>Gravitational constant</td>
<td>$g$</td>
<td>m/sec$^2$</td>
<td>L T$^{-2}$</td>
</tr>
<tr>
<td>Powder bed height</td>
<td>$h$</td>
<td>M</td>
<td>L</td>
</tr>
<tr>
<td>Blade length</td>
<td>$l$</td>
<td>M</td>
<td>L</td>
</tr>
</tbody>
</table>
where \( m \) is the mass (weight) of the wet mass and \( \rho \) 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 the 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 \( \rho \), wet mass viscosity \( \eta \), fill ratio \( h/d \sim m \times V_b/\rho \), 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

\[
N_p = b \times (Re \times Fr \times h/d)^a
\]

or

\[
\log N_p = \log b + a \times \log(Re \times Fr \times h/d)
\]

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 \( \Delta P \) (which can be observed in real time as a true indicator of the target end-point) for any point on the line.

ACKNOWLEDGMENT

Selected excerpts and figures from M. Levin, “Granulation: End-Point Theory, Instrumentation, and Scale-Up, Education Anytime, CD-ROM Short Course, AAPS 1999” are reprinted with permission.

APPENDIX

List of Symbols and Dimensions

\[
a, b \quad \text{Slope and intercept of a regression equation}
\]

\[
d \quad \text{Impeller (blade) diameter or radius (m); dimensional units [L]}
\]

\[
g \quad \text{Gravitational constant (m/ sec\(^3\)); dimensional units [L T\(^{-2}\)]}
\]

\[
h \quad \text{Height of granulation bed in the bowl (m); dimensional units [L]}
\]

\[
H \quad \text{Bowl height (m); dimensional units [L]}
\]

\[
l \quad \text{Blade length (m); dimensional units [L]}
\]

\[
n \quad \text{Impeller speed (rev/sec); dimensional units [T\(^{-1}\)]}
\]

\[
P \quad \text{Power required by the impeller or motor (W = J/sec); dimensional units [M L\(^2\) T\(^{-5}\)]}
\]

\[
R_b \quad \text{Radius of the bowl (m); dimensional units [L]}
\]

\[
q \quad \text{Binder liquid addition rate}
\]

\[
s \quad \text{Amount of granulating liquid added per unit time (kg); dimensional units [M]}
\]

\[
t \quad \text{Binder addition time (sec); dimensional units [T]}
\]

\[
V_p \quad \text{Particle volume (m\(^3\)); dimensional units [L\(^3\)]}
\]

\[
V_m \quad \text{Wet mass volume (m\(^3\)); dimensional units [L\(^3\)]}
\]

\[
V_b \quad \text{Bowl volume (m\(^3\)); dimensional units [L\(^3\)]}
\]

\[
w \quad \text{Wet mass; dimensional units [M]}
\]

\[
\rho \quad \text{Specific density of particles (kg/m\(^3\)); dimensional units [M L\(^{-3}\)]}
\]

\[
\nu = \eta/\rho \quad \text{Kinematic viscosity (m\(^2\)/sec); dimensional units [L\(^2\) T\(^{-1}\)]}
\]

\[
\eta \quad \text{Dynamic viscosity (Pa sec); dimensional units [M L\(^{-1}\) T\(^{-1}\)]}
\]

\[
\tau \quad \text{Torque (N-m); dimensional units [M L\(^2\) T\(^{-2}\)]}
\]

\[
\varphi = \eta \times n \times d^2/\Delta \tau \quad \text{Dimensionless “viscosity factor” relating net torque } \Delta \tau \text{ and dynamic viscosity } \eta
\]

\[
Fr = n^2 \times d/g \quad \text{Froude number. It relates the inertial stress to the gravitational force per unit area acting on the material. It is a ratio of the centrifugal force to the gravitational force}
\]

\[
N_p = P/(\rho \times n^3 \times d^2) \quad \text{Newton (power) number. It relates the drag force acting on a unit area of the impeller and the inertial stress}
\]

\[
\text{Re} = d^2 \times n \times \rho/\eta \quad \text{Reynolds number. It relates the inertial force to the viscous force}
\]
$\Psi \text{Re} = \frac{d^2 \times n \times \rho / \tau}{\text{m}^3 / \text{s}}$ “Pseudo Reynolds number” (m$^3$/s); dimensional units [L$^{-3}$ T]. Note: this variable physically is a reciprocal of volume flow rate
$Ga = \frac{Re^2}{Fr}$ Galileo number

ARTICLES OF FURTHER INTEREST

**Fractal Geometry in Pharmaceutical and Biological Applications**, p. 1791.
**Scale-Up and Post Approval Changes (SUPAC)**, p. 3188.

REFERENCES

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