ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 52 (2001) 279–288

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Review article

New trends in the production of pharmaceutical granules: the classical batch concept and the problem of scale-up

Hans Leuenberger*

Institute of Pharmaceutical Technology, Pharmacenter of the University of Basel, Basel, Switzerland

Received 5 February 2001; accepted in revised form 28 June 2001

Abstract

The moist agglomeration process, i.e. the wet massing, screening, and subsequent drying is often a critical unit operation. The correct amount of granulating liquid and the correct monitoring and detection of the granulation kinetics are important issues. The method to monitor the kinetics needs to be robust and should be applicable for any batch size. In this context, the theory of scale-up and the monitoring of the moist agglomeration process are reviewed.

It has to be kept in mind that the production of granules in the pharmaceutical industry is still based on a batch concept. This concept offers many advantages with respect to quality assurance as a batch can be accepted or rejected. From experience, it is well known, however, that the scale-up of the batch size may lead to problems. This fact is due to the variety of the equipment involved and to the fact that there is a lack of well-known 'scale-up invariant' parameters. A survey of the granulation end-point detection procedure shows that the majority of the equipment manufacturers offer mixer/kneaders for the moist agglomeration process instrumented with a power consumption device. In this review, this and other approaches are discussed and emphasis is placed on how to best use the power consumption method.

The question of robust formulations leads to the conclusion that, for a robust dosage form design, new concepts such as percolation theory have to be applied. A typical example is presented, which illustrates the effect of a percolation phenomenon.

Keywords: Granulation end-point detection; In-process control; Dimensional analysis; Robust dosage form design; Percolation theory

1. Introduction

New trends in the production of pharmaceutical granules: the classical batch concept and the problem of scale-up. What are the new trends? In the past, the batch concept was never seriously questioned. This situation has changed especially since production costs have become an issue. Thus, today the whole production process is analyzed to identify critical steps and to find out, whether there is a chance to save money and to increase productivity. It is evident that the scale-up process is a critical step leading to additional costs, especially when there are unforeseen problems. Thus, it is not surprising that the number of recent publications treating the scale-up process has considerably increased. In addition, scale-up problems are nowadays carefully analyzed by the registration authorities and in case of doubts about the quality of the production batch, expensive bioequivalence studies between small-scale and large-scale batches, i.e. manufactured with the small and large size equipment, have to be done. What are the reasons for the differences in quality between a small batch and a large batch? There are several possible explanations. In the early phase of the development, only a limited amount of the drug substance is available. Thus, small sized production equipment is chosen for the small batch size. However, the most critical point is the following: the formulation and the process are optimized using, in general, small-scale equipment. Subsequently, the formulation is 'frozen', i.e. during the clinical studies it is no longer possible to change the process and/or the formulation. For this reason, the formulation needs to be robust and has to lead to the same quality of the product using small and large-scale equipment. Thus, the scale-up process is an extremely important step. Unfortunately, in many cases the variety of the equipment involved does not facilitate the task of scale-up. During the scale-up process, the quality of the granules may change. A change in the granule size distribution, final moisture content, friability, compressibility, and compactibility of the granules may strongly influence the

* Institute of Pharmaceutical Technology, Pharmacenter of the University of Basel, Klingelbergstrasse SO, CH-4056, Basel, Switzerland.
Tel.: +41-61-267-1500; fax: +41-61-267-1516.
E-mail address: hans.leuenberger@unibas.ch (H. Leuenberger).

0939-6411/01/$ - see front matter
PII: S0939-6411(01)00200-4

properties of the final tablet, such as tablet hardness, tablet friability, disintegration time, dissolution rate of the active substance, etc. In order to identify critical steps of the batch granulation and the scale-up process, the paper is structured as follows. Fundamental aspects of the classical batch-type moist agglomeration process and of the scale-up exercise are reviewed. The term 'reviewed' needs an acceptable definition in this context: the author of this paper has been often asked as an invited speaker to focus his presentation on his own research work that the audience can take advantage of his personal experience and his personal approach. The content of this paper complies to a large extent with this idea, i.e. the paper is not a comprehensive review discussing the different approaches of the different research groups in detail. However, other approaches and concepts are mentioned without elaborating the merits and weaknesses. It is suggested that the reader of this paper consult directly the original papers cited. It is important that the reader can make his own unbiased choice of his preferred approach. Thus, just the general ideas of the different types of approaches including important boundary conditions will be summarized. Without the intention to blame anybody, it is also of interest to study the list of references of the individual research papers including the references that may have been consciously or unconsciously omitted. In fact, different types of approaches should be encouraged. The author of this paper usually advises his PhD students to develop first their own ideas and then to consult the literature, to see whether the idea is really new and original. Thus, a replication of an earlier work can be avoided. On the other hand, it can be of interest to replicate an existing research work for validation purposes and/or to start one's own projects in this research field.

For the better understanding of the subsequent sections, fundamental approaches on the micro- and macrolevel are reviewed in the following section.

2. Fundamentals

Fundamental research work in the area of the moist agglomeration process goes back to Newitt and Conway-Jones [1] and Rumpf [2] describing at the microscopic level the mathematical models for the liquid bridge forces and Ennis et al. [3] for the dynamic viscous forces, which take place during the moist agglomeration process. The following equations describe the cohesive stress σ_c for the pendular liquid bridge force [1,4]:

$$\sigma_c = A\pi\gamma/x(1 + \mathrm{tg}(\theta/2)) \quad (1)$$

where A is the constant taking into account the packing and the shape of the particles; γ the interfacial tension between the granulating liquid and the particle and θ the half center angle defining the extent of the liquid bridge between two spherical isometric particles of diameter x. The cohesive stress for the force of the liquid bridge in the funicular

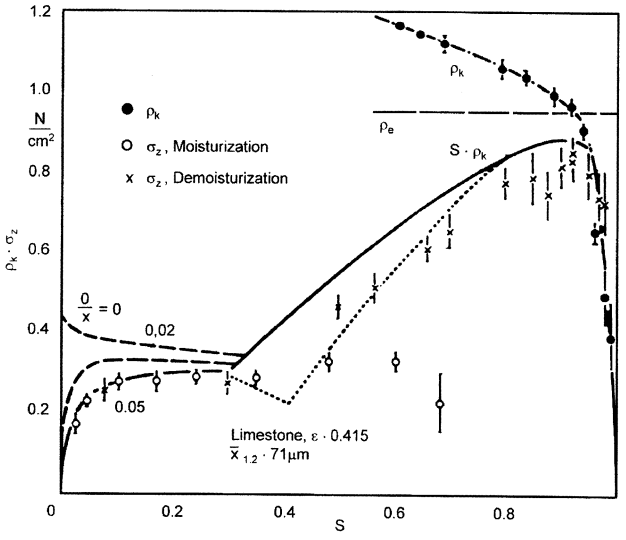

Fig. 1. Tensile strength of a moistened limestone powder bed according to Schubert [5].

state [2] reads as:

$$\sigma_c = Sp_e \quad (2)$$

where S is the degree of saturation of the inter-particulate void space with the granulating liquid and p_e = entry suction potential. The model of Ennis et al. [3] predicts that the collisions will result in coalescence when the viscous Stokes number St_v is less than some critical Stokes number St_v^*:

$$St_v = 8\rho ru/9\eta \text{ and } St_v^* = (1 + 1/e)\ln(h/h_a) \quad (3)$$

where ρ is the granule density, r the harmonic mean granule radius of the two spheres, u the half relative velocity of impact, η the viscosity of the granulating liquid, h the thickness of the liquid surface layer, h_a the characteristic height of the surface asperities and e the coefficient of restitution [3].

Schubert [5] describes the relation between the tensile strength of moistened limestone and the degree of saturation with water (see Fig. 1).

Leuenberger was able to show the link (see Figs. 1 and 2) between the microscopic forces and the power consumption

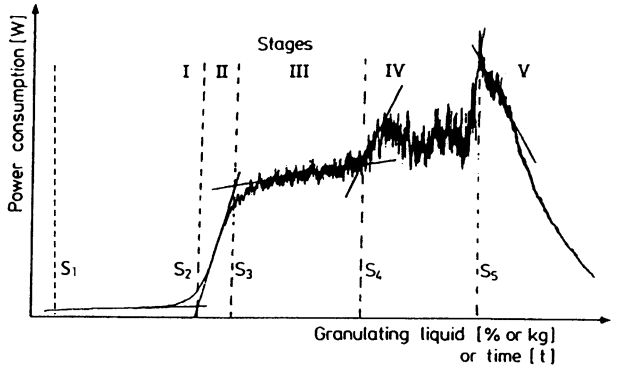

Fig. 2. Division of a power consumption curve according to Leuenberger [4].

profile, measured during the constant addition of granulating liquid to the powder bed [4,6],

$$dN/dV = \mu\sigma_c\kappa \quad (4)$$

where dN/dV is the volume specific energy consumption, μ the apparent friction coefficient and κ the shear rate.

It has to be kept in mind that the moist agglomeration process is a superposition of different processes as first described by Sastry and Fuerstenau [7] and recently modified by Litster and Ennis, see e.g. [8]. Among the fundamental approaches, the Population Balance Models have also to be addressed.

Due to the fact that fast computation can be performed today with personal computers, this discipline has evolved considerably and covers fluidized bed agglomeration, as well as drum agitation and high-shear granulation [9–11] since the early work of Sastry. The goal of the Population Balance Models is to simulate real agglomeration processes from first principles. It is evident that such an approach is an ambitious one. Thus, in practice, the mathematical model needs to be adapted to the experimental findings. Another approach is not to improve the mathematical models but to adapt the experimental set-up to fit better an existing mathematical model. This point can lead to controversial discussions among people from industry and academia: a typical example is the use of glass ballotini, i.e. nicely spherical particles with a smooth surface as a starting material for moist agglomeration experiments. Both approaches have merits and weaknesses and will not be further discussed in this paper. A point of discussion concerns the merits of purely descriptive research papers. Today, it is generally accepted that the 'art' of agglomeration has become a science with lesser room for papers with descriptive contents.

Another research area, which is not treated in this paper, is related to the production of spherical granules by the extrusion process. A lot of excellent work has been done by Newton et al. [12]. The agglomeration processes including dry agglomeration techniques such as tabletting and the roller compaction process are comprehensively reviewed in the books of Pietsch [13,14].

The topics for the following sections are dedicated to the classical batch granulation process in a bowel (planetary or high-shear mixer), to the questions related to the scale-up exercise and to the problem of robust and non-robust formulations. Emphasis is placed on the specific approach and on the underlying concept of the Basel research group. Questions related to the control of processes in the fluidized bed, i.e. the moist agglomeration and the drying process are not treated.

3. Monitoring and controlling the batch agglomeration process with respect to the scale-up exercise: approach and concept

The scale-up process of the batch-type moist agglomeration process is analyzed taking into account mathematical considerations of the scale-up theory [15–20], the search for scale-up invariants, the establishment of in-process control methods [20–23] based e.g. on the power consumption method, as well as the design of a robust dosage form. In this respect, new concepts such as the percolation theory [24] play an important role.

In small-scale equipment, the use of the torque measurement as an in-process control is often more sensitive than the measurement of the power consumption. The measurement of the torque is also used to control the in situ production of pharmaceutical pellets in a rotary fluidized bed system [25–27]. Both the power consumption and the torque measurement methods are today used in industry and by many research groups (see e.g. [28–40]). Both methods can also be successfully applied to the melt agglomeration process [41,42]. It has to be kept in mind that in too many cases the focus for the in-process control of the moist agglomeration process was put on the 'end-point detection'. In this respect, it is important to realize that the measurement of the power consumption profile or the torque as a function of the amount of granulation liquid added can provide an earlier signal (landmark, control signal!) such as the steepest ascent of the power consumption profile, which can be used to control very rigorously the wet agglomeration process (see e.g. [4,20,21,40]).

In practice, the 'early signal' (power consumption threshold detection, or peak detection) indicates a well defined and reproducible 'cohesiveness' of the powder mass, which can be used to fine tune the moist agglomeration process by adding from this 'point of reference' a constant amount of granulation liquid. Thus, minor changes in the particle size distribution of the starting material and 'seasonal effects' (different relative humidities in winter, summer) leading to differences in the moisture content of the starting material can be taken into account.

4. Theoretical considerations related to the scale-up process

4.1. The principle of similarity

4.1.1. The definition of similarity and dimensionless groups

The important concept for scale-up is the principle of similarity [15–20]. When scaling up any mixer/granulator (e.g. planetary mixer, high-speed mixer, pelletizing dish, etc.), the following three types of similarity need to be considered: geometric, kinematic, and dynamic similarity. Two systems are geometrically similar when the ratio of the linear dimensions of the small scale and scaled-up system is constant.

Two systems of different size are kinematically similar when in addition to the systems being geometrically similar, the ratio of velocities between corresponding points in the two systems are equal. Two systems of different size are dynamically similar when *in addition* to the systems

being geometrically and kinematically similar, the ratio of forces between corresponding points in the two systems are equal.

4.1.2. Similarity criteria

There are two general methods of arriving at similarity criteria:

- (A) When the differential equations or in general the equations, that govern the behavior of the system are known, they can be transformed into dimensionless forms.
- (B) When differential equations or in general equations, that govern the behavior of a system, are not known, such similarity criteria can be derived by means of dimensional analysis.

Both methods yield dimensionless groups, which correspond to dimensionless numbers [15], e.g. Reynolds number, *Re*; Sherwood number, *Sh*; Froude number, *Fr*; Schmidt number, *Sc* etc. [16]; Nusselt number, *Nu*.

The classical principle of similarity can then be expressed by an equation of the form:

$$\pi_1 = F(\pi_2, \pi_3, \ldots) \tag{5}$$

This equation may be a mechanistic (case A) or an empirical one (case B):

- (A). $\pi_1 = e^{-\pi_2}$ with the dimensionless groups:

  $$\pi_1 = \frac{P(x)}{P(0)}$$

  where $P(x)$ is the pressure at level x and $P(0)$ the pressure above sea level ($x = 0$).

  $$\pi_2 = \frac{E(x)}{RT} \quad \text{with } E(x) = Mgx \tag{6}$$

  where $E(x)$ is the molar potential energy; M the molecular weight; g the gravitational acceleration, x the height above sea level and RT the molar kinetic energy.
- (B)

  $$\pi_1 = a(\pi_2)^b(\pi_3)^c \tag{7}$$

  The unknown parameters a, b, and c are usually determined by non-linear regression calculus.

4.2. Buckingham's theorem

For a correct dimensional analysis, it is necessary to consider Buckingham's theorem, which may be stated as follows [19,20]:

The solution to every dimensionally homogeneous physical equation has the form $F(\pi_1, \pi_2, \pi_3\ldots) = 0$, in which π_1, π_2, π_3, ….. represent a complete set of dimensionless groups of the variables and the dimensional constants of the equation.

If an equation contains n separate variables and dimensional constants and these are given dimensional formulas in terms of m primary quantities (dimensions), the number of dimensionless groups in a complete set is $(n - m)$.

4.3. Scale-up and monitoring of the wet granulation process

4.3.1. Dimensionless groups

As the behavior of the wet granulation process cannot be described so far adequately by mathematical equations, the dimensionless groups have to be determined by a dimensional analysis. For this reason, the following idealized behavior of the granulation process in the high-speed mixer is assumed:

- the particles are fluidized;
- the interacting particles have similar physical properties;
- there is only a short-range particle–particle interaction;
- there is no (macroscopic) system property equivalent to viscosity, i.e. (a) there are no long-range particle–particle interactions and (b) the viscosity of the dispersion medium air is negligible.

According to Buckingham's theorem the following dimensionless groups can be identified:

- Power number

  $$\pi_1 = \frac{P}{r^5\omega^3\rho}$$

- Specific amount of granulation liquid

  $$\pi_2 = \frac{qt}{V\rho}$$

- Fraction of volume loaded with particles

  $$\pi_3 = \frac{V}{V^*}$$

- Froude number (centrifugal/gravitational energy)

  $$\pi_4 = \frac{r\omega^2}{g}$$

- Geometric number (ratio of characteristic lengths)

  $$\pi_5 = \frac{r}{d}$$

List of symbols:

P	Power consumption.
r	Radius of the rotating blade (first characteristic length of the mixer).

ω Angular velocity.
ρ Specific density of the particles.
q Mass (kg) of granulating liquid added per unit time.
t Process time.
V Volume loaded with particles.
V^* Total volume of the vessel (mixer unit).
g Gravitational acceleration.
d Diameter of the vessel (second characteristic length of the mixer).

The following remark has to be made: if the viscous forces play an important role, i.e. in the case of highly viscous binders or in order to study properly the dynamic agglomeration events on the microscopic level, the Stokes number St_v [3] has to be introduced. The Stokes number describes the ratio of granule collisional energy to the viscous dissipation energy brought about by the interstitial binder. In the case of high viscous binders, the (macroscopic) power consumption profile changes as the liquid bridges are no longer mobile [20].

Based on the above-defined boundary conditions using only low viscous granulating liquid the following scale-up equation can be established:

$$\pi_1 = a(\pi_2)^b(\pi_3)^c(\pi_4)^d(\pi_5)^e \quad (8)$$

In general, however, it may not be the primary goal to know exactly the empirical parameters a, b, c, d, and e of the process under investigation, but to check or monitor pragmatically the behavior of the dimensionless groups (process variables, dimensionless constant) in the small- and large-scale equipment. The ultimate goal would be to identify scale-up invariants.

5. The principle of the power consumption method

5.1. The power consumption method

The principle of power consumption method was described in detail in Refs. [5,20–23,40]. In the majority of our experiments in Basel, a Diosna V 10 as a high-shear mixer was used keeping constant impeller (270 rpm) and chopper speed (3000 rpm) during the experiments. However, it is no problem to use other types of high-shear mixers such as the Glatt-Powrex Vertical Granulator or the horizontal high-shear mixers of Lödige.

If it is the goal to study the agglomeration process in the bowel, it is important to measure the so-called 'native' granule size distributions as a function of the amount π of granulating liquid added. For this purpose, the green, i.e. still moist, granules have to be dried very carefully. Thus, to reduce the possible side effects due to the friability of more or less already dried granules in a fluidized bed equipment and/or in order to prevent secondary agglomeration during the drying process in a dish dryer, on the granule size distribution the following process was adapted: (1) the granules are dried only for 3–5 min in a fluidized bed (Glatt Uniglatt) and (2) subsequently for 15–25 min in a dish dryer to obtain moisture equilibrium corresponding to 50% relative humidity of the air at ambient temperature (20°C). The particle size distributions were determined according to DIN 4188 using ISO-norm sieve sizes [23]. If the reader is interested in a literature study it is important to check whether 'native' granule size distributions have been measured or if the granule size distribution was measured after screening through a sieve.

Nowadays, most of the mixer/granulators types offered in the market are equipped or can be equipped with the option to measure the power consumption or torque profile during the moist agglomeration process. Concerning the measurement of the power consumption profile or torque profiles, different approaches are possible. It has to be kept in mind that power consumption profiles and torque measurement yield the same result [36,37]. Already the first attempts to monitor the granulation process were made by measuring the power consumption or torque of a planetary mixer [38,39]. In the case of results obtained with very small-scale equipment, such as mixers used in a kitchen, the signal-to-noise ratio has to be carefully analyzed. If the signal-to-noise ratio is low, the results have to be treated with caution. It is evident that the no-load power consumption has to be subtracted. If power consumption profiles are studied in the literature, it is important to note the type of mixer, the formulation, and last but not least, whether the granulating liquid was added in the beginning as a bolus or continuously added with a pump. It also has to be clarified, if after the addition of the granulating liquid, the wet powder was still massed for a certain time or not. The Basel group has adopted the following concept to *characterize a* formulation: the power consumption is measured as a function of the low viscous granulating liquid added continuously with a pump to the dry powder mix containing the well soluble binder till a suspension is obtained (see Fig. 2).

5.2. Typical materials (example)

The physical characteristics of typical starting materials are compiled in Table 1. Polyvinylpyrrolidone was added in a dry state at a level of 4% (w/w) to the powder mix of lactose (86% w/w) and corn starch (10% w/w). As a granulating liquid, demineralized water was used and pumped to the powder mix at a constant rate of 15 g min^{-1} kg^{-1}. It has to

Table 1
Physical properties of lactose (L) and corn starch (MS)

	Lactose (L)	Corn starch (MS)
Bulk density (g/cm^3)	0.58	0.49
Tapped density (g/cm^3)	0.84	0.65
True density(g/cm^3)	1.54	1.5
S_m (mass specific surface) (cm^2/g)	3055	
Mean diameter (μm)	40	25

be kept in mind that the solubility of the components plays an important role and influences the power consumption profile.

6. Evidence for scale-up invariants based on the power consumption

6.1. How to monitor and control the moist agglomeration process

In the case of the wet granulation process in a mixer/kneader, the granulation process can be easily monitored by the determination of the power consumption [4,20–23,40] (Fig. 2) profile.

The typical power profile consists of five different phases (Fig. 2).

- Phase I (S_1–S_2): up-take of the added amount of granulating liquid by the components to saturate the moisture content (equilibrium moisture content at 100% relative humidity of the air).
- Phase II (S_2–S_3): start of the formation of liquid bridges (pendular state) between the primary particles.
- Phase III (S_3–S_4): plateau phase, i.e. filling up the interparticulate void space with the granulating liquid (transition from the pendular to the funicular state). The liquid bridges are mobile.
- Phase IV (S_4–S_5): funicular state with isolated 3-dimensional clusters (snowballs) having already reached the capillary state.
- Phase V ($>S_5$): transition from the capillary state (i.e. void space between the primary particles completely occupied by the granulating liquid) to a suspension.

Usable granulates can be produced in a conventional way only within the plateau region S_3–S_4 according to the nomenclature in Fig. 2. It is important to realize that the liquid bridges of Phase III are mobile and thus the granulation liquid needs to have a low viscosity. Fig. 3 indicates that the change of the type of mixer changes the power consumption profile. The important increase in the power consumption of the Glen mixer for amounts of granulating liquid $S > S_4$ can be related to the build-up of large snowballs in the planetary mixer between the wall and the impeller blade. However, the important plateau phase can be well recognized in both cases. However, the actual power consumption signal (absolute amount of power used) of mixers of different type, can differ greatly for a given granulate composition.

The important point is now whether the power consumption profile as defined by the parameters S_3, S_4, and S_5 is independent of the batch size. For this investigation, mixers of the planetary type (Dominici, Glen, Molteni) were used.

The batch size ranged from 3.75 up to 60 kg. To obtain precise scale-up measurements the excipients, which are used (10% w/w corn starch, 4% w/w polyvinylpyrrolidone as binder, and 86% w/w lactose) need to belong to identical lots of primary material. As can be seen from Fig. 4 the

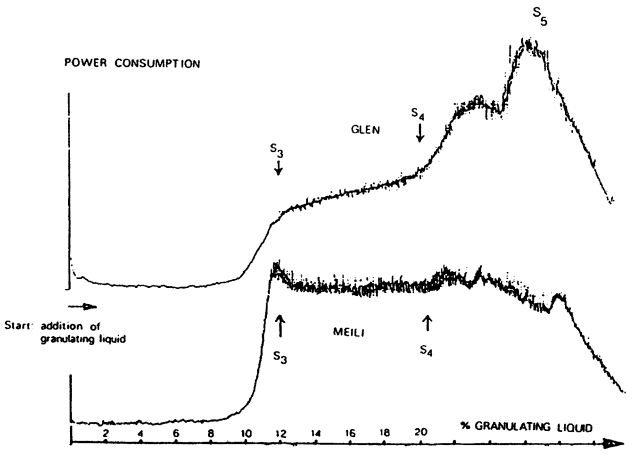

Fig. 3. Power consumption profiles of two types of a mixer/kneader.

amount of granulating liquid is linearly dependent on the batch size. During the scale-up exercise, the rate of addition of the granulation liquid was enhanced in proportion to the larger batch size. Thus, the power profile, which was plotted on the chart recorder showed the characteristic S_3, S_4, and S_5-values independent of batch size within the same amount of time since the start of the addition of granulation liquid. This fact is not surprising as in terms of scale-up theory, the functional dependencies of the dimensionless group numbers π_1 and π_2 were measured:

$$\pi_1 = F(\pi_2) \tag{9}$$

The other numbers π_3, π_4, and π_5 were kept essentially constant. From these findings, one can conclude that the chosen uncritical relative amount of granulating liquid per amount of particles to be granulated is a constant [20–23]. It is evident that the first derivative of the power consumption curve is a scale-up invariant and can serve as an in-process control and for a fine-tuning of the correct amount of granulating liquid (see Fig. 5). These findings led to the construction of a control device prototype [5,23] at Sandoz Ltd (today: Novartis Ltd) as a result of a fruitful cooperation between H. Leuenberger (Pharmaceutical Development

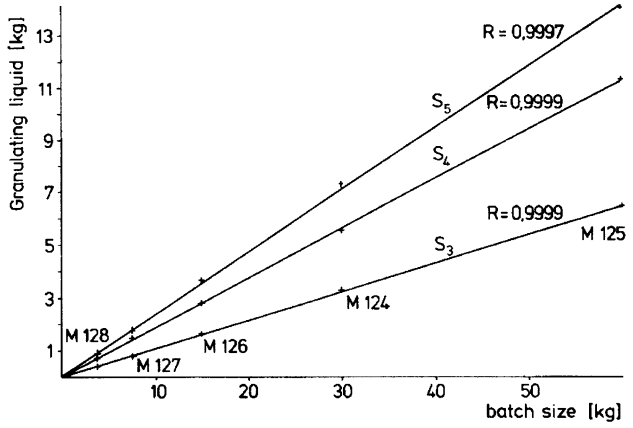

Fig. 4. Scale-up precision measurements with identical charges [20].

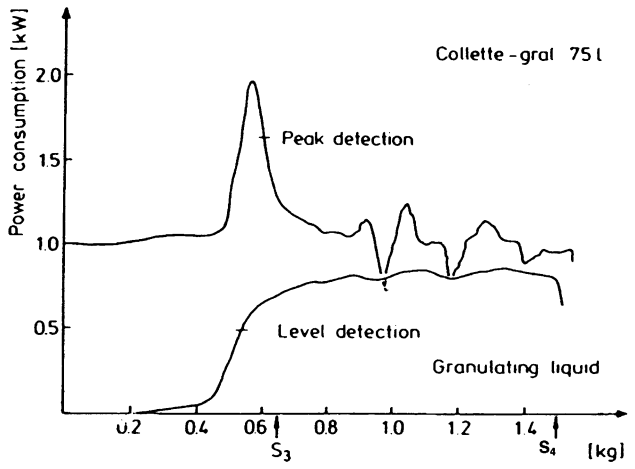

Fig. 5. Power consumption profile of a high-speed mixer (Collette-Gral 751) with peak and level detection [4].

Department), J. Werani (Pharmaceutical Manufacturing Department), and M. Dürrenberger (Engineering Department) as early as 1982 [5].

The control device was then successfully commercialized by Collette Ltd, which instrumented at that time all the Collette Gral mixers used world wide by Sandoz Ltd in order to guarantee a higher homogeneity of the batch to batch quality, i.e. between the sites of manufacture (Brazil, Spain, Switzerland, USA, etc.) as well as a function of the time. In 1985, Holm, Schaefer, and Kristensen, from the Danish School of Pharmacy in Copenhagen suggested using the power control profile as well as its first derivative to determine the end-point of the granulation process [28]. The Copenhagen group (see e.g. Refs. [29,30]) and also the group in England with York et al. (see e.g. Refs. [31,32]) have since that time invested a lot of research work in the area of process control and scale-up based on mixer torque rheometer and/or power consumption measurements. In 1999, Landin et al. [31] published the results of a study using the dimensionless numbers of Power, Reynolds, and Froude to analyze the scale-up behavior of a dicalciumdihydrate formulation with pregelatinized starch as a binder in planetary mixers with a size capacity between 5 and 200 l.

It is recommended that the power consumption profile be measured in parallel with the temperature of the moistened powder bed as an 'in-process control' to avoid an excessive temperature increase (drug stability, undesired melting of components, etc.) however, the temperature profile may not be a very reliable and versatile parameter to detect the granulation endpoint [33]. In place of the already discussed power consumption/torque measurements, other approaches were studied e.g. the frequency analysis of the power consumption [34], the use of fast Fourier transform technique [35], or sophisticated moisture sensors based on near infrared spectroscopy [43] during the moist agglomeration process. To the knowledge of the author of this paper, none of these concepts have led so far to a control device, which proved to be the method of choice. The effort to look at alternatives to replace the method of measuring the power consumption profile indicates, quite clearly, that the power consumption/torque measurements are not always satisfactory. This statement is correct. In many cases, the power/torque measurements are just used as a fingerprint for batch documentation and not for control purposes.

For a successful application of the control device [4,20,23,40] based on the power consumption method, it is important to apply strictly the following rules:

1. The formulation and the wet agglomeration process needs to show, if possible, an ideal power consumption profile (see Fig. 2). Such a profile can only be obtained if the components (drug substance, excipients) are not too soluble in the granulating liquid. It is important that the power consumption profile shows an increase before the end-point, i.e. before the point of no return is reached.
2. In order to keep constant the amount of binder in the formulation, an easily water-soluble binder (PVP, pregelatinized starch, etc.) should be added to the dry premix.
3. As a granulating liquid, a low viscous solvent, preferably deionized water, should be used.
4. It is an absolute prerequisite not to add the granulating liquid at the beginning as a bolus but to add the granulating liquid with a pump at a constant speed to be able to 'fine-tune' the necessary amount of granulating liquid on the basis of an early signal (not endpoint) as discussed in the previous sections.
5. The validation of the moist agglomeration process with the control device needs to include the subsequent screening and drying process.
6. An excellent check is the higher homogeneity of the yield of the granule size distribution (see Table 2). Nevertheless, other granule properties such as the compression profile and the properties of the final tablets should be tested too.

With this method the Manufacturing Department at Sandoz Ltd was able to increase the mean yield (see Table 2) of the granule size fraction between 90 and 710 μm by

Table 2
Comparison between the manual and the automatic mode of controlling the moist agglomeration process [23]

Type of mode	Yield (% w/w) 90–710 μm	% Undersize <90 μm	% Undersize <710 μm
Manual mode $n = 20$ batches	82.03 ± 2.42	6.80 ± 0.51	88.30 ± 2.05
Automatic mode $n = 18$ batches	91.45 ± 0.36	5.40 ± 0.35	96.80 ± 0.31

10%, and what is even more important, could reduce the standard deviation of the mean yield by an order of magnitude [23].

6.2. The use of power consumption method in dosage form design

Robust formulations are today an absolute prerequisite. Concerning the production of granules, the granule size distribution should not vary from batch to batch. The key factors are the correct amount and the type of granulating liquid. The interpretation of the power consumption method can be very important for an optimal selection of the type of granulating liquid. The possible variation of the initial particle size distribution of the active substance and/or excipients can be compensated in the case of an intelligent in-process control method, e.g. based on the power consumption profile. However, the formulation may not be very robust if the volume-to-volume ratio of certain excipients such as maize starch and lactose correspond to a critical ratio or percolation threshold [24,44–48].

With dosage form design, it is often necessary to compare the performance of two different granule formulations. These two formulations differ in composition and consequently vary also in the amount of granulating liquid required.

Thus, the following question arises: how can the quantity of granulating liquid be adjusted to achieve a correct comparison?

The answer is not too difficult as it is based on identified physical principles. A correct comparison between two formulations is often a prerequisite as the dissolution process of the active substance in the final granulate or tablet can be affected both by the amount of granulating liquid and by the qualitative change (excipients) in the formulation. In order to calculate corresponding i.e. similar amounts of granulating liquid in different compositions, it is necessary to introduce a dimensionless amount of granulating liquid π. This amount π can be defined as the degree of saturation of the inter-particulate void space between the solid material.

$$\pi = \frac{S - S_2}{S_5 - S_2} \tag{10}$$

where S is the amount of granulating liquid (in l), S_2 the amount of granulating liquid (in l) necessary which corresponds to a moisture equilibrium at approximately 100% relative humidity and S_5 the complete saturation of inter-particulate void space before a slurry is formed (amount in l)

Power consumption is used as an analytical tool to define S values for different compositions. Thus, the granule formation and granule size distribution of a binary mixture of excipients are analyzed as a function of the dimensionless amount of granulating liquid π. This strategy allows an unbiased study of the growth kinetics of granules consisting of a single substance or binary mixture of excipients. Thus, it is important to realize that the properties of the granule batches are analyzed as a function of the dimensionless amount of granulating liquid π [5,6].

Less dense and smaller granules are obtained with an amount of granulating liquid close to S_3. Harder and denser granules can be produced with an amount of granulating liquid close to S_4. It could be shown [47] that the growth of the mean granule diameter follows a first-order kinetics in the range between the saturation levels S_3 and S_4 (plateau), i.e. where the pendular state still dominates. It could be shown that between S_3 and S_4 an exponential growth of the mean particle size occurs. For saturation levels exceeding S_4 ($\Pi >$ approximately 60%) the system becomes over-wetted. Thus, the measurement of the complete power consumption profile between S_1 and S_5 is important in order to determine the growth kinetics as a function of the dimensionless amount of granulating liquid π, i.e. as % liquid saturation S. It is evident that it is not possible that the granulating liquid can saturate the inter-particulate pore space to an extent that exceeds $\Pi = 100\%$, which was reported for the case of calcium hydrogen phosphate using different binders and a different approach [49].

If excipients are used, which exhibit a high plasticity after being moistened such as microcrystalline cellulose quite spherical granules can be achieved for a liquid amount S close to S_4 in a high-shear mixer. If a rotary granulator [25,27] is used, a direct pelletization of microcrystalline cellulose is possible with a rather narrow size distribution of the final pellets. It is recommended to equip such a rotary granulator in order to measure the torque exerted on the rotating bottom plate during the addition of granulating liquid. The mean size of the pellets is related to the torque value (see Fig. 6). An alternative approach is to characterize separately the rheological properties of the excipients used [50].

6.3. Robust formulations and dosage form design

6.3.1. The effect of percolation theory

A percolation phenomenon can be best explained in the

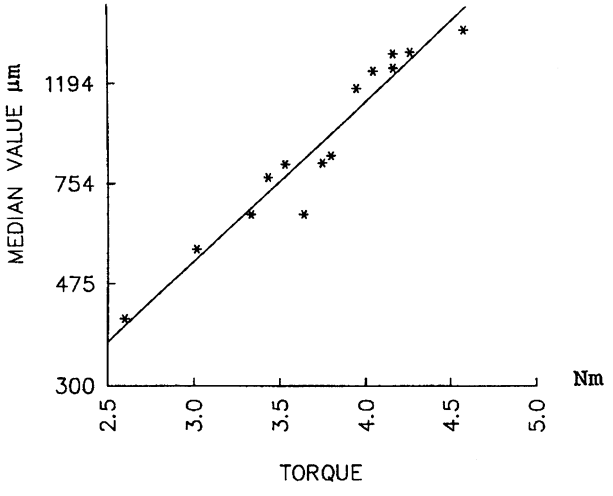

Fig. 6. Mean pellet size as a function of the torque measured [25].

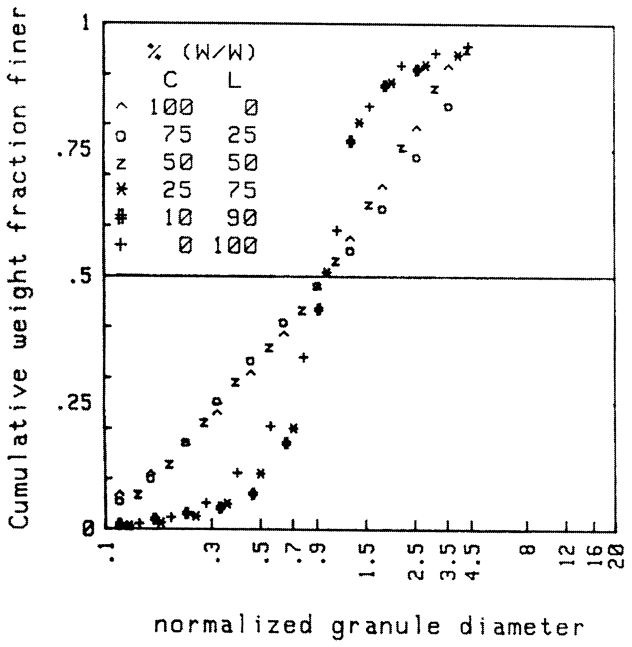

Fig. 7. Cumulative particle size distribution of the agglomerates at a fixed normalized amount $\pi(=0.62)$ of granulating liquid for different ratios of the binary powder mixture consisting of lactose (L) and corn starch (MS).

case of a binary mixture consisting of two substances with very different physical properties, such as an electrical conductive material and an electrical isolator.

Thus, with a mixture between Al_2O_3 (an electrically insulating material) and copper powder, electrical conductivity of the Al_2O_3/copper tablet is only observed if the copper powder forms an electrical pathway between the electrodes attached to the surface of the tablet produced. The critical ratio where conductivity is measured corresponds to the so-called percolation threshold p_c [24]. In the case of a fixed normalized amount π of granulating liquid (see Fig. 7), it is interesting to note that the granules obtained from a lactose/corn starch powder mixture lead to granule size distributions equivalent either to the granule size distribution of lactose (L) or corn starch (MS). This result can be interpreted based on percolation theory (Fig. 7), i.e. the properties differ for compositions below or above a critical ratio p_c of components between lactose and corn starch.

This result can have a tremendous effect if e.g. the particle size distribution of the starting material changes and influences the exact percolation threshold p_c. Thus, if the formulation is close to p_c concerning the ratio of the excipients lactose to corn starch the resulting granule size distribution can exhibit a linear or an S-shape (see Fig. 7) corresponding to a processing below or above p_c. In order to develop robust formulations, it is important that the formulation does not contain critical ratios or percolation thresholds [44–48,51] i.e. the theory of percolation is taken into account.

References

[1] D.M. Newitt, J.M. Conway-Jones, A contribution to the theory and practice of granulation, Trans. Inst. Chem. Eng. 36 (1958) 422–442.
[2] H. Rumpf, Grundlagen und Methoden des Granulierens. 1. Teil: Begriffe, Anwendung und Eigenschaften der Granulate, Chem. Ing. Tech. 30 (1958) 144–158.
[3] B.J. Ennis, G.J. Tardos, R. Pfeffer, Powder Technol. 65 (1991) 257–272.
[4] H. Leuenberger, Granulation, new techniques, Pharm. Acta Helv. 57 (3) (1982) 72–82.
[5] H. Schubert, Kapillardruck und Zugfestigkeit von feuchten Haufwerken aus körnigen Stoffen, Chem. Ing. Tech. 45 (1973) 396–401.
[6] H. Leuenberger, Design and optimisation approaches in the field of granulation, drying and coating, in: D.J.S. Crommelin, K.K. Midha, T. Nagai (Eds.), Pharmacy World Congress '93, Tokyo, Proc. 53rd Int. Congress Pharm. Sci 1993, Medpharm, Scientific Publishers, Stuttgart, 1994, pp. 493–511.
[7] K.V.S. Sastry, D.W. Fuerstenau, Mechanisms of agglomerate growth in green pelletization, Powder Technol. 7 (1973) 97–105.
[8] S.M. Iveson, J.D. Litster, K. Hapgood, B.J. Ennis, Nucleation, growth and breakage phenomena in agitated wet granulation process: a review, Powder Technol. 117 (2001) 3–39.
[9] C.A. Biggs, C. Sanders, A.C. Scott, A.W. Willemse, A.C. Hoffmann, T. Instone, M.J. Hounslow, Coupling granule properties and granulation rates in high-shear granulation, Seventh International Symposium on Agglomeration, Albi, France, May 29–31, Preprints, vol. 1, 1, 2001, pp. 307–316.
[10] S. Heinrich, M. Peglow, M. Ihlow, L. Morl, Particle population modeling in fluidized bed-spray granulation – analysis of the steady-state and unsteady behaviour, Seventh International Symposium on Agglomeration, Albi, France, May 29–31, Preprints, vol. 1, 2001, pp. 295–305.
[11] A.A. Adetayo, J.D. Litster, S.E. Pratsinis, B.J. Ennis, Population balance modelling of drum granulation of materials with wide size distribution, Powder Technol. 82 (1995) 37–49.
[12] J.M. Newton, S. Boutell, J. Chatchawalsaisin, Preparation of spherical granules by extrusion/spheronization without microcrystalline cellulose, Seventh International Symposium on Agglomeration, Albi, France, May 29–31, Preprints, vol. 1, 2001, pp. 337–342.
[13] W. Pietsch, Size Enlargement by Agglomeration, Wiley, Chichester, 1991.
[14] W. Pietsch, Agglomeration Processes – an Industrial Survey, Wiley-VCH, Weinheim, 2001.
[15] M. Zlokarnik, Dimensional analysis, scale-up, in: M.C. Flickinger, W. St. Drew (Eds.), Encyclopedia of Bioprocess Technology: Fermentation, Biocatalysis and Bioseparation, Wiley, Chichester, 1999, pp. 840–861.
[16] Dimensionless groups, see CRC Handbook of Chemistry and Physics, R.C. Weast (Ed.), CRC Press Inc., Boca Raton, FL, USA, e.g. 67th edition (1986–1987), pp. F307–324.
[17] Pharmaceutical Manufacturers' Association, 115, 154th Street, N.W. Washington DC, 20005; Remington's Pharmaceutical Sciences, 15th (Ed.), Mack, Easton, PA, 1975, p. 1429.
[18] R.W. Johnstone, M.W. Thring, Pilot Plants, Models and Scale-up Methods in Chemical Engineering, McGraw-Hill, New York, NY, 1957 p. 12.
[19] H. Leuenberger, in: H. Sucker, P. Fuchs, P. Speiser (Eds.), Pharm. Technologie, G. Thieme Verlag, Stuttgart, 1978, pp. 80–92.
[20] H. Leuenberger, Scale-up of granulation processes with reference to process monitoring, Acta Pharm. Technol. 29 (4) (1983) 274–280.
[21] H. Leuenberger, Moist agglomeration of pharmaceutical processes, in: D. Chulia, M. Deleuil, Y. Pourcelot (Eds.), Powder Technology and Pharmaceutical Processes, Handbook of Powder Technology, vol. 9, Elsevier, Amsterdam, 1994, pp. 377–389.
[22] H. Leuenberger, Design and modification of powders – a must in

pharmaceutical technology, Proceedings of the Second World Congress Particle Technology, September 19–22, 1990, Kyoto, Japan, Society of Powder Technology, Japan, vol. III, pp. 317–328.
[23] M. Dürrenberger, J. Werani, The control of the granulation process by power consumption measurement in pharmaceutical production, in: C.E. Capes (Ed.), Proceedings of the Fourth International Symposium on Agglomeration, Toronto, June 2–5, 1985, Iron and Steel Society of the United States, ISBN No. 0-932897-00-2, pp. 489–496.
[24] H. Stauffer, Introduction to Percolation Theory, Taylor and Francis, London, 1985.
[25] H. Leuenberger, B. Luy, J. Studer, New developments in the control of the moist agglomeration and pelletization process, S.T.P. Pharma 6 (1990) 303–309.
[26] J. Kristensen, T. Schaefer, P. Kleinebudde, Direct pelletization in a rotary processor controlled by torque measurements. I: Influence of process variables, Pharm. Dev.Technol. 5 (2000) 247–256.
[27] J. Kristensen, T. Schaefer, P. Kleinebudde, Direct pelletization in a rotary processor controlled by torque measurements. II: Effects of changes in the content of microcrystalline cellulose, AAPS Pharmsci. 2 (3) (2000) (article 24).
[28] P. Holm, T. Schaefer, H.G. Kristensen, Granulation in high-speed mixers. Part. VI. Effect of process conditions on power consumption and granule growth, Powder Technol. 43 (1985) 213–223.
[29] H.G. Kristensen, T. Schaefer, Granulation, a review on pharmaceutical wet granulation, Drug Dev. Ind. Pharm. 13 (1987) 803–872.
[30] H.G. Kristensen, Particle agglomeration in high shear mixers, Powder Technol. 88 (1996) 197–202.
[31] M. Landin, P. York, M.C. Cliff, R.C. Rowe, Scale-up of a pharmaceutical granulation in planetary mixers, Pharm. Dev. Technol. 4 (1999) 145–150.
[32] A. Faure, I.M. Grimsey, R.C. Rowe, P. York, M.C. Cliff, Applicability of a scale-up methodology for wet granulation processes in Collette Gral high shear mixer-granulators, Eur. J. Pharm. Sci. 8 (1999) 85–93.
[33] G.J.B. Horsthuis, J.A.H. Van Laarhoven, R.C.B.M. von Rooij, H. Vromans, Studies on upscaling parameters of the Gral high-shear granulation process, Int. J. Pharm. 92 (1993) 143–150.
[34] K. Terashita, S. Watano, K. Miyanami, Determination of end-point by frequency analysis of power consumption in agitation granulation, Chem. Pharm. Bull. 38 (1990) 3120–3123.
[35] A. Ohike, K. Ashikara, R. Ibuki, Granulation monitoring by fast Fourier transform technique, Chem. Pharm. Bull. 47 (1999) 1734–1739.
[36] H. Leuenberger, H.P. Bier, H. Sucker, Theory of the granulation – liquid requirement in the conventional granulation process, Pharm. Tech. Int. 3 (1979) 61–68.
[37] H.P. Bier, H. Leuenberger, H. Sucker, Determination of the uncritical quantity of granulating liquid by power measurements on planetary mixers, Pharm. Ind. 41 (1979) 375–380.
[38] N.-O. Lindberg, L. Leander, L. Wenngren, H. Helgesen, R. Reenstierna, Granulation in a change can mixer, Acta Pharm. Suec. 11 (1974) 603.
[39] D.N. Travers, A.G. Rogerson, T.M. Jones, Torque arm mixer for studying wet massing, J. Pharm. Pharmacol. 27 (Suppl 3P) (1975).
[40] H. Leuenberger, How to monitor and control the moist agglomeration process, in: M.-R. Angel (Ed.), Data Acquisition and Measurement Techniques, Interpharm Press, Buffalo Grove, 1998, pp. 141–157.
[41] A. Johansen, T. Schaefer, H.G. Kristensen, Evaluation of melt agglomeration properties of polyethylene glycols using a mixer torque rheometer, Int. J. Pharm. 183 (1999) 155–164.
[42] T. Schaefer, Melt agglomeration with polyethylene glycols in high shear mixers, Dr Pharm. Thesis, The Royal Danish School of Pharmacy, Copenhagen, 1996, p. 98.
[43] J. Ratanen, O. Antikainen, J.-P. Mannermaa, J. Yliruusi, Use of near-infrared reflectance method for the measurement of moisture content during granulation, Pharm. Dev. Technol. 5 (2000) 209–217.
[44] H. Leuenberger, L. Holman, M. Usteri, S. Winzap, Percolation theory, fractal geometry, and dosage form design, S. Pharm. Acta Helv. 64 (2) (1989) 34–39.
[45] J.D. Bonny, H. Leuenberger, Matrix type controlled release systems: II. Percolation effects in non-swellable matrices, Pharm. Acta Helv. 68 (1993) 25–33.
[46] H. Leuenberger, The application of percolation theory in powder technology, Adv. Powder Technol. 10 (1999) 323–352.
[47] H. Leuenberger, M. Usteri, G. Imanidis, S. Winzap, Monitoring the granulation process: granulate growth, fractal dimensionality and percolation threshold, Bolletino Chimico Farmaceutico 128 (2) (1989) 54–61.
[48] H. Leuenberger, Percolation theory and robust formulations, in: Y. Jin, M. Kwauk, G. Jimbo, Y. Kousaka, (Eds.), Powder Technology Proceedings '96 China–Japanese Symposium on Particuology, May 24/25, 1996, Beijing, pp. 37–41.
[49] M. Ritala, P. Holm, T. Schaefer, H.G. Kristensen, Influence of liquid bond strength on power consumption during granulation in a high shear mixer, Drug Dev. Ind. Pharm. 14 (1988) 1041–1060.
[50] P. Luukkonen, T. Schaefer, L. Hellén, A.M. Juppo, J. Yliruusi, Rheological characterization of microcrystalline cellulose and silicified microcrystalline cellulose wet masses using a mixer torque rheometer, Int. J. Pharm. 188 (1999) 181–192.
[51] R. Luginbühl, H. Leuenberger, Use of percolation theory to interpret water uptake, disintegration time and intrinsic dissolution rate of tablets consisting of binary mixtures, Pharm. Acta Helv. 69 (1994) 127–134.