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Scale-up of Granulation Processes with Reference to Process Monitoring*

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Summary

Process monitoring has recently become an important part for validation and quality assurance purposes. The granulation process can be easily monitored by the determination of the power consumption of the mixer used. The paper shows, that process monitoring can facilitate the scale-up exercise of the classical wet agglomeration process, the granulation with a high speed mixer and the subsequent fluidized bed drying of the granules. The theory of scale-up is reviewed and applied for the scale-up of the granulation process. The paper shows, that there is an experimental evidence for scale-up invariables.

Zusammenfassung

Prozeßüberwachung mit automatischer Registrierung stellt heute ein wesentliches Hilfsmittel zur Prozeßvalidierung und zur Qualitätssicherung dar. Der Granulierprozeß kann aufgrund der kontinuierlichen Leistungsmessung am Mischer/Granulator leicht überwacht werden. Die Arbeit zeigt, daß die Prozeßüberwachung das Scale-up-Prozedere bei der klassischen Feuchtgranulation wie auch im Falle der Granulation im Hochleistungsmischer und beim anschließenden Trocknen der Granulate erleichtert. Im Hinblick auf die Anwendung beim Granulieren wird auf die Grundlagen der Scale-up-Theorie eingegangen. Es konnte dabei gezeigt werden, daß Scale-up Invarianten gesucht werden müssen und auch experimentell nachweisbar sind.

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1 Introduction

Process monitoring has recently become an important part for validation and for general quality assurance purposes. The American Pharmaceutical Manufacturers Association defines the quality of a product as follows (1):

1. The quality of a product is its degree of possession of those characteristics designed and manufactured into it which contribute to the performance of an intended function when the product is used as directed.
2. The quality of medicinal and related products is the sum of all factors which contribute directly or indirectly to the safety, effectiveness and acceptability of the product.
3. Quality must be built into the product during research, development and production.

The third statement includes problems associated with the scale-up exercise. Among the quality parameters the bioavailability of a drug is considered as one of the most important ones. There is a number of factors which directly or indirectly influence the bioavailability of an oral solid dosage form:

A) Factors related to the dosage form:
   Desintegration time
   Dissolution rate of the active substance
B) Factors related to the active substance:
   Polymorphic crystal form
   Particle size
   Hydrated or anhydrous form
   Wettability, Solubility
   Stability (heat, moisture sensitive drugs)

All these factors mentioned can be influenced by the granulation process and/or by a change of the granulation process during scale-up. Though

scale-up is a very important task fundamental investigations in the field of pharmaceutics are missing.

2 Scale-up methods

2.1 Empirical and semiempirical methods

2.1.1 The state of art

The method of "trial and error" is still the most widely used technique. This method depends on the skill and experience of the pharmaceutical scientist, who is in charge of the scale-up exercise. A more sophisticated approach may be used by applying experimental design (2). This procedure yields linear or quadratic equations, which show the sensitivity of a quality parameter chosen to smaller variations of the process factors (Fig. 1). Such an approach is used by MERCK SHARP and DOME (3). The main advantage is that they know exactly how critical a certain process is. Without this mathematical tool a pharmaceutical scientist will adapt the process during scale-up according to the results he has obtained. This procedure is often less expensive but may be more risky. It is clear, however, that the latter method can be best and safely applied using some kind of process monitoring. An example is given in the following section.

2.1.2 The scale-up of the drying process in a fluidized bed dryer

The final moisture content of a granulate is a very important factor and can be decisive for an uncritical tablet production. The drying process can be

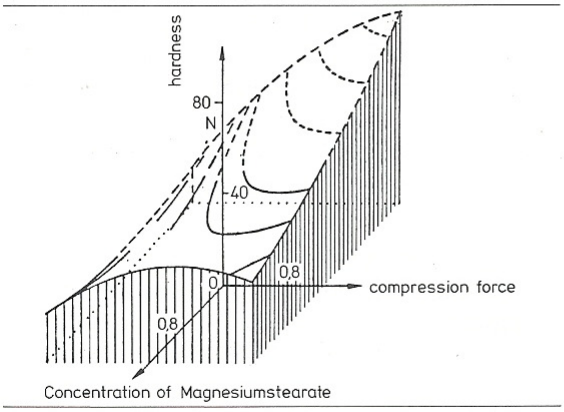

Fig. 1 Response surface of the quality parameter hardness of a tablet as a function of the compressional force and the concentration of magnesium stearate in the formulation (2)

easily monitored by means of the temperature change at the surface of the granules. This change of temperature can be explained most simply by means of the two-capillary model. The fine capillary draws liquid out of the coarse capillary by capillary action. This liquid is transported to the surface of the granulate which thus remains moistened. This state of dynamic equilibrium on the surface of the material is characterized by a constant temperature T_k, the "wet bulb temperature" on the granulate surface. In the second stage of drying the fine capillaries are no longer able to maintain an adequate supply of liquid on the surface and begin to dry out. The temperature on the surface of the material therefore rises. The granulate has a residual water content which is specific to the composition and corresponds to a certain temperature on the granulate surface. Thus this phenomenon may be used for monitoring and controlling the drying process: The dryer is switched off at an end temperature T_e, which has been established in preliminary experiments (4):

T_e then corresponds to the sum of the wet bulb temperature T_k in the first drying stage and a quantity ΔT:

$$T_e = T_k + \Delta T \quad (1)$$

T_e is established with laboratory scale batches of ca. 5 kg batch size. The next batch size may be 15 kg or 30 kg in the pilot plant dryer. The pharmaceutical scientist has now to adapt the switch-off temperature T_e to get the same final moisture content:

$$T_e \text{ (5 kg batch)} = T_k + \Delta T \quad (2)$$

$$T_e^* \text{ (30 kg batch)} = T_k + \Delta T^* \quad (3)$$

This fact is not surprising, as even in the case of geometrically similar scaled-up fluidized bed drying, it is difficult to measure T_e exactly at the same (i. e. the corresponding) place within the fluidized bed. This fact raises the question of the importance of the principle of similarity in scale-up processes (5).

2.2 The principle of similarity

2.2.1 The definition of similarity and dimensionless groups

The important concept for scale-up is the principle of similarity (6). 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. Two systems are *geometrically* similar when the ratio of the linear dimensions of the small scale and scaled-up system are 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.

2.2.2 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 behaviour 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 π_1, π_2 etc., which correspond to dimensionless numbers, e. g. REYNOLDS number Re, FROUDE number Fr, NUSSELT number Nu, SHERWOOD number Sh, SCHMIDT number Sc etc. (5, 7).

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

$$\pi_1 = F(\pi_2, \pi_3, \ldots) \qquad (4)$$

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

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

$$\pi_1 = \frac{P(x)}{P_0}$$

$P(x)$ = pressure at level x above sea level ($x = 0$)
P_0 = pressure at $x = 0$

$$\pi_2 = \frac{E(x)}{RT}$$

$E(x) = M \cdot g \cdot x$ = molar potential energy
M = molecular weight
g = specific gravity
x = height above sea level
RT = molar kinetic energy

B) $$\pi_1 = a\pi_2^b \pi_3^c \qquad (5)$$

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

2.2.3 BUCKINGHAM's theorem

For a correct dimensional analysis it is necessary to consider BUCKINGHAM's theorem which may be stated as follows (8, 9):

1. The solution to every dimensionally homogeneous physical equation has the form $F(\pi_1, \pi_2, \pi_3 \ldots) = 0$, in which $\pi_1, \pi_2, \pi_3 \ldots$ represent a complete set of dimensionless groups of the variables and the dimensional constants of the equation.
2. If an equation contains n separate variables and dimensional constants, and these are given dimensional formules in terms of m primary quantities (dimensions), the number of dimensionless groups in a complete set is $(n - m)$.

3 Scale-up and monitoring of the wet granulation process (high speed mixer)

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 behaviour 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 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:

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

$$\pi_2 = \frac{\dot{q}\,t}{V\rho}$$ Specific amount of granulation liquid

$$\pi_3 = \frac{V}{V^*}$$ Fraction of volume loaded with particles

$$\pi_4 = \frac{r\,\omega^2}{g}$$ FROUDE number (Centrifugal/gravitational energy)

$$\pi_5 = \frac{r}{d}$$ Geometric number (ratio of characteristic lengths)

List of symbols:

P = Power consumption
r = Radius of the rotating blade
ω = Angular velocity
ρ = Specific density of the particles
$\dot{q}$ = Amount of granulating liquid added per unit time
t = Process time
V = Volume loaded with particles
V* = Capacity of the mixer vessel
g = Gravitational acceleration
d = Second characteristic length of the mixer

In principle the following scale-up equation could be established:

$$\pi_1 = a\pi_2^b\,\pi_3^c\,\pi_4^d\,\pi_5^e$$

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

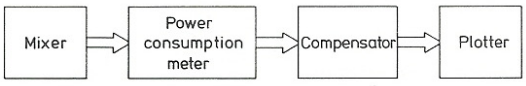

Fig. 2 Block diagram of measuring equipment

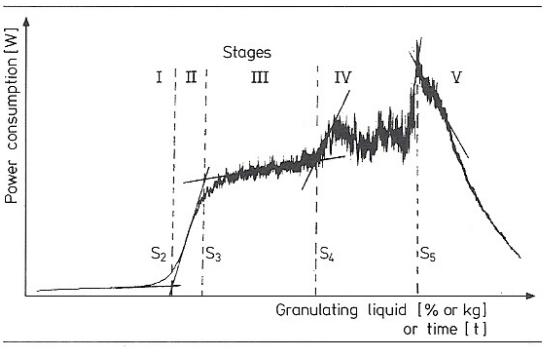

Fig. 3 Division of a power consumption curve

4 Experimental evidence for scale-up invariables

4.1 Conventional wet granulation process

In the case of conventional wet granulation, the granulation process can be easily monitored by the determination of the power consumption (4, 10, 11, 12) (Fig. 2).

The typical power profile consists of five different phases (Fig. 3). Usable granulates can be produced in a conventional way only within the plateau region S_3–S_4 according to the nomenclature in Figure 3. As Figure 4 indicates, changing the type of mixer has only a slight effect on the phases of the kneading process.

However, the actual power consumption of mixers of different type, differs greatly for a given granulate composition.

The important point is now, that the power consumption profile as defined by the parameters

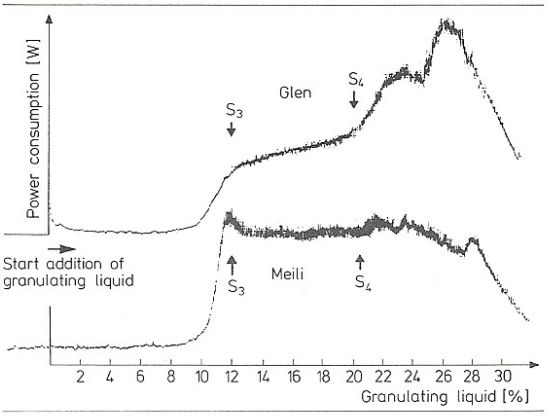

Fig. 4 Power consumption curves of two types of mixer

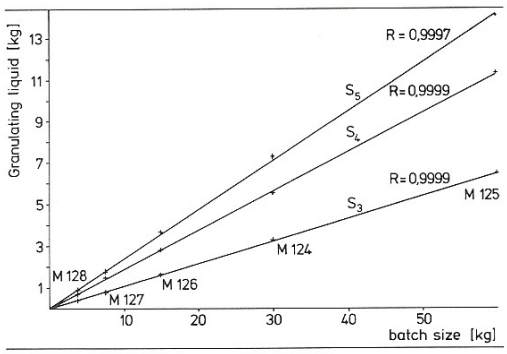

Fig. 5 Scale-up precision measurements with identical charges

S_3, S_4, 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 kg up to 60 kg. To obtain precise scale-up measurements the excipients which were used, belonged to identical lots of primary material (10% (W/W) corn starch, 4% (W/W) polyvinylpyrrolidone as binder, and 86% (W/W) lactose). As can be seen from Figure 5 the 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, 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 (compare section 3.1):

$$\pi_1 = F(\pi_2)$$

The other numbers π_3, π_4, π_5 were kept essentially constant. From these findings one can conclude that the correct amount of granulating liquid per amount of particles to be granulated is a scale-up invariable (7). It is necessary, however, to mention that during this scale-up exercise only a low-viscous granulating liquid was used. The exact behavior of a granulation process using high-viscous binders and different batch sizes is unknown.

4.2 Granulation with a high-speed mixer (COLLETTE-GRAL, LÖDIGE etc)

The granulation process can be monitored by means of measuring the power consumption profile. This "fingerprint"-information may be part of a batch record and is useful for validation and quality assurance purposes. It is interesting that the power consumption profile of a given granulate composi-

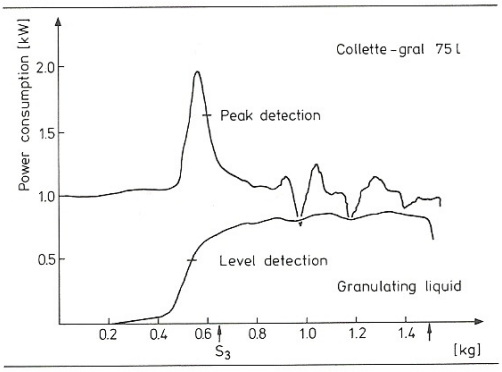

Fig. 6 Power-consumption profile of a high-speed mixer (COLLETTE-GRAL 75 l) with peak and level detection (4)

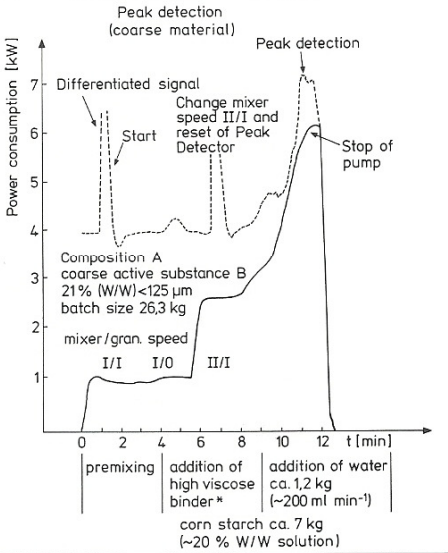

Fig. 7 Power consumption profile (coarse material, high viscous binder added manually with subsequent finetuning of the amount of granulating liquid)

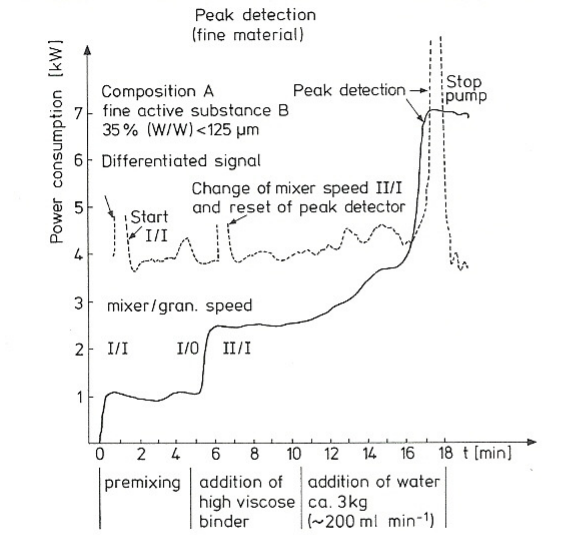

Fig. 8 Power consumption profile (fine material, high viscous binder added manually with subsequent finetuning of the amount of granulating liquid)

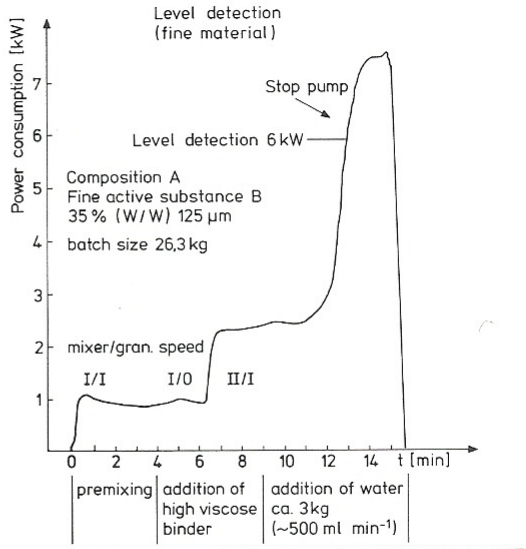

Fig. 9 Power consumption profile (fine material, increased speed of the pump, power level threshold detection mode)

tion in a high-speed mixer is very similar to one obtained by means of a planetary mixer (Fig. 6). The power consumption meter developed by SANDOZ laboratories can be used to control and determine the necessary amount of granulating liquid. Essentially there are two possibilities (12):

1. the peak detection method
2. the level (threshold) detection method

The first method uses the differentiated signal of the power consumption profile. The peak which can be identified on Figure 6, describes the steepest ascent of the power consumption during the second phase (compare Fig. 3). Because of the electronic time constant of the control unit, the peak represents quite well the starting point of the plateau region, i. e. the parameter S_3. It is known from experience that within this plateau-region usable granulates can be produced (4). Measurements with low viscous binders have shown that the parameter S_3 is a scale-up invariable.

In case of the second method, a threshold level of the absolute power consumption is switching-off the granulation process. It is clear that this absolute amount of power consumption is a function of batch size and of the type of the mixer used. Thus, it is necessary to adapt empirically the threshold level of the power consumption to the batch size and to the mixer. Again the power consumption profile can be used as a "fingerprint" information for the batch record.

4.3 Experience with a high-viscous binder

So far another important dimensionless group $\pi_6 = d_i/d_f$, i. e. the ratio of the characteristic dimension d_i of the starting material and d_f of the final granulate was not considered. For quality assurance purposes it is important to know the behavior of this dimensionless group variable with reference to the final quality of the granulate. To quantify the influence of π_6 on π_1 (power consumption) and π_2 (amount of granulating liquid) the other dimensionless groups were kept constant. Thus the experiment was done with batches of equal size in the same high-speed mixer (LÖDIGE 125 l). The fineness of the active substance B in the composition A differed for the two batches as follows: batch I: 21 % (W/W) < 125 µm and batch II: 35 % (W/W) < 125 µm. In addition the assumption was made that the level of power consumption describing the correct e. g. "snow ball consistency" of the granulating material is the same for both batches. After a dry premixing phase an identical amount of high viscous binder was added manually to both batches. In order to "finetune" the exact amount of granulating liquid necessary, demineralized water

was added by a pump (ca. 200 ml min^{-1}). The pump stopped as soon as the peak detector became active (Fig. 7, 8). The important point is that the additional amount of demineralized water to finetune the necessary amount of granulating liquid differs by a factor of 2.5! Thus there are different π_2-values of granulating liquid but similar π_1-values of the power consumption at switch-off time. As a consequence, equivalent results were obtained using the power level detection method where the threshold level was set to 6 kW. To shorten the process time the pump speed was set to 500 ml min^{-1} (Fig. 9). The same composition and batch-size were used. This result leads to a still open question which might be worth further discussions and investigations:

Is a reasonably normalized power consumption number π_1, e. g. $\pi_1{}^* = \pi_1/\pi_3$ i. e. $\pi_1 = PV^* / r^5\omega^3 V\rho$ the very scale-up invariable of choice?

An affirmative answer indeed would mean that the scale-up of the granulation process should be done by means of process monitoring using power input measurement for endpoint determination.

5 Literature

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