Granulation, New Techniques[1]

By *H. Leuenberger, Pharmacy Research and Development, Sandoz AG, CH-4002 Basle*

1. Introduction

Today the pharmacist who is working in the industry receives nearly each week some prospectus on an new granulation technique. Sometimes it is quite difficult to realize, whether the technique, which is described in the prospectus, is really new or whether it is a known technique, which is somehow modified.
To understand the modern granulation processes in detail still a lot of research work has to be done. In the following paragraphs a review on different granulation techniques is given. The differences between these techniques are interpreted by the results of recent research work on granulation, which was conducted at the Sandoz Laboratories in Basle. These findings are mainly based on the theoretical interpretation of power consumption measurements, which were obtained during the agglomeration process [1, 2].

2. Measurement of the Power Consumption of a Conventional Mixer

Figure 1 is a diagrammatic representation of the measurement principle. A compensator deducts the no-load consumption from the measurement signal, and the resultant power consumption curve is practically equivalent to a torque measurement [2]. In order to simplify the evaluation, a filter circuit was used to smooth the power-consumption curve. With a granulate composition commonly used in pharmacy (10% maize starch, 4% polyvinylpyrrolidone as binder, and 66% lactose) the typical power-consumption curve presented in Figure 2 is obtained. The curve can be divided into five phases, in relation to the quantity of granulation liquid (water) added.
In the first phase the solid components are moistened without any observable increase in the power consumption, which remains the same as in the dry premixing phase. There is no perceptible agglomeration of the primary particles in this first phase. As further granulation liquid is added, power consumption increases sharply, to an extent dependent on the granulate composition, and the solid particles begin to agglomerate. During the third phase power consumption levels off. According to our nomenclature, this plateau region lies between the two measurement parameters S_3 and S_4. In our experience usable granulates can be produced only within this plateau region. If the volume of granulation liquid is less than S_3, the agglomerate particles are too soft and disintegrate on drying, and at S_4 the kneading mass is too moist for further processing. In the following fourth phase power consumption rises further, showing large low-frequency fluctuations, and with further continous addition of granulation liquid, power consumption reaches a maximum. During the fifth and last phase power consumption falls steeply, and the kneading mass, which was still firm in the fourth phase, disintegrates and slowly passes into a suspension.

Figure 1

Block diagram of measuring equipment

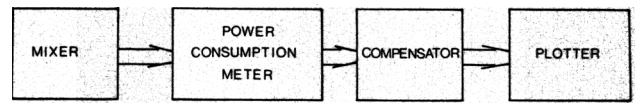
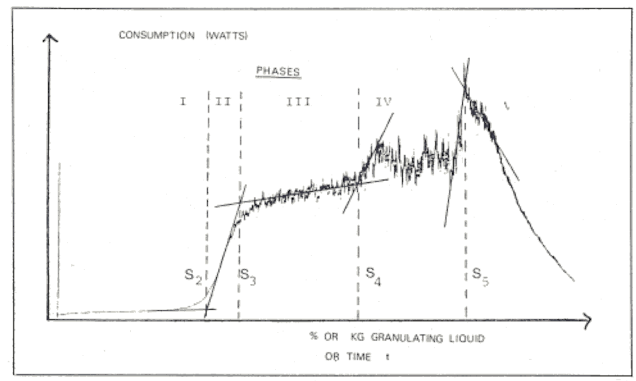


Figure 2

Parametric division of a power-consumption curve



These five phases were obtained with practically all the compositions investigated. As Figure 3 indicates, changing the type of mixer also has only a slight effect on the phases of the kneading process. However, the actual power consumption of mixers of different type (Glen planetary mixer, Meili Z-blade mixer) differs greatly for a given granulate composition. Nevertheless, kneading phases 1–3 which are important in practice are clearly recognizable with

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Figure 3

Power-consumption curves of two types of mixer

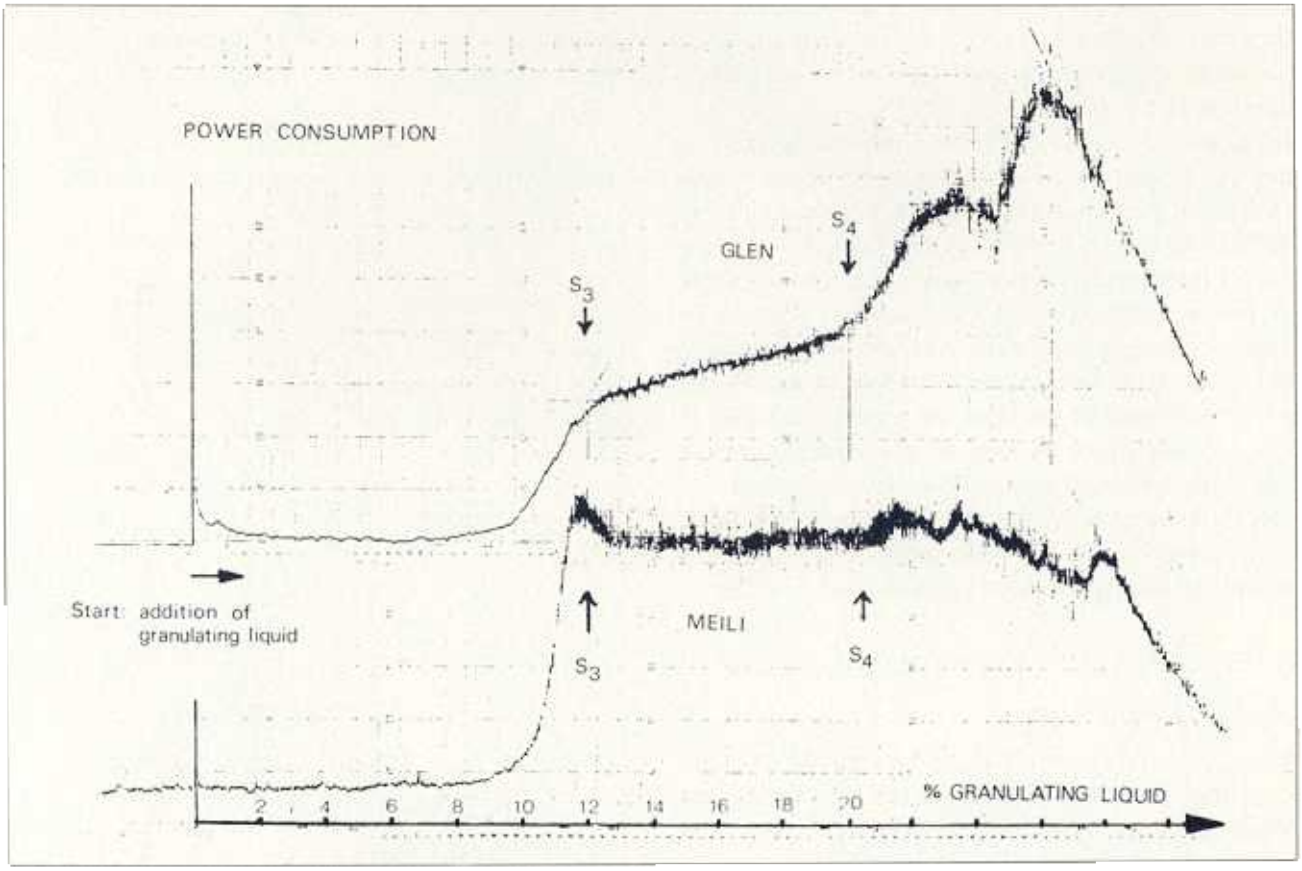
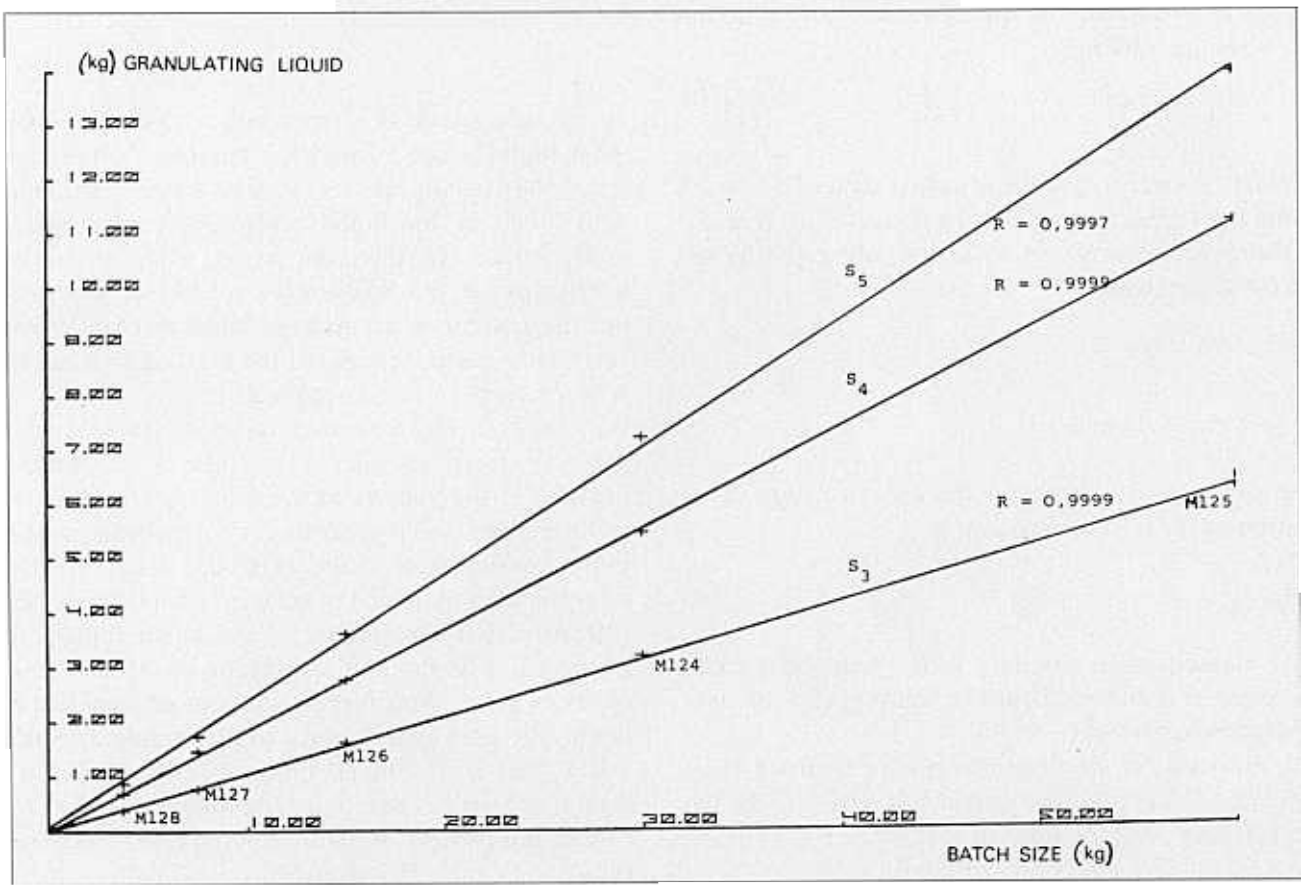


Figure 4

Scale-up precision measurements with identical charges



both machines. Furthermore, the power consumption curve, as defined by the parameters S_3, S_4 and S_5, is also independent of batch size (Fig. 4). It may then be asked whether a theoretical explanation can be found for this evidently quite generally valid power-consumption curve.

It has already been established that measurement of the power consumption of the mixer is essentially equivalent to measurement of the torque applied to the mixing arm. For the purpose of our investigation we are interested at present not in the absolute value of power consumption or torque, but only in its relative changes during the addition of granulation liquid. In the mixing process, changes in torque and power consumption occur as the result of a change in the cohesive force or the tensile strength of the agglomerates in the moistened powder bed. It should therefore be possible to interpret the power consumption curve on the basis of the cohesive forces developed during the moist agglomeration process.

3. The Cohesive Forces Involved in Agglomeration

3.1 The Liquid Bridges

Rumpf [3], and *Newitt* et al. [4] have put forward the view that the cohesive force operating during the moist agglomeration process originates from the liquid bridges between the solid particles.

According to *Pietsch* and *Rumpf* [5] the cohesive force H depends on the surface tension α of the granulation liquid, the contact angle δ, the particle separation a and the particle diameter x in the following manner:

$$H = \alpha \Pi x \sin\beta \left[\sin(\beta + \delta) + \frac{x}{4}\left(\frac{1}{R_1} + \frac{1}{R_2}\right)\right] \quad (1)$$

Where R_1 and R_2 are the principal radii of curvature and β is the sector angle of the liquid bridge (Fig. 5). The radii of curvature R_1 and R_2 are given by the following equations:

$$R_1 = \frac{x(1-\cos\beta) + a}{2\cos(\beta + \delta)} \quad (2)$$

$$R_2 = \frac{x}{2}\sin\beta + R_1\{\sin(\beta + \delta) - 1\} \quad (3)$$

In dimensionless notation the cohesive force F_H is given by the following equation:

$$F_H = \frac{H}{\alpha x} = f\left(\beta, \delta, \frac{a}{x}\right) \quad (4)$$

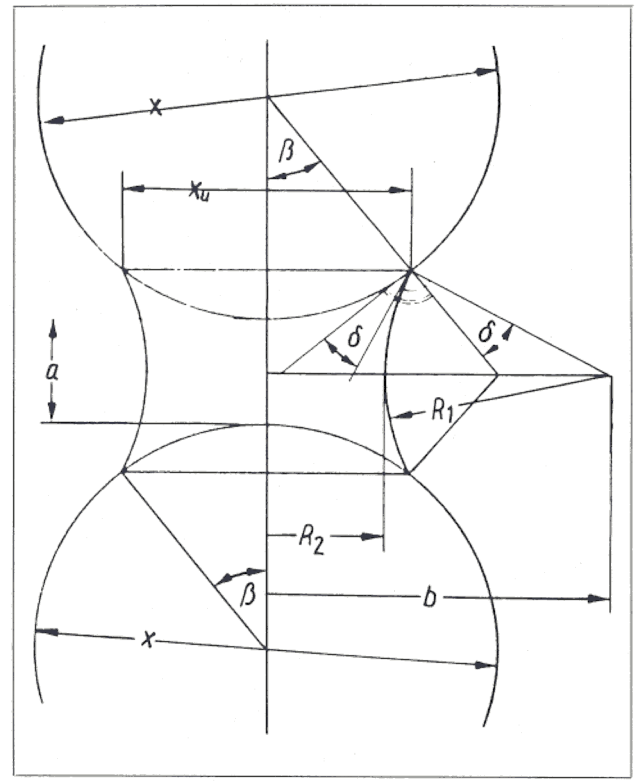
A mathematical solution which can be exactly expressed is obtained for the limiting case of solid particles in contact ($\frac{a}{x} = 0$).

In this case the meridian line can be regarded as an arc of a circle [4]. This estimate is adequate for the qualitative interpretation of the power consumption curve. Table 1 shows the cohesive force values F_H in relation to the sector angle β for ideal wettability ($\delta = 0$) and particles in contact ($\frac{a}{x} = 0$).

F_H values are given for rhombohedral packing of spheres for β values of 5° to 30°, and for cubical packing for β values of 5° to 45°.

Figure 5

Model of a liquid bridge between two spheres of equal size



In the calculations it is important to note that even when liquid bridge formation is minimal the cohesive force rises steeply, passes through a maximum, and slowly falls as the liquid bridges become progressively larger. In this case when, after an initial wetting phase, the first bridges are formed throughout the powder mass. A large build-up of cohesive force must occur, leading to the marked increase in power consumption seen in Figure 2.

According to the estimated values in Table 1, the cohesive force changes very little with further increase in the volume of the liquid bridge. This is confirmed by the appearance of a plateau in the power-consumption curve. On the basis of our interpretation it may be assumed that within this plateau region the volume of the liquid bridges is increased, without any significant changes in the cohesive force. With further addition of granulation liquid, the pore spaces begin to fill completely with liquid, that is, the liquid bridges slowly disappear. *Rumpf* et al. [6, 7] developed the following theory to explain this process. Within the liquid-filled space the capillary pressure P_K is exerted.

Table 1

Cohesive force F_H for cubical or rhombohedral packing, assuming $\frac{a}{x} = 0$ and ideal wettability ($\delta = 0$) [4], for various values of the half-sector angle β:

β	F_h cubical	Filled pore space (%)	F_H rhombohedral	Filled pore space (%)
5°	1.51	0.063	4.26	0.033
10°	1.44	0.084	4.09	0.461
20°	1.34	1.131	3.78	5.78
30°	1.24	4.68	3.5	24.3
45°	1.11	18.21		

This value is equal to the maximum possible transmissible tensile stress in the agglomerate. Since only the liquid-filled space S contributes to the tensile strength σ_z the following equation holds:

$$\sigma_z = S P_K$$

In the limiting case, in which the pores are filled with liquid to an S value of 100%, the capillary pressure and the cohesive force become zero.

3.2 A Theoretical Estimate of the Quantity of Granulation Liquid

Using concepts which have already been evolved, it is also possible to make a theoretical estimate of the quantity of granulation liquid required in the granulation process [1]:

$$W = \frac{\gamma \varepsilon \varrho_L}{\varepsilon \varrho_L + (1-\varepsilon)\varrho_s} + \delta_H \qquad (5)$$

In the equation (5) we take into account that cohesive forces arise even before the entire pore space is filled.

Selection of the value 0.1821 for the coefficient γ corresponds to the complete filling of the wedge volumes – i.e. the complete development of the liquid bridges in an idealized cubic packing of isometric spheres. In the limiting case of rhombohedral packing of isometric spheres, γ would be 0.243. In the calculation, the mean value $\bar{\gamma} = 0.213$ is used since it may be assumed that neither of the sphere packings corresponding to the limiting values will occur in practice.

In equation (5) the additional term δ_H corresponds to the equilibrium moisture uptake of the solid materials, which are exposed to a relative humidity of 100% since granulation liquid is added in the agglomeration process.

The appropriate value can be obtained by means of adsorption isotherm measurement. For the practical calculation the value ε of the porosity which was used corresponded to the porosity obtained by tamped density measurements.

Figure 6

Experimental granulating liquid range S_3–S_4 and calculated liquid requirement

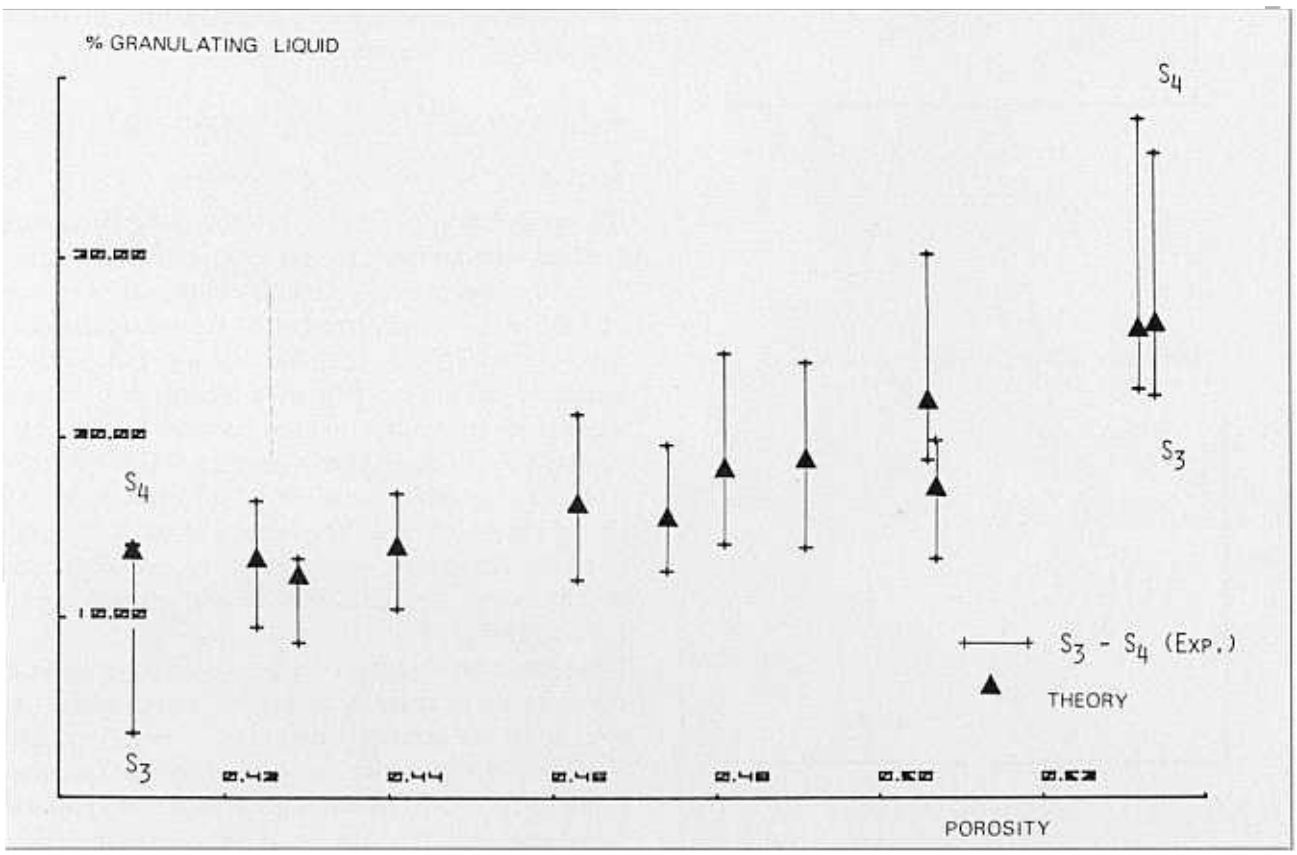


Figure 7

Effect of the quantity of granulation liquid on the particle size of the granulates

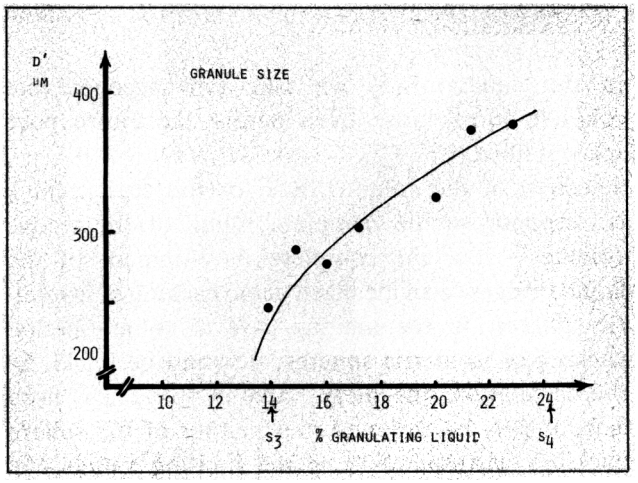


Figure 8

Effect of the quantity of granulation liquid on the quantity of fines < 100 µm and on the fineness parameter n

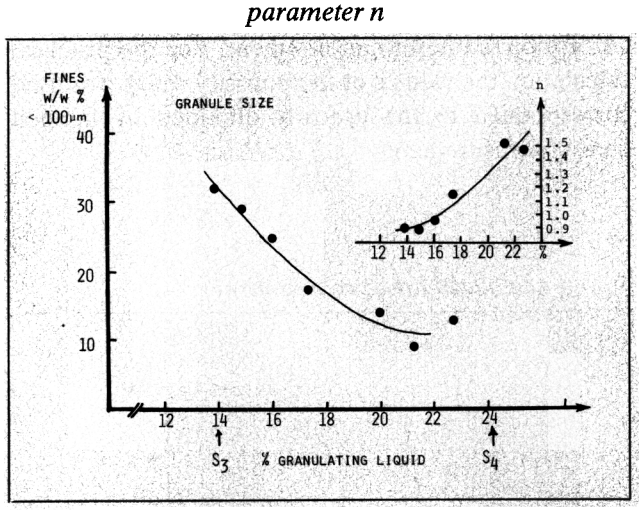


Figure 9

Resistance of the granulates to abrasion

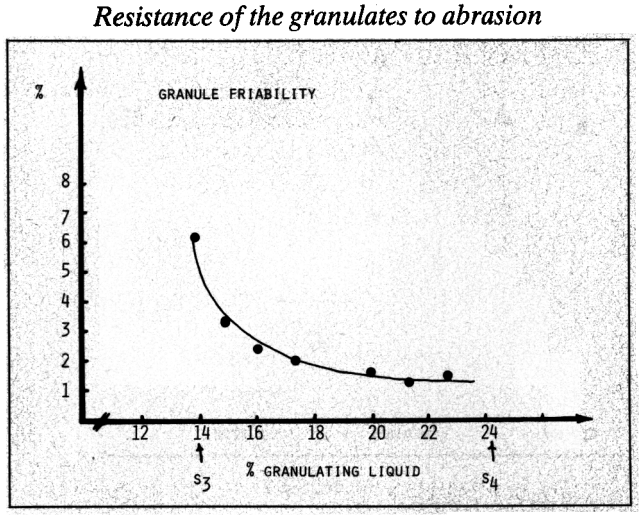


Figure 6 compares theory and experiment, i.e. the experimentally determined range of weights of granulation liquid giving satisfactory results and the calculated weights, for various tamped densities. In practically every case the calculated value lay between the two values S_3 and S_4, i.e. was within the acceptable range.

3.3 The Effect of the Quantity of Granulation Liquid

In order to gain exact knowledge of the granulation process in practice it is important during the development work to determine the full range of acceptable quantities of granulation liquid, in order to assess the processing properties of the granulates and their effect on the solid dosage form.

Figures 7 and 8 show the effect of the quantitiy of granulation liquid on the particle size of the granulates. Larger quantities of granulation liquid produce a narrower particle size range and coarser granulates; i.e. the proportion of fine granulate particles below 100 µm decreases. At the same time the fineness parameter *n* in the Rosin-Rammler-Sperling-Bennet particle size distribution increases, i.e. we obtain a narrow particle-size range. Another major quality criterion is the resistance of the granulate to abrasion. It would not be appropriate here to enter into details of the various possible methods of measurement, but there is qualitative agreement on the important fact that the granulates produced with a small proportion of granulation liquid are soft and porous and subject to large weight losses on abrasion (Fig. 9).

Granulates produced with a large quantity of granulation liquid are considerably harder.

4. The Controlled Granulation and Drying Process

4.1 Control of the Granulation Process

The granulation process is controlled by measuring the first differential of the power measurement signal (Fig. 10). This peaks in phase II of the agglomeration process at the steepest point of the power-measurment curve (Fig. 11). Together with a threshold value detector, this peak can be used directly as a control signal and may, for example, be used to start two clocks. One of these clocks may control the further addition of granulation liquid for a certain predetermined period of time. The second clock may determine the duration of that part of the kneading time which follows the detection of the control signal (peak detection, Fig. 11).

Since the control signal does not reach its peak until the steepest increase is measured during phase II, this signal in principle describes a quite specific condition of the particulate solid material. The time elapsing before the signal is given depends upon the initial state, e.g. the fineness of the starting material.

Figure 10

Control unit to measure the necessary quantity of granulation liquid [2] developed by Sandoz Electronic Department (9650 Elektron. Entwicklung, Sandoz Ltd. CH-4002 Basle) [15]

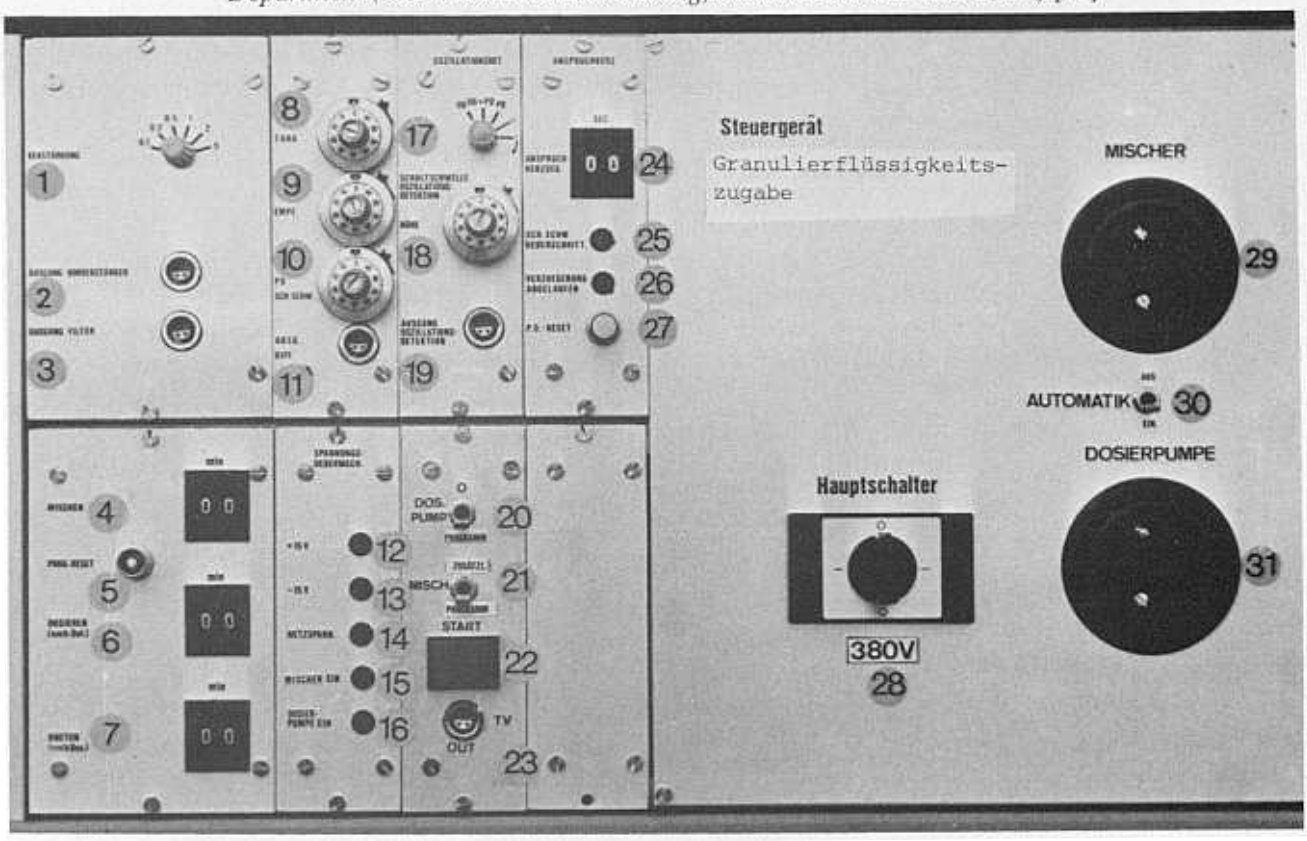
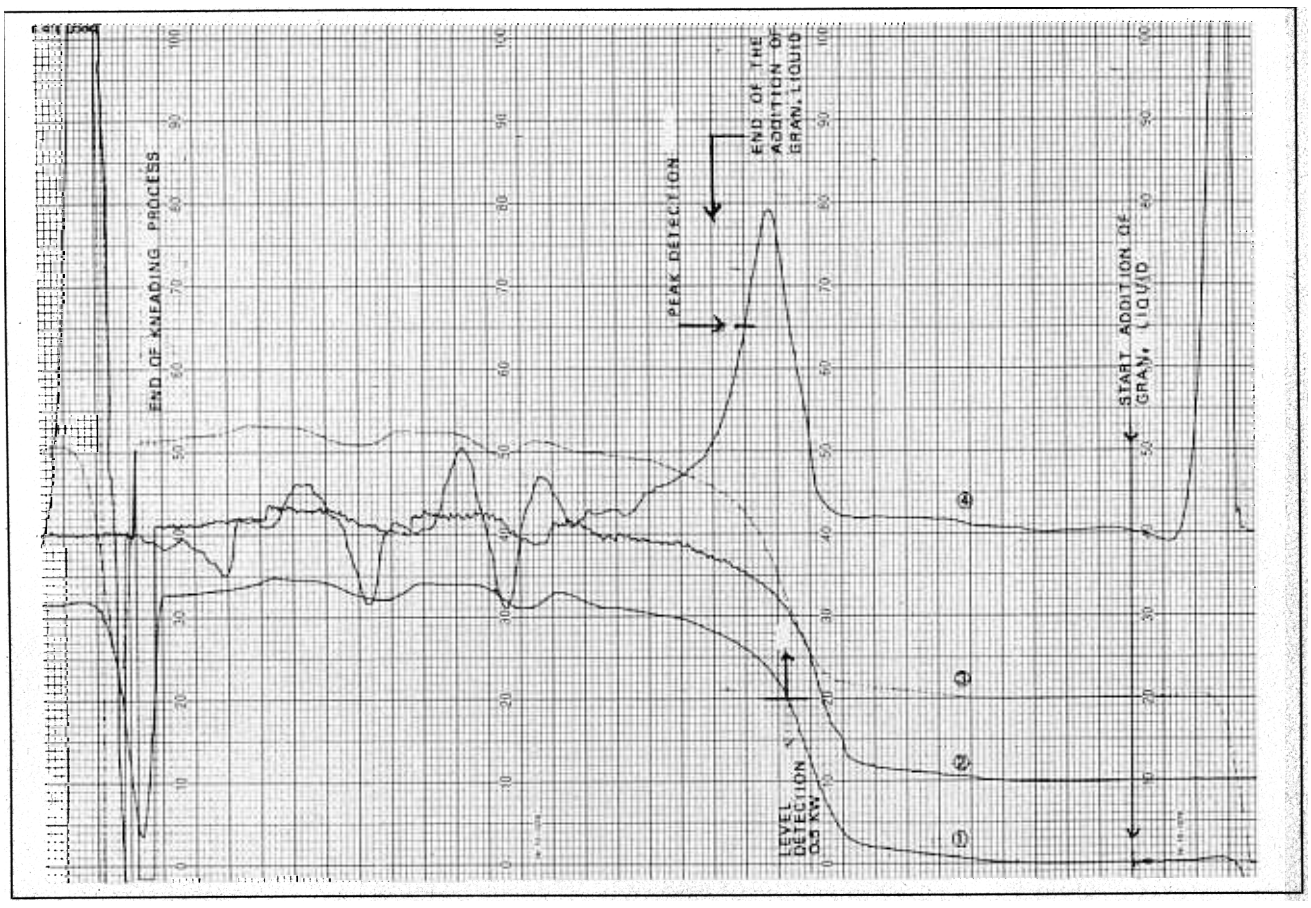


Figure 11

Power-consumption profile of a high-speed mixer (Collette-Gral 75 l) with peak and level detection



Quality variations in the starting material which are relevant to the granulation process may therefore be detected with this equipment. If these variations are not unduly large, the quantity of granulation liquid required to be added is thus automatically corrected by this signal operated by the particulate material itself. However, this very elegant method of control can be used only if the composition actually does display the typical first three phases of agglomeration. In special cases, the typical phases of agglomeration may be absent. However, this does not contradict the theory which has been advanced, but actually indirectly supports it, as in the system, where the granulation liquid is a solvent for the starting material the initial pore structure is destroyed. Thus the typical agglomeration phases which are based on the filling of the pore space with granulation liquid will not appear.

In such cases it would be necessary to establish whether another more suitable granulation liquid could equally well be used. If this is not possible, the power measurement can still be used simply for documentation of the batch, or as a further alternative, it is possible to interrupt the agglomeration process at a predetermined absolute power-consumption value (level detection, Fig. 11).

4.2 Control of the Drying Process in the Fluidized Bed

The drying process may be most simply explained by means of the two-capillary model (Fig. 12):

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 at the surface of the material represents the first phase of drying, and is characterized by a constant temperature (known as the wet bulb temperature at the granulate surface). The rate of drying is constant in the first stage.

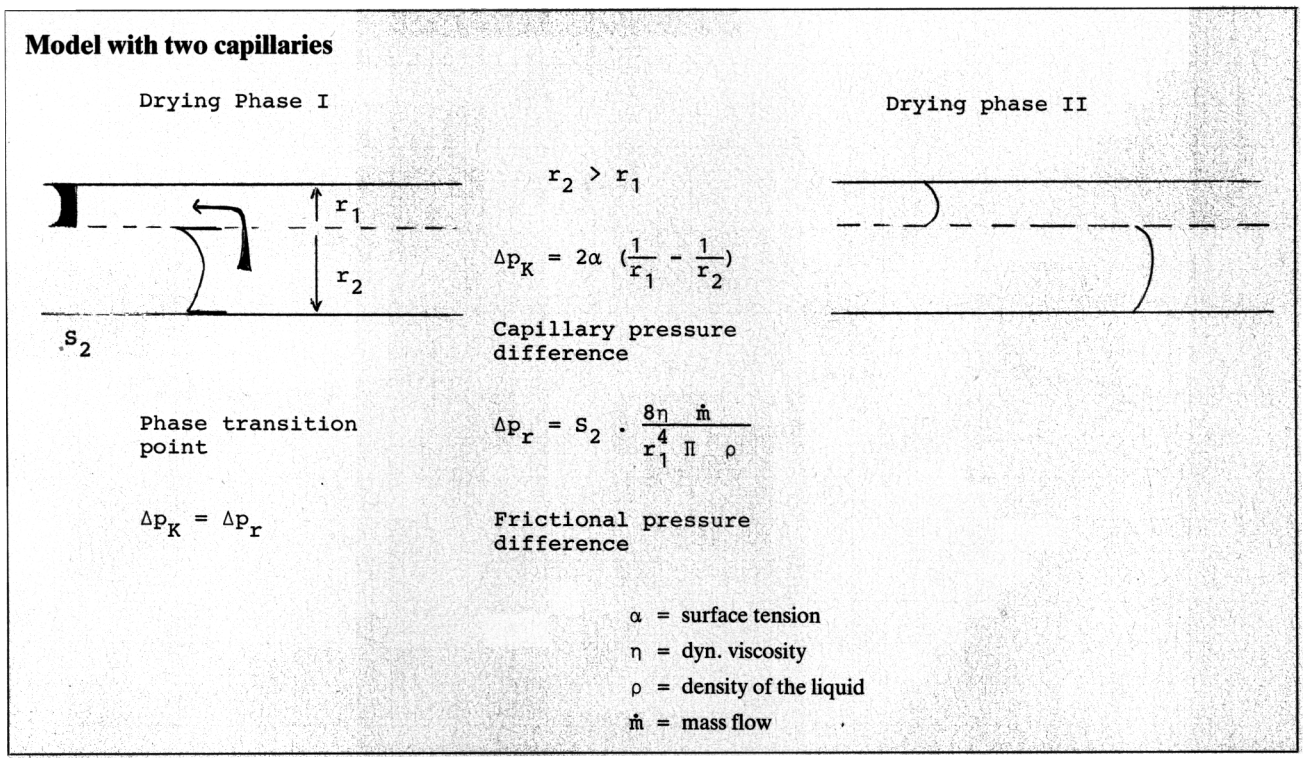
In the second stage of drying the fine capillaries are no longer able to maintain an adequate supply of liquid to the surface and begin to dry out. The temperature at the surface of the material therefore rises. In the second stage of drying the granulate has a residual water content which is specific to the composition and corresponds to a certain temperature at the granulate surface. This phenomenon may be directly used for controlling the drying process, e.g. by keeping a running check on the temperature in the fluidized bed dryer, and switching off the dryer when a specified end temperature T_e, established in preliminary experiments, is reached. This end temperature T_e then corresponds to the sum of the wet bulb temperature T_K in the first drying stage and a quantity ΔT.

$T_e = T_K + \Delta T$

It has been found in practice that the endpoint drying temperature T_e established empirically for a specific composition provides adequate reproducibility of the final moisture content of the granulate.

In addition to the method described above, there are a number of other methods (8). The difference lies mainly in the detail of the design and in the expense associated with it.

Figure 12



5. Can the Physical Principles of Conventional Moist Granulation be Applied to Other Granulation Processes?

In the following paragraphs an attempt will be made to apply the results obtained in the first two sections of this paper to other granulation processes, and to high-light differences.

5.1 Granulation in Fluidized Beds

When granulation liquid is sprayed into a fluidized bed, the dry powder particles are wetted and form–together with the binder–relatively loose and very porous agglomerates. Densification of these agglomerates is brought about solely by the capillary forces present in the liquid bridges. It is therefore important that the quantity of liquid sprayed into the bed should be relatively large compared with that used in conventional moist granulation. During the spraying a proportion of the liquid bed is immediately lost by evaporation, so that the system has little tendency to pass beyond the liquid bridge phase. The particle size of the granulate may be controlled by adjusting the quantity of granulation liquid and the rate at which it is fed–i.e. the droplet size. The mechanical strength of the particles depends principally on the composition and the binder used. In general the granulates obtained are softer and more porous when the rather more volatile ethanol or water-ethanol mixtures are used instead of water.

5.2 Granulation in the Rapid Mixer

In rapid mixers such as the Diosna, Collette-Gral or Lödige the solid particles are fluidized by the high rotational speed of the stirring blade.

The charge should therefore not be too high a proportion of the capacity of the mixer. The quantity of granulation liquid should also be limited, in order to avoid the formation of extensive particle-liquid bridge-particle agglomerates. In comparison with conventional moist granulation, therefore, the quantities of liquid used are in the phase II region–i.e. in the region in which none of the more extensive agglomerates have yet been formed (aggregation phase).

If more than theoretically necessary quantity of granulation liquid is added to the powder charge the larger agglomerates (snowballing effect) must be broken down again by using a chopper, which is usually supplied by the manufacturer of the equipment. Without the use of the chopper a very wide particle size distribution would result. As already mentioned, agglomeration of the solid particles is brought about by the forces acting within the liquid bridges during granulation. The fluidization results, as in fluidized bed granulation, in the formation of a structured agglomerate formed by layers («Aufbauagglomerat»). However in contrast to the fluidized bed process, in the rapid mixer the agglomerates are highly densified by collisions with the stirrer blade and the walls. The process should therefore be thought of as a dynamic equilibrium, as described in the following paragraph.

Only granules containing primary particles which are really firmly bound to one another survive the force of the collision. The high-rotational speeds, and the energy so injected, therefore, result not only in densification but also in disintegration of the larger and weaker agglomerates.

The more weakly bound particles split off and attach themselves at another point. The exact relationships between the rotational speed–i.e. the centrifugal energy injected–and the properties of the granulates have not yet been investigated.

Because of the densification effect, a difference is to be expected between rapid mixers rotating in the horizontal plane and in the vertical plane. In mixers rotating vertically, the force of gravity acting on the charge has an additional effect on densification.

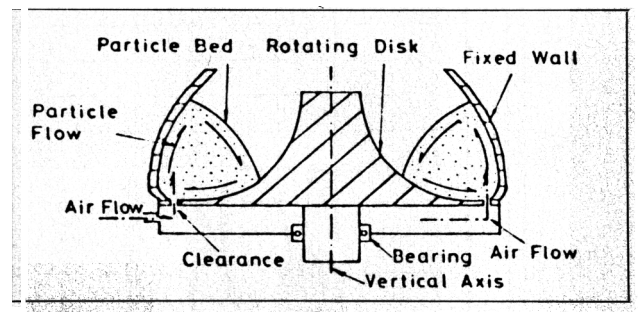
5.3 Other Granulation Methods

There are quite a number of granulation processes incorporating minor modifications, such as the use of fluidized bed granulators incorporating a chopper, V-mixers incorporating baffle plates, intensifier bars, etc. In general these accessories increase densification or the disintegration of agglomerates. I do not wish to go into the details of briquetting, which is purely a densification process. This process must also be operated with the correct moisture content of the material to allow capillary forces to operate.

A novel factor is introduced, however, in the process illustrated in Figure 13 [10].

Figure 13

Centrifugal fluidizing type coating vessel [10].



This is a system in which the primary particles are fluidized by injection of air at a certain rate and the particles are caused to agglomerate by spraying in granulation liquid. In this equipment the floor of the granulator can be made to rotate at a high speed, so that particles coming into contact with the floor experience a tangential force which leads to a secondary densification and rounding of the agglomerates.

The equipment is therefore specially suitable for the production of pellets, and leads on to the discussion of the pelletizing dish.

5.4 The Pelletizing Dish

Both in mineral treatment and in fertilizer manufacture the granulation dish is used very successfully on a large scale [11]. The main reason for the success of the method is that it is *continous* and can achieve a very high throughout, while, as will be shown below, it produces a relatively narrow particle size range. As in rapid mixers and fluidized bed granulators, agglomerates are formed by addition of granulation liquid and individual development of particle agglomerates held together by liquid bridges. However, the subsequent densification is produced not by collision of the particle with the stirrer arm and the walls, as in the rapid mixer, but by the weight of the particles themselves as they roll on the dish. The high density of ores is a very favourable factor in this process. The effect of gravity can also be controlled within certain limits by varying the tilt of the granulation dish. However, an important feature of the granulation dish is that the agglomerates are rounded by the rotational movement. The rounding can also be made use of in the following manner to achieve particle size uniformity [11]:

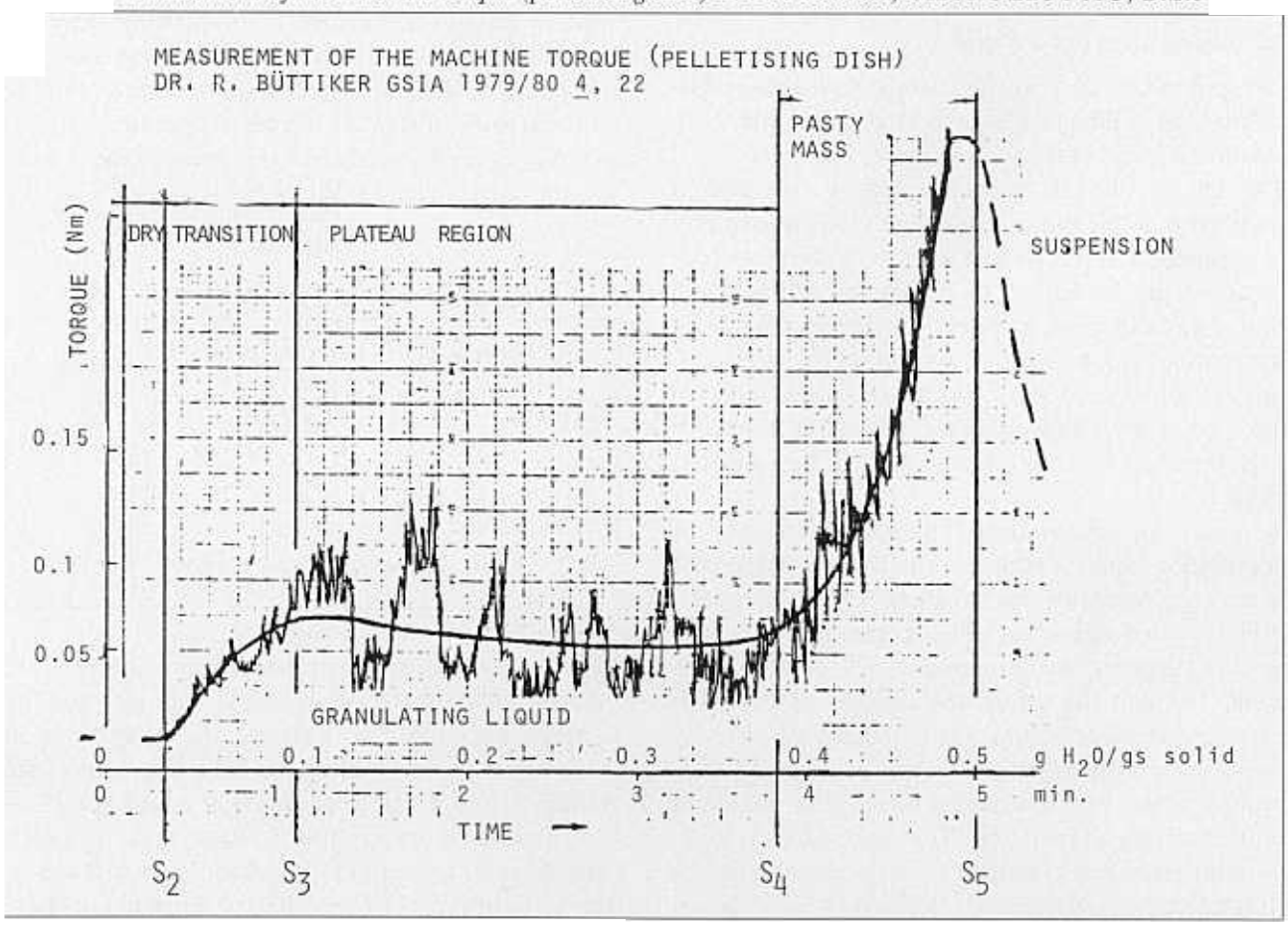
The granulation nuclei and the small agglomerates occur near to the floor of the dish and are transported to a higher level by the greater frictional force acting on those particles which at an early stage are still irregular. Since the larger, well-rounded granules more easily roll on to the smaller, more irregular granules, they move–one could almost say that they swim–towards the surface of the bed, and then–when they have reached a well-defined particle size–are carried out of the dish. During this process there are changes in the machine torque with the quantity of granulation liquid added, and these changes can be divided into the same agglomeration phases as can the power consumption curve in the conventional moist granulation (Fig. 14) [12].

5.5 Dry Agglomeration

The term dry granulation is applied generally to manufacture of granulates by briquetting and compaction. The type of dry agglomeration mentioned here, however, is concerned, in the narrower sense, with the agglomeration properties of finely-divided solids in the dry state. The powders involved are those which tend to agglomerate spontaneously under fairly normal conditions of temperature,

Figure 14

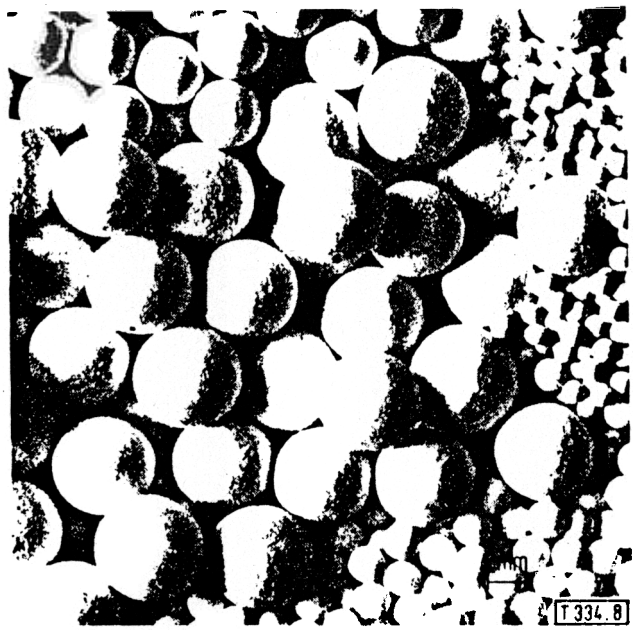
Measurement of the machine torque (pelletizing dish) Dr. R. Büttiker, CIBA-GEIGY AG, Basle



pressure, and humidity [13]. In pharmaceutical practice this phenomenon is generally a nuisance, especially in its effect on the storage properties of powders. Though usually a disadvantage, this may under some circumstances be turned to advantage, as shown by research carried out at the Max Planck Institute in Munich [14]. This work was mostly carried out on inorganic materials such as ZnO, CuO, alpha-Al_2O_3, and UO_2, which are used in nuclear technology. If these powdered materials are agitated, for example in a tumbler mixer, well-rounded pellets are formed without any further processing (Fig. 15).

Figure 15

Al_2O_3-spheres with a diameter of 0.075 and 3 mm [14]



According to the Max Planck Institute this process can also be applied to common pharmaceutical raw materials. Since the operating conditions are not yet accurately known, a substantial amount of basic work still has to be carried out on this process. The relatively long process time, up to ten hours and more, constitutes a further disadvantage of the method. This method will therefore only be of interest in pharmaceutical manufacturing if the process times for normal pharmaceutical materials can be shortened, and provided that no laborious pretreatment of the starting materials is necessary.

6. Differences Between the Various Granulation Techniques

The following table summarizes the various agglomeration and granulation processes. A rough classification may be made on the basis of the binding forces acting during agglomeration and of the type of further densification:

- Formation of extensive agglomerates which are later compacted and subdivided.
- Formation of isolated structured agglomerates through the action of liquid bridges or liquid drops.
- Formation of isolated structured agglomerates which are densified by mechanical impact and by rolling action.

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Granulation processes and principles

Granulation process	Densification by: Binding forces	+ Additional effects	Agglomerate type	Application of power measurement to investigation of principles and/or quality control
1) conventional moist granulation	liquid bridges	mechanical (e.g. double-Z intensive kneader, pressing through sieves, perforated screen)	extensive agglomerates later subdivided and shaped (perforated plate, sieve)	measurement of agglomeration kinetics and process control both possible
2) fluidised bed granulation	liquid bridges	--	isolated structured agglomerates	?
3) rapid mixer	liquid bridges	mechanical (collision)	isolated structured agglomerates or subdivision of extensive agglomerates by chopper	under investigation
4) briquetting	van der Waal's forces capillary liquid	mechanical compression		
5) dry agglomeration	van der Waal's forces capillary liquid	rolling movement weight of charge	isolated structured agglomerates	
6) granulating/ pelletising dish	liquid bridges	weight of charge rolling movement	isolated structured agglomerates (layer-by-layer growth)	torque measurement shows behaviour analogous to (1)

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