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GRANULATION

A REVIEW ON PHARMACEUTICAL WET-GRANULATION

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ABSTRACT

Recent developments in pharmaceutical wet granulation techniques are reviewed with the main emphasis on granulation in fluidized beds and high shear mixers. The following items are dealt with: Fundamentals of granule growth, granulation methods and equipments, granulation variables, scaling-up and end-point control.

INTRODUCTION

Granulation is a process of size enlargement whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified[1]. This definition comprises size enlargement by agitation of moistened powders in mixing equipments, compression, extrusion and globulation[2]. In the pharmacy world, the term granulation usually refers to processes whereby aggregates with sizes ranging from ab. 0.1 to ab. 2.0 mm are produced by agitation of moistened powders. Pelletization may be synonymous to granulation, but in pharmacy this term usually refers to the manufacture of aggregates with a narrow size range using agitation or extrusion.

The pharmaceutical industry benefits from wet granulation by improvement of one or more of the properties of powders: Flow and handling, bulk density, dust formation, appearance, solubility and resistance to segregation. Wet granulation serves primarily to prepare powders for tabletting. Granulation can also serve to prepare medicinal products in a granular form for use by the patient directly or for the preparation of instant products. Important aspects are further to facilitate encapsulation and to reduce environmental hazards for the working personnel.

For decades granules have been processed on a purely empirical basis and often in a small scale. Reproducibility of the granule characteristics was of less importance while tablet compression ran smoothly. This situation has changed completely today. The increasing scale of manufacture, the need for fast running processes and GMP and validation requirements have stressed the necessity to develop controllable granulation processes having as few processing steps as possible and preferably completed in a closed circuit[3,4]. This has largely been accomplished by the introduction in the 60's of fluidized bed techniques and in the 70's of high shear mixers. Granulation by spray drying and continuous granulation methods are available, but are less wide spread than the two former methods because their benefits rely on a larger scale of manufacture than is normal in most pharmaceutical industries. There is no doubt, however, that continuous granulation in the future will gain a more dominating position in pharmacy along with appropriate equipment being developed.

The introduction of modern granulation equipments has given rise to an interest in basic research on wet granulation. Experiences have shown that many formulation and process variables influence the performance characteristics of the final product[5].

The need for fast running processes has caused significant interest in instrumental methods for granulation end-point control. The increasing scale of manufacture gives rise to problems in scaling-up from laboratory to production scale.

An extensive technical literature on granulation has been reviewed in a number of monographs on size enlargement methods, e.g. Capes[6,7], Pietsch[8], Sherrington and Oliver[2] and Kapur[9]. These monographs present fundamentals of size enlargement methods, equipments and applications to different industrial areas.

It is notable that the concern of a great part of the literature on the fundamentals of granulation is powders that are insoluble in the liquid phase. They are often agglomerated in equipments with a mode of action that differs from that of the equipment normally used in the pharmaceutical industry.

The wet phase of pharmaceutical granulation technology has been reviewed by Record[10] who covers all generally used equipments. Aulton and Banks[11] have reviewed fluidized bed granulation. Anderson et al.[3] have described the principles of improved tablet production systems including modern granulation equipments. The literature on the characterization of granulations and the interactions between granule and tablet characteristics are reviewed by Fonner et al.[5].

The aim of the present paper is to review recent developments in pharmaceutical wet granulation. Emphasis is given to granulation in fluidized beds and high shear mixers because these equipments today are the most wide-spread in the pharmaceutical industry, and also because they have been the concern of the authors' own research.

FUNDAMENTALS OF GRANULE GROWTH

Granulation Mechanisms

Wet granulation proceeds by different mechanisms for agglomerate growth and degradation which are dependent on the granulation equipment as well as the properties of the feed material, especially its particle size distribution[12]. In the manufacture of pharmaceutical products wet granulation normally concerns fine powders with wide size distributions. Agglomerate formation and growth of these powders can be described adequately by the two growth mechanisms[2,6,9]:

(i) Nucleation of particles

(ii) Coalescence between agglomerates

"Ball growth", a rapid formation of large agglomerates, is considered to be uncontrolled growth by coalescence. It occurs when the feed material becomes overwetted, especially when the material rolls and slides over inclined surfaces.

Agglomerate formation and growth require the presence of liquid, viz. a binder solution, in order to establish a binding strength which suffices to resist the degrading forces exerted by the agitation. It is likely that most wet granulation processes operate in a balance between agglomerate growth and degradation. The binding strength in the moist agglomerate is therefore a significant factor to granule growth. Powders with uniformly sized particles produce relatively weak agglomerates that are likely to break. These powders show granule growth by layering of feed particles or fines from the degradation of the agglomerates[2,6].

Figure 1 outlines agglomerate formation and growth by nucleation of completely wetted particles. The surface tension of the liquid tends to reduce the total surface free energy by reduction of the air-liquid interfacial area. Hence, loose agglomerates or nuclei are formed due to mobile liquid bondings between particles. Nucleation is most evident with fine particles and may account for growth of agglomerates up to mm size[6].

If agitation is insufficient to assure the distribution of the liquid phase, or if wetting of the particles is incomplete due to the solid-liquid tension, nuclei may be formed by immersion of the particles into the liquid droplets. This is followed by consolidation of the assembly because of the liquid surface tension.

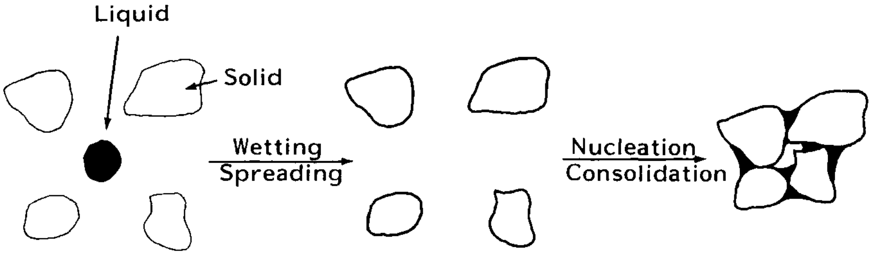

FIGURE 1

Nucleation of particles.

In this case the droplet size must affect the final granule size distribution. It is likely that this mechanism is significant to granule growth in fluidized beds where it has been shown that the droplet size of the atomized binder solution affects the granule size[13]. In high shear mixers, the very intense agitation contributes to the spreading of the liquid. The droplet size of the atomized binder solution has therefore no effect upon the granule size[14]. The larger lumps occurring even in high shear mixers are likely to be formed by local overwetting of the feed material and formation of the lumps by immersion and consolidation as described above.

Granule growth can also proceed by coalescence between colliding agglomerates, Figure 2. At the moment of collision a bonding strength is established in the area of contact between the agglomerates. The strength must suffice to withstand the separating forces due to the bending moment caused by the mass and velocity of the two agglomerates. Growth by coalescence is favoured by feed materials having fine particles and wide size distributions[6], because these materials give rise to high agglomerate strengths.

In the literature there is general agreement that growth by coalescence requires free liquid in the agglomerate surface. The liquid may contribute to the necessary bonding strength. It is likely, however, that the primary effect of the surface liquid is

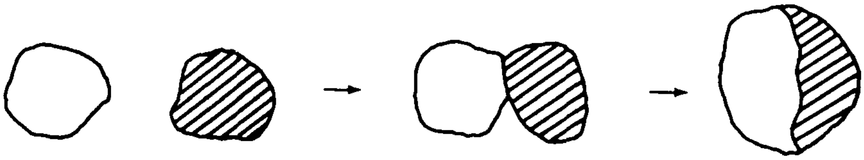

FIGURE 2
Granule growth by coalescence

to improve the surface plasticity of the agglomerate and thus to create a larger area of contact[15,16].

The free surface liquid can be supplied by the addition of binder solution in the first stages of the process. During wet massing, liquid is forced to the agglomerate surface because of consolidation of the agglomerate. Kristensen et al.[17] have shown that granule growth during wet massing in a high shear mixer did not occur unless there was a simultaneous consolidation of the moist agglomerates. Therefore, consolidation of the moist agglomerates is a basic mechanism involved in granule growth.

Consolidation of the agglomerates proceeds due to the contracting forces exerted by the liquid phase (surface tension, capillary pressures). These forces are supported by forces provoked by the agitation of the mass. The particles of a moist agglomerate are never fully constrained, but possess freedom of movement which allow them to adjust to relatively dense packing configurations[9]. The consolidation is revealed by measuring the intragranular porosity of dried samples taken during granulation. It may be referred to by the term densification of agglomerates. The rate of consolidation and the final level reached during granulation depend of course on the properties of the feed material, especially its particle size distribution, particle shape, surface roughness, etc. It has been shown that granulation of pharmaceutical feed materials in a high shear mixer may result in intragranular porosities below 25%[18] and that the rate of densification depends on the particle size distribution[16]. Mixers with less intensive agitation produces granules of higher porosities[19,20].

Granule growth proceeds by nucleation and coalescence with a growth rate which is strongly dependent on the amount of liquid phase. The growth rate is usually described in terms of the mean granule size measured by sieve analysis of dried samples taken during the process. In many cases the log normal distribution gives the best fit to the cumulative granule weight distribution. The distribution is therefore described by the geometric weight mean diameter, d_{gw}, and the geometric standard deviation, s_{gw}, which is the ratio between the diameters, corresponding to the 50% and 15,9% weight distribution, respectively[5].

The content of fines in dried samples taken during granulation can also give information about the agglomeration. This approach has been used to detect growth by nucleation in the early stages of granulation in high shear mixers[17,21].

Liquid saturation

Newitt and Conway-Jones[22] described the states of moist agglomerates having an increasing content of liquid phase:

1. The pendular state
2. The funicular state
3. The capillary state

The three states are distinguished by the relative amount of liquid phase as expressed by the liquid saturation S. S is the ratio of pore volume occupied by liquid to the total volume of pores available in the agglomerate. S may be expressed as the percentage ratio.

In the pendular state, i.e. low S, the particles are held together by liquid bridge bondings. According to Rumpf[23] increasing amounts of the liquid phase give rise to increasing volumes of the liquid bridges. Above ab. 25% of S the voids begin to fill and the state changes from the pendular to the funicular state. In this state the particles are held together by liquid bridge bondings and pressure deficiencies due to liquid surface tension. In the capillary state, i.e. S > ab. 80%, the bonding strength relies upon the capillary pressure of the liquid.

The liquid saturation depends on the amount of liquid and the intragranular porosity according to the equation[17]:

$$S = \frac{H(1 - \varepsilon)}{\varepsilon} \rho \qquad (1)$$

H is the ratio of the mass of liquid to the mass of solid particles. For an agglomerate of particles that are insoluble in the liquid, H is the humidity on dry basis. ε is the intragranular porosity and ρ the particle density. The equation presupposes that the liquid density is unity.

On an empirical basis Kristensen et al.[17] have shown that liquid saturation of the agglomerates is an important factor to granule growth. Granulation of common qualities of lactose and dicalcium phosphate in a high shear mixer showed that the effects of process conditions (impeller rotation speed, process time, liquid amount and liquid addition rate) upon granule growth could be described adequately by the effect of S on the mean granule size. Figure 3 shows the effect of S upon the content of fines and d_{gw} in experiments with dicalcium phosphate. The two graphs demonstrate that the effects of the process conditions depend largely upon their effect on S. According to eq.(1) S is controlled by the liquid content and the intragranular porosity.

Experiments with lactose gave similar results though in the wet massing stage S remained constant, because the lactose granules were not further densified. Accordingly, d_{gw} did not change. The quality of lactose used in these experiments was densified to the final porosity level early in the process.

Schaefer et al.[24,25] have verified the basic correlation between S and d_{gw} in a comparison between granulation in two high shear mixers of horizontal and vertical types. The different liquid requirements for granule growth could be attributed to differences between the densification of the granules in the two mixers. Describing the liquid requirements in terms of S, the results obtained in the two mixers agreed well.

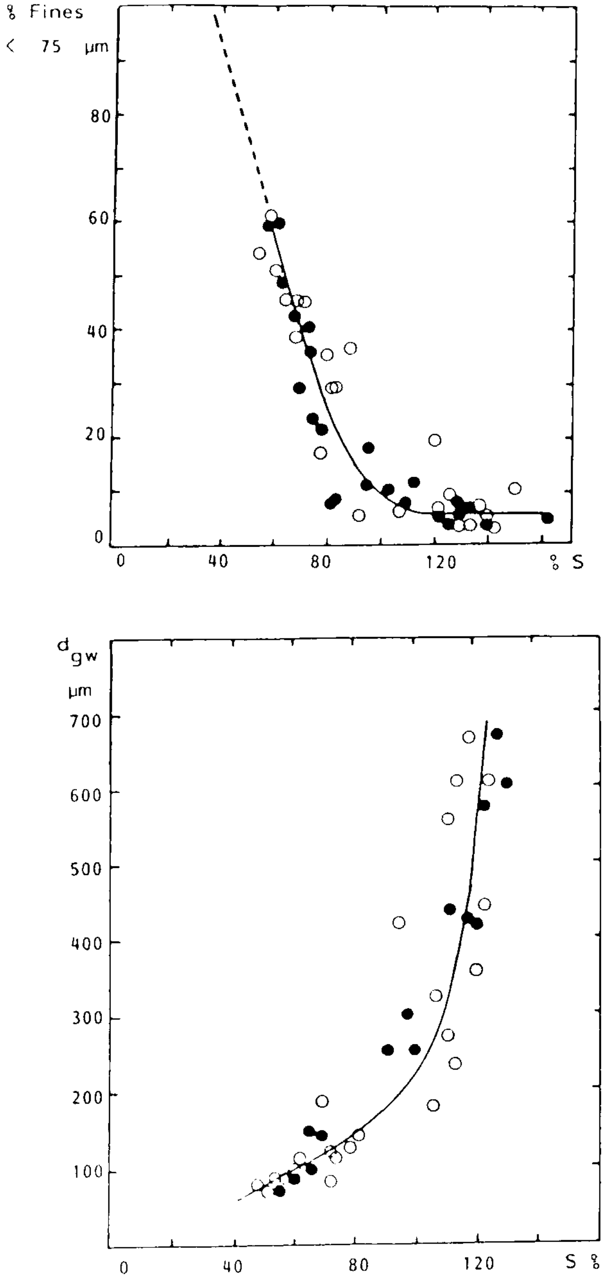

FIGURE 3

Effect of liquid saturations on content of fines and mean granule size of dicalcium phosphate granulation during wet massing in Fielder PMAT 25. o: Impeller speed 250 rpm. ●: Impeller speed 500 rpm.

In a following comparison between high shear mixers available in Danish pharmaceutical industries[26,27] it was found that the correlation between S and d_{gw} applied to mixers of the same type and with different capacity. Comparing different types of mixers, the correlation failed, however.

It is supposed that the correlation between S and d_{gw} is a characteristic of the actual feed material so far granulation in a particular type of mixer is considered. It has been shown that the correlation is influenced by the particle size distribution of the feed material[16]. When the mean particle size of dicalcium phosphate was reduced, the liquid requirements in terms of S were increased. It may be possible to evaluate the effect of the particle size on the liquid requirements on the basis of the correlation between S and d_{gw}.

The liquid saturation of granules can be estimated by measurements of H, ε and ρ, cf. eq. (1), of samples taken during granulation. The sample humidity is measured by drying and corrected for the amount of dissolved binder which contributes to the total liquid volume. ρ can be measured by a gas pycnometer and ε by a pycnometer using mercury as immersion liquid[18,28].

It shall be noted that measurements of the intragranular porosity are likely to be biased because mercury can penetrate larger pores of the agglomerate. It means that the measured value is too low, and that the estimated value of S becomes too high. For the purpose of a particular granulation process, this error is of less importance, but it may invalidate comparisons between granules of different feed materials.

Liquid Requirements

In pharmaceutical practice it is well known that granulation proceeds within a narrow range of liquid contents, especially when granulation in high shear mixers is considered[29]. The liquid amount required to run an uncritical granulation process depends on a large number of factors which include feed material properties (particle size distribution, particle shape and surface roughness, solubility in the liquid and ability to absorb the liquid), liquid characteristics (viscosity, surface tension and solid-liquid tension) and the equipment and its mode of action[6].

It would be a great advantage to industry if the required amount of liquid could be predicted on the basis of knowledge about the feed material and the equipment. Little progress has been made, however, in this direction, probably because of the large number of factors influencing the liquid requirements and their interactions.

A few guidelines can be found in the literature. Linkson et al.[30] examined published data on granulation of insoluble materials in conventional equipments. They found that satisfactory granulation in general required between 50% and 55% v/v liquid phase. Record[10] stated that granulation in high shear mixers normally requires 2/3 to 3/4 of the liquid for more traditional equipments. It is supposed that high shear mixers granulate with less liquid because of pronounced densification of the granules due to the intense agitation.

Kapur[9] stated that in theory the amount of liquid should equal or just exceed the liquid content corresponding to 100% liquid saturation. Thus, the theoretical liquid content W on wet basis is[6]:

$$W = \frac{1}{1 + \frac{1 - \varepsilon}{\varepsilon} \frac{\rho}{\rho_L}} \tag{2}$$

ρ_L is the density of the liquid phase. The equation was fitted to published data on agglomeration by tumbling methods by Capes et al.[31]. Two equations were derived for powders with mean particle sizes below 30 µm and above 30 µm, respectively. The estimated values of the porosity function $1 - \varepsilon/\varepsilon$ were 1.85 and 2.17, which values correspond to ε = 35% and ε = 32%, respectively. The two estimates could predict the liquid requirements with an accuracy of about 30%, only. It is likely, however, that the accuracy can be improved by the use of the actual values of the final granule porosity.

Leunberger et al.[32] studied liquid requirements for granulation in a planetary mixer. They simplified eq.(2) and presented it in a form which takes into account that cohesiveness in the wet mass may appear before the agglomerates are saturated:

$$W = \frac{\bar{\Upsilon}\ \varepsilon\ \rho_L}{[1 - \varepsilon]\rho_S} + \delta_H \qquad (3)$$

where $\bar{\Upsilon}$ is a constant expressing the degree of saturation of the agglomerates. It was given the value 0.213. δ_H is the equilibrium humidity of the feed material at 100% humidity. W expresses the liquid requirements as the proportion of liquid to the dry feed material.

Eq.(3) was tested in experiments on granulation of mixtures of lactose and starch. Estimates of ε were obtained from tapped density measurements of the dry feed material[32,33,34]. It was shown that the liquid requirements according to eq(3) agreed well with the estimates of the uncritical quantity of liquid obtained by recording the power consumption during granulation in a Glen planetary mixer and a Meily Z-mixer[32].

Though it is usually assumed that satisfactory granulation requires 100% liquid saturation, cf. eq.(2), it does not apply to all feed materials. It has been shown that some qualities of lactose and dicalcium phosphate exhibit significant growth by coalescence at liquid saturations far below 100%[16,17,35]. Glass spheres being an extreme showed agglomeration at liquid saturations of ab. 10%[35].

It is supposed that the mean particle size and size distribution of the feed material have a pronounced effect upon the liquid requirements as expressed in terms of the liquid saturation. Experimental evidences about this effect are, however, limited.

The present knowledge about agglomeration of fine powders does not allow the prediction of the liquid requirements with an accuracy which suffices for a proper control. The approach by Leunberger et al.[32] is promising. Further research is needed with respect to the effects of the particle characteristics upon the correlation between liquid saturation and mean granule size.

Today, the realistic alternative to prediction of the liquid requirements is the implementation of instrumental methods for the monitoring of the granulation process as demonstrated by Leunberger et al.[32] and Paris and Stamm[36].

Agglomerate strength and deformability

The strength of moist agglomerates has been studied extensively by Rumpf and his coworkers, theoretically as well as experimentally. The results concerning the strength due to mobile liquid bondings are reviewed in all major monographs on agglomeration. The tensile strength, σ_t, of an agglomerate in the funicular and capillary states can be approximated by the equation[6,37]:

$$\sigma_t = S\,C\,\frac{1-\varepsilon}{\varepsilon}\,\frac{\gamma}{d}\,\cos\Theta \qquad (4)$$

C is a material constant that for uniformly sized spheres is 6. γ is the surface tension of the liquid phase, Θ the contact angle of the liquid to the solid surface and d the particle diameter.

The equation predicts the maximum tensile strength of an agglomerate. It is presupposed that the agglomerate consists of uniformly sized particles and that the liquid phase is freely movable. The agglomerate strength relies on liquid bindings entirely.

Powders with irregular particles and wide size distributions produce agglomerates, the strength of which deviates from that predicted by eq.(4)[23,38]. Kristensen et al[39] have shown that particle interactions may contribute significantly to the strength. Figures 4 and 5 show a comparison between the tensile strength of moist samples of lactose and dicalcium phosphate as measured by a diametrical compression test[39] and the maximum strength predicted

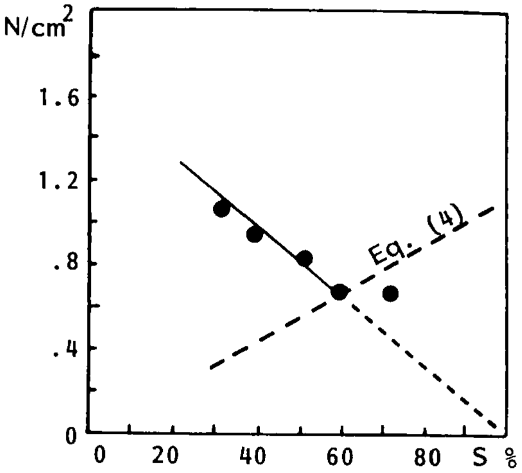

FIGURE 4
Tensile strength of moist samples (ε = 30%) of lactose (d_{gw} = 56 µm) compared to the maximum liquid binding strength cf. eq.(4). Liquid phase Kollidon VA 64, 10%, γ = 45 mN/m, θ ~ 0°.

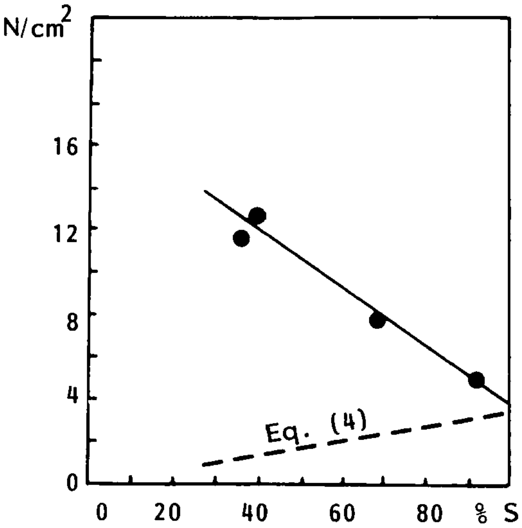

FIGURE 5
Tensile strength of moist samples (ε = 37%) of dicalcium phosphate (d_{gw} = 14µm) compared to the maximum liquid binding strength cf. eq.(4). Liquid phase Kollidon VA 64, 10%, γ = 45 mN/m, θ ~ 0°.

by eq.(4). Due to the method of measurement the results concern brittle samples only. It appears that the tensile strength in both cases is significantly higher than the strength due to mobile liquid bondings, cf. eq.(4). Further, the tensile strength is reduced as the liquid saturation is increased. It means that increasing S reduces the particle interactions, which are supposed to be due to interlockings and friction between particle surfaces. The tensile strength in log scale showed an approximately linear increase against $1/\varepsilon$.

Figure 4 shows that the tensile strength of the lactose samples depends mainly on the liquid bonding strength when S becomes larger than ab. 60%. It was at the same limit of saturations that the moist samples changed from being brittle into a state with plastic deformation[35]. The same observation was made for samples with 37% and 43% porosity. Figure 5 shows that particle interactions dominate the tensile strength of dicalcium phosphate samples so far they are unsaturated. Stress-strain records showed accordingly that the samples remained brittle until S was increased to 90 to 100%[35]. The same results appeared from measurements on samples with 43% and 50% porosity.

Granulation of the two materials in a high shear mixer[16,35] showed that granule growth by coalescence was significant for lactose in the range of saturations above ab. 25%. When S became ab. 70% the growth rate was very high and the mass appeared overwetted. In contrast, granulation of dicalcium phosphate required more than 80% to 90% saturation for growth by coalescence.

The experiments with the two materials demonstrated that granule growth by nucleation occurred when there was sufficient liquid phase to establish bridge bondings. Growth by coalescence became significant when the amount of liquid phase expressed in terms of the liquid saturation was sufficient to improve plastic deformation of the agglomerates. This means that in the stages of the process where growth by coalescence becomes significant, the strength of the agglomerates depends mainly upon the mobile liquid bonding strength, cf. eq.(3).

The above results are an experimental verification of the theoretical work on coalescence mechanisms by Ouchiyama and Tanaka[15,40]. They showed that a large deformability is essential for growth by coalescence. The deformability can be described by the stress-strain record of the agglomerate[39]. The maximum stress σ_{cr} and the corresponding strain l_{cr} are measures of the deformability. The effect of the deformability upon the growth rate is formulated mathematically by the equation[15,16]:

$$\delta^{2/3} = A \frac{{l_{cr}}^3}{\sigma_{cr}} \qquad (5)$$

A is a constant and δ a measure of the potential to grow by coalescence, and hence a measure of the growth rate. Strictly, δ defines the limiting granule size beyond which growth by coalescence is hindered because of the effects of the mass and velocity of the colliding agglomerates.

Eq.(5) outlines a very complex correlation between granule growth and the properties of the feed material, the content of liquid phase, the granule porosity and liquid saturation. During wet granulation the moist agglomerates are densified to an extent which depends on the packing properties of the feed particles and the action of the mixer. By densification, the agglomerates gain strength and the liquid saturation is increased. In addition, excess liquid is forced to the agglomerate surface by effects of capillary pressures and consolidation. At a certain stage of the process, the growing liquid saturation and the free surface liquid suffice to improve the plastic deformation behaviour which means that l_{cr} is increased. According to eq.(5) the effect of l_{cr} overrules the effect of σ_{cr}, because l_{cr} enters the equation as l_{cr}^3. It is supposed that this presents the explanation of the close correlation between S and d_{gw} which has been discussed above and claimed to be characteristic to the particular feed material.

Eq.(5) demonstrate further that growth by coalescence of feed materials that produce moist agglomerates which are primarily brittle is delayed by the growing tensile strength. This effect has been demonstrated experimentally by granulation of different qualities of dicalcium phosphate in a high shear mixer[16]. Independent of the quality, the moist agglomerates remained brittle as long as they were unsaturated. Growth by coalescence was found to correlate with the tensile strength in agreement with eq.(5).

The discussion above shows that the tensile strength of moist agglomerates has a pronounced effect upon granule growth. The effect can, however, be described qualitatively only. Feed materials with fine particles and wide size distributions, i.e. cohesive powders, are likely to produce agglomerates that are primarily brittle. Though agglomeration by the nucleation mechanism will occur at relatively low liquid saturations, almost complete saturation is required to see significant growth by coalescence. These materials are experienced to densify during wet massing in high shear mixers, because of their resistance to consolidation. Granulation becomes very sensitive to the liquid content and process time, because there is only a narrow margin between complete liquid saturation and overwetting caused by densification.

Feed materials that are non-cohesive are easily densified to the final level early in the wet granulation process[16,35]. These materials produce relatively weak agglomerates that may become deformable at saturations below 100%, especially when the feed particles are rounded and have smoothed surfaces. An example is granulation of a lactose quality with $d_{gw} = 56$ µm which in a high shear mixer showed growth by coalescence at a wide range of saturations above ab. 25%[17]. The process was accordingly very robust to variations in the amount of binder solution.

The presentation above presupposes some degree of ideality with respect to uniformity of the liquid distribution in the moistened feed material, and that the liquid phase is freely movable. It is well experienced that the method of liquid addition can affect the granule size distribution and give rise to the presence of large lumps because of local overwetting. Deposition of moist material on the wall of the mixer may as well affect the granule growth and the final granule size, because the mass becomes inhomogeneous.

GRANULATION METHODS AND EQUIPMENTS

In the pharmaceutical industry the processes ordinarily used for granulation are fluidized bed granulation and wet massing. The main emphasis, therefore, is given to these processes. A more complete review of processes and equipments used for pharmaceutical granulation is presented by Record[10].

Fluidized bed granulation of pharmaceuticals was first described by Wurster[41] in 1959, and during the 1960s fluidized bed granulators were installed in many pharmaceutical companies. Although different types are commercially available, all standard equipments are similar to that described in Figure 6. Air is drawn by a ventilator through a material container of a conical shape. The ventilator sets moving the particles up in the central part of the bed and down again at the wall. The fluidizing air is heated to a temperature typically ranging from 40 to 80 °C; binder solution is added by spraying, and when liquid addition is finished the granules are dried in the same equipment. Fluidized bed batch granulators for granulation of pharmaceuticals are available with capacities from about 1 to 800 kg.

The greatest merit of the method is that it meets the requirements of GMP very well[42], since mixing, wetting and drying are combined in a single process. The ventilator gives rise to a pressure below atmospheric within the equipment, thus reducing the risk of cross-contamination and escape of toxic material. From the standard fluidized bed granulators the fluidizing air is blown into the atmosphere, and therefore pollution of air by dust and by solvents might be a problem. In order to retain dust of highly toxic materials a secondary high-efficiency filter is necessary[10].

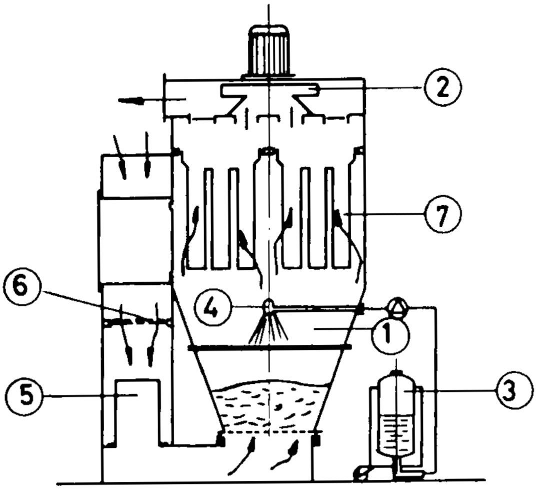

FIGURE 6
Fluidized bed granulator. Material container (1), ventilator (2), binder solution (3), nozzle (4), heating elements (5), inlet air filter (6), outlet air filter (7).

Pollution of air by solvents can be prevented by using a specially constructed fluidized bed operating in a closed system, where the solvent is recovered by cooling[43].

Another disadvantage of fluidized bed granulators is the enhanced risk of explosion due to the large amount of oxygen conveyed by the fluidizing air. The explosion might involve dusts, solvents or hybrid mixtures of dusts and solvents being ignited by a spark induced by electrostatic charging[44]. Different methods of preventing explosions in fluidized bed granulators and driers are discussed by Bartknecht[45] and Külling[44,46].

Wet massing is accomplished in mixers equipped with mechanical agitators of different sizes and shapes rotating at different speeds[10]. The Z-blade and planetary mixers are examples of mixers, where the agitators rotate at rather low speeds. The distinction between low speed mixers and high speed mixers is somewhat arbitrary[47]. Mixers such as Lödige®, Diosna®, Fielder® and Baker Perkins®, which are equipped with an impeller rotating at moderately high speed, normally in the range of 100-500 rpm, are called high speed or high shear mixers. The higher mixing intensity in high shear mixers results in denser granules when compared to low speed mixers[19].

In a high shear mixer (Figure 7), mixing, densification and agglomeration of wetted materials are achieved as a result of shearing and compaction forces exerted by the main impeller. Most of these mixers are additionally equipped with a chopper rotating at a very high speed (1000-3000 rpm) in order to cut lumps into smaller fragments. The binder solution might be poured or pumped into the bowl within a few minutes, but a more uniform liquid distribution and thus a more controllable granule growth is obtained when the liquid is atomized onto the powder[48]. After liquid addition the material is normally wet massed for a few minutes in order to obtain further densification and granule growth. It is a disadvantage of the process that the granules at the end of wet massing have to be transferred to a drying equipment, for example a fluidized bed drier.

High shear mixers might be either horizontal, vertical or changeable bowl mixers[10,26,47]. Schaefer et al. have compared different types of high shear mixers[24-27]. Granule growth mechanisms in the horizontal mixers might differ from the vertical type, since granules are rolling down the inner wall of the cylindrical mixing chamber. It is difficult to conclude, however, whether the differences in size distributions of granules produced in horizontal and vertical mixers, respectively, are due to differences in the construction and rotation speeds of the mixing tools or are caused by the horizontal mixing bowl[27]. Imanidis and Leuenberger[49] found differences in power consumption of the impeller motor during granulation in a horizontal and a vertical mixer, respectively. The differences were ascribed to a higher densification of the granules in the vertical mixer, where granules are assumed to be thrown extensively against the wall by the centrifugal forces. In the pilot scale mixers examined[27] similar differences in densification were found at low impeller speed only. A

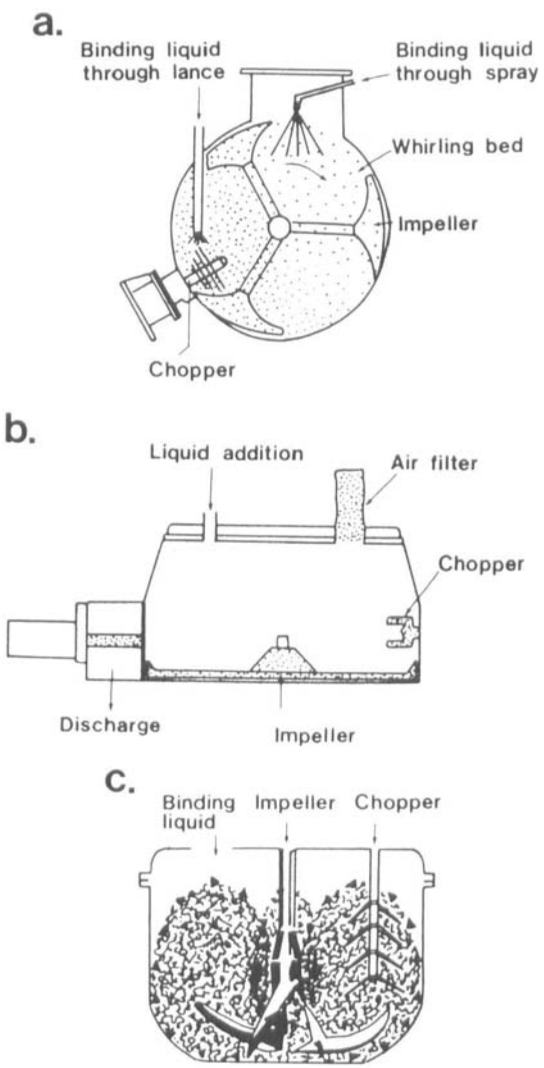

FIGURE 7
Different types of high shear mixers. (a) Horizontal mixer, (b) Vertical mixer, (c) Changeable bowl mixer (from[26]).

production scale changeable bowl mixer gave granules of physical properties similar to those obtained in vertical production scale mixers[27]. Thus, the major advantage of changeable bowl mixers seems to be a reduced risk of contamination, since the seals are kept away from the product.

It was shown that the energy consumed in a high shear mixer is converted completely into heat in the moist mass[35]. The temperature increase depends on the rotation speeds as well as the size and shape of the mixing tools[26,27]. The rise in temperature during the process can be more than 40 °C[27]. In the Baker Perkins Granulators the rise in temperature can be extremely high due to a higher energy input. In such mixer type Flanders et al.[50] obtained a temperature of 110 °C during a melt granulation process without heating. The use of high shear mixers, therefore, might give rise to problems when using heat sensitive materials. In order to reduce the rise in temperature some high shear mixers are equipped with a cooling jacket.

During the last decade high shear mixers have gained an increasing interest in the pharmaceutical industry at the expense of fluidized bed granulators. Aulton and Banks[11] have discussed the reasons for this change and have concluded that wet massing is a simple, robust technology, whereas fluidized bed granulation is much more delicate. In practice, many existing formulations cannot be easily transferred to fluidized bed granulators without lengthy and expensive development work.

Many of the problems can be ascribed to the lack of shear forces in a fluidized bed. Densification of voluminous materials and fluidization of cohesive materials might therefore be difficult to achieve in a fluidized bed granulator. Accordingly granules obtained from fluidized bed granulators are generally found to be more porous than those obtained from high shear mixers[34,51,52,53]. That might be advantageous in some formulations resulting in better dissolution and compression characteristics[11]. Once the development problems are overcome, fluidized bed granulation is advantageous, too, since the granule growth is easy to control and the reproducibility is very good[54]. The optimal choice of granulation methods will therefore depend on the physical properties of the starting materials and the demands to the final product.

Several modifications of granulation equipments have been constructed to combine the advantages of a fluidized bed granulator and a high shear mixer, e.g. by introducing mechanical agitation into a fluidized bed or by combining a high shear mixer with a drier. Lenkeit et al.[55] describe a high shear mixer equipped with a drying-air-system. However, this method is not widely used, probably because of the inefficiency of the drying procedure compared to a fluidized bed.

The method of mechanical agitation in a fluidized bed seems to be more convenient. Ormós et al.[56-59] described laboratory scale fluidized bed granulators equipped with different mechanical agitators. It is also possible to modify a commercially available fluidized bed granulator by equipping it with a chopper similar to that of a high shear mixer[60]. Mechanical agitation makes it possible to fluidize materials with poor fluidization characteristics and to increase the moisture content of the bed. The resulting granules have a denser structure and a narrower size distribution. Similar effects are obtained in the vibrofluidization granulation process where vibration energy is transferred by a vibrating air distributor plate[61].

The modification most commonly used in the pharmaceutical industry is the rotary fluidized bed granulator[62-64]. In this type of granulator a rotating disk is installed in the bottom of the bed instead of the air distributor plate ordinarily used (Figure 8). The rotation speed as well as the diameter of the air slit can be varied. Due to the rotating disk rounded granules of a high density are obtained, and thus the process is suitable for production of pellets[63,65]. A disadvantage is, however, that the material is not uniformly fluidized, and consequently the temperature varies within the bed[62].

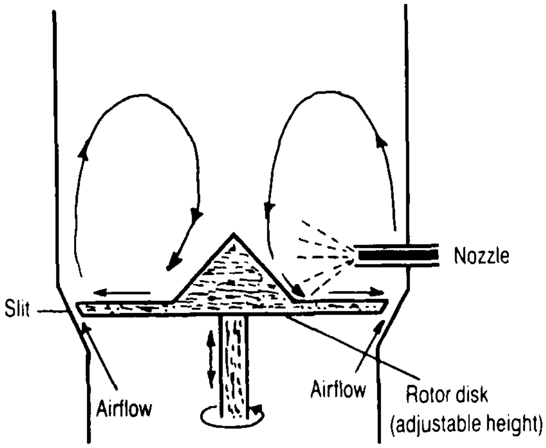

FIGURE 8
Schematic diagram of the product-handling section of a rotary fluidized bed granulator (from[64]).

Although the modifications described above seem to be suitable for special purposes, the results published are not sufficient to conclude whether some of the equipments might generally be preferable to ordinary fluidized bed granulators or high shear mixers.

Other granulation methods are mentioned to be advantageous to fluidized bed granulation and high shear mixing. Bartsch described a method named Topo-granulation where a drug is deposited on the surface of a carrier material in a one-step vacuum system[66]. Another method is microgranulation being a coating process by which small particles are made free-flowing by coating with a binder[67]. Agglomeration is prevented by using an amount of binder solution smaller than that necessary for ordinary granulation. Microgranulation might improve the content uniformity and dissolution rate and reduce tablet weight variation when compared with wet massing[67-69]. Although both methods might be favourable for special purposes, they do not seem to be generally applicable.

Since batch sizes in the pharmaceutical industry ordinarily are rather small, granulation of pharmaceuticals is mainly carried out in batch granulators. Another reason is that the GMP requirements are easier to comply with in batch granulators where process variables are easier to control compared to continuous granulators[3]. In case of large volume products continuous granulation processes might be of interest, however. Continuous fluidized bed granulators are described in laboratory scale[58,59,70] as well as pilot scale[71,72], but they are only rarely used in the pharmaceutical industry. Extrusion followed by spheronization is a common method for preparation of pellets[73-77]. However, extrusion might be used for continuous production of granulations of ordinary size distributions, too[78]. Continuous extrusion processes seem to gain increasing interest. Provided that further research on the effect of process variables is done, it is likely that extrusion might be a granulation process of the future besides fluidized bed granulation and high shear mixing.

GRANULATION VARIABLES

Agglomeration is caused by complex interactions of several parameters, and a knowledge of the effect of each is therefore necessary for controlling the granulation process. Aulton and Banks[11] distinguish between apparatus variables, process variables and product variables. Apparatus variables are related to the construction of the granulation equipment and process variables to the procedure being used, and these variables are closely related to the actual process. Product variables are related to the starting materials and the applied binder and binder solvent, and thus product variables influence any granulation process, although to a varying extent. Detailed reviews of the effects of granulation variables in fluidized beds[11] and in high shear mixers[47] are given in the pharmaceutical literature. Only the main variables will be discussed below.

Apparatus variables

In a fluidized bed granulator the air distributor plate and the shape of the container influence the particle motion in the bed. However, proper fluidization can be obtained by different distributors as well as by varying container shapes. By an appropriate choice of these parameters the effect of the construction of the bed on granule properties seems to be insignificant. Accordingly Ormós et al.[79] found no effect of varying the design of the air distributor plate.

The position of the nozzle in a fluidized bed granulator affects the wetting of the material. If the position is too high, spray drying of the binder solution might occur, on the other hand a low position might result in clogging of the nozzle. In practice, nozzle height variations within a rather wide range have slight effect only on granule properties. Within that range it is sufficient to maintain a combination of nozzle height and spray angle that brings about a proper wetting of the bed surface without wetting the wall of the apparatus[80].

While the fluidized state in a fluidized bed granulator is nearly independent of the construction of the apparatus, shear forces in a high shear mixer are very dependent on the mixer construction. Consequently, apparatus variables are more essential when using high shear mixers. Size and shape of the mixing chamber, impeller and chopper differ in different high shear mixers. However, high shear mixers are constructed on a rather empirical basis, and only few results on the effect of mixer construction are published.

Schaefer et al.[26,27] compared two sets of mixing tools in a 25-litre Diosna mixer, the standard tools being similar to those shown in Figure 7b and a set consisting of a specially constructed impeller and chopper. The specialized tools were similar to those used in the vertical Lödige mixer, the impeller of which is of a ploughlike shape. The standard tools resulted in a considerable amount of wetted mass adhering to the wall and the lid of the bowl, whereas no appreciable adhesion was found when using the specialized tools. The difference was ascribed to a more appropriate movement of the mass caused by the specialized tools. It is assumed that the ploughlike impeller lifts the mass and throws it down into the central part of the bowl, whereas the mass is thrown against the wall to a greater extent by the standard tools. Further, the amount of lumps was found to be considerably lower when using the specialized tools. The extremely low amount of lumps is most likely due to less adhesion to the bowl as well as a larger comminution effect of impeller and chopper.

Richardson[81] calculated the relative volume swept out by the impeller and chopper, respectively, in Diosna mixers of varying sizes assuming that it is related to their work input on the material. The wet massing time necessary to obtain a certain granule size was found to be shorter, the higher the relative swept volume. When comparing high shear mixers of different types, Schaefer et al.[27] found differences in densification, which were ascribed to differences in the relative swept volume of the impellers. Thus, the relative swept volume seems to be an appropriate parameter when comparing the effect of size and construction of the mixing tools.

The effect of the chopper on granule properties in different types and sizes of mixers was examined[26,27], and the comminution effect was found to differ rather considerably. It was concluded that the chopper seems to be undersized in many high shear mixers.

The results indicate that there is a general need of optimizing the construction of high shear mixers. Relatively few attempts have been made to compare the properties of granules made by different granulation methods[19,53,68,69,82-88]. This is clearly an area within wet granulation methods that calls for further research.

Process variables

In fluidized bed granulation agglomeration is controlled by the moisture content of the bed. If the moisture content is too high, the bed becomes overwetted and defluidizes rapidly, and if the moisture content is too low, no agglomeration will occur. The possible range of variation in moisture content is narrow, and it is necessary therefore exactly to control the process variables affecting the moisture content.

At any given time, the moisture content of the granules depends on wetting and evaporation, which are primarily controlled by liquid flow rate and inlet air temperature. Granule size was found to be proportional to liquid flow rate and inversely proportional to air temperature[89]. Ormós et al.[90] describe equations for calculation of the equilibrium liquid flow rate at which liquid supply is balanced by evaporation, and the critical liquid flow rate above which fluidization is impossible due to overwetting. Ordinarily a liquid flow rate between these values is used.

Other variables influencing evaporation are flow rate and humidity of the inlet air. Since granule size and moisture content are increased during liquid addition, the flow rate of the fluidizing air has to be increased simultaneously in order to keep the bed expansion constant[91,92], and that might complicate the control of the moisture content. The effect on evaporation of varying the air humidity can be eliminated by varying the inlet air temperature so that the ΔT-value, i.e. the difference between the drying air temperature and the wet bulb temperature is kept constant[89].

Provided that a proper balance between liquid addition and evaporation is established, droplet size of the atomized binder solution is the most important process variable in fluidized bed granulation. Droplet size is easily varied when using a binary nozzle[93]. Several authors have shown that increased atomizing air flow rate or air pressure result in a smaller granule size. Schaefer and Woerts[93] derived an empirical droplet size equation on basis of estimation of the sizes of droplets obtained by atomization of different binder solutions at varying air-to-liquid mass ratios. As can be seen in Figure 9 a linear correlation was found between the droplet size calculated from the equation and granule size. The correlation depends on the applied binder solution.

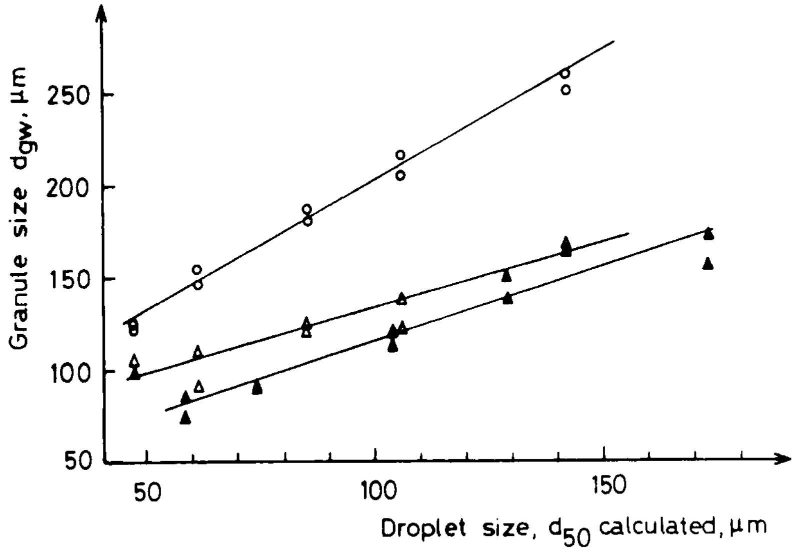

FIGURE 9
Correlation between droplet size calculated from an empirical droplet size equation[93] and granule size at the end of the granulation phase in a fluidized bed granulator (from[13]). Binder solutions: o: gelatine 4%, Δ: Kollidon 25 (PVP) 10%, ▲: Methylcellulose 2%.

Thus granule size in fluidized bed granulation can be varied in a simple and reproducible way by varying the air flow rate to the nozzle.

When granulating in a high shear mixer the mechanical forces exerted on the moist mass by the mixing tools are essential, and thus the most important process variables are impeller speed and wet massing time. Chopper speed might be an important variable, too, but the effect of chopper speed depends on the size and shape of the chopper[26,27]. In order to produce granulations of varying porosities and size distributions it is essential that rotation speeds of the impeller as well as the chopper can be varied continuously[27].

Figure 10 shows the effect of the impeller speed on agglomeration during liquid addition. Dicalcium phosphate is granulated in two different high shear mixers, a 5-litre horizontal Lödige

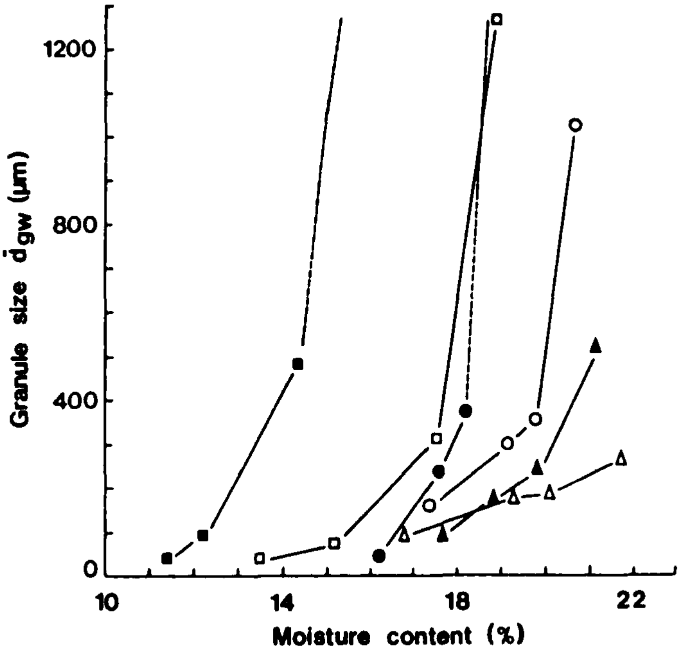

FIGURE 10
Effect of moisture content on granule size of dicalcium phosphate granules during liquid addition in two types of high shear mixers. Mixers: Fielder PMAT 25 VG (□, ■), Lödige M 5 GR (o,●,Δ,▲). Impeller speed: 100 rpm (o,Δ), 250 rpm (□,●,▲), 500 rpm (■). Liquid flow rate: 25 g/min (o,●), 75 g/min (Δ,▲), 100 g/min (□,■) (from[24]).

mixer and a 25-litre vertical Fielder mixer[24]. As can be seen granule growth begins at a lower moisture content at high impeller speed. This effect was ascribed to an effect of impeller speed on porosity and consequently on liquid saturation. Further it is seen that granule growth begins at a lower moisture content in the Fielder mixer due to a higher densification in that mixer. When plotting the correlation between liquid saturation and granule size instead the marked effects of impeller speed and type of mixer nearly disappear.

The effect of wet massing time on intragranular porosity and granule size in a high shear mixer is shown in Figure 11. Moist

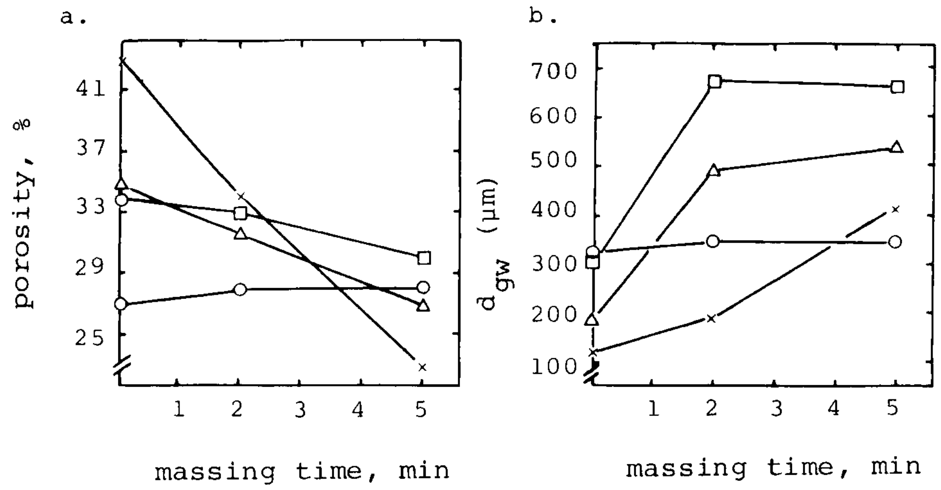

FIGURE 11
Effect of wet massing time on intragranular porosity (a.) and granule size (b.) in a high shear mixer, Fielder PMAT 25 VG. Impeller speed: 250 rpm. Chopper speed: 3000 rpm. Starting materials: Lactose, o. Dicalcium phosphate: x. Dicalcium phosphate/corn starch 85/15 w/w%: Δ. Dicalcium phosphate/corn starch 55/45 w/w%: □. (from[94]).

lactose agglomerates are easily densified and therefore the minimum porosity was reached during liquid addition, and no further densification is seen during wet massing. Dicalcium phosphate granules are difficult to densify, which results in a marked fall in porosity during wet massing. The addition of starch to dicalcium phosphate facilitates densification, but results in a higher final porosity. A fall in porosity during wet massing increases the liquid saturation, and therefore granule growth is obtained in the case of dicalcium phosphate and mixtures of dicalcium phosphate and starch. In the case of lactose liquid saturation is unchanged, and consequently no granule growth occurs. Thus wet massing time primarily is of importance, if the starting material is difficult to densify. This observation explains the contradictory findings of the effect of wet massing time[51,95].

At a given amount of binder solution liquid flow rate will affect the processing time. A lower flow rate prolongs the processing time, which might result in a lower porosity. This explains that a larger granule size can be seen at a lower liquid flow rate, if moisture content is unchanged (cf. Figure 10).

Contrary to fluidized bed granulation the droplet size of the atomized binder solution is of less importance in high shear mixers, where liquid is distributed by mechanical agitation. However, it might be favourable to atomize the binder solution instead of pouring it into the bowl in order to obtain a homogeneous liquid distribution[26,48].

Product variables

In practice variations in the physical properties of the powders to be granulated give rise to problems. Thus it might be necessary to change one or more process variables as well as the amount of liquid when changing the formulation. Even at unchanged formulation inevitable variations in particle size from batch to batch of the same material make it difficult to control the granulation process.

The most important physical properties of the starting material seem to be the size and size distribution of the particles. Since free surface liquid is necessary in order to obtain agglomeration, the amount of liquid to be used will depend on the surface area of the powder. A smaller particle size results in a larger surface area. This explains why several authors have found that a decreasing particle size results in a smaller granule size at a constant amount of liquid[96-98] or that a larger amount of liquid has to be used in order to keep granule size constant when the particle size decreases[80,99-103].

When using water absorbing materials such as starches, absorption results in incomplete wetting of the surface and therefore the amount of liquid has to be increased[32,80,97]. Lindberg et al.[104] examined the effect of the water content of the starch on granulation. They concluded that it is inexpedient to use a constant amount of binder solution when granulating starches, because variations in water content of the starch in that case will affect granule size distribution.

If the particle size is so small that the powder becomes cohesive, further problems might occur. As previously mentioned fluidization of cohesive materials is difficult or impossible to achieve, and fluidized bed granulation might therefore not be an appropriate method. Is high shear mixing used instead, densification of the material will be very dependent on impeller speed and wet massing time, and thus the amount of liquid is very critical.

In Figure 11 densification of dicalcium phosphate proceeded slowly contrary to lactose. The difference between the two materials, however, was primarily due to differences in particle size. Kristensen et al.[16] examined different qualities of dicalcium phosphate and found densification to be very dependent on mean particle size and size distribution. Correspondingly, lactose might be difficult to densify, too, when the particle size becomes smaller than used for the experiments in Figure 11[99,102].

Linkson et al.[30] examined the effect of particle size distribution of silica sand on granule growth in a rotating drum. A wide size distribution resulted in strong agglomerates of a low intragranular porosity, whereas a narrow size distribution resulted in weaker agglomerates of higher porosity. These results were confirmed by wet massing of lactose[103]. An increasing content of starch gives rise to weaker granules[97]. Thus in a fluidized bed granulator Schaefer et al.[54] found a remarkable attrition at a content of starch of 80% and Higashide et al.[42] found an increasing content of starch in the finest size fraction of granules consisting of a mixture of lactose and starch.

The effect of starch on granule strength is caused by the relatively narrow size distribution of starches as well as the rounded particle shape preventing interlocking. However, only little is known about the effect of particle shape on agglomeration. In general an irregular particle shape will favour interlocking and thus increase granule strength. The granule strength is especially important when using granulation methods where large mechanical forces are involved. In the case of fluidized bed granulation particle shape might influence fluidization characteristics, needle-shaped or plate-shaped particles being difficult to fluidize.

It is complicated to clarify the effects of the physical properties of different starting materials, since the physical properties normally differ in many respects. It might be favourable, therefore, to carry out experiments using narrow size distributions when comparing granulation of different materials, thus reducing or eliminating the effect of particle size.

Ormós and Pataki[105] granulated size fractions of between 0.1 and 0.2 mm of five different materials with an aqueous gelatine solution in a laboratory scale fluidized bed granulator. The results are shown in Figure 12. The highest growth rate is seen if the material is soluble in the binder solution, such as sodium chloride and sodium nitrate, and the lowest growth rate was found for polyethylene being insoluble and poor wettable. Thus solubility and wettability are physical properties affecting granule growth, too. Jaiyeoba and Spring[106] found solubility and wettability to have a larger effect on mean granule size than the particle size of the third component of a ternary mixture.

When the powder is semisoluble in the binder solution, the amount of solution has to be lower, since the volume is increased by dissolution of powder, and the amount of powder is reduced[107,108]. Since the smallest particles are dissolved first, the reduction in surface area can be relatively large[109]. Recrystallization of dissolved material during drying will increase the strength of the granules[107].

If the starting material is poorly wettable, granule formation and growth are difficult to achieve, which results in a smaller granule size[110-112]. The wetting of the powder is likely to be more important in a fluidized bed granulator due to the lack of shear forces[110]. Wettability might be improved and granule size thus be increased by using another solvent[112,113], or by adding a surfactant to the binder solution[110,114]. Bode-Tunji and

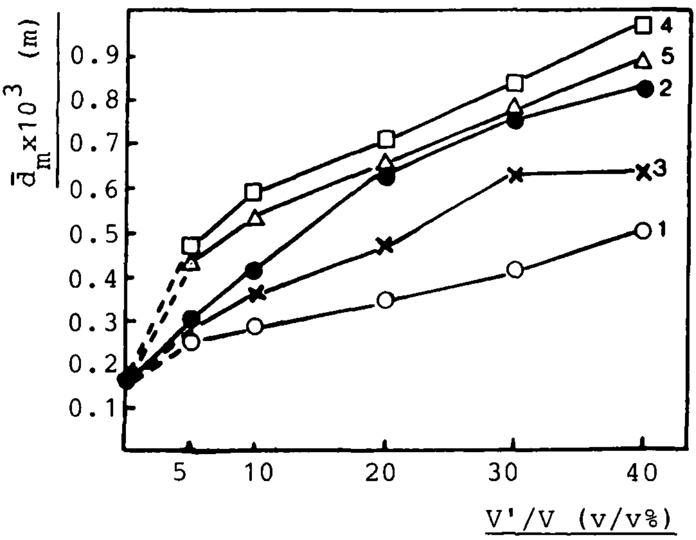

FIGURE 12
Effect of the relative amount of binder solution on the size of granules produced from 0.1-0.2 mm size fractions in a laboratory scale fluidized bed granulator. Starting materials: polyethylene (1), glass beads (2), sand (3), sodium chloride (4), sodium nitrate (5) (from[105]).

Jaiyeoba[114] compared the effect of three surfactants on wettability and found that a higher HLB value resulted in a larger granule size. The effect of surfactant might depend on its concentration. At low concentrations of different surfactants granule size was found to decrease, whereas an increase was found at higher concentrations[115]. It has to be considered that addition of a surfactant might influence other properties of granules and tablets. El-Arini and Polderman[116] found that addition of sodium lauryl sulphate to fluidized bed granulations resulted in granules and tablets which were weaker and had shorter disintegration times. Similar results were found by wet massing, where surfactants improved disintegration and dissolution[115].

The results published hitherto show that the effect of the starting material on granule formation and growth is a complex interaction between different physical properties. It is difficult to make an experimental design, where only one of these factors is varied. This explains why the knowledge of the effect of the starting material is rather unsystematical. Further research in this field is needed to obtain such a knowledge that on basis of data of the material it will be possible to predict the optimum amount of liquid and the optimum process variables.

As discussed previously granule growth is primarily controlled by the liquid saturation of the granules. The liquid saturation depends on the amount of liquid added as well as on the densification of the granules. The optimum amount of liquid for granulation of a given starting material, therefore, will depend on the apparatus variables and process variables affecting densification. Record[10] for example states that the quantity of liquid necessary in a high shear mixer is normally about two-thirds to three-quarters of that used in low shear mixers.

Ordinarily a binder has to be added in order to keep the granules together by solid bridges after drying. As mentioned above solid bridges are formed by recrystallization when a material is semisoluble, and if so a binder might possibly be avoided.

Distribution of the binder into the starting materials in a dry state before wetting might result in a smaller granule size[112,117] and an increased content of lumps[99] indicating an inhomogeneous distribution of the binder. Therefore, the binder is normally dissolved in the liquid before liquid addition.

In a fludized bed granulator mechanical forces are too low to obtain a uniform distribution of the binder solution without spraying. This means that only binder solutions of a rather low viscosity can be used. Although spraying might be favourable in a high shear mixer, too, shearing forces makes it possible to obtain a uniform distribution of solutions of low viscosities without atomization by a proper choice of process variables.

The distribution of binder within a granule depends on the granulation method as described by Seager et al.[20,118]. In granules prepared by wet massing the binder is distributed as a sponge-like matrix. The same matrix of binder is seen in a granule from a fluidized bed granulator, but further the surface of the granule is coated with a shell of binder. Ragnarsson and Sjögren[53] compared fluidized bed granulations with granulations prepared by wet massing. They found tablets compressed from fluidized bed granulations to be stronger, and these findings were ascribed to the surface shell of binder resulting in stronger bondings.

During fluidized bed granulation drying occurs simultaneously to liquid addition and therefore the effects of binders differ from the effects obtained by high shear mixing. In both methods particles are held together by liquid bondings. In a fluidized bed granulator, however, evaporation of solvent results in an increasing concentration of binder in the liquid bridge, and consequently the liquid bondings become viscous and immobile. Therefore, the adhesive forces are markedly increased, and the agglomerates are stabilized[70,119]. The higher the binder concentration, the more viscous the liquid bondings, and this explains why granule size increases at increasing binder concentration in fluidized bed granulation[13,70,91,120-127].

In a high shear mixer on the other hand evaporation of solvent occurs to a less extent and liquid bondings therefore are normally mobile. Granules are stabilized instead by densification and deformation. Consequently Ritala et al.[128] found only a slight effect of the concentration of five different binders on granule growth during the liquid addition phase in a high shear mixer. However, a higher binder concentration resulted in a lower power consumption, since the binder acts more effectively as a lubricant, when its concentration is increased.

If the binder solutions are highly viscous such as starch paste, the binder will be inhomogeneously distributed, and that might result in weaker granules due to insufficient bonding forces[129,130]. Leuenberger and Imanidis[49,131] found that the power consumption curve obtained from a high shear mixer was strongly affected by addition of a highly viscous starch paste, because liquid bondings were not freely mobile. Accordingly it seems to be inexpedient to use highly viscous binder solutions, since the use of such binders makes it difficult to control the granulation process.

The type of binder is essential in fluidized bed granulation. Evaporation during the process results in agglomerates being partly held together by solid bridges of binder,but if the binder is too weak, the agglomerates are broken down and re-agglomeration occurs by further liquid addition followed by break-down etc.[132].

Several binders have been used for fluidized bed granulation of pharmaceuticals, and granule growth is found to be affected by the type of binder[13,96,119,120,126,133,134] as can be seen in Figure 13. Droplet sizes of the atomized binder solutions depend on the viscosity of the solution[93]. Consequently, the effect of different binders on granule size might be due to varying droplet sizes.

However, the effect of type of binder seen in Figure 13 could only partly be explained by differences in viscosity affecting droplet size. Granule growth is also affected by the actual viscosity and adhesion forces in the wet agglomerates, where the properties of the binder solution are changed due to evaporation of solvent. This might explain why gelatine and Kollidon 90 seem to possess the best agglomeration properties of the binders in Figure 13.

Massoud and Bauer[135] have described an apparatus for determination of adhesion forces of binder solutions in the course of drying, and thus the results might possibly simulate the changes of adhesion forces in a fluidized bed granulator. They found a higher increase in adhesion forces when using gelatine or Kollidon 90 instead of Kollidon 25 in accordance with the effect of the same binders on granule growth (cf. Figure 13). Several authors have found that gelatine gives rise to larger granule size than low molecular types of PVP[96,126,133,134].

Gelation of gelatine solutions might explain the good agglomeration properties of this binder. Gelation begins at a temperature below 30-40 °C dependent on the concentration of the gelatine

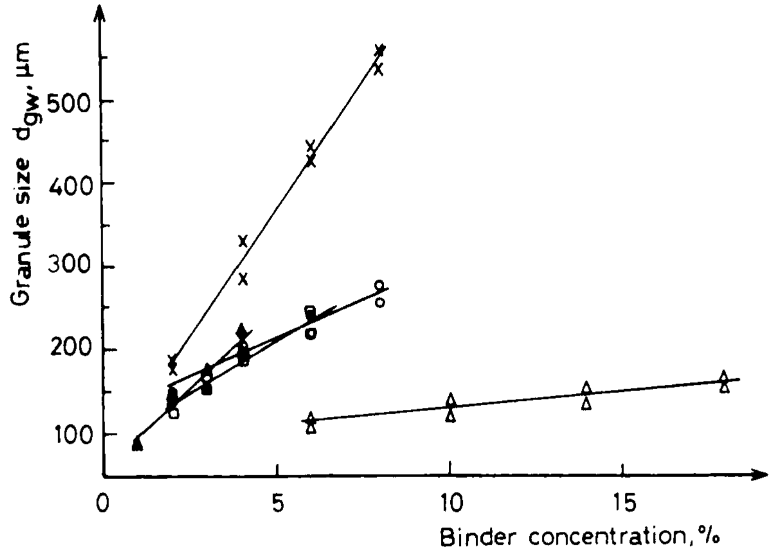

FIGURE 13
Effect of concentration of binder in the binder solution on granule size in a fluidized bed granulator, Glatt WSG 15. Air-to-liquid mass ratio at the nozzle: 1.15. Binders: o: Gelatine, Δ: Kollidon 25 (PVP), x: Kollidon 90 (PVP), □: Sodium carboxymethylcellulose, ▲: Methylcellulose (from[13]).

solution. Since the bed temperature during liquid addition normally is below that level, gelation will be caused by cooling of the solution as well as by evaporation of solvent. When the gelation begins, adhesion forces are increased thus promoting agglomeration, and by further gelation strong agglomerates are formed kept together by immobile liquid bondings. Gelation can be delayed by increasing the inlet air temperature and consequently the bed temperature.

Ritala et al.[128] compared five binders in a high shear mixer. Kollidon VA 64, Methocel E 5, Methocel E 15 and Kollidon 90 gave rise to granule growth at the same liquid saturation. Kollidon 90, however, resulted in a lower intragranular porosity, and consequently the amount of liquid necessary to obtain a given liquid saturation was lower. The effect of Kollidon 90 on densification was assumed to be due to a higher surface tension of the solution. Use of hydrolysed gelatine (Protein S) gave rise to granule growth at a lower liquid saturation. This effect was ascribed to a starting gelation of the solution.

In a high shear mixer evaporation of solvent is much lower than in a fluidized bed, and the effect of droplet size of the atomized binder solution on granule growth is insignificant. The type of binder and the viscosity of the binder solution seem to be of less importance when using a high shear mixer.

For reasons of economy and in order to avoid pollution and risk of explosion, water is ordinarily used as binder solvent, if the physical and chemical properties of the material and binder permit it. As previously mentioned, solubility and wettability of the material and thus granule growth might be changed by using another solvent[113]. The volatility of the solvent will affect the liquid saturation of the agglomerates especially when a granulation method of high evaporation rate is used. Accordingly a smaller granule size was obtained in a fluidized bed granulator when using an organic solvent instead of water[112,136]. Granule formation and growth are assumed to be affected by the lower surface tensions of organic solvents. However, no systematical comparisons of the effects of different binder solvents on granulation are described in the literature.

In order to eliminate the drying stage of wet granulation, granules can be produced by a melt granulation process. It is indicated that melt granulation requires only 1/3 to 1/5 of the heat energy consumed by wet granulation and drying[137]. Melt granulation implies the use of binders which melt or soften at relatively low temperatures[138] thus acting like a binding liquid. Polyethylene glycols are commonly used[137,139-141] as binders for melt granulation but also the use of stearic acid[138] and different waxes[50,142] is described. The amount of binder has to be rather high (normally between 10 and 20% w/w of the starting material), since a sufficient number of liquid bridges of molten binder is necessary in order to form agglomerates.

The equipment for melt granulation can be a rotating drum or pan[137,139], a low shear mixer[138,141], a high shear mixer[50,140,142] or a fluidized bed granulator[143,144].

The binder is added either in molten form or in powder form. In the latter case the materials are heated by hot air or by a heating jacket to above the melting point of the binder. When using a high shear mixer with an extremely high power input, the temperature can be raised by friction without any heating[50,142]. Dry granules are obtained by cooling the agglomerates to room temperature.

Kinget and Kemel[140] carried out factorially designed experiments in order to elucidate the effects of some process and product variables. The effect of binder concentration, particle size of the starting material and impeller speed were similar to those obtained in ordinary wet granulation. The viscosity of the molten binder can be relatively high making distribution of the binder difficult, which might result in a wide size distribution.

Melt granulation is a way of producing sustained release dosage forms[142], and solid dispersions can be prepared by dissolving a drug in the molten binder[140,141].

SCALING-UP OF GRANULATION PROCESSES

Before scaling-up it is necessary to have a detailed knowledge of the influence of all major variables so that the increased size of the apparatus and the increased weight of the product are the only unknown factors.

Leuenberger[100] describes the principles of applying experimental design to scaling-up of granulation processes. This procedure yields equations, which show the sensitivity of a quality parameter to small variations of granulation variables. This mathematical tool, however, might be difficult to use for granulation processes, since wet granulation cannot be described adequately by mathematical equations. In practice therefore the method of "trial and error" is still the most widely used technique.

Many of the problems encountered by scaling-up are due to the fact that the ratio of the linear dimensions of the small scale and scaled-up system is not constant, i.e. the equipments are not geometrically similar. That might result in differences in particle motion and in the dynamic forces involved in the process, and those differences might affect granule growth as well as the physical properties of the final granules.

As discussed in a previous section the liquid saturation of the agglomerates during a wet granulation process is an essential parameter controlling the granule growth. It has to be aimed at, therefore, that liquid saturation is kept constant by scaling-up. Liquid saturation depends on moisture content as well as intragranular porosity (cf. Eq.(1)). Since the porosity might affect the properties of the final granules such as strength and bioavailability, changes in intragranular porosity by scaling-up are normally undesirable. The porosity might be influenced by the processing time, and if so it might be favourable to make a choice of process variables that results in a constant granulation time by scaling-up.

In case of a constant porosity, moisture content has to be kept constant, too, in order to obtain a constant liquid saturation. When using a granulation method where evaporation of water during the granulation phase of the process is inconsiderable, a constant moisture content is obtained by using the same specific amount of liquid, i.e. the amount of liquid has to be increased proportional to the amount of powder. Accordingly the amount of liquid was found to be linearly dependent on the batch size when scaling-up in planetary mixers[100]. Scaling-up of granulation processes in fluidized bed granulators and high shear mixers seems to be more complicated, although only a few experiments involving scaling-up are described in the pharmaceutical literature.

In fluidized bed granulation scaling-up is complicated by the fact that the moisture content is the result of a balance between liquid addition and evaporation. The ratio of the depth of the bed to the diameter of the air distributor plate is typically larger in production scale equipments[64]. The increase in volume of fluidizing air, therefore, is not proportional to batch size. Consequently, the liquid flow rate must be based on the increase in air volume instead of the increase in batch size. An increase in liquid flow rate proportional to the batch size might result in overwetting, since the air volume and consequently the drying capacity of the fluidizing air are relatively lower by scaling-up[64]. If necessary the drying capacity of the air can be increased by increasing the air temperature. When scaling-up from laboratory to pilot scale the relative increase in air flow rate was found to be only slightly lower than the relative increase in batch size[145].

Gore et al.[52] and Ceschel et al.[146] examined scaling-up of fluidized bed granulation processes by the "trial and error" method. Since several process variables were varied simultaneously, and moisture content was not kept constant, the experiments give no general information about scaling-up in fluidized bed granulators.

The effect of scaling-up on intragranular porosity is not examined in fluidized bed granulators. It is mentioned by Jones[64] that a 20% increase in bulk density can be expected when scaling-up from 8 kg to 500 kg. Further the critical water content was mentioned to be lower in production scale equipments. Both findings might indicate that scaling-up in fluidized bed granulators results in a lower intragranular porosity.

As mentioned before droplet size of the atomized binder solution is an important parameter in fluidized bed granulation, and although no experimental verification exists it is assumed essential to keep the droplet size constant by scaling-up.

On basis of the present insufficient knowledge of scaling-up in fluidized bed granulators it can be concluded that process variables have to be chosen in such a way that droplet size, moisture content and intragranular porosity are kept constant in equipments of different scale.

Scaling-up in high shear mixers were examined by Richardson[81] and by Schaefer et al.[26,27]. Richardson examined scaling-up in Diosna mixers by comparing a 25-litre machine with a 600-litre machine. Granulation time was found to be appreciably longer in the 600-litre scale due to dimensional differences between the mixing tools[81].

Schaefer et al.[26,27] granulated dicalcium phosphate in nine different high shear mixers of sizes ranging from 5 to 300 litres. Scaling-up was found to result in a less homogeneous liquid distribution, a wider granule size distribution and a higher intragranular porosity due to a less intimate contact between the mixing tools and the wetted mass in a larger mixer. Consequently, it seems to be inconvenient that impeller and chopper speeds are reduced at increasing mixer size in most commercially available high shear mixers.

Figure 14 shows the effect of scaling-up in Diosna mixers on the intragranular porosity during wet massing. As can be seen scaling-up results in a higher porosity. Densification is assumed to depend on the work input on the material. The work input in a high shear mixer depends on the size and shape of the mixing tools and on their rotation speeds. Richardson[81] related the work input to the relative volume swept out by the impeller and chopper, respectively, and found that the relative swept volume decreased by scaling-up, explaining why wet massing time had to be longer in the production scale mixer.

In Table 1 the relative swept volume is calculated at two levels of impeller speed by dividing the volume swept out per second by the volume of the mixer. In Diosna mixers scaling-up results in a marked decrease in relative swept volume explaining the higher porosity found by scaling-up (cf. Figure 14). The specific power consumption was found to be lower in larger machines in accordance with the smaller relative swept volume and the lower densification observed by scaling-up[27].

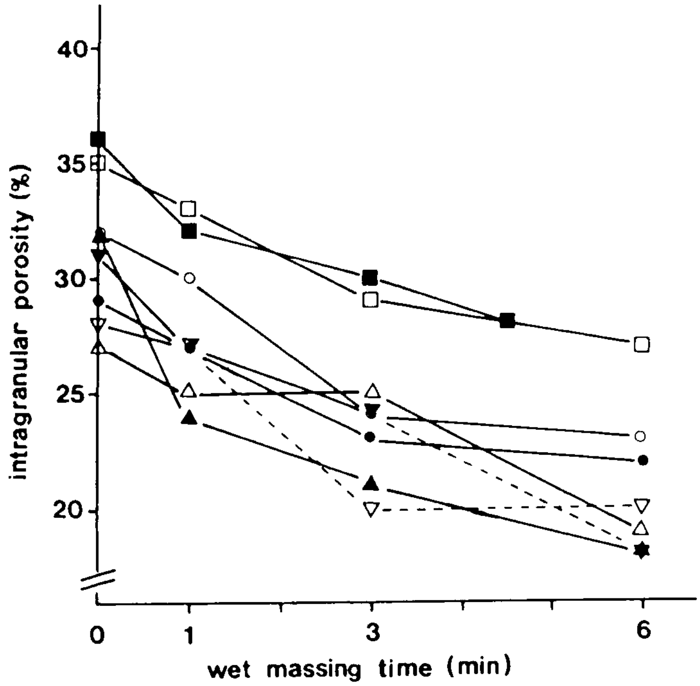

FIGURE 14
Effect of wet massing time on intragranular porosity by scaling-up in Diosna high shear mixers. The dotted lines indicate a marked adhesion to the mixing bowl. ▼, ∇ = Diosna P 25 with standard tools. ▲, Δ = Diosna P 25 with specialized tools. ●, o = Diosna P 50. ■, □ = Diosna P 250. ▼, ▲ = Impeller speed 300 rpm. ● = Impeller speed 288 rpm. ■ = Impeller speed 190 rpm. ∇, Δ = Impeller speed 150 rpm. o = Impeller speed 144 rpm. □ = Impeller speed 95 rpm. ▼, ▲, ●, ■ = Chopper speed 3000 rpm. ∇, Δ, o, □ = Chopper speed 1500 rpm (from[26]).

In Fielder mixers only a slight decrease in relative swept volume is seen by scaling-up, and consequently differences in porosity were smaller[26]. Thus it seems to be favourable that high shear mixers are constructed in such a way that the relative swept volume is constant in mixers of different size. The Fielder mixers are therefore considered to be more suitable for scaling-up than the Diosna mixers. Scaling-up, however, is likely to be less dependent on the relative swept volume, when using materials being less cohesive than the quality of dicalcium phosphate used in the

TABLE 1
The angle of inclination of the impeller blade and the relative vertical volume swept out by the blades in Fielder and Diosna high shear mixers of different scale (from[27])

		Relative swept volume/sec.	
	Angle of	Impeller speed	
Mixer type	inclination	Low level	High level
Fielder PMA 25	29°	0.75	1.51
Diosna P 25 (standard tools)	36°	1.37	2.74
Fielder PMA 65	30°	0.71	1.42
Diosna P 50	39°	1.08	2.16
Fielder PMA 150	30°	0.61	1.23
Diosna P 250	54°	0.52	1.03

experiments. Further it might facilitate scaling-up in Fielder mixers that the angle of inclination of the impeller blade (cf. Table 1) is nearly constant contrary to Diosna Mixers.

In laboratory scale and pilot scale the relative swept volume is higher in Diosna mixers than in Fielder mixers (cf. Table 1) resulting in lower porosities of the granules produced in Diosna P 25 and P 50. In production scale where the relative swept volumes are similar, no clear differences in porosities were found[27]. These results emphasize that the relative swept volume is a useful parameter when designing high shear mixers.

As mentioned before the high power input in a high shear mixer results in a marked heat development, specially when the relative swept volume is high. That might result in a marked loss of evaporation of water during wet massing in laboratory scale and pilot scale. In production scale, evaporation was found to be slight due to the lower relative swept volume and the smaller relative surface area of the mixing bowl[27].

If the mixer is too small, shearing and compaction forces exerted by the mixing tools might be too low to allow direct scaling-up. Scaling-up from a 5-litre to a 50-litre Lödige mixer, therefore, was found to be impossible[26]. However, prolonging the wet massing time in the 5-litre machine might result in proper scaling-up[24].

It was found[27] that the same relative amount of binder solution could be used in machines of sizes ranging from 5 to 300 litres, because the differences in porosities were partly compensated by the larger evaporation of water being related to the stronger densification. Liquid saturation at the end of the process therefore was within the same range in all machines, and consequently granule growth was similar. However, the differences in porosities might be inconvenient affecting the properties of the final granules as discussed above.

The final conclusions concerning scaling-up in high shear mixers are that process variables have to be chosen in order to keep moisture content and intragranular porosity constant. Due to the inexpedient construction of many high shear mixers giving rise to large differences in relative swept volume, direct scaling-up might be impossible. As described by Richardson[81] it might be necessary to use varying granulation times instead in order to keep densification and evaporation nearly constant in mixers of different scale.

END-POINT CONTROL OF WET-MASSING METHODS

Control of wet-granulation methods with respect to the amount of binder solution and wet-massing time is essential to assure the manufacture of granules with the desired characteristics like granule size, distribution, flowability, density and friability. These characteristics are influenced by variations in properties of the feed material and their effect upon the liquid requirements. With high-shear mixers, the very short processing times give rise to a potential risk for overmassing or overwetting.

The robustness of granulation by wet-massing methods against variations in feed material properties is clearly dependent on the granulation equipment and its operation as well as the formulation being processed. There is, however, a general need for techniques that are capable of controlling the amount of binder solution and process time required to achieve the desired granule characteristics, i.e. the granulation end-point.

With fluidized bed granulation the possibilities for control differ greatly from those of wet-massing methods, cf. the preceding sections. No method has been devised yet for end-point control of fluidized beds.

The control of wet-massing methods must be based upon a process parameter providing information about the stages of the process and which is simple to measure. A variety of control parameters has been considered in the past. They include electrical methods (ammeters for motor current, power consumption meters), machine characteristics (torque, tachometery, sound emission) and mass properties (temperature, light reflections, conductivity and probes inserted in the mass).

The conductivity of the wet mass was examined by Spring[147], however, the correlation with granule properties was not evident. The conductivity depends on the formation of a continuous medium. In consequence, changes in conductivity are related to the mixing state more than to the strength of the mass.

The temperature of the wet mass may grow significantly during massing, especially with high shear mixers. It is simple to measure using thermoresistant probes inserted in the mass. Holm et al.[35] showed that the temperature changes in a high-shear mixer represent the complete conversion into heat of the energy consumed by the mass during agitation. The temperature rise is influenced by the loss of heat to the machine parts and the surroundings. It was shown that the temperature increased independently of the granule growth. Thus, records of the mass temperature are not suited for end-point control.

Light reflection methods, which are commercially available, have been used to evaluate the mixing of dyes[148] and to measure the humidity in powders[149]. It is possible that light reflection provides a suitable method.

The consistency of wet masses was examined with the aim to detect physical changes relevant to granulation. Alleva and Schwartz[150] measured the resistance against movement of a probe inserted in the mass. They demonstrated characteristic differences between commonly used tablet excipients. Schildcrout[151] used a Plasti-Corder rotational rheometer and showed that the torque readings changed with time when a premixed liquid-powder mass was examined. Njikam and Spring[102] used a shear box technique to examine the strength of moist masses and Harrison et al.[152] measured the force required to press the mass through a narrow die. Though, these investigations demonstrate characteristic effects of liquid addition to feed materials and effects of wet-massing, they are inconclusive with respect to the prediction of liquid requirements.

The most successful approaches to the granulation end-point control have been based upon instrumentations that monitor changes in the consistency or strength of the wet mass during granulation, i.e. instrumentations for torque measurements and power consumption of the motor driving the agitators, and probes that reflect the resistance against flow of the wet mass. Commercial devices that are available include the Diosna-Boots Probe and power consumption meters (Gralomatic® Collette, Meinke Load Controller® and Baker-Perkins GD200®).

During granulation, the strength of the moistened mass grows due to effects of mobile liquid bondings between particles and consolidation of the agglomerates. As the strength is increased the torque of the mixer blades or paddles increases and is hence an indirect measure of the bed strength.

Figure 15 demonstrates the correlation between torque and the related machine parameters for a normally loaded induction motor.

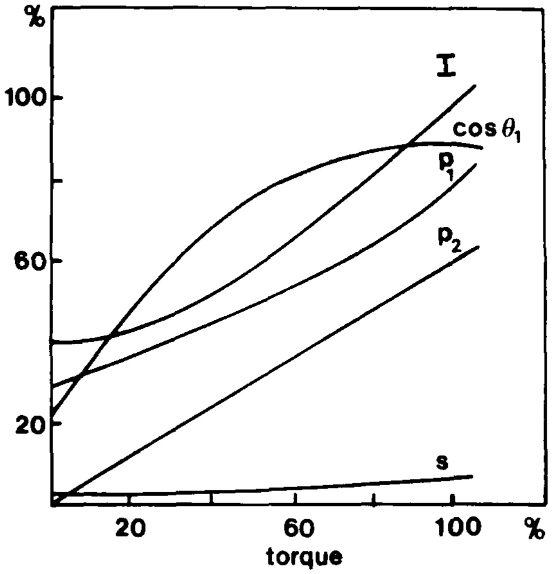

FIGURE 15
Correlations between torque and related parameters for a three phase induction motor in the range of normal load[47]. I: Motor current, P_1: Power consumption of the motor, P_2: Transmitted power to the motor shaft, θ_1: Phase difference between current and applied voltage, S: Slip.

Monitoring a granulation process by electrical methods, i.e. motor current and power consumption gives signals that are likely to correlate with torque readings. The slip is the difference between syncronous speed and operating speed divided by the syncronous speed. Also slip measurements are likely to correlate with the torque. As discussed below, there is experimental evidence for these correlations.

Torque measurements

Lindberg et al.[153] measured the bending moment of one of the mixer arms in an Artofex PH-15 change can mixer using a strain gauge technique. At the same time they recorded the power consumption of the motor driving the rotating bowl. It was shown that bending moment and power consumption changed simultaneously with the visible changes in the consistency of the mass. Further, the bending moment and power consumption correlated with granule size. A similar technique was applied by Travers et al.[154,155]. The torque increased with increasing liquid content to a plateau which was judged to present the appropriate range of liquid contents.

Instrumentation of a Tripas PL-25 planetary mixer was described by Lindberg et al.[156,157]. A bar was attached to the top of the mixer paddle and the bending of this was monitored using strain gauges. The granulation of lactose was shown to be monitored adequately by the instrumentation. Compression of wet mass on the bottom and the sides of the bowl disturbed, however, the signal from the instrumentation.

Lindberg et al.[99,158,159] described a different approach to the instrumentation of a planetary mixer. A Kenwood 707A domestic-type mixer was reconstructed so that the bowl became freely movable on ball bearings. Torque readings were obtained by a strain gauged steel beam which prevented the rotation of the bowl. Also this study showed a close correlation between granule size and torque readings. The instrumentation was an improvement of a previous instrumentation of the planetary mixer where the torque was monitored simply by the stretching of a coil spring[160]. Also, an instrumentation of a C-100 Hobart mixer for monitoring the torque on the paddle has been described[161,162].

The potential of torque measurements for granulation end-point control is well documented in the above mentioned papers. It is demonstrated that torque measurements are reproducible and sensitive to variations in process and product variables and that the torque readings correlate with granule growth[99,159,162].

Instrumentations for torque readings are described for conventional equipments like the planetary mixers. With high shear mixers, difficulties with a reliable transmission of signals from the sensing device clearly call for a different approach. By normal load of the motor driving the main impeller the slip of a three phase induction motor is approximately proportional to the torque[163], cf. Figure 15. Slip measurements are described by Andersson and Lindberg[164]. They measured the change in rotation speed of the motor impeller shaft of a Diosna P-25 high shear mixer using an optical incremental encoder. The potential of slip measurements for end-point control was demonstrated[21,164,165]. Lindberg et al.[104] showed further that changes in power consumption were coincident with changes in the impeller rotation speed.

Probe measurements

In addition to torque measurements, changes in the consistency of the wet mass can be monitored by measuring the bending moment on a probe inserted in the mass. This approach was developed in the Boots Company, UK, in order to overcome the difficulties encountered at the change from conventional granulation to granulation in high shear mixers[29]. The probe (Diosna-Boots Probe®) consists of a small cylindrical target lowered to within 15-18 mm of the impeller blade. During rotation, the movement of the mass generates a signal by means of an arrangement of strain gauges positioned on the probe shaft. The probe is fixed to the lid of the mixer bowl of the high shear mixer. The criterion for end-point indication is that a pre-set number of signals generated must be greater than a pre-set value and must occur within a pre-set time[81].

The Diosna-Boots Probe has been tested in the production plant and in mixers with different capacity[101,166]. A detailed description of the end-point control is given by Richardson[81].

Recently, Staniforth et al.[167] described the use of a probe vibration technique for the end-point control of granulation in a Fielder PMAT 25 high shear mixer.

It is supposed that the end-point control by probe measurements demonstrates changes in the wet mass which are basically the same as the changes demonstrated by torque and slip measurements. There is, however, neither experimental comparison between the two types of control, nor with the power consumption measurements discussed below.

Power consumption measurements

The power consumption of the mixer motor is of interest in relation to granulation end-point control because the force opposed to the mixer blades by rotation through the wet mass is related to the torque and the power consumption of the motor, cf. Figure 15. Hunter and Ganderton[19] demonstrated early the benefits of power consumption measurements in a comparison between different granulation machines. Lindberg et al.[153] showed that the bending moment on the mixer arm in an Artofex PH-15 correlated with the power consumption of the motor driving the rotating bowl. Flesch[168] claimed the advantage of using power consumption measurements in the in-process control of granulation in a Diosna P-600 high shear mixer. It was, however, the fundamental work by Leuenberger et al.[32,34,49,101,169] that gave evidence for the potential of power consumption measurements for the end-point control. It was shown[101] that simultaneous readings of power consumption and the torque in a planetary mixer were closely related. Recently, Holm et al.[35,47,94] and Ritala et al.[128,170] have also demonstrated the benefits of power consumption measurements for the end-point control.

The power consumption of the induction motors of A.C. asyncronous type mainly used in granulation machines is affected by several components[164]: Ohmic loss in stator and windings, iron loss, frictional loss and stray load loss. Only changes in power consumption are needed for monitoring a granulation process. Therefore, iron and stray load losses are excluded, because they are approximately invariant at constant rotation speed. The ohmic loss, in contrast, varies by the load. The frictional loss due to viscosity of the gear box and friction in bearings and seals can be excluded from the recorded changes in power consumption by running the system warm before the measurements are initiated[35].

The power consumption is related to the three phase auxiliary current I and voltage V by the expression:

$$P_1 = \sqrt{3}\, I\, V \cos\theta_1 \qquad (6)$$

where θ_1 is the phase difference between current and applied voltage. The equation demonstrates that measurements of the motor current are not directly comparable to torque and power consumption measurements for the end-point control. Although motor current has been suggested for the control[34], Kay and Record[171] mentioned that motor current measurements had been tried in the control of Diosna mixers. The recorded changes were, however, too insensitive for a reliable control of critical formulations.

End-point control

Measurements of torque, power consumption and changes in rotation speed are related control parameters, cf. Figure 15 and experimental comparisons[101,104,153]. It is likely that the record obtained by the Boots-Diosna Probe also reflects the strength of the wet mass and hence is a related parameter, though there is no experimental support for this assumption.

These techniques provide indirect measurements of the changes in consistency or rheological properties of the wet mass. If it can be accepted that the recorded changes are closely correlated with the granule growth process, measurements of the torque of the mixer blades or paddles should present the most reliable control technique. It is so, because the torque is proportional to the resistance by the mass against rotation. Measurements of the motor power consumption are easy to achieve with the commercially available power consumption meters. The technique suffers, however, from the many factors affecting the record, primarily the frictional losses which are dependent on the temperature of the gear box etc. Probe measurements are supposed to correlate with torque measurements, but they are experienced to be affected by the position of the target in the mass and the mass flow pattern. Moreover, the signals are much more difficult to interpret than the signals from torque sensing devices. From that point of view, one would suggest torque measurements as the first candidate for end-point control techniques. The crucial point of this approach

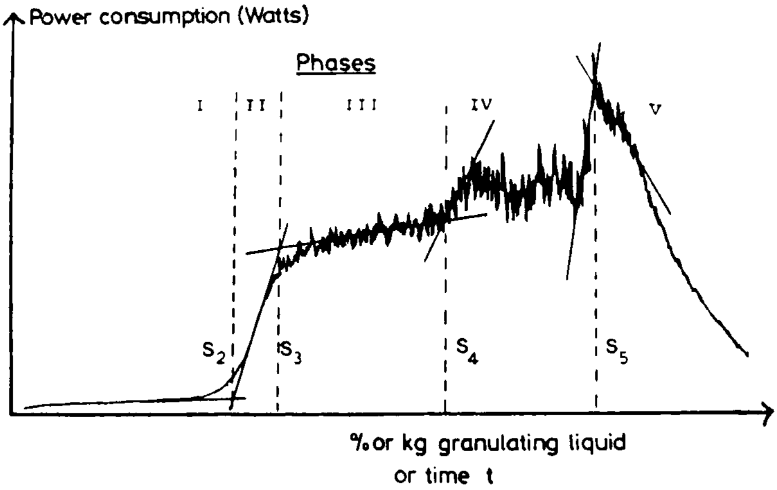

FIGURE 16
Parametric division of a power consumption curve[32]

is that radio transmission of signals from torque sensing devices in high shear mixers until now has been rather expensive.

Figure 16 shows a power consumption record obtained during continuous liquid addition to a mixture of corn starch and lactose in a planetary mixer[32]. The curve is divided into five phases related to the amount of liquid added. During phase I particles are moistened without any significant increase in power consumption. In phase II, the power consumption increases markedly and the particles begin to agglomerate. In phase III, the curve shows a plateau between the parameters S_3 and S_4, which indicates the appropriate range of liquid quantities for granulation. Further addition of liquid increases the power consumption in phase IV until a peak is passed and the mass in phase V becomes doughy and later on a suspension.

Profiles similar to the curve in Figure 16 were reported by Rogerson et al.[155] recording the bending moment in a paddle mixer during granulation of a powdered sucrose. Lindberg et al.[21] who recorded the change in rotation speed in a Diosna P-25 during granulation of lactose presented also a similar profile. Leuenberger[34] claimed that the characteristic phases of the curve in Figure 16 can be found in most power consumption records, independently of the mixer type, and independently of variations of the feed material properties. There is, however, evidence that the power consumption profiles depend on the formulation being granulated and the type of mixer as shown by Hunter and Ganderton[19] and Holm et al.[94] .

The strategy for end-point control by power consumption measurements suggested by Leuenberger et al.[32] applied to the profile shown in Figure 16. They demonstrated in planetary mixers that the estimated values of S_3 and S_4 were proportional to the batch size and that the range S_3-S_4 of liquid quantities described the uncritical liquid requirement for granulation. A technique for prediction of the uncritical quantity of liquid based upon tapped density measurements of the feed material was described[34]; see also the section above on liquid requirements.

The correlation between power consumption records and the mean granule size was demonstrated by Holm et al.[35,94] by granulation in a Fielder PMAT 25 of lactose, dicalcium phosphate and mixtures of the latter with corn starch. Correlation curves have also been presented by Ritala et al.[128,170] studying the effect of different binders upon the wet granulation in a Fielder PMAT 25.

The energy consumption during granulation, i.e. the cumulated power consumption, is converted completely into heat in the wet mass[35]. This led to the assumption that the power consumption curve of a particular process is controlled by the ability of the agglomerates to absorb energy and transform it into heat. The power consumption is consequently controlled by the deformability of the agglomerates. The agglomerate deformability is essential to granule growth by coalescence, too. This explains the experienced relationship between power consumption and granule growth.

Since the power consumption is supposed to be controlled by the deformability of the agglomerates, a highly deformable mass should have a high power consumption and vice versa. The deformability depends as described above on the bonding strength and the brittle/plastic deformation behaviour. In the case of dicalcium phosphate, which produces agglomerates that are primarily brittle[16], it is to expect that the power consumption is influenced only by the bonding strength, because the agglomerates are brittle. Ritala et al.[128,170] showed in experiments with different binder solutions that there was a correlation between power consumption and granule porosity and liquid surface tension which applied to equation (4) for the maximum liquid bonding strength. They suggested accordingly that the power consumption curve is a direct presentation of the growing liquid bonding strength in the agglomerates. Consequently, the power consumption curve obtained by granulation of a feed material producing brittle agglomerates is proportional to the porosity function $(1 - \varepsilon)/\varepsilon$. This is the only parameter of eq.(4) which varies provided that the agglomerate surfaces contain free liquid as is the case when growth by coalescence is significant.

The supposed correlation between power consumption and porosity function was investigated by granulation of dicalcium phosphate in a Fielder PMAT 25 mixer using three slightly different quantities of a Kollidon 90 binder solution and constant process conditions[170]. Figure 17A shows the power consumption curves recorded during liquid addition (until ab. 7 min) and wet massing. The granule growth during wet massing is shown in Figure 17B. Figure 17C shows the correlation between power consumption and porosity function for the wet massing phase of the three experiments.

It shall be noted that the correlation shown in Figure 17C does not apply to all granulation processes. It is characteristic for the described process that the agglomerates were primarily brittle and that they were densified continuously during the entire process. It is also important that the experiments were performed so that deposition of wet mass on the sides of the mixer

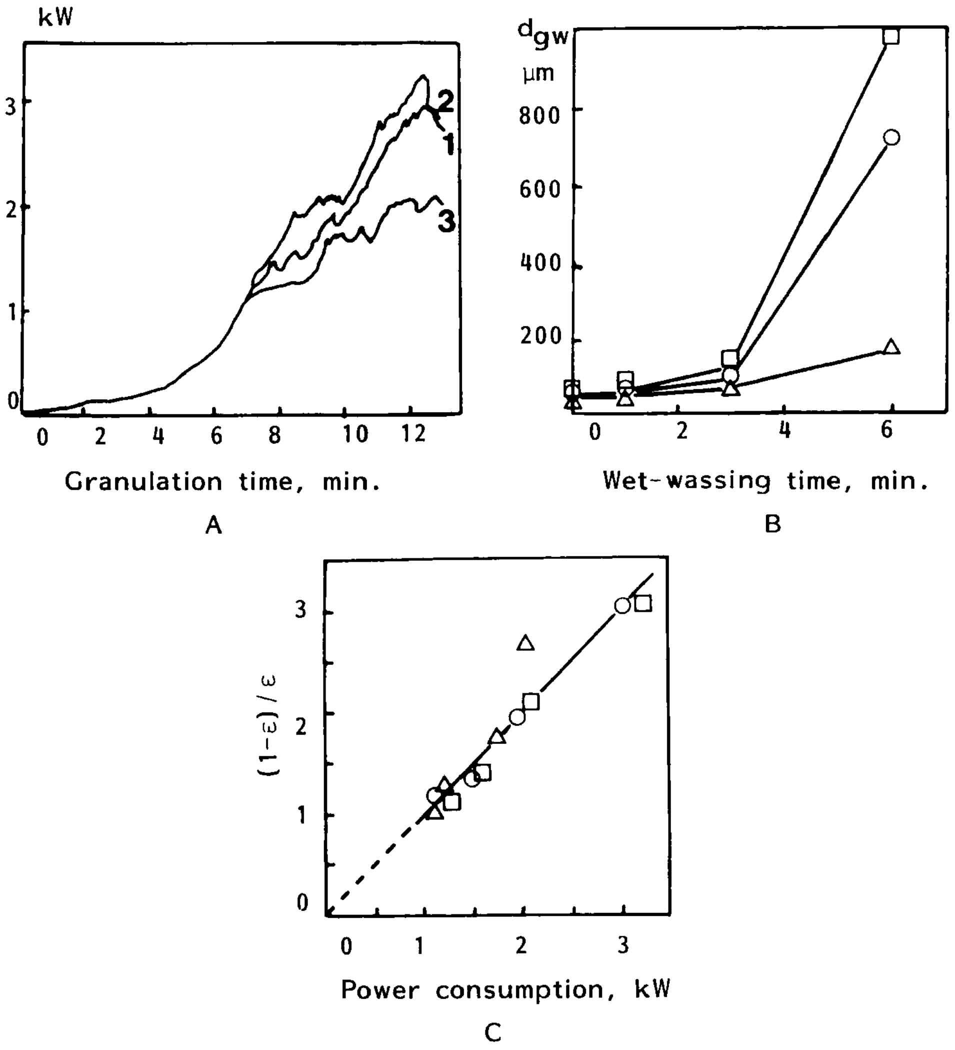

FIGURE 17

Granulation of dicalcium phosphate (d_{gw} = 21 µm) with a 3% Kollidon 90 in Fielder PMAT 25[170]. A: Power consumption records during liquid addition and wet massing. 1: 18.0% w/w binder solution, 2: 17.5% w/w solution, and 3: 17.2% w/w solution.

B: Granule growth in the wet massing stage. □: Curve 1 in A, ○: Curve 2 in A, and Δ: Curve 3 in A.

C: Correlation between power consumption and porosity function $(1-\varepsilon)/\varepsilon$. Symbols as in B.

bowl was insignificant. In the case of a feed material that is easily consolidated to its final porosity or that exhibits plastic deformation, the correlation fails because the plastic deformation gives rise to heat development and hence a growing power consumption despite the constant porosity level.

A general conclusion of these observations is that the power consumption curve is influenced by the densification of the agglomerates. The curve shown in Figure 16 demonstrates therefore that the lactose-corn starch mixture is densified to its final level during phase II, and that the plateau in phase III is likely to be due to an approximately constant granule porosity. The addition of liquid in phase IV gives rise to an improved deformability and hence an increasing power consumption.

This interpretation applies also to the power consumption curves presented by Holm et al.[35,94]. They showed that lactose (d_{gw} = 56 µm) was densified to the final level early in the process and that the power consumption curve had a shape similar to that in Figure 16. With dicalcium phosphate (d_{gw} = 14 µm) the densification proceeded slowly during the entire process. Accordingly, the power consumption curve did not show a plateau.

According to the discussed effect of liquid saturation on granule growth, densification of the granules is essential to provide the conditions required for growth by coalescence. It means that the liquid saturation suffices to assure plastic deformation of the agglomerate surfaces. The densification is therefore a very fundamental part of the granulation process. It can be detected by the power consumption curve or better by the differentiated curve as suggested by Bier et al.[101] and Holm et al.[35].

A procedure for the end-point control based upon power consumption records is to apply a pre-set power consumption value for the termination of liquid addition and another pre-set value for the termination of wet-massing. The pre-set values are determined by a calibration of the actual granulation process. It is expected that the procedure leads to granules with the predetermined granule size distribution and porosity. Difficulties which may arise in practical work are the effects of deposition of wet mass on the sides and bottom of the mixer bowl and also the effects of liquid addition and liquid distribution in the wet mass upon the power consumption record.

There is, however, only little evidence in the literature on the proper end-point control procedure. Especially, there is a need for investigations on the effects of the particle size distribution of the feed material on granule growth as well as the power consumption.

CONCLUDING COMMENTS

The research on pharmaceutical wet granulation has increased considerably in recent years, probably because of the introduction of new granulation equipments and the increasing scale of manufacture. Significant problems in production practice are the specification of starting material properties in relation to the actual granulation method, control of the liquid quantity required to run an uncritical process, the scaling-up from laboratory to production scale, and the control of the granulation end-point defining a product with the desired characteristics. Though progress has been made, nearly every aspect of wet granulation needs further research.

A part of the literature on pharmaceutical wet granulation describes processes that comprise wet granulation, drying and milling of the dried product. This literature has largely been omitted in the present review, because it is inconclusive with respect to the wet phase of granulation and the general understanding of the process. Another difficulty met at the interpretation of experimental results is that they may have been heavily influenced by sub-optimal experimental conditions. For example, when deposition of a moist mass on the wall of the bowl of a high shear mixer is significant, the liquid distribution becomes non-uniform. This affects the experimental results and probably also the reproducibility of the experiment.

The fundamental issues of wet granulation seem to be fairly well understood, at least on a qualitative basis. The physical prerequisites to granule formation and growth are established, but investigations on the effects of physical properties remain to be done, e.g. mean particle size and size distribution, solubility and wettability, upon liquid requirements and granule growth. Investigations are also needed in the field of interactions between the physical properties of starting materials, granulation equipment and its mode of action, and the properties of the final granulation. The investigations can probably be based upon studies of the consolidation or densification of agglomerates during the process and the effects of liquid saturation upon granule formation and growth. An improved method for measuring the granule porosity should, however, be devised for that purpose.

Studies on granulation in high shear mixers indicate that there is a general need of optimizing their construction. This is valid especially with regard to the scaling-up from laboratory to production scale where difficulties met in practical work are likely to attribute to the mixer design. The choice of granulation machinery and comparisons between different granulation methods are other fields which need further research.

Granulation end-point control including the control of the liquid requirements has been subject to a number of studies on instrumental methods. Reliable methods have been devised, so that the paramount need in this field seems to be an evaluation of the methods in the production plant.

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