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Fluid bed agglomeration with a narrow droplet size distribution

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Abstract

In the fluid bed agglomeration processes liquid distribution influences the agglomerate growth. We developed a new nozzle that produces uniform droplets, which allows droplets to be easily controlled in size independently of liquid- and airflow of the nozzle. It was found that the spray rate and the mixing in the spray zone determine the average granule size and that there is linear relation between the number of droplets of which a granule consists and its volume, at the early stage of the process. The nucleation ratio factor introduced in this paper depends on the material properties of binder liquid and powder particles and is a useful parameter to describe the binder liquid efficiency. The decline of the growth rate of granules during the agglomeration process was due to the less sufficient rewetting of granules resulting in less growth. A linear relation was found between tracer mass added to the binder liquid and the granule mass in an early stage of the process. Solubility of the tracer was found not to influence its distribution. The new nozzle proves to be a good tool to study the effect of wetting and growth of granules.

Keywords: Fluid bed; Agglomeration; Nozzle

1. Introduction

Granulation, binding fine powder particles together to form a large porous structure, is an often-used process in powder processing industries. Granulation of small particles improves the handling properties of the powder such as the enhancement of the flowability or reduction of dust formation, which is important if the material is toxic or there is a risk of dust explosion. Other improvements of the granulated powder are: a higher dissolution rate by reducing lump formation and flotation of the powder, higher bulk density resulting in lower transport costs and a better compactability for the tabletting process. The 'wet' granulation fluid bed process is commonly used in the pharmaceutical industry. A binder liquid is sprayed upon a moving bed of particles where the liquid binds the particles by capillary forces. The binder liquid, mostly water with some polymer, evaporates and the binder solidifies between the particles forming a strong solid bond. The pharmaceutical entity can be added premixed with the excipients before the

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granulation, during granulation suspended in the binder liquid, or added to the granules after the granulation. The powder and binder liquid properties together with the type of apparatus used determine the final properties of the granule product. For instance, the wet granulation process performed in high shear equipment such as a high-speed mixer will produce denser granules than in low shear equipment like the fluid bed granulator (Iveson and Litster, 1998). This is due to the fact that mechanisms of growth depend on the apparatus used. The choice of granulation equipment should therefore depend on the desired product properties.

Uniformity between batches is a necessity, especially in the pharmaceutical industry. Good process control is therefore inevitable, which can only be achieved with a good fundamental knowledge of the mechanisms involved in granulation. Unfortunately granulation is still an art rather than a science (Iveson and Litster, 1998).

1.1. Trends in pharmacy

Over the past decades, there has been an increase of the potency of new drugs, resulting in very low levels of active components in tablets and capsules entering the market. Typical examples of these type of drugs are estrogens, corticosteroids, anti-hypertensives (like cilazapril or moxonidine) and anti-psychotics (risperidon; Reynolds, 1996). We expect this trend of increasing drug potency and resulting low dosage formulation, such as small peptides, to continue with the influence of 'the new biotechnology' (Wrighton et al., 1996). The granules required for producing these tablets will consist largely of excipients, like starch, lactose, microcrystalline cellulose or salts, and only a small amount of the active drug component. Such low dosage applications bear an increased risk of an inadequate uniformity of the active component (Graves et al., 1995).

More recently the Barr decision (or Wolin decision) in 'The US versus Barr Laboratories case' again stressed the attention to the homogeneity of powder blends. This gave rise to an enormous discussion within the pharmaceutical field on the predictive value of blend homogeneity and different pitfalls in powder sampling (Graves et al., 1995; Berman et al., 1996; Geutensberger et al., 1996; Muzzio et al., 1997).

The homogeneity of powder blends will, as the trend to an increase of drug potency develops, become a challenge for industry. A major effort should be made to improve both blend quality and validation methods to overcome future problems in achieving homogenous powder blends. The subject of this paper is improving fundamental knowledge about the fluid bed granulation process, which is necessary to achieve better blend quality.

1.2. Fluid bed granulation

In the late 1970s, Scheafer and Worts wrote a series of articles (Scheafer and Worts, 1977a,b, 1978a,b,c) to describe important mechanisms which determine the granule growth process in a fluid bed. One of the major conclusions which can be drawn from their work, is that there is a relationship between droplet size and granule size. This indicates that rupture of granules is of minor consequence, because the droplet size granule size relation is preserved during the process. In the early 1990s, Waldie (1991) did some supplementary experiments were he introduced large droplets (diameter of ~ 3 mm) in to a fluid bed, and also found a relationship between droplet size and primary granule size. Although the granules were fairly large, 3–5 mm, they are believed to be representative of the mechanisms involved. Once again it can be concluded that rupture of granules is not significant. If the binder added to the spraying liquid results in enough strength between the particles, rupture will not occur. From the point of view of the fluid bed apparatus this result was to be expected, because the apparatus is a low shear device. This is also illustrated by the high porosity (ε) of granules ($\varepsilon = 0.4–0.5$) made in the fluid bed compared to high shear devices ($\varepsilon = 0.2–0.3$), because densification of the granules by external forces within the fluid bed plays only a minor role.

Schaafsma et al. (1998b) stated that in low shear granulation rupture is of no consequence

regardless of the low shear device used if binder properties are chosen well. They performed granulation in a shaking perti-disc, which was considered to have the same growth mechanisms involved as the fluid bed granulation. This enabled them to study the growth of single granules in more detail. The growth of granules can be described as unsaturated liquid flow from the interior of the wet granule to its surface. The binder liquid should have good wetting properties with a contact angle of considerably less than 90°, so that capillary action can occur. Furthermore, the transport by mixing of primary powder particles to the granule should be fast in respect to the liquid flow from the core of the granule to its surface.

If we consider full-scale granulation we have to take into account not only primary growth (nucleation), growth by engulfment of particles by a droplet, but also rewetting of granules (secondary growth). The secondary growth depends on a number of factors, which are difficult to analyse due to their complexity and inter-dependence. For instance, the wetting of granules depends on the residence time in the spray zone and the fraction of granules in the spray zone (Schaafsma et al., 1998a). During granulation processes, mixing intensity of the fluid bed will change as the granule size distribution alters, resulting in different wetting. The complexity of these mechanisms is of little consequence in existing processes, provided they perform in a reproducible and robust manner. However, if a new process is developed it is important to know how mixing and rewetting affects the results so that the new process can be developed from expertise rather than trial and error. Furthermore, if the process is changed, for instance scaled-up, problems in acquiring the desired quality are likely to occur.

Since droplet size directly influences granule size, it is important to understand the liquid distribution process. The distribution of binder or any substance added to the sprayed liquid (e.g. pharmaceutical entity) depends on the binder liquid distribution in the fluid bed. This influences the granule properties for further processing such as tabletting, homogeneity, and dissolution of granules.

In order to study the primary growth (nucleation) and secondary growth in a full-scale process we developed a new nozzle, which is able to produce virtually mono-disperse droplets in a fluid bed granulator. By adding soluble and non-soluble tracers to the binder liquid we can evaluate the effect of solubility and binder properties on the distribution of components in a granule mixture. The soluble and non-soluble tracers represent an active entity.

2. Materials and methods

2.1. Materials

α-Lactose monohydrate 200 Mesh powder (DMV Veghel, Holland) was agglomerated using water containing 8–20% polyvinylpyrolidone (PVP, MW ~24 500, Fluka). For tracer experiments a mixture containing 85% α-lactose monohydrate 200 Mesh and 15% maize starch (National Starch, USA) was used with a binder of 3% w/w hydroxypropylcellulose (HPC; Klucel-EP, Aqualon/Hercules). Two different types of tracer were used, a soluble tracer, fluorescein sodium, and a non-soluble tracer, iron(III)oxide particles with diameters less than 2 microns.

2.2. Analysis

Mechanical sieves (Retsh) were used to measure granule size distribution. The equivalent granule diameters (projection) were also determined using an image analysing computer system (Quantimet 520+, Cambridge instruments).

The iron(III)oxide particles were analysed by mass spectrometry. The granules containing fluorescein sodium were dissolved in water, after which the concentration of fluorescein was measured by means of a spectrofluormeter (excitation 495 nm, emission 515 nm, SLM Aminco SP 500C, US).

Confocal laser micoscopy (Biorad MRC600, UK; Inoue, 1990) was used to study the distribution of components within the granule. Fluorescing and light reflection of granules containing fluorescein sodium was measured. The granules

were cut in half and the flat cross section was measured a few microns below the surface to overcome light scattering by the lactose crystals.

2.3. Fluid bed

A schematic diagram of the experimental set-up is shown in Fig. 1. The product chamber is a conical cylinder made from stainless steel. The air distributor is a bronze sintered plate (Poral, France). A cyclone was used to remove lactose fines from the process air.

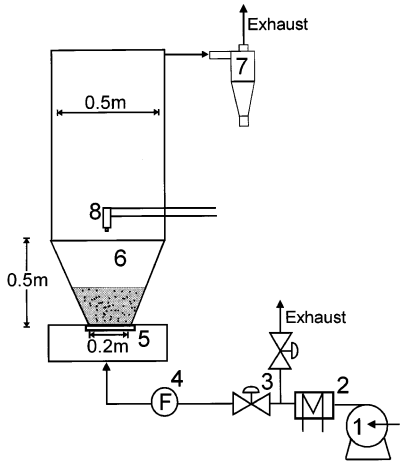


Fig. 1. Experimental set-up: 1, roots blower; 2, heater; 3, control valves; 4, mass flow meter; 5, wind box; 6, product chamber; 7, cyclone; and 8, actuator driven nozzle.

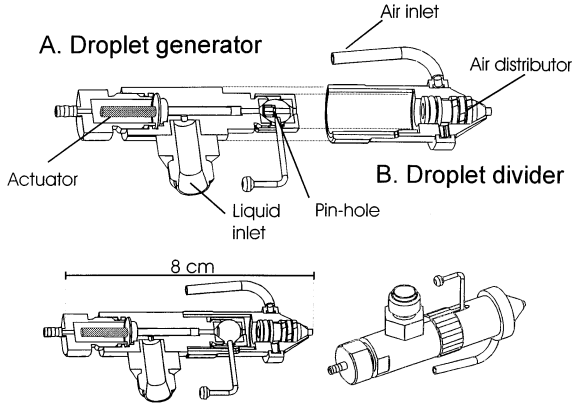


Fig. 2. The actuator driven nozzle.

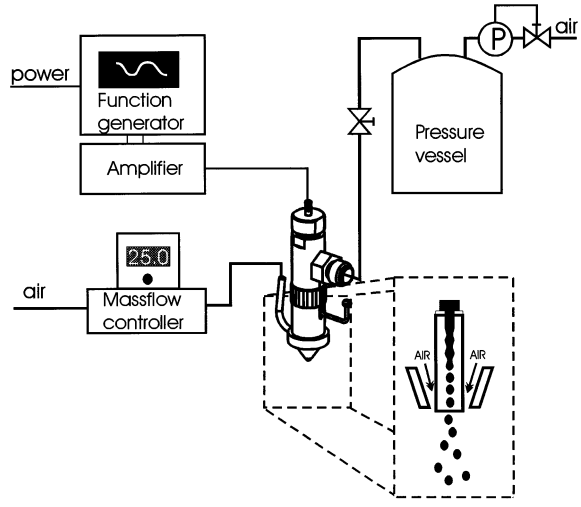


Fig. 3. Scheme of the actuator driven nozzle.

The binder liquid was top sprayed upon the fluid bed, which consisted of 2.5 kg lactose or a lactose starch blend. The fluidisation velocity was 0.32 m/s measured at the distributor plate. The spray time was varied between 1 and 80 min. After the experiment the whole batch was sieved mechanically. No fragments of granules were found and no granules were found below the lower sieve (200 or 315 micron).

2.4. The multilayer actuator driven nozzle

A nozzle for spraying uniform droplets was developed. The size of the nozzle is small (Fig. 2), so it can easily be fitted into a small fluid bed. Fig. 2 depicts the nozzle that consists of a droplet generator (A) and a droplet divider (B). The droplet generator brakes up the droplets from a liquid current by means of a ceramic multilayer actuator (Philips components, type D31). The droplet divider (B) can be mounted onto the droplet generator and spreads the formed droplets by means of an air current. A schematic picture of the nozzle equipment is shown in Fig. 3.

When an electric sinusoidal frequency is put on the actuator of the droplet generator, a repeating shock wave passes through the liquid, which results in the breaking up of the laminar liquid jet into droplets with a narrow size distribution. The

mechanism of the liquid jet break up into droplets is described for Newtonian liquids by Weber (Levebvre, 1988). By changing the frequency of the wave function the droplet size is controlled. The average droplet size can be calculated according to Eq. (1),

$$d_d = \left[\frac{6\phi_v}{\pi f_w}\right]^{\frac{1}{3}} \quad (1)$$

Here, d_d (m) is the droplet diameter; ϕ_v (m^3/s) is the liquid throughput of the nozzle; and f_w is the frequency (1/s) of the actuator. The nozzle has a plate with a small orifice, the pin-hole, which can be varied from 35 to 300 μm. The size of the pin-hole determines the liquid jet diameter and the range in which a stable droplet size break-up occurs. The stable regime of droplet break-up is a droplet diameter of about twice the pin-hole diameter. The frequency that should be applied depends on the throughput of the liquid. The throughput of liquid lies between the 2- and 50-g/min of water, depending on the pin-hole diameter and the pressure at which the liquid is sprayed. The droplet size can be controlled independently of the liquid and airflow. During initial testing of the nozzle, the airflow through the droplet divider was set between 10 and 13 m^3/min. A higher airflow resulted in break-up of droplets and a lower airflow resulted in too much droplet coalescence by partial over-wetting at the bed surface due to a narrow spraying angle. The droplet size was measured by laser diffraction (Helos Sympatec, Germany). The average droplet size calculated (Eq. (1)) was within 4% of the measured value. The droplet size distribution could not be measured accurately by laser diffraction apparatus, because the droplet distribution was found to be narrower than the apparatus could determine. The droplet volume distribution (d_{10}–d_{90}) was found to be less than 20% of the measured droplet diameter. Droplet sizes, liquid flows and densities applied in the experiments in this paper are listed in Table 1.

3. Results and discussion

3.1. Granulation by spraying mono-sized droplets

Lactose was granulated for 4 min by spraying a 13% w/w PVP solution. This short period minimised the chance of rewetting granules. There was no significant difference in the granule size distribution plot for granules made with 2–4 min spraying and thus no significant rewetting of granules has occurred. All granules were above the 315-micron sieve, indicating that no granule break-up had occurred. The granules are spherical in shape and no fragments were found. However, when a 3% w/w PVP binder liquid was used, granules were broken at the sieves and it was not possible to measure an accurate granule size distribution. This result shows that the binder gives strength to the granule and sufficiently binder should be available in the granule to withstand rupture forces during processing.

Comparisons of granule sizes by image analysing or sieve measurement show a similar size distribution (Fig. 4). There are some differences in size distribution at the larger granule sizes. This may be explained by the orientation of the oval granules, which can pass a sieve on their smallest orientation but are registered by image analysis on their largest projected orientation. For very broad granule size distributions segregation made it difficult to obtain a representative sample

Table 1
Droplet sizes and liquid flows

Binder concentration (w/w)	Liquid flow (g/min)	Droplet size (μm)	Density (kg/m^3)
13% PVP	4.60	195	1022
20% PVP	6.10	226	1028
20% PVP	11.57	337	1028
3% HPC	6.92	200	1003

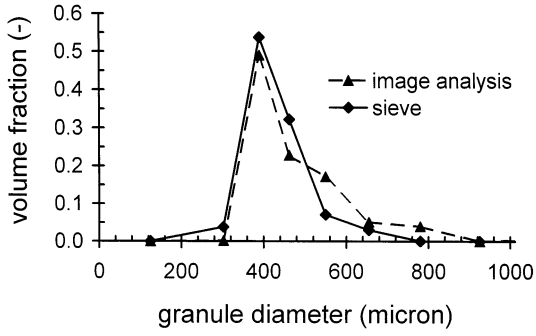


Fig. 4. Volume distribution of granules after 4 min spraying by sieving and image analysing technique, 13% w/w PVP binder liquid, inlet temperature fluid bed 40°C.

to use for image analysis. Fig. 5 shows the volume frequency and cumulative volume distributions of granules after 4 min of spraying.

Several authors (Scheafer and Worts, 1977b; Waldie, 1991; Schaafsma et al., 1998b) showed a linear dependence between droplet size and granule size, which is expected to be true for the granules produced in these experiments. There is much coalescence of droplets and granules at the spray surface, resulting in a shift of the average granule size, with respect to the initial droplet-granule size relation. The several peaks of the distribution plot (Fig. 5) represent granules, which were formed by one or more droplets. The surface renewal at the spray surface, together with the spray area and spray rate, determines the chance

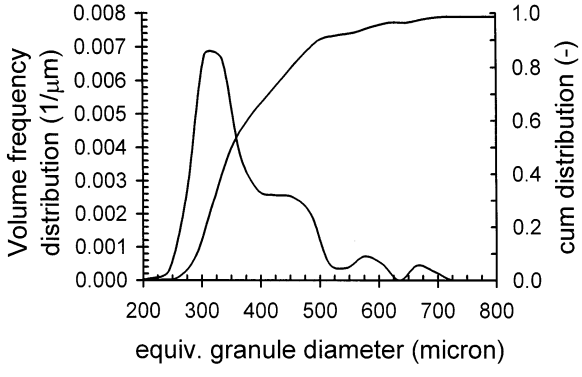


Fig. 5. Volume frequency distribution and cumulative volume fraction, less than size, distributions after 4 min spraying by image analysing technique, 13% w/w PVP binder liquid, inlet temperature fluid bed 40°C.

of coalescence and thus the average granule size. A possible mechanism of growth at the wetting (spray) surface is depicted in Fig. 6, where granules may be formed by one droplet (A), coalescence of droplets (B) or coalescence of wet granules (C).

The peak of the smallest granule size in Fig. 5 consists of granules formed by a single droplet. Granules originating from two or more droplets form peaks at larger granule sizes. Eq. (2) describes the relation between the granule size at a peak and the number of droplets it consist of:

$$\frac{\pi}{6}d_a^3 = K\frac{\pi}{6}d_d^3 N_d \quad (2)$$

Where d_a is the agglomerate diameter at a peak; N_d is number of droplets of which the agglomerates are formed; and K is the nucleation ratio which is a constant that depends on the material properties such as particle size distribution and the wettability of the powder. From the peaks in distribution plots of several short granulation experiments with 13% PVP binder, coalescence of granules and/or droplets at the spray surface could be determined. Fig. 7 shows the relation of the relative agglomerate volume, which is the agglomerate volume divided by the droplet volume, and N_d. The linear relation between the relative agglomerate volume and the number of droplets confirms our assumption that the granules grow by coalescence of droplets or granules. The slope of the line in Fig. 7 is the nucleation ratio (K), which has a value of 5.87. Note that the slope starts not in the origin, which is probably due to the effect that the droplet has to have a certain volume before it can bind particles by the mechanism of unsaturated capillary suction (Schaafsma et al., 1998b).

Granulation experiments by spraying two different droplet sizes, 226 and 336 micron containing 20% w/w PVP dissolved in water, onto lactose were performed. The binder solution was sprayed for 2–3 min, to minimise the chance of rewetting granules. Fig. 8 shows the volume and cumulative frequency distribution of the granules after 3 min spraying with a droplet size of 226 micron obtained by image analysing technique. Once again, the several peaks in the distribution plot are gran-

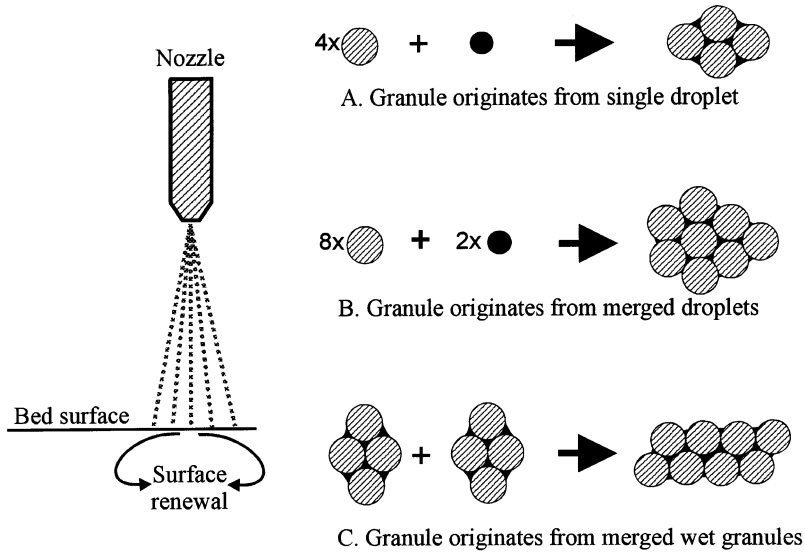


Fig. 6. Mechanism of wetting powder at spray surface.

ules formed by one or more droplets. There is more coalescence of droplets and/or granules than sprayed with 13% PVP binder liquid Fig. 5, due to the higher spray rate spraying with 20% PVP (Table 1). The granule size originating from the two initial droplet sizes (numbered 1) and granules sizes formed by coalescence of two to four droplets (numbered 2–4) is shown in Fig. 9. All granules are lying on a straight line, confirming the assumption that the peaks in the distribution plot originate from merged droplets or coalescence of granules. The slope in Fig. 9 represents the nucleation ratio, which is the ratio of granule volume to liquid volume. The nucleation ratio is independent of the droplet size and its value is 6.58 for 20% PVP binder liquid solution. The granules were spherical in shape and the primary particle size determined their surface roughness, as is shown in Fig. 10(A). Granules originating from the coalescence of two droplets or granules can be seen in Fig. 10(B, C). The photos of the granules confirm the proposed mechanism of growth by coalescence of droplets and granules at the spray surface (Fig. 6).

When α-lactose monohydrate was granulated for a longer period, up to 80 min, spraying a 13% w/w PVP solution, no fragments of granules were found and no brake-up of granules was observed. At the early stage of the granulation process there is a nearly linear growth (Fig. 11). The growth rate decreases slowly during the granulation process. This might be explained by less effective rewetting of granules compared to wetting of primary particles. Rewetting of granules is expected to be less effective because a part of the binder liquid is sucked into a dry granule and is not available for binding other particles. This mechanism is depicted in Fig. 12. Sieve analyses of the lactose granules at several stages show a

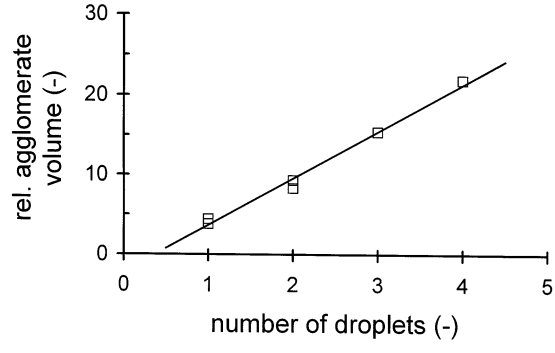


Fig. 7. Relation between merged droplets and relative granule volume, 13% w/w PVP binder liquid, and inlet temperature fluid bed 40°C.

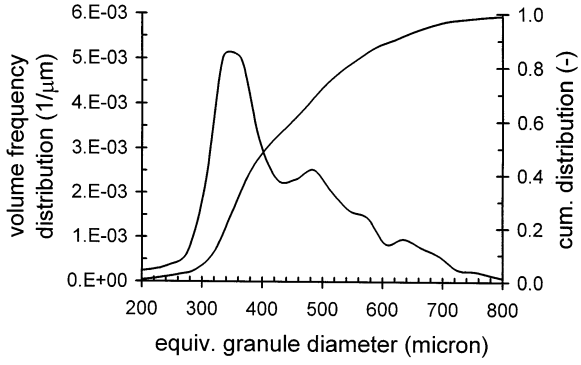


Fig. 8. Volume and cumulative frequency distribution of lactose granules after spraying 3 min 20% w/w, PVP binder liquid, droplet diameter 226 μm, inlet temperature fluid bed 50°C.

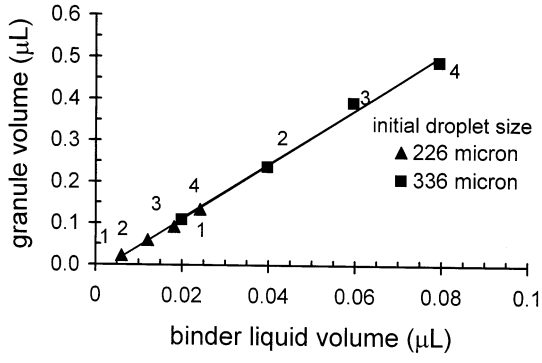
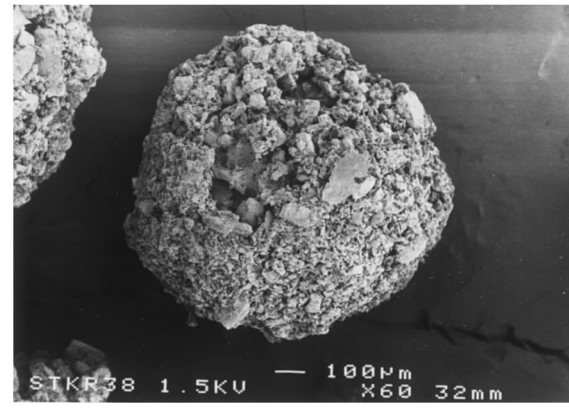


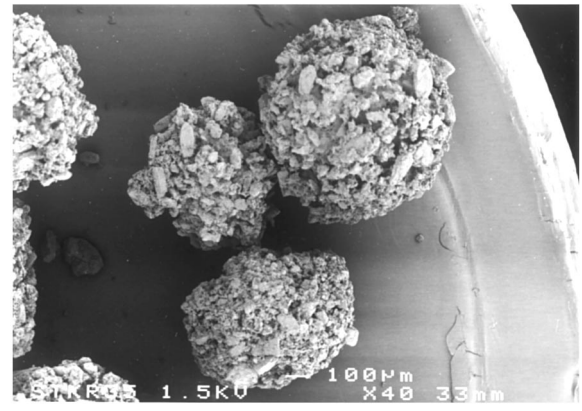
Fig. 9. Relation between droplet volume and granule volume, numbers represent the number of droplets the granule consists of 20% w/w PVP binder liquid, inlet temperature fluid bed 50°C.

shift the granule size during the granulation process (Fig. 13). The first peak of the smallest granules consists of granules formed by primary wetting, powder wetted once by droplets. The second peak consists of granules, which are rewetted by one or more droplets and are therefore grown larger.

The nucleation ratio (K) can also be calculated from the relation between the granule mass and the amount of binder liquid sprayed (Fig. 11), if the granule porosity and density of the primary particles and binder liquid are known (Eq. (3)).

$$\frac{m_a}{\rho_p(1-\varepsilon)} = K\frac{m_l}{\rho_l} \tag{3}$$





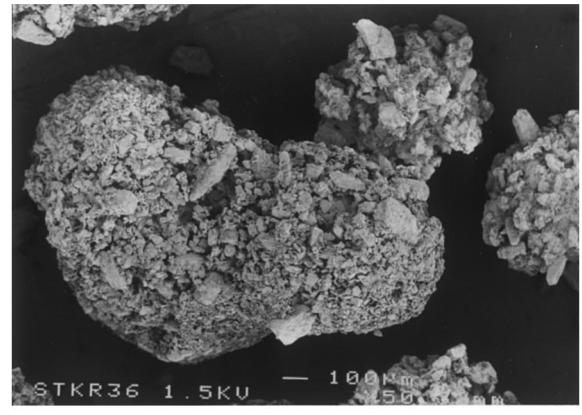


Fig. 10. Granule photos: (A) granule formed by one droplet (shape is spherical); (B) two small granules formed by one droplet, one large granule formed by two droplets with twice the volume of the small granules (shape is spherical); and (C) coalescence of wet granules (shape is not spherical).

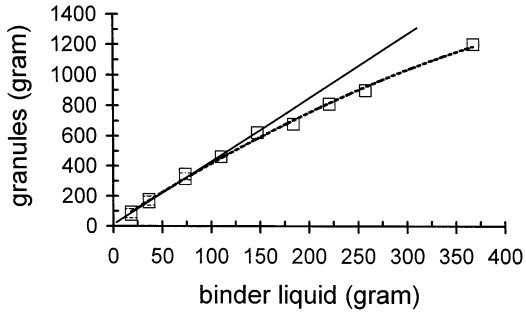


Fig. 11. Growth curve of lactose granules, 13% w/w PVP binder liquid, inlet temperature fluid bed 40°C.

Here, m_a is the dry agglomerate mass; ρ_p the density of the primary particles; ε the porosity of the agglomerate; m_l the binder liquid mass; and ρ_l the density of the binder liquid. The nucleation ratio calculated according to the slope of Fig. 11 is 5.90, for the measured average granule porosity of 0.5, and is in accordance with the calculated nucleation ratio (value 5.87) from Eq. (2). The physical meaning of nucleation ratio is related to the wetting saturation (Schaafsma et al., 1998b) and the porosity of a granule.

$$K = \frac{1}{S_w \varepsilon} \tag{4}$$

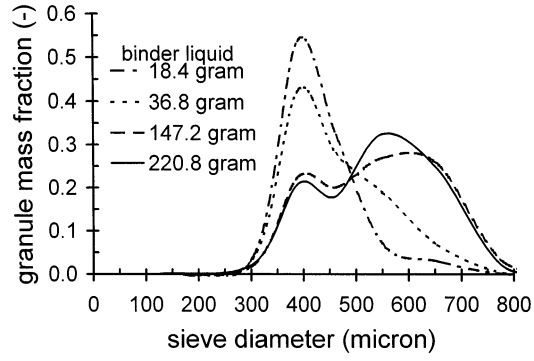


Fig. 13. Granule mass distribution at several stages during the granulation process, 13% w/w PVP binder liquid, inlet temperature fluid bed 40°C.

Here S_w is the wetting saturation reflects the wettability of the powder, and is approximately given by the droplet volume divided by the pore volume of a granule if no drying occurs. According to Schaafsma et al. (1998b) a granule will grow until the primary particles are not able to attach to the liquid in the pores at the surface of the granule. The relative amount of liquid present at that stage is called the wetting saturation. The S_w depends on the contact angle of the binder liquid and the pore structure of the granule.

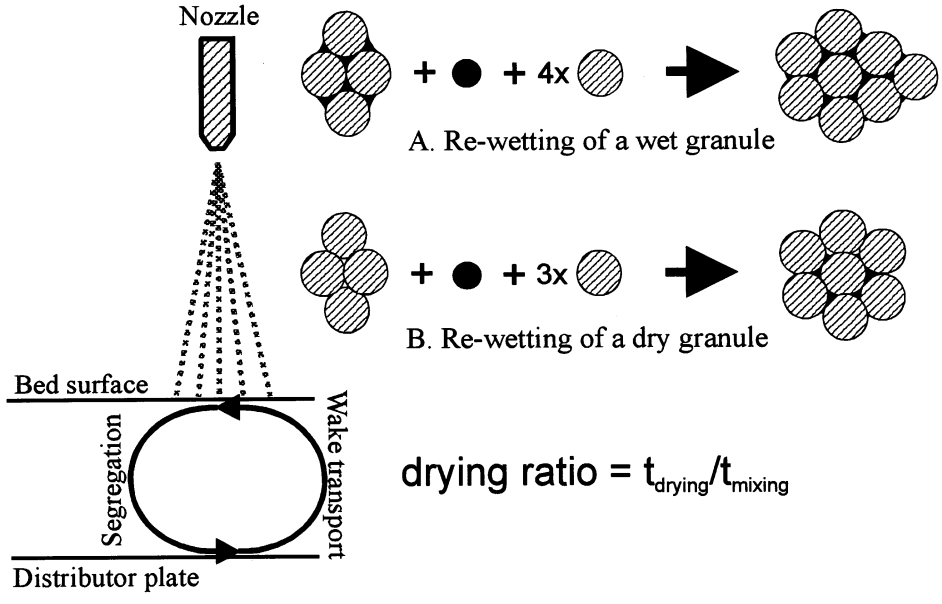


Fig. 12. Mechanism of rewetting granules.

In general, granulation is performed with smaller droplets than applied in these experiments (Scheafer and Worts, 1977b; Gore et al., 1985; Schaafsma et al., 1998a). Coalescence of granules and/or droplets at the spray surface is surely occurring in those processes because of the higher spray rates and the larger number of smaller droplets that are sprayed on the bed surface. The coalescence of droplets at the spray surface will result in an apparently different granule size–droplet size relation. This can be explained by the fact that the average granule diameter (d_m) measured by sieve or image analysis is larger than the granule diameter (d_a) originating from one droplet (d_d; Table 2). The true nucleation ratio can be determined from the granule mass–binder liquid mass relation (Fig. 11, Eq. (3)) as this value is not influenced by the coalescence of droplets. The volume distribution plot can determine the amount of coalescence. The fraction of coalescent droplets (F_c) is approximately one minus the cumulative volume fraction distribution of the peak formed by one droplet, as the other peaks originate from two or more droplets (Table 2). Table 2 shows that the fraction of coalescent droplets (F_c) is related to the number rate of droplets sprayed. This is expected as the chance of coalescence is related to the number rate of droplets, droplet size and the spray area (which was kept constant for all droplet spray rates and sizes in these experiments).

The nucleation ratio factor can be used to develop a suitable binder liquid for powder that has to be granulated. The better the binder liquid binds particles, which is reflected in a high nucleation ratio, the less liquid has to be used to granulate the same amount of material. This saves time and money. Furthermore, coalescence of droplets at the spray surface can be determined. The coalescence of droplets and granules at the spray surface will result in a broader granule size distribution because granules may be originating from a single to several droplets resulting in a broader size distribution than the initially droplet size distribution. Spraying large droplets with less coalescence would be an alternative way to prepare the granules with a narrow size distribution. In the future the nucleation ratio can be used to develop a population balance for fluid bed granulation if effectiveness of rewetting on growth and the coalescence of granules and droplet at the spray surface are taken into account as well.

3.2. Distribution of tracer

In the short granulation experiments (spraying 20% w/w PVP solution as mentioned above) 0.5‰ w/w fluorescein sodium was added as tracer to the binder liquid. The granule sieve fraction and the relative tracer concentration are shown in Table 3 for the two different sprayed droplet sizes. The tracer concentration was independent of the droplet size and sieve fraction. Only the lowest sieve contained fines, which consist of non-granulated material, and resulted in an apparently lower tracer concentration. The relation between tracer mass and granule mass is shown in Fig. 14. The data have been obtained collecting 100 granules of each sieve starting above 425 micron and determining the average granule mass and tracer mass. The powder below sieve 425 consisted of a large amount of fines and particles could not be collected accurately. There is a linear relation between the granule mass and tracer mass, which confirms the linear relation between droplet size and granule size. To study the distribution of tracer within the granule we made a picture of a granule by means of a confocal laser fluorescence

Table 2
Granule size and coalescence

Binder concentration (w/w)	d_d (μm)	d_a (μm)	d_m (μm)	Spray rate of droplets (number/s)	F_c
13% PVP	195	304	358	19300	~0.49
20% PVP	226	350	408	16400	~0.42
20% PVP	336	593	600	9400	~0.21

Table 3
Fluorescein tracer

Sieve (μm)	Droplet diameter 226 μm		Droplet diameter 336 μm	
	Mass fraction	Relative tracer conc.	Mass fraction	Relative tracer conc.
Fines < 425	0.156	0.66	0.003	0.98
425–600	0.723	0.95	0.034	1.05
600–710	0.116	0.99	0.352	1.04
710–850	0.005	0.99	0.264	1.02
> 850	–	–	0.349	1.03

microscopy (Fig. 15). The tracer is found mainly near the surface of the granule, indicating that the tracer was moved during capillary drying phase to the granule surface. This is consistent with data of large granules (diameter ~5 mm; Schaafsma et al., 1998b). The binder is expected to migrate to the granule surface as well, which may influence the strength of the granule. Eventually the non-uniform distribution within the granule may contribute to a broader distribution of binder and tracer (or active entity) when granules are brittle and break up during processing. Break-up of granules should therefore be prevented.

A non-soluble tracer Fe_2O_3 was suspended in a 3% w/w HPC binder liquid and sprayed for a short period (4 min) on a fluid bed containing 15% w/w starch and 85% w/w lactose. The granule sieve fraction and the relative tracer concentration are shown in Table 4. The distribution of the tracer was uniform for the large sieve fractions, the lower sieve fraction collected a lot of non-granulated fines and some small granules. The lowest sieves contained not enough material for analysis.

The binder liquid distribution corresponds with the uniform distribution of tracers in the granules. It shows also that rupture is of minor consequence because the relation between granule mass and tracer mass is preserved, which would be not valid if granules were fragmentised. The solubility of the tracer does not seem to influence the distribution between granule size fractions. The tracer experiments confirm the linear relation between the droplet mass and the granule mass, as this relation is true for tracer mass and granule mass as well. The tracer is uniformly distributed be-

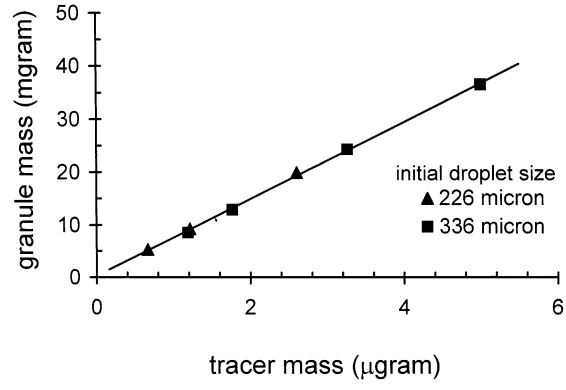


Fig. 14. Relation between granule mass and tracer mass, for one granule, 20% w/w PVP binder liquid, droplet diameter 226 and 336 μm, inlet temperature fluid bed 50°C.

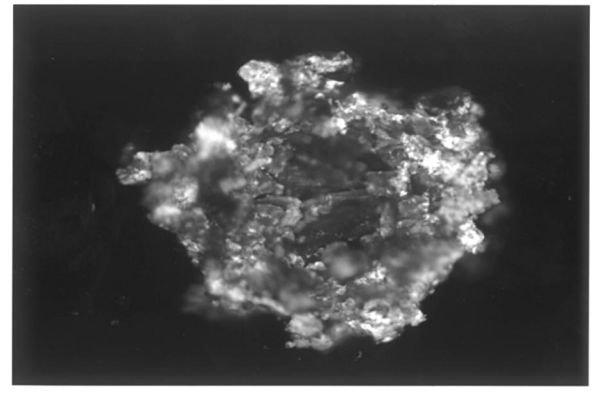


Fig. 15. Fluorescein distribution in cross-section of granule measured by confocal laser microscopy, 20% w/w PVP binder liquid, and droplet diameter 226 μm.

Table 4
Fe_2O_3 tracer

Sieve (μm)	Mass fraction	Relative tracer conc.
Fines < 75	0.006	na[a]
75–106	0.004	na
106–150	0.002	na
150–212	0.008	0.10
212–300	0.018	0.12
300–500	0.644	0.90
500–600	0.184	1.04
600–710	0.093	1.13
> 710	0.053	1.12

[a] na, not analysed.

tween the granule fractions at the early stage of a granulation process, but this will probably not hold during the whole process as rewetting is bound to occur. Rewetting is expected to be less effective as was shown earlier by the longer spray experiments of spraying 13% PVP binder liquid.

4. Concluding remarks

By developing a nozzle which produces uniform droplets, we were able examine in more detail the granule growth mechanism in the fluid bed granulation process. The newly developed nozzle also seems a promising tool to study other aspects of fluid bed granulation, like the influence of drying conditions on the product properties and the effects of bed mixing intensities on granule growth. This is because the nozzle eliminates the influence of the droplet size distribution. The results in this paper show a direct relation between droplet size and granule size at the early stage of the growth process, which is not always measured when looking at the average granule size, because coalescence of droplets and granules takes place in the wetting zone. Rupture of granules does not occur in the fluid bed granulator if the proper binder concentration is chosen. The nucleation ratio introduced can be used to develop new binders and test their wetting and binding capability. A tracer added to the binder liquid is uniformly distributed throughout the granule size fractions at an early stage of the granulation process. This uniformity is not expected to hold during the process of growth because of the less effective rewetting of dried granules.

Preventing rewetting would be a promising method to control granulation and produce well-defined, uniformly sized granules with a uniform component distribution. It would result in a granule size distribution, which is controlled only by the droplet size distribution. The concentration of an active entity added to the binder liquid will be directly related to the granule mass. Whether or not it is possible to avoid rewetting to achieve controlled granulation in a fluid bed remains to be proven.

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