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Research paper

Qualitative proof of liquid dispersion and penetration-involved granule formation in a high shear mixer

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Abstract

The origination of granules in the early seconds is an important aspect of high shear granulation. To elucidate these mechanisms, a substandard amount (1.5% w/w) of an aqueous hydroxypropyl cellulose solution was added to four different lactose mixtures: (1) lactose 100 M ($d_{4,3} \sim 170$ μm), (2) lactose 200 M ($d_{4,3} \sim 50$ μm), and (3, 4) 10% magnesium stearate/lactose 100 or 200 M. Between 1 and 15 s after binder addition samples were taken, which were immediately frozen in liquid nitrogen. The frozen sample was sieved into granular (>280 μm) and non-granular-material (<280 μm). The binder distribution in these fractions was determined. The observed binder distribution behaviour revealed that three different nucleation mechanisms can occur: (I) For lactose 100 M holds that all the binder is initially located in the granules. These granules are subsequently broken again. (II) The lactose 200 M granules also contain 100% of the added binder liquid. Contrary to lactose 100 M the lactose 200 M granules remain intact during the process. It is argued that in both cases liquid penetration is responsible for the accumulation of all liquid in the granules. A theoretical evaluation also confirmed that liquid penetration leads to the formation of the primary granules (III) No liquid penetration is possible in the hydrophobic magnesium stearate/lactose mixtures and the binder is completely dispersed in the non-granular material.

Keywords: High shear granulation; Nucleation; Dispersion; Liquid penetration; Binder distribution; Granule breakage

1. Introduction

Wet granulation is widely employed in various industries to improve one or more of the characteristics of the powder. One of the frequently used granulation equipment is the high shear mixer. The term high shear implies that the mass is intensively blended in the mixer, suggesting good mixing abilities of the apparatus [1]. This is certainly true when various powders are dry-mixed. Paradoxically, addition of binder liquid, necessary for granulation, often results in demixing of the powders [1–5]. The demixing is revealed as a granule size-dependent variation in composition of the granules with respect to active, filler and also the binder. High shear granulation is used in the pharmaceutical industry for the production process of a solid formulation (e.g. tablet, capsule). The poor distribution of an active substance is especially problematic in this field, since the content uniformity of intermediate and end products are essential requirements for product quality.

Since little is known about the mechanisms involved in the formation of non-homogeneous granules, a research project focused on granule inhomogeneity was started. Previous publications on this subject showed that breakage behaviour of the granules prevented the poor distribution of an active [6,7]. Once granule breakage is minimal, granules grow by layering, especially during the initial stage of the granulation process when a large amount of ungranulated powder is still present. During layering preferential adherence of the smallest (drug) particles on the granules causes the inhomogeneity [6,8]. This preferential growth leads to accumulation of the smallest (drug) particles in the larger granules and depletion of these particles in the ungranulated material.

The granule inhomogeneity is manifested already after 1 min of granulation and also the largest extent of growth occurs during this first minute [6]. However, there is still

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Nomenclature

f_g	mass fraction granular material [−]
C_g	concentration paracetamol in the dried granules [mg/g]
C_b	concentration paracetamol in the binder solution [mg/g]
M_b	mass of added binder [g]
k	binder dispersion rate [s^{-1}]
d_g	granule diameter [m]
R_d	radius of a liquid droplet [m]
R_{pore}	Pore radius [m]
$t_{280\ \mu m}$	theoretical penetration time necessary for a granule of 280 μm [s]
V_l	volume of liquid in a granule [m^3]
V_g	volume of a granule [m^3]
t	penetration time [s]
μ	viscosity [Pa s]
ε_g	porosity granule [−]
ε_p	porosity powder bed [−]
γ	surface tension [N/m]
Θ	contact angle [−]

lack of detailed information about this initial stage of the granulation process (nucleation). In order to unravel the inhomogeneity phenomena, comprehensive knowledge about the mechanisms of granule growth during the nucleation process is indispensable.

In wet granulation, granules exist due to the presence of liquid bridges between primary particles. Hence, the formation of granules will strongly depend on the mixing of the binder liquid with the powder. Based on a literature survey a schematic overview is given of the possible ways that the liquid can be mixed with the powder (Fig. 1). The nucleation process starts with two separate phases, a liquid and a solid phase. The mixing action of the impeller and chopper blades disperses the liquid continuously into smaller liquid volumes. If these volumes are too small to assemble several primary particles, the binder is homogeneously dispersed over the primary particles. In literature this mechanism of liquid mixing is called the *distribution mechanism* [9] or the *mechanical dispersion mechanism* [10]. When liquid volumes come into contact with the powder, penetration of the liquid into the powder bed can occur. Provided that the liquid volume is large enough to embed several particles, granules can be formed by liquid penetration or immersion [9,11]. Depending on the strength of these freshly formed granules, granules may break or remain intact during the process. It should be noted that the proposed mechanisms are based on measurements done at least 1 min after the start of liquid addition. This means that there is no information about the early seconds of the process. In a previous study of the authors it was shown that after a process time of 1 min the process was already completed for a large degree with respect to granule inhomogeneity and size. Hence, it seems that especially the events that occur within the first minute are of paramount importance for the continuing granulation process. Moreover, it is indistinct at which process and formulation conditions the proposed mechanisms in Fig. 1 are valid. The aim of this study is to investigate both theoretically as experimentally, how granules are formed during the initial seconds of the high shear granulation process and which mechanisms are involved.

2. Experimental

2.1. Materials

For the experiments four different powder mixtures were used: (1) lactose 100 M with a weight mean particle size of 170 μm, (2) lactose 200 M with a weight mean particle size of 50 μm, (3) a mixture of 10% magnesium stearate and

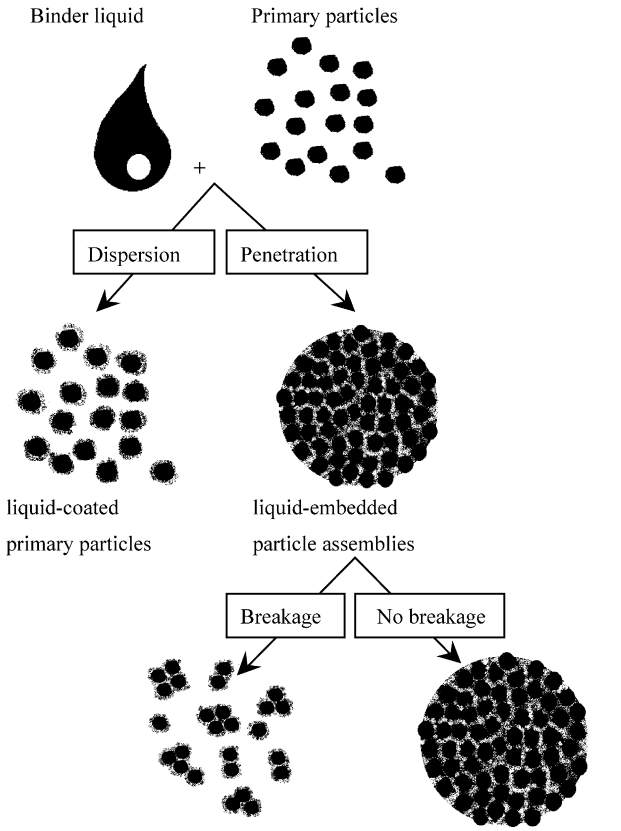

Fig. 1. Schematic overview of the possible nucleation mechanisms in the high shear mixer proposed in literature. See text for explanation of the different mechanisms. In order to prevent confusion it is necessary to use a consistent terminology for the different aspects that are important for nucleation. The term binder distribution refers to the location of the binder in the powder mixture, whereas binder dispersion refers to the scattering of pure binder liquid volumes into smaller volumes. Breakage is a term for the fragmentation of the granular material.

lactose 100 M and (4) a mixture of 10% magnesium stearate and lactose 200 M. The mixture of magnesium stearate and lactose was dry-mixed for 10 min in the high shear mixer prior to granulation. Lactose was obtained from DMV (Veghel, The Netherlands) and magnesium stearate from Peter Greeven Fett Chemie (Venlo, The Netherlands). An aqueous solution of 15% (w/w) hydroxypropyl cellulose (Klucel EP, Aqualon, Wilmington, USA) and 1% (w/w) paracetamol (BuFa, Uitgeest, The Netherlands) was used as the binder. The viscosity of this solution was 1.0 Pa s (Brookfield rheometer DV-III).

2.2. Methods

To evaluate the nucleation behaviour, approximately 15-g binder solution was added to 1000 g of a powder mixture. Hence, the percentage of binder liquid is only 1.5% which is approximately a 10th of the amount of binder which is normally used for granulation. This was done to assure that there is excess of powder with respect to the binder liquid. This means that the availability of the powder is no limiting factor for liquid penetration. To trace the location of the binder and to measure the binder content, approximately 1% of paracetamol was dissolved in the binder solution. The binder was added by a syringe in one go. The powder mixture was rotating in the high shear mixer (Gral 10, Machines Colette, Wommelgem, Belgium) during binder addition. The impeller and chopper were operated at 430 and 1500 rpm, respectively. This corresponds with a tip velocity of 5 m/s for the impeller and chopper. The mixer was stopped at different time points after addition of the binder. The mixture was immediately poured into liquid nitrogen to freeze the process. This frozen powder mixture was hand-sieved into two fractions, one fraction larger than 280 μm and one fraction smaller than 280 μm. Both fractions were weighed to determine the mass fraction of the material larger than 280 μm (f_g). The sieve size of 280 μm was arbitrarily chosen as the cut-off size between granular and non-granular material. The fraction larger than 280 μm is regarded as granular material and/or binder lumps, because the primary particle size of the lactose is smaller than 280 μm. The fraction smaller than 280 μm is regarded as non-granular material. All the materials larger than 280 μm was plate-dried. The concentration of paracetamol in the original binder solution and in the powder fraction larger than 280 μm was analysed with a HPLC method with UV detection at 254 nm (column; Nucleosil 100 C18, 5 μm, 250 × 4.6 mm; Chrompack, The Netherlands). The amount of paracetamol in this fraction is a measure for the total amount of binder. The percentage of binder still present in the granules >280 μm relative to the total amount of binder liquid added is calculated with the following equation;

$$\text{Percentage of binder (\%)} = \frac{f_g C_g (1000 + M_b)}{M_b (C_b + C_g)} \quad (1)$$

in which f_g is the mass fraction of the material larger than 280 μm, C_g the concentration of paracetamol in the dried granules, C_b the concentration of paracetamol in the binder and M_b the total mass of the added binder. The number 1000 (g) in Eq. (1) equals the filling grade of the bowl. The liquid/solid ratio (w/w%) of the fraction larger than 280 μm was also determined, which is expressed as,

$$\text{Liquid/solid ratio} = \frac{C_g}{C_b} \quad (2)$$

The experiments were done in triplicate.

3. Results

Earlier work has demonstrated that lactose 100 M form granules, which cannot survive the shear forces in the process [7]. Fig. 2a indicates what happens during the first seconds after liquid addition for lactose 100 M. The amount of binder in the fraction >280 μm rapidly decreases in the first 15 s. After 15 s almost no coarse particles are present any more, meaning that the binder is distributed over the powder with a size smaller than 280 μm. The mass percentage and the liquid/solid ratio of the material larger than 280 μm is shown in Fig. 2b. The value of approximately 0.1 indicates that a relatively large fraction of

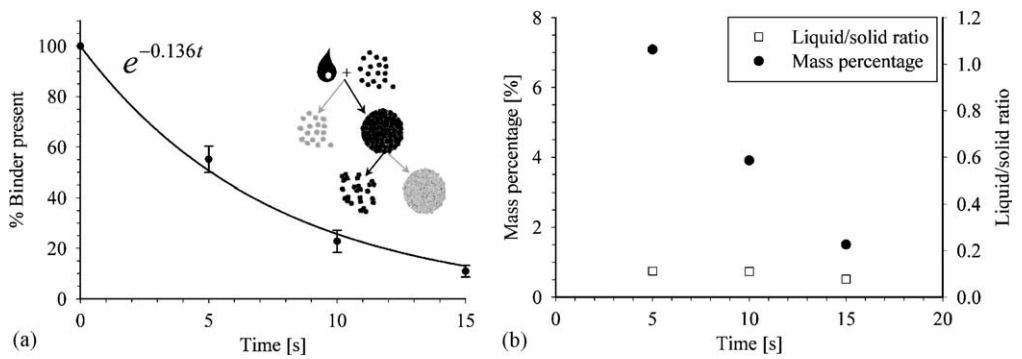

Fig. 2. (a) Influence of process time on the binder percentage that is present in the fraction >280 μm for the lactose 100 M mixture. The insert depicts a schematic representation of the nucleation mechanism. (b) The mass percentage of powder that is larger than 280 μm and liquid/solid ratio (w/w%) of the material present in this fraction (● mass percentage, □ liquid/solid ratio).

the material larger than 280 μm is solid. Hence, granules are formed already 5 s after binder addition. However, the decrease in mass percentage indicates that the granules also disappear. Obviously, they are not strong enough to withstand the impacts of the impeller and chopper arms and are consequently broken down. In fact this confirms the earlier referred findings. After 15 s practically no granules are present anymore and the binder is homogeneously distributed over the lactose 100 M particles.

The insert in Fig. 2a, which is deduced from Fig. 1, schematically shows the nucleation behaviour of lactose 100 M. First of all, several primary particles are embedded by binder liquid resulting in agglomerates. The embedding of the primary particles occurs by liquid penetration into the porous powder bed. The shear forces break down these newly formed agglomerates.

Addition of the same amount of binder to lactose 200 M clearly leads to completely different binder distribution behaviour than observed for lactose 100 M. Fig. 3a shows that after 5 s the complete amount of binder is present in the fraction larger than 280 μm. Contrary to the results of lactose 100 M, even after 300 s still 75% of the total amount of binder is located in this fraction. Fig. 3b shows that the mass percentage of the material larger than 280 μm varies between 9 and 12%. This means that only a small mass fraction of the powder mixture (~10%) contains almost all the binder, while approximately 90% of the powder contains no binder. This means that the binder is not homogeneously distributed over the powder mix.

Fig. 3b shows that the liquid/solid ratio of the lactose 200 M granules decreases slightly in time. Part of the binder is distributed to the fraction smaller than 280 μm. However, the mass of the solid in the fraction larger than 280 μm increases. Hence, the granules are picking up ungranulated material, which explains the mass increase. This indicates that the granules grow by layering. An earlier study showed that layering growth could introduce inhomogeneity, expressed as poor distribution of the drug substance in the granules, provided that there is a particle size difference between filler and drug substance [8]. Hence, it is possible that this type of nucleation mechanism is correlated with the inhomogeneity phenomena.

The insert in Fig. 3a schematically illustrates the observed nucleation behaviour of lactose 200 M. Similar to the granule formation of lactose 100 M, granules are formed in the early seconds by liquid penetration. The difference however is that the lactose 200 M granules are not broken down, whereas the lactose 100 M granules were susceptible for breakage. Hence, a change of lactose 100 M to lactose 200 M has a dramatic effect on the nucleation behaviour. The only difference between lactose 100 M and 200 M experiments is the primary lactose size. It is illustrated here that a decrease in the particle size results in a considerable increase in the granule strength and can even lead to a shift from breakage to no breakage behaviour of the granules.

To confirm the role of penetration in the granule formation, magnesium stearate was mixed with lactose to coat the lactose 100 M and 200 M particles with magnesium stearate. Magnesium stearate is a hydrophobic compound. The contact angle of water on magnesium stearate is 120°. It is therefore unlikely that binder volumes of an aqueous solution of HPC can penetrate this hydrophobic mixture and form granules. Hence, there is no wetting. The results for the binder distribution in the powder mixture of 10% magnesium stearate/lactose 100 M is shown in Fig. 4a. Compared to the lactose 100 M experiments, addition of 10% magnesium stearate to lactose 100 M does not seem to influence the binder distribution to a great extent. Again the amount of binder located in the fraction larger than 280 μm rapidly decreases, faster than observed for the lactose 100 M experiment. However, the influence of magnesium stearate on the liquid/solid ratio is pronounced. Although, an L/S ratio of 0.1 was observed for the lactose 100 M experiment,

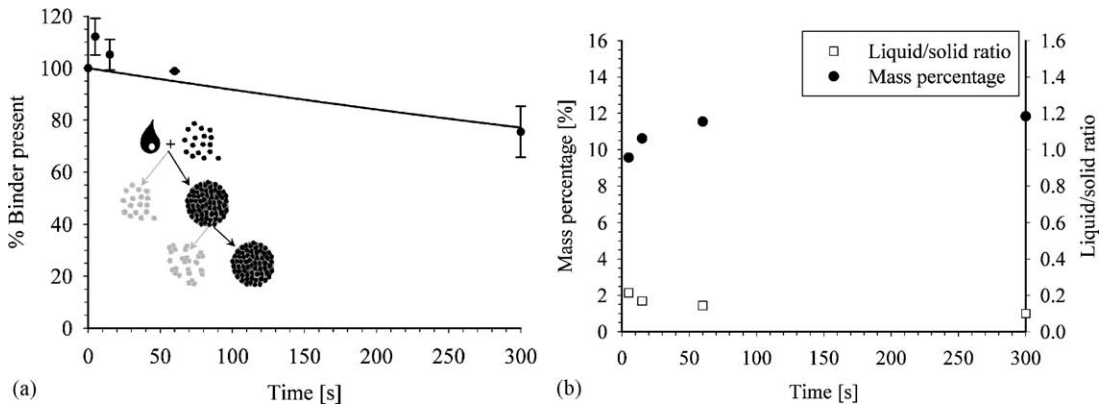

Fig. 3. (a) Influence of process time on the binder percentage that is present in the fraction >280 μm for the lactose 200 M mixture. The insert depicts a schematic representation of the nucleation mechanism. (b) The mass percentage of powder that is larger than 280 μm and liquid/solid ratio (w/w%) of the material present in this fraction (● mass percentage, □ liquid/solid ratio).

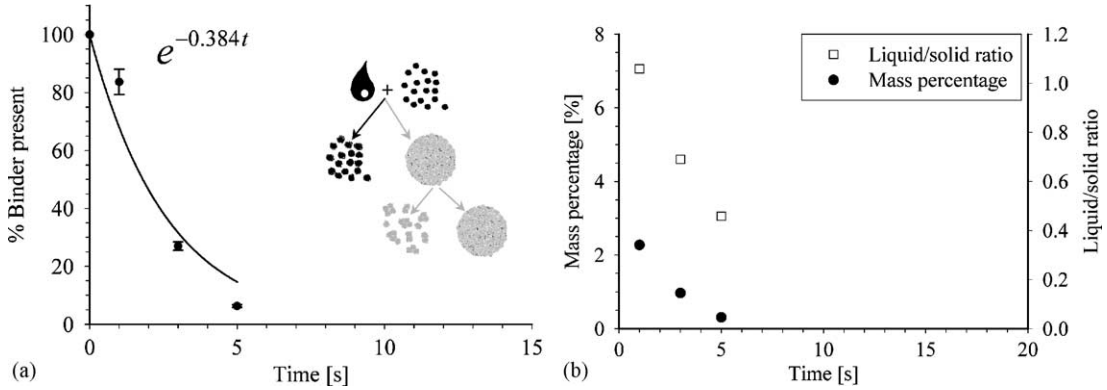

Fig. 4. (a) Influence of process time on the binder percentage that is present in the fraction >280 μm for the 10% magnesium stearate/lactose 100 M mixture. The insert depicts a schematic representation of the nucleation mechanism. (b) The mass percentage of powder that is larger than 280 μm and liquid/solid ratio(w/w%) of the material present in this fraction (● mass percentage, □ liquid/solid ratio).

addition of magnesium stearate results in an L/S ratio between 1.0 and 0.5. This indicates that the material largely consists of binder liquid. An L/S ratio of approximately 0.2 for a standard granulation process of lactose will result in over-wetted granules. Hence, an L/S ratio between 1.0 and 0.5 in fact reflects a wet paste.

The influence of the magnesium is even more pronounced for lactose 200 M. Fig. 5a shows that after 15 s almost no binder is present anymore and the L/S ratio is enormously increased. The inserts in Figs. 4a and 5a show that the nucleation mechanism for the magnesium stearate/lactose mixtures is controlled by complete dispersion of the binder. The ultimate result, distribution of the binder liquid to the ungranulated material, is the same for both the lactose 100 M and the lactose/magnesium stearate experiment. However, it is noted that there is a substantial difference between the cause of both results. The high L/S ratios observed for the magnesium stearate/lactose mixtures suggest that the binder is present as almost pure binder volumes. These binder volumes are completely dispersed by the mechanical action of the mixer arms, resulting in distribution of the binder liquid to the ungranulated material. For the nucleation mechanism of lactose 100 M holds that the distribution of the binder is induced by the breakage of the granules.

4. Evaluation/discussion

In low shear granulation processes, like drum and fluid bed granulation, a strong correlation between droplet size after spraying and granule size has been found, indicating that (drop) penetration plays a role [12,13]. Even in the high shear mixer this correlation was found when spraying a low viscosity binder (<100 mPa s) under special conditions [10]. However, it is more common and convenient, especially on a large-scale and for highly viscous binder solutions, to add the binder by pouring. If the binder is added to the powder mixture by pouring, for a short time period much larger volumes of binder liquid are present in the high shear mixer than is the case with spraying. This results in a larger average granule size for pour-on experiments [14]. The mechanical agitation of the powder mixture by the impeller and chopper blades is responsible

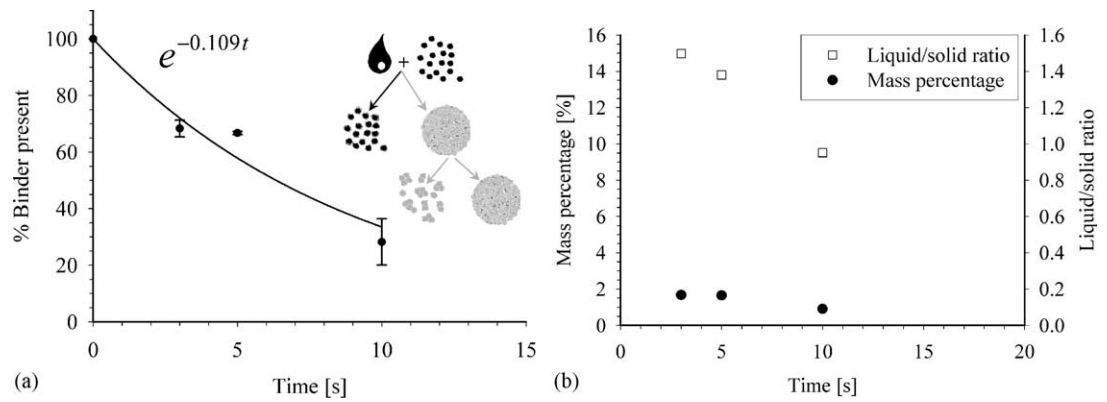

Fig. 5. (a) Influence of process time on the binder percentage that is present in the fraction >280 μm for the 10% magnesium stearate/lactose 200 M mixture. The insert depicts a schematic representation of the nucleation mechanism. (b) The mass percentage of powder that is larger than 280 μm and liquid/solid ratio (w/w%) of the material present in this fraction (● mass percentage, □ liquid/solid ratio).

for the dispersion of the binder. Whether and to what degree penetration of these larger binder volumes will also take place in the high shear mixer during the pour-on experiments depends on the kinetics of the binder dispersion and the rate of penetration. The result of the lactose 100 M and 200 M experiments actually showed (see Figs. 2 and 3) that granules can be formed by penetration. The penetration time for a droplet into a porous substrate is determined by [15,16]:

$$t = 3.55 \frac{r_d^2}{\varepsilon_p^2 R_{pore}} \frac{\mu}{\gamma \cos \Theta} \tag{3}$$

in which R_{pore} is the radius of the capillary, γ the liquid surface tension, Θ the contact angle, μ the viscosity of the solution, ε_p the porosity of the powder bed and r_d is the radius of the liquid drop covering the powder. This equation was validated for a static situation, where a liquid drop was placed on a powder bed and the penetration time was determined [10,15–17]. For simplicity reasons it is assumed in the further discussion that this equation can also be applied in the dynamic situation of the high shear mixer. Of course there are some major differences compared to the static situation. In case of the static situation the available time for penetration of the liquid is unlimited. In the high shear mixer the contact time of the liquid with the powder may be very short, because the penetration process is ended if the binder liquid is further dispersed by mechanical action. Hence, it is assumed that the rate of the binder dispersion is the critical step for penetration to occur in the mixer. The available penetration time is defined as the time period that a liquid volume (V_l) can penetrate the powder, until the binder liquid is further dispersed. The size of a granule, which is formed by penetration of this liquid volume, is determined by the following relationship between the liquid volume (V_l) and the total volume of the granule (V_g)

$$V_g = \frac{V_l}{\varepsilon_g} \tag{4}$$

in which ε_g is the porosity of the granule. It is assumed that the total void volume of the granule is filled with liquid (100% saturation). The volume of a granule is given by Eq. (5)

$$V_g = \frac{1}{6} \pi d_g^3 \tag{5}$$

And the volume of the liquid is described by Eq. (6)

$$V_l = \frac{4}{3} \pi r_d^3 \tag{6}$$

d_g is the diameter of the granule and r_d is the radius of the binder liquid volume that has penetrated assuming that this was a droplet. The granule size after liquid penetration can be calculated by combining Eqs. (4)–(6)

$$d_g = \frac{2 r_d}{\varepsilon_g^{1/3}} \tag{7}$$

It is likely that the porosity of the dry powder mixture (before penetration) and the granule (after penetration) will be different. (The capillary pressure difference will pull the particle in the granule together and the impact forces acting on the granule result in densification.) For that reason different values are used for the powder bed porosity (ε_p) and the granule porosity (ε_g). Combination of Eqs. (3) and (7) leads to the following equation to calculate the granule size after liquid penetration

$$d_g = 1.06 \left(\frac{\varepsilon_p^2 R_{pore} \gamma \cos \Theta}{\mu \varepsilon_g^{2/3}} t \right)^{1/2} \tag{8}$$

In order to obtain an indication of the characteristic penetration time necessary to get a granule with a size of 280 μm, Eq. (8) is rewritten. The size of 280 μm was chosen, because this is the cut-off size between granular and non-granular material used in the experiments. The penetration time necessary to obtain a granule with a size of 280 μm is given by

$$t_{280} = 6.97 \times 10^{-8} \frac{\mu \varepsilon_g^{2/3}}{\varepsilon_p^2 R_{pore} \gamma \cos \Theta} \tag{9}$$

Fig. 6 shows the granule size as a function of the available penetration time the indicated conditions. It can be calculated that a penetration time of 0.17 s and a liquid volume of 0.0023 μl is required in the high shear mixer to obtain granules of 280 μm. This is a remarkably short time and small binder volume.

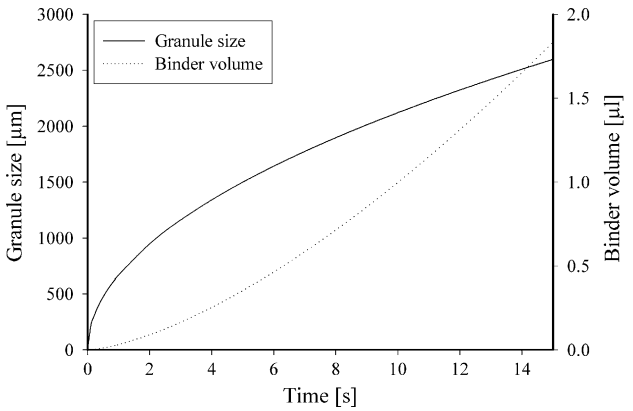

Fig. 6. The influence of the available penetration time on the size of the granules and the binder volumes necessary to form these granules. The granule size was calculated with Eq. (8). The values used for the calculations are: viscosity (μ), 1 Pa s; pore radius (R_{pore}), 15 μm; porosity of the powder bed (ε_p), 0.5; porosity of the granule (ε_g), 0.2; surface tension (γ), 0.044 N/m and contact angle (Θ), 34°. The values for the surface tension and contact angle correspond with real measured values for an aqueous HPC solution and lactose [22].

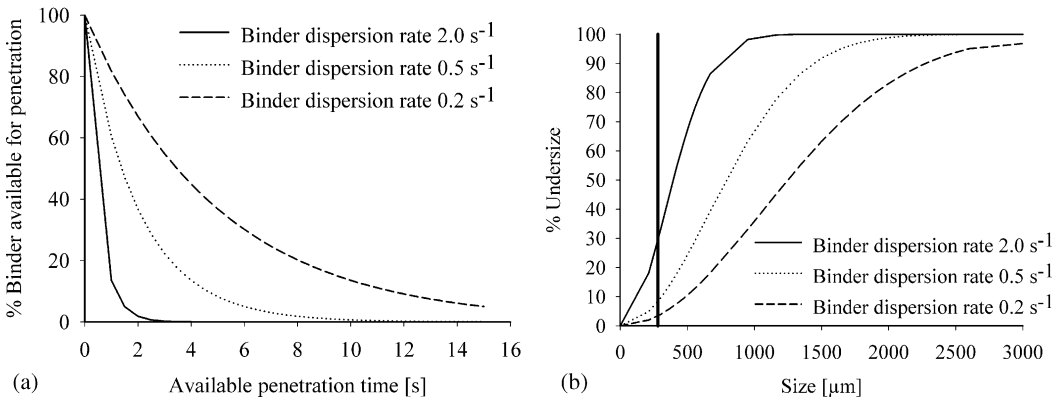

Fig. 7. (a) First-order binder dispersion curves expressed as the percentage of binder that is still available for penetration in sufficiently large volume to form granules; (b) influence of the binder dispersion and penetration rate on the nuclei size distributions after the penetration process is completed. The vertical line represents the cut-off size (280 μm) between granular and non-granular material (see text for explanation).

Another prerequisite for penetration to occur in the high shear mixer is that the available penetration time of the binder droplets with the powder is sufficiently long and that the binder volumes are large enough to assemble several primary particles. Whether this is the case will depend on the binder dispersion rate. Two possible dispersion scenarios can be proposed:

- The binder liquid is dispersed gradually from relatively large volumes into smaller and smaller volumes.
- The binder liquid is dispersed instantaneous into volumes insufficiently large to form granules.

This instantaneous dispersion of the binder is not observed in this study. In several other studies it was also argued that this instantaneous distribution of the binder is impossible [14,18–21]. On the other hand, when the binder dispersion is not instantaneous and droplet volumes persist, large enough to assemble several primary particles, granules can be formed by penetration. Hence, an important parameter in the nucleation process is the kinetics of binder dispersion. Some simulated first-order kinetics of the binder dispersion are shown in Fig. 7. The figure shows the percentage of the binder that is still available in sufficiently large volumes (theoretically >0.0023 μl) to form nuclei. It is noted that this is a theoretical definition and representation of the binder dispersion behaviour. However, the binder distribution behaviour observed for the magnesium stearate/lactose experiments (Figs. 4a and 5a) can be interpreted as indications for the binder dispersion rate, since the binder was present as almost pure liquid fragments. The values for the binder dispersion rate derived from Figs. 4a and 5a are 0.384 and 0.109 s^{-1}, while the theoretical values used for the calculations in Fig. 7 vary between the 2.0 and 0.2 s^{-1}. This means that the values used for the calculations corresponds fairly well with the experimental values, which indicates that the values for the theoretical first-order binder dispersion rates shown in Fig. 7 are realistic.

In the high shear mixer the binder dispersion and the penetration are not separate processes, but occur simultaneously. Actually, the mechanism of granule formation depends on the balance between the binder dispersion rate and the penetration rate. To combine these processes in the nucleation model some assumptions have to be made. Therefore, it is assumed that liquid volumes still present at a certain time point have also had the ability to penetrate during this time period. The influence of this assumption on the nucleation model is illustrated with the following example. It can be calculated from the first-order kinetics shown in Fig. 7a that for the lowest binder dispersion rate 37% of the binder is still present after 5 s. According to Fig. 6 the nuclei size after a penetration time of 5 s is 1500 μm. Hence, assuming that the total volume has penetrated during these 5 s, 37% of the nuclei that are formed are larger than 1500 μm. For the intermediate binder dispersion rate holds that 8% of the total binder volume is available after 5 s, so 8% of the nuclei are larger than 1500 μm. No nuclei larger than 1500 μm can be formed for the highest binder dispersion rate, because no binder is present after 5 s. By combining the binder dispersion process with the penetration process in this manner, it is possible to calculate a theoretical nuclei size distribution. The size of the nuclei at a certain penetration time is calculated with Eq. (5), while the percentage undersize of the nuclei at this time point is determined by the dispersion rate,

$$\%\ \text{undersize} = (1 - e^{-kt})100\% \tag{10}$$

in which k is the binder dispersion rate. Note that it is assumed that the total volume of binder will completely penetrate to form nuclei. The fact that for lactose 200 M after 60 s 100% of the binder is still located in the fraction larger than 280 μm implies that this assumption seems realistic (Fig. 3). Moreover, the binder present at a certain process time should be available in sufficiently

large volumes to form nuclei with this (time-corresponding) size. Hence, the liquid volumes are no restriction for the nuclei size. The results of the aforementioned calculations for the different binder dispersion rates are shown in Fig. 7b. The figure illustrates that the lowest binder dispersion rate leads to the formation of the largest granules. This is a logical consequence of the fact that binder liquid is available for penetration for a longer time period. For all the binder dispersion rates holds however that the largest part of the binder liquid is converted into granules larger than the cut-off size of 280 μm. Hence, the model predicts that in case of good wetting abilities of the binder, liquid penetration is involved in the formation of the granules. This conclusion is also experimentally observed for lactose 100 M and 200 M. In both experiments granules were formed by liquid penetration already in the early seconds of the process. The strength of these freshly formed granules determined the subsequent event, granule breakage for lactose 100 M and no granule breakage for lactose 200 M.

It is clear that in case of no wetting of the binder (contact angle exceeding 90°), not any liquid penetration is predicted by the model. This conclusion corresponds with the observed nucleation behaviour for the lactose/magnesium stearate experiments. In these experiments no granules were formed by liquid penetration and the liquid was completely dispersed over the primary particles.

The experimental and modelistic evaluation of the granulation behaviour in the early seconds of the high shear granulation process shows that, two rate-processes, binder dispersion and liquid penetration determine the granule formation. The balance between both processes is influenced by the formulation characteristics. When the binder liquid can wet the powder particles, penetration-involved nucleation is the predominate mechanism of granule formation. Complete binder dispersion occurs when there is no wetting. Once the granules have been formed by liquid penetration the strength of the granules determines whether they survive the shear forces.

5. Conclusion

In this study nucleation experiments with a substandard amount of binder were performed to investigate the mechanisms of granule formation in the early seconds of the high shear granulation process. Based on these results three different nucleation mechanisms could be qualified:

- penetration-involved nucleation and granule breakage (lactose 100 M)
- penetration-involved nucleation and no granule breakage (lactose 200 M)
- dispersion-involved nucleation (lactose/magnesium stearate)

The importance of each mechanism is determined by the formulation and process characteristics. The influence of wetting abilities on the nucleation behaviour could be qualitatively predicted by a model, which is based on the process of liquid penetration and binder dispersion. Future experiments will be focused on a more quantitative prediction of the influence that formulation and process variables (impeller speed, primary particle size, and viscosity) have on the nucleation mechanisms.

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