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Relationship between inhomogeneity phenomena and granule growth mechanisms in a high-shear mixer

K. van den Dries [a,*], H. Vromans [a,b]

[a] *Department of Pharmaceutics, Organon, AKZO-NOBEL, P.O. Box 20, 5340 BH Oss, The Netherlands*
[b] *Faculty of Pharmacy, Department of Pharmaceutics, University of Utrecht, P.O. Box 80082, 3508 TB Utrecht, The Netherlands*

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Abstract

A poorly understood phenomenon observed during high-shear granulation is the poor distribution of a drug in the granulate. To investigate the causes of this inhomogeneity, lactose of three different particle sizes was granulated with 0.1% micronized estradiol (5 μm) in a 10 l high-shear mixer. An aqueous solution of HPC was used as binder. Granulation with the largest lactose particles (141 μm) yielded a homogeneous granulate. However, at a prolonged process time demixing was observed. Contrary to the largest particles, granulation with the smaller lactose particles (50 and 23 μm) already leads to demixing in the first minute, although to a lesser extent. It was concluded that granulation with the largest particles resulted in breakage behavior of the granulate, thereby preventing demixing. However, once granules are strong enough (smaller particle size and prolonged process time) to survive the shear forces demixing is observed. Theoretical calculations of dynamic and static granule strength were used to explain the influence of lactose particle size and process time on breakage behavior. It was argued that once granules survive, preferential growth of the small estradiol particles in favor of the larger lactose particles causes the demixing. The extent of demixing depends on the particle size difference. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: High-shear mixer; Granule strength; Demixing; Particle size; Granulation; Porosity

Nomenclature

$d_{3,2}$	surface mean diameter (μm)
DP	demixing potential (%)
F_{bond}	bonding force (N)
F_v	viscous force of a liquid bridge (N)
h	interparticle gap distance (μm)

* Corresponding author. Tel.: +31-412-661511; fax: +31-412-662524
E-mail address: kaspar.vandendries@organon.com (K. van den Dries).

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S	liquid saturation (–)
St_{def}	Stokes deformation number (–)
v_c	collision velocity (m/s)
v_i	tip velocity (m/s)
v_p	relative velocity of the moving particles (m/s)
Greek symbols	
γ	surface tension (N/m)
ε	porosity (–)
μ	viscosity (Pa s)
ρ_g	granular density (kg/m^3)
σ_c	static granule strength (Pa)
σ_{impact}	impact pressure (Pa)
σ_v	dynamic granule strength (Pa)

1. Introduction

In the pharmaceutical industry, high-shear granulation is a commonly used unit operation in the production process of a solid dosage form (tablet, capsule). During the high-shear granulation process, a binder solution is added to the mechanically agitated powder mix, which results in the size enlargement by the formation of liquid bridges between primary particles. The powder mix is agitated by a mixer arm that rotates at high speed in a bowl. Often a chopper, which functions as a breakage device, is also situated in the bowl.

Although granulation is intended to yield a homogeneous product, there are indications that this is certainly not always the case. The demixing of a low dose drug during (high-shear) granulation is an interesting phenomenon (Selkirk, 1976; Warren and Price, 1977; Oijle et al., 1982; Egermann and Reiss, 1988; Vromans et al., 1999). Often the large size fractions exhibited the highest drug concentration. However, the opposite, where the highest content was found in the smallest size fractions, has also been observed (Oijle et al., 1982). The unequal distribution of the drug may eventually affect the content uniformity of the formulation. However, not only the drug substance is susceptible to demixing, but also pharmaceutical filler materials (e.g. corn starch) show tendency for demixing (Vegt de et al., 2001).

Authorities tend to demand that intermediate products should also meet the content uniformity specifications, forcing industries to pay more attention to the manufacturing process. This results in an increasing interest from the pharmaceutical industry in fundamental research concerning the mechanisms of demixing during granulation. Despite the fact that there is an increasing understanding about the granule growth mechanisms, the mechanisms of demixing are still poorly understood.

Several mechanisms concerning the demixing of the drug substance during granulation have been proposed in the literature. These mechanisms may also play a role during high-shear granulation. At least two properties of the drug substance seem to be of importance: solubility and particle size.

Dissolution of the drug substance is suspected to play a role during massing and drying of the granulate. Oijle et al. (1982) observed a relation between solubility of the drug and the drug concentration in different sized granules. Drug dissolution in the overwetted regions and distribution of the drug containing binder solution results in either an increase or a decrease in drug content in different size fractions of the granulate.

Other authors relate solubility of the drug substance or diluent with intragranular drug migration during drying (Selkirk, 1976; Warren and Price, 1977). They suggest that fluid and the solute is drawn to the surface of the granule as drying proceeds, which results in a solute-enriched crust. Abrasion of the granules during dry screen-

ing results in a high concentration of the drug or diluent in the fines.

Egermann and Reiss (1988), Vromans et al. (1999) were the first who related demixing of the drug substance with granule growth mechanisms. Inhomogeneity of the granulate was attributed to a difference in primary particle size between drug substance and diluent. When drug particles were smaller than the diluent particles, the largest granule fraction exhibited the highest drug content. When, on the other hand, the drug particles were coarser than the diluent, the highest concentration was found in the smallest size fractions. They postulated that granule strength is, amongst other factors, determined by the primary particle size and the strongest granules are formed by the smallest primary particles. The high-shear forces may induce breakage of the large granules, promoting the formation of granules from small particles that can survive the shear forces.

The aim of this study was to investigate the influence of primary particle size on the growth of the granules and the demixing of the drug substance in the granulate and to establish whether there is an interrelationship between granule growth mechanisms and the demixing of a drug substance in the granulate. For that purpose different grades of lactose, varying in primary particle size, were granulated at different impeller and chopper rates with a low-dosed poorly soluble micronized drug. Current knowledge about granule growth mechanism was tested on the experimental data. A simple theoretical model to predict dynamic and static granule strength was used to predict the granule growth mechanism and to explain the observed drug-distribution behavior in the granulate.

2. Theoretical considerations

The influence of the (primary) particle size on the granule growth in a high-shear mixer is complicated. It is known that particle size affects the different stages of granule growth (Iveson and Litster, 1998a; Ennis, 1991; Hapgood, 2000). A key parameter in these different growth stages is wet granule strength. The initial granules that are formed during the nucleation stage are too weak to resist the high-shear forces and continuous breakage and coalescence occur (Vonk et al. 1997). As the process proceeds, densification leads to granules that are strong enough to survive the shear forces and further growth occurs by coalescence and layering of the granules. The rate of densification depends on the deformation of the granules, which is also a function of granule strength.

Rumpf (1962) has derived a general relationship for the tensile strength of a granule, which is a function of porosity, particle size and bonding forces between particles:

$$\sigma = \frac{9}{8}\frac{1-\varepsilon}{\varepsilon}\frac{F_{\text{bond}}}{d_{3,2}^2}, \tag{1}$$

in which ε is the porosity, $d_{3,2}$ the surface mean diameter and F_{bond} the bonding force between particles. The bonding forces can consist of van der Waals, electrostatic or liquid bridge forces. In wet granulation liquid bridges are the most important binding forces. The forces acting between two particles due to a liquid bridge may be both capillary and viscous in nature, i.e. static and dynamic, respectively. For a static liquid bridge, the tensile strength of a wet granule is determined by the capillary pressure difference along the circumference of the granules. The strength of the granule is then given by (Rumpf, 1958)

$$\sigma_c = 6S\frac{1-\varepsilon}{\varepsilon}\frac{\gamma}{d_{3,2}}, \tag{2}$$

in which S is the liquid saturation level and γ the surface tension of the binder solution. However, under dynamic conditions the viscous forces exceed the capillary forces in a liquid bridge. In high-shear granulation continuous collisions of granules with the impeller, chopper, wall and other granules lead to deformation of the granules, resulting in a relative displacement of the associated particles. The viscous force of a liquid bridge is given by Reynolds' lubrication equation:

$$F_v = \frac{3\pi\mu d_{3,2}^2 v_p}{8h}, \tag{3}$$

in which μ is the viscosity, v_p the relative velocity of the moving particles and h the interparticle gap

distance. Incorporation of the viscous force (F_v) into Eq. (1) leads to the following description of the strength of a granule under dynamic conditions:

$$\sigma_v = \frac{9}{8}\frac{1-\varepsilon}{\varepsilon}\frac{3\pi\mu v_p}{8h}. \quad (4)$$

The interparticle gap distance (h) can be estimated by the Kozeny model to determine the pore diameter. The pore space between particles in a granule is represented as a bundle of cylindrical capillaries having the same surface area as the particle assembly:

$$\frac{4}{h} = 6\frac{1-\varepsilon}{\varepsilon}\frac{1}{d_{3,2}}. \quad (5)$$

Substituting h in Eq. (4), the model for the tensile strength of a granule under dynamic conditions becomes

$$\sigma_v = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\mu v_p}{16 d_{3,2}}. \quad (6)$$

An assumption in this model is that the tensile strength is independent of the liquid saturation and only depends on the number of contact points between particles. This is consistent with the viscous force of a single liquid bridge between two moving particles. Ennis et al. (1990) have shown that above a certain liquid bridge volume, the viscous force is independent of the liquid bridge volume. The strength of a dynamic liquid bridge can be attributed to the viscous force at the contact point with the smallest interparticle gap distance and is relatively insensitive to the surrounding fluid. A characteristic tip velocity is used as an estimate for the relative velocity of the moving particles (v). Both the dynamic and the static model show that the tensile strength of a granule increases with a decreasing particle size and porosity. Many authors use the static granule strength to describe the granulation process (Leuenberger et al., 1979; Ritala et al., 1988; Vonk et al., 1997; Vromans et al., 1999). An approach is to compare the static strength of the granules with the impact pressure of the impeller/chopper blades (Vonk et al., 1997; Vromans et al., 1999), where the impact pressure is given by

$$\sigma_{impact} = \tfrac{2}{3}\rho_g v_i^2, \quad (7)$$

in which v_i is the tip velocity and ρ_g the granular density. When the impact pressure exceeds the static strength of the granule breakage occurs.

Another way to reflect the process is to compare the externally applied kinetic energy on the granules with the energy required for deformation of the granule (Iveson and Litster, 1998b; Tardos et al. 1997). The ratio of both is given by the Stokes deformation number (St_{def}):

$$St_{def} = \frac{\rho_g v_c^2}{2\sigma_v}, \quad (8)$$

in which v_c is the representative collision velocity and σ_v the dynamic granule strength, which is calculated with Eq. (6). It is assumed that the collision velocity equals the tip speed of the chopper (Iveson et al., 2001b). The differences between both models is that the second model takes into account the dynamic conditions in a granulator and recognizes that the applied energy can be absorbed by deformation of the granules.

3. Materials and methods

3.1. Materials

Micronized estradiol was supplied by Diosynth (Akzonobel, Oss, The Netherlands). Because estradiol exhibits a poor aqueous solubility (3 μg/ml), only a minimal part of estradiol is dissolved in the binder solution (0.06%). HPC (Klucel EP) was obtained from Aqualon (Wilmington, DE) and lactose 100M, 200M and 450 M was from DMV (Veghel, The Netherlands). Some powder characteristics of the excipients are shown in Table 1.

3.2. Granule preparation

For all the granulation experiments, the same composition of the binder solution was used, and so the viscosity was kept constant. The viscosity, determined by a Brookfield rheometer (model DV III), was 3.2 Pa s. Because of particle size

Table 1
Particle sizes and density characteristics of the excipients

Materials	Weight mean diameter, $d_{4,3}$ (μm)	Surface mean diameter, $d_{3,2}$ (μm)	Tapped density (g/cm^3)	Tapped bed porosity
Lactose 100M	141	23	0.90	0.42
Lactose 200M	50	8	0.85	0.45
Lactose 450M	23	6	0.77	0.50
Estradiol	5	1.5	–	–

Table 2
Formulations used for the granulation experiments

Excipient	Lactose 100M (%)	Lactose 200M (%)	Lactose 450M (%)
Estradiol	0.1	0.1	0.1
HPC	1.7	2.1	3.0
Lactose	98.2	97.8	96.9
Water[a]	8.0	10.0	14.0

[a] Percentage of dry powder.

differences between lactose 100M, 200M and 450 M, the optimum amount of binder solution necessary to obtain an acceptable granulate varied with the granulation of each lactose grade, leading to different percentages of binder in the formulation (Table 2).

The high-shear mixer used for the granulation process was a Gral 10 (Machines Colette, Wommelgem, Belgium) with fixed chopper rate settings (1500 or 3000 rpm) and variable impeller rate settings (0–650 rpm). The typical batch size was 1 kg dry matter. The lactose and estradiol were dry-mixed in the Gral 10 for 5 min (impeller 430 rpm, chopper 3000 rpm). The homogeneity of the dry-mix was checked by taking at least 10 samples from different spots in the bowl. The chemical assay was performed by HPLC. This revealed that a homogeneous mixture was obtained with an RSD $< 3.0\%$. The binder solution was added by pouring the binder solution onto the rotating powder mass. For each time point (1, 4, 7, 10 and 15 min), a different batch was produced to prevent influences of sampling. The granulate was dried on plates at 40 °C at reduced pressure (Elbanton, The Netherlands).

3.3. Granule characterization

The granule size distribution was determined by sieve analysis of the dry granulate with a series of 16 ASTM standard sieves in the range 75–4750 μm. A sample of about 100 g was sieved for 10 min on a vibrating sieve (Retsch, Germany) at an amplitude of 1.5 mm. The sieve fractions above 3150 μm consist of large lumps and were not used for further analysis. Omission of these sieve fractions did not influence the outcome of the experiments. The other size fractions were weighed and subsequently analyzed for estradiol content. Measurements were done in duplicate. The distribution of estradiol in the granulate is expressed as the demixing potential:

$$\mathrm{DP}\ (\%) = \frac{100}{\bar{p}} \sqrt{\sum \frac{w(p-\bar{p})^2}{100}}, \tag{9}$$

where $\bar{p}$ is the average concentration, p and w the actual concentration and the weight of a particular sieve fraction, respectively. The porosity and pore size distribution of the granulate was determined by mercury intrusion porosimetry (Autopore II 9220, Micromeretics, USA).

4. Results and discussion

4.1. Drug distribution

4.1.1. Primary particle size

Fig. 1a shows the (in)homogeneity of the estradiol granulate as a function of both primary particle size of lactose and process time. A high DP is always associated with an increase in the drug concentration in the large granules and a decrease in the drug concentration in the small

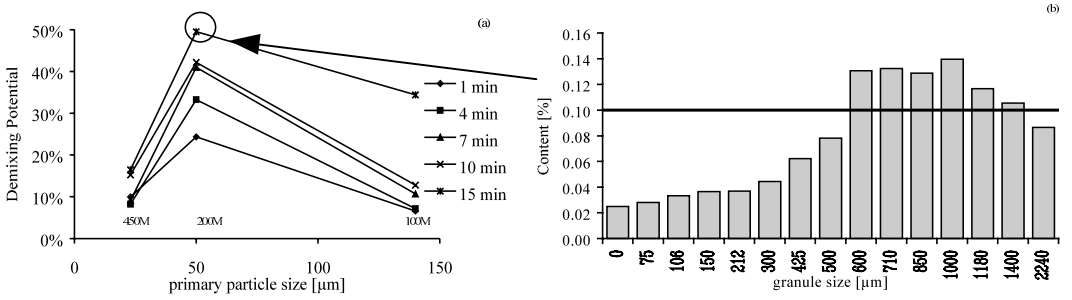

Fig. 1. (a) The influence of the primary particle size of lactose on the drug distribution in a granulate for different process times (process conditions: impeller, 430 rpm; chopper, 3000 rpm). (b) A typical example of a poor distribution of estradiol (lactose 200M, process time 15 min, process conditions: impeller, 430 rpm; chopper, 3000 rpm).

granules (Fig. 1b). On basis of the results of Egermann and Reiss (1988), Vromans et al. (1999), it was expected that the large particle size difference between lactose 100M (~ 141 μm) and estradiol (~ 5 μm) would lead to a poor distribution of estradiol. However, the distribution of estradiol is remarkably good. Only at a granulation time of 15 min there is a sudden increase in inhomogeneity. At this point, the drug accumulates in the largest size fractions.

A decrease in primary particle size of lactose to 50 μm (lactose 200M) has a dramatic effect on the demixing behavior of estradiol in the granulate. Already during the first minute demixing is observed and, as the process proceeds, there is a steady increase in DP. When the primary particle size is further reduced to 23 μm (lactose 450M), an improvement of the homogeneity is observed compared to the lactose 200M results. This latter improvement is consistent with the idea that a small difference in primary particle size between diluent and drug substance should result in a good distribution. It is, however, not clear why the homogeneity of the lactose 100M granulate is in most cases better than that of the lactose 450M granulate.

4.1.2. Process conditions

The influence of the impeller and chopper speed on the demixing potential and granule growth profiles for the different lactose grades is shown in Fig. 2. Clearly, lactose 100M exhibits a deviating behavior with respect to granule growth and especially demixing, when compared to lactose 200M/450M. For lactose 100M, no demixing is observed during the initial time points. However, as the process proceeds, a sudden increase in DP is observed. This increase depends on the impeller and chopper speeds. An increase in impeller or a decrease in chopper speed exhibits a negative tendency on the granulate homogeneity. When a smaller particle size of lactose is used, a completely different demixing behavior is observed. Variations in impeller and chopper speed have almost no effect on the distribution of estradiol in the lactose 200M/450M granulate. There is a large contrast in demixing behavior between lactose 100M and lactose 200M/450M. This contrast, although less pronounced, is also observed for the growth curves. At first instance, a very rapid growth is observed for all the lactoses in the very first minute. Furthermore, it is noticed that further growth does not occur for lactose 100M. Whereas a steady growth phase is observed for the other two lactoses until a plateau phase is reached after approximately 10 min. During the lactose 100M granulation experiments some wall adhesion of the granulate was observed. Keningley et al. (1997) associated this wall adhesion with the formation of loose aggregates. This so-called crumb behavior occurs when the granules are too weak to form permanent granules, but instead are constantly broken down and reforming. The wall adhesion was almost not observed with the lactose 200M and 450M experiments, suggesting that stronger permanent granules are formed.

Fig. 2 also shows the influence of variation in impeller and chopper rate on the granule growth

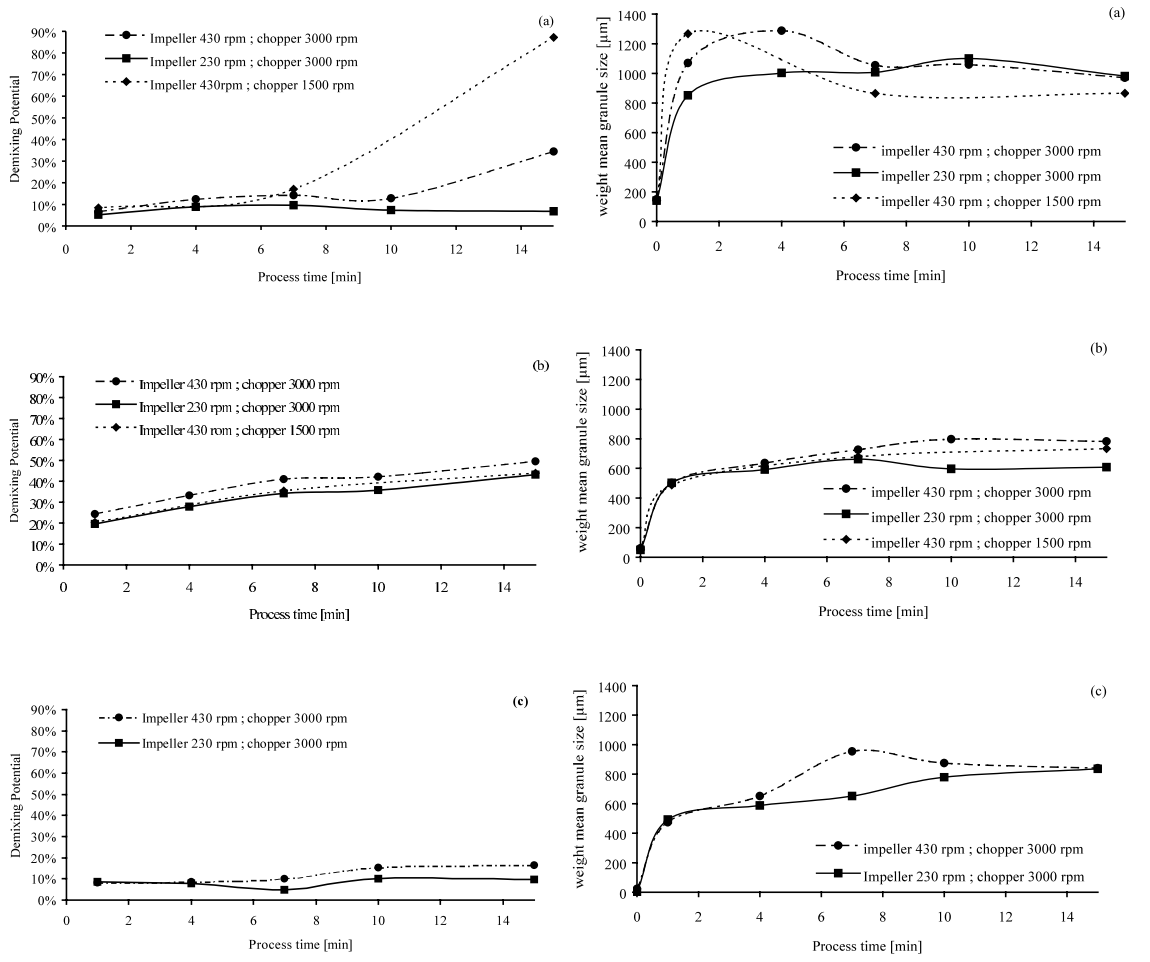

Fig. 2. The distribution of estradiol, expressed as demixing potential (DP) and the granule growth curves for lactose 100M (a), 200M (b) and 450M (c) granulate as a function of both the impeller and chopper speed.

of lactose 100M, 200M and 450M. Only the first time points of the growth curves for lactose 100M show a pronounced influence of the impeller and chopper rate on the mean granule size. A decrease in the chopper rate from 3000 to 1500 rpm leads to an increased mean granule size after 1 min for the lactose 100M granulate. According to a study of Hoornaert et al. (1988), the initial increase in mean granule size with a lower chopper rate is due to the formation of lumps. Initial lumps, which originate from the direct method of binder addition, are broken down by the chopper. The growth of lactose 200M/450M is hardly influenced by a change in impeller or chopper rate. Even on a granule size distribution scale there are almost no differences (data not shown), while the variations in impeller and chopper speed are large. The difference in growth and demixing behavior between lactose 100M and 200M/450M suggest a difference in growth mechanism between lactose 100M and 200M/450M.

4.2. Porosity

The porosity of the granulate was measured with mercury porosimetry. To increase the distinction between intergranular and intragranular porosity, the large size fraction of the granulate

(between 1000 and 1180 μm) was used for the porosity measurements. For lactose 200M and 450M, two distinctive pore classes can be distinguished in the intrusion plot. The large pores (> 10 μm) can obviously be attributed to the intergranular voids, while the intragranular porosity was determined from the intrusion volume for the pore sizes between 8 and 0.1 μm. These results are consistent with the pore size measurements from other studies (Knight et al., 1988; Scott et al., 2000). For lactose 100M, it was not possible to distinct between the intra- and intergranular porosity, indicating that only large pores exist (> 30 μm). To observe a trend in porosity of the lactose 100M granulate, it was assumed that the intergranular porosity does not change during the process. This seems reasonable since the same sieve fraction was used for all the measurements. Therefore, changes in total porosity can be attributed to a change in intragranular porosity. This porosity of the lactose 100M granulate, which must not be intermingled with the intragranular porosity, was determined from the intrusion volume of pores of size within 30 and 90 μm.

Although no intragranular porosity can be determined at $t = 0$, it is assumed that the initial porosity will approximate the tapped powder bed porosity, which corresponds roughly with a porosity of 0.5. The porosity of the different lactose granulates is already decreased to approximately 0.15, after only 1 min mixing (Fig. 3). The fast densification corresponds with the rapid growth phase of the granulate (Fig. 2). During the following phase, which is the steady growth phase, there is only a small decrease in porosity. The differences in porosity as a function of the impeller and chopper speed are relatively small, especially when compared with the rapid decrease in porosity during the first minute of the granulation process. However, the general trend is that a higher impeller and chopper speed leads to a lower porosity value.

4.3. Theoretical growth behavior and homogeneity

In an attempt to explain the previously discussed results, the granule growth and breakage behavior as a function of the primary particle size

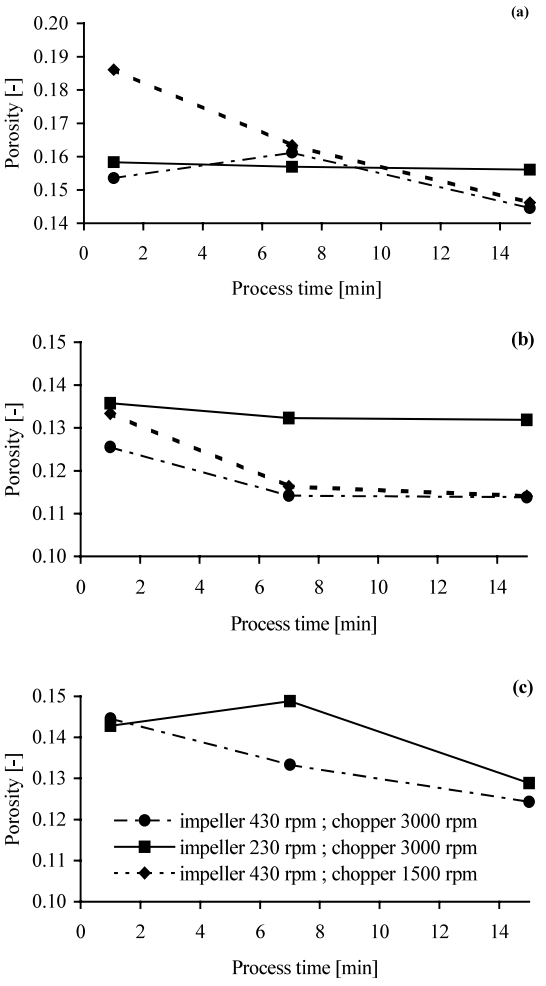

Fig. 3. The porosity for lactose 100M (a), 200M (b) and 450M (c) as a function of the process time at different impeller and chopper rates. For clarity reasons, the porosities at $t = 0$ min are not shown.

was theoretically investigated. Earlier work on demixing (Vromans et al., 1999) already related inhomogeneity phenomena in high-shear granulation with granule strength and growth. Besides, the results show a large influence of particle size of lactose on demixing and, to a lesser extent, on granule growth. Rumpf (1962) recognized that a decrease in primary particle size results in an increase in static wet granule strength. Fig. 4 shows the results of the calculations of the static granule strength (Eq. (2)) as a function of porosity. The impact pressure of the chopper and the

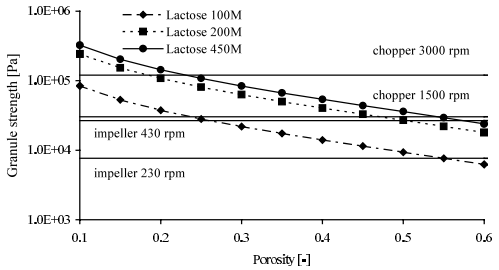

Fig. 4. The influence of the porosity on the static strength of the granules for lactose 100M, 200M and 450M. The impact pressure of the impeller and chopper was also calculated (horizontal lines). Impeller speed 430/230 ~ 5/3 m/s; chopper speed 3000/1500 rpm ~ 11/5 m/s. Values used for calculations: saturation = 90%; $d_{3,2} = 23$, 8, 6 μm; $\rho = 1500$ kg/m^3.

impeller are given by Eq. (7). When the strength of the granules exceeds the impact pressure, no granule breakage is expected. The calculations of the impact pressure indicate that the chopper has the highest impact pressure, which strengthens the observation that the chopper functions as a breakage device. According to these theoretical data, a decrease in primary particle size and porosity can result in a shift from breakage to no breakage behavior of the granulate. The experimentally observed crumb behavior of lactose 100M granulate, indicating continuous breakage of the granulate, is indeed to be expected from Fig. 4 depending on the characteristic impeller and chopper speed. The smaller particles of lactose 200M and 450M yield already at higher porosities sufficient strength and consequently result in no breakage behavior. Prolonged mixing results in further densification and hence in stronger granules.

It is a restriction of the static model that it does not take into account the dynamic conditions, which actually exist in the high-shear granulation process. Although Iveson and Litster (1998c) have shown that also under dynamic conditions, a decrease in particle size results in an increase in wet granule strength, there are still almost no theoretical predictions of wet granule strength and granule breakage under dynamic conditions. In this paper, an attempt is made. For that purpose, a model that describes the different granule growth behaviors under dynamic conditions, the so-called growth regime map of Iveson and Litster (1998b), is used. Originally, the growth regime map was intended to predict the growth behavior of the granules. In addition, this map can also be used to predict breakage or no breakage behavior of the granulate under dynamic conditions. According to the growth regime map, an increase in dynamic granule strength, resulting in a decreasing St_{def} (Eq. (8)), can lead to a shift from crumb behavior (breakage) to steady/induction growth (no breakage). The theoretical calculation of the wet granule strength as a function of porosity and particle size (Eq. (6)) was used to calculate the St_{def}. The boundaries between breakage behavior and no breakage behavior ($St_{def} \sim 0.04$) was experimentally established by Iveson et al. (2001b). Fig. 5 shows that the order of magnitude calculation predicts a similar impact of primary particle size on growth behavior as earlier obtained with the static approach. Crumb behavior for lactose 100M is expected at a high porosity and, as the process proceeds, densification of granulate can lead to a shift no breakage behavior. A decrease in chopper speed shows a shift for the lactose 100M curve, and so a transition to no breakage behavior can be expected at a higher porosity. Whereas smaller lactose particles yield stronger granules. Both lactose 200M and 450M immediately start with no breakage. It is clear that the static and the dynamic model yield qualitatively the same conclusions; a variation in primary particle size of lactose can lead to a different growth behavior of

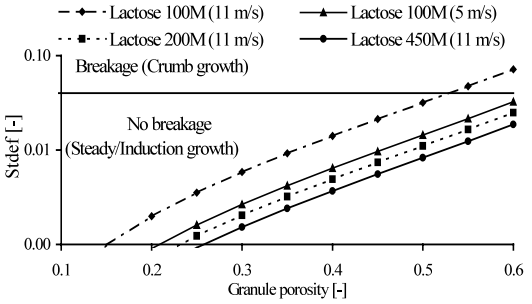

Fig. 5. The influence of the porosity on the St_{def} calculated for a chopper rate of 3000 rpm (11 m/s) for lactose 100M, 200M and 450M and calculated for a chopper rate of 1500 rpm (5 m/s) for lactose 100M. Values used for calculations: $\mu = 3$ Pa s; $d_{3,2} = 23$, 8, 6 μm; $\rho = 1500$ kg/m^3; v = chopper speed (chopper speed is used for calculations, because it exhibits the highest tip velocity).

the granulate, depending on porosity and impact forces.

Now the question arises what the relationship is between granule growth behavior and demixing. The crumb behavior of the lactose 100M granulate, indicating continuous breakage and coalescence, prevents an uneven drug distribution. As the process proceeds, the granule strength increases through densification of the granules. At a certain point, the lactose 100M granules are strong enough to withstand the forces in the high-shear mixer and demixing is observed. For lactose 200M and 450M, this is already the case during the first minute of granulation, because the initial granules are stronger.

One important parameter that influences the drug distribution in a granulate is wet granule strength. Another parameter that is important for the demixing of estradiol in the granulate is the primary particle size difference between estradiol and lactose. The reason why a large difference in primary particle size of estradiol and lactose stimulates demixing is unclear. In a previous study (Vromans et al., 1999), it was argued that the smaller particles in a powder mixture are the first to form granules that are strong enough to resist the forces in the process. Therefore, the largest granule particles will consist of the smallest primary particles (estradiol). It is not likely that the small amounts of estradiol and a relatively small difference in estradiol concentration between granules, varying from 0.01 to 0.05%, will influence granule strength to an extent that it can influence the breakage behavior of granules. According to the hypothesis of Vromans reducing the breakage of the granules should prevent or minimize the demixing, while the opposite was observed for lactose 100M. It is also difficult to explain why there is a sudden increase in the DP for lactose 100M at prolonged time points, while the initial drug distribution was good. There may, however, be another mechanism that can play a role in addition to the wet granule strength.

Nowadays it is assumed that granule growth can occur by coalescence and layering of the granules (Iveson et al. 2001a). For the layering growth, the most important parameter that will determine the extent of growth is the surface wetness of the granules, which is correlated with the densification of the granules. Surface asperities on a granule may disable the layering of large (primary) particles, while small particles can penetrate the pores and adhere to the granule. A granule can be surface dry for large (lactose) particles, while the granule is surface wet for the small (estradiol) particles leading to a preferential growth of the small (estradiol) particles, which results in the observed demixing. The extent of the preferential growth and the demixing will depend on the particle size difference. A prerequisite for preferential growth is that granules remain intact during the process, and so granule breakage will prevent demixing.

For lactose 200M/450M, no breakage behavior is expected, and so preferential growth of the estradiol causes the demixing. The observed demixing of the estradiol in the lactose 200M granulate is larger than for the lactose 450M granulate, because the particle size difference between estradiol and lactose 200M is also larger than for lactose 450M.

Continuous breakage, observed during the initial time points for the lactose 100M granulate, will prevent the preferential growth. Strengthening of the granules during the process due to densification will decrease the amount of breakage. For the lactose 100M granulate, the sudden increase in DP at a process time of 15 min is associated with a decrease in the porosity, indicating an increase in granule strength. Now the preferential growth and the large particle size difference can promote the demixing.

5. Conclusion

The experiments show a strong correlation between granule growth and demixing mechanisms, in which the primary particle size plays an essential role. First, differences in primary particle size influence the wet granule strength. Breakage or crumb behavior of the granules, consisting of the largest lactose particles, retards the densification and prevents the demixing. A decrease in lactose particle size leads to stronger granules, which can resist the high-shear forces and demix-

ing is observed. A theoretical model to determine the dynamic granule strength was proposed, in addition to the existing static model. An order of magnitude analysis with this model showed a reasonable agreement between experimental and theoretical data. Once granules survive, a second phase in granule growth (preferential growth) is responsible for the further observed demixing phenomena. A difference in primary particle size between lactose and estradiol results in demixing of estradiol. Preferential growth of the micronized estradiol particles in favor of the lactose particles explains the demixing behavior of estradiol in the varying lactose granulates.

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