Universiteit Utrecht

The paradox of high shear granulation; the formation of non-homogeneous granules

"*De paradox van het granuleren in een snelkneder; de vorming van niet-homgene granules*"
met een samenvatting in het Nederlands

Proefschrift

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Je kan niet altijd
de sterkste zijn

soms doet het
gewoon
te pijn

Ton van den Dries

Voor Astrid

& mijn ouders.

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Preface

Wet granulation is a process of particle size enlargement, used in the agricultural, mineral, food, detergent and pharmaceutical industry, to improve one or more of the powder characteristics. Mixing powder with liquid induces the particle size enlargement. The liquid is responsible for the assembly of several primary powder particles, hereby forming agglomerates. The mixing action can be performed by tumbling (drum granulation), intensive mechanical agitation (high shear mixer) or through fluidisation (fluid bed granulation). In the pharmaceutical industry granulation is often used as an intermediate process step in the production pathway of a solid formulation. Logically, the incorporation of an additional step in this pathway should imply that this step offers additional benefits. For granulation the following advantages are claimed.

- Improved compaction properties of the granules with respect to the pure powders.
- Prevention of dust formation, which is important in the pharmaceutical industry since (highly) active materials are used.
- Minimising the potential to segregate, which prevents content uniformity problems.
- Increasing the flowability leading to improvement of the handling properties.

A major disadvantage is that granulation can introduce inhomogeneity. The inhomogeneity is expressed as a granule size-dependent variation in composition. The formation of non-homogeneous granules has been observed in high-shear, fluid bed and drum granulation.

In many industries the inhomogeneity phenomena do not pose a problem, because granules are processed in such large quantities that the bulk unit is homogeneous or homogeneity is not a critical specification. In the pharmaceutical industry granules are used in relatively small quantities. When only 50 mg of granules are used for a solid formulation (e.g. tablet, capsule) content uniformity of these formulations is a major challenge.

In spite of the importance, still little is known about the cause of the inhomogeneity phenomena. One of the reasons for the relative lack of attention is that regardless of granule inhomogeneity the

end product often still meets the content uniformity specifications. In this case, the granule homogeneity does not seem to be an important issue, since granulation is only an intermediate process step. However, the tendency is that federal authorities are demanding that also the intermediate products should require a certain quality.

A clear example of the intensified regulations is the lawsuit of the United States of America vs. Barr laboratories (civil action No. 92-1744, February 1993). The actual lawsuit against Barr laboratories was filed because of invalidated manufacturing and cleaning processes, the lack of failure investigation, incomplete annual reviews and failure to explain retesting. The FDA used the issue of content uniformity as major support for their arguments.

In the court's rulings Judge Wolin's interpretation of blend testing was; *"Blend testing is necessary to increase the likelihood of detecting inferior batches. Blend content uniformity testing cannot be waived in favour of total reliance on finished product testing, because finished product testing is limited."* Although the court's ruling were restricted to blend analysis, it emphasises the importance of testing the quality of intermediates and that it is insufficient to test the quality of the end-product only. The current code of federal regulations contains the following GMP guideline for sampling and testing of in-process materials and drug products (CFR-21 §211.110);

"§ 211.110 Sampling and testing of in-process materials and drug products.

(a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:"……(3) Adequacy of mixing to assure uniformity and homogeneity;"

It is obvious that a poor distribution of the drug substance in the granules cannot assure uniformity and homogeneity. The FDA has recently launced a new initiative towards quality regulation, called process analytical technology. Process analytical technologies are systems for analysis and control of manufacturing processes based on timely measurements of critical quality parameters and performance attributes process materials. This implies that also the future regulations will be focused on quality testing throughout the process.

This discussion indicates that the production of homogeneous granules is essential to assure the quality of the drug product, which signifies the importance to identify and investigate the mechanisms that are responsible for the inhomogeneity.

Another reason to acquire more fundamental insights into granulation is given by the drug development process. In the early phase of development drug substance is scarce. Hence, the use of numerous trial-and-error experiments to fully develop a high-quality product should be avoided. Understanding of the granulation mechanisms can help to facilitate the optimisation and up scaling processes.

The aim of this research project was to elucidate the mechanisms involved in the formation of non-homogeneous granules. Although the occurrence of the inhomogeneity phenomena is observed in different equipment, the mechanisms underlying these phenomena will differ between equipment. This thesis is focused only on the high shear mixer.

2

Granulation in a high shear mixer

2.1 Inhomogeneity phenomena

In granulation often a multi-component powder mixture is used as starting material. Wet granulation of this mixture can result in a non-homogeneous distribution of the different components in the granules. Most studies on granule inhomogeneity are focused on the demixing of a drug substance. This seems a logical consequence of the fact that homogeneity is a very important issue in the pharmaceutical industry. Of course the inhomogeneity is not only restricted to active compounds. Hence, also filler materials show tendency for demixing [Vegt et al., 2001, Oostra et al., 2002].

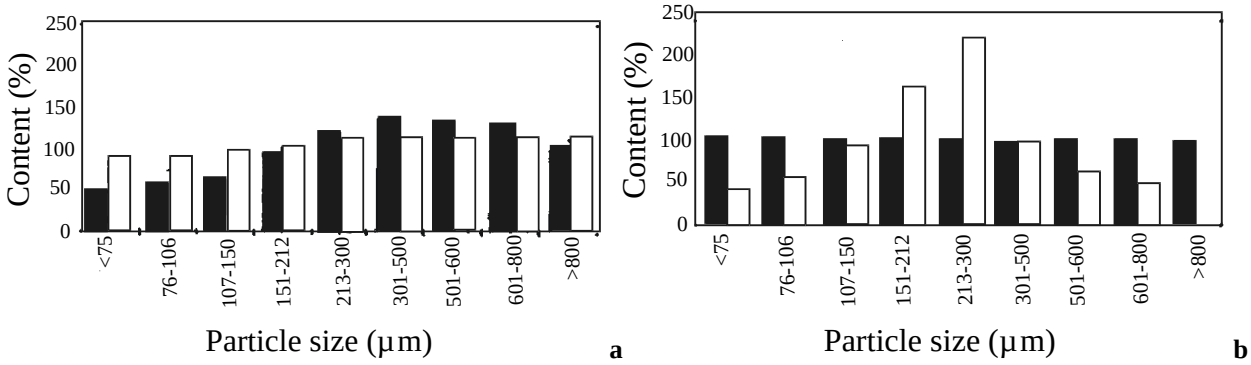


Figure 2-1 *typical examples of (poor) drug distributions in the granules. Each curve respresents a different granulate.* ***(a)*** *Open bars: content of steroid in granules composed of micronized steroid and lactose 200M processed in a 75-L high shear mixer at 75 rpm. Closed bars; same composition process in a 75-L mixer at 235 rpm.* ***(b)*** *Open bars; content of steroid in granules composed of unmicronized steroid and lactose 200M processed in a 10-L mixer at 430 rpm. Closed bars; content of steroid in granules composed of micronized steroid and micronized lactose processed at same conditions.*

Different profiles of the drug distribution in the granules have been observed in literature. Some are illustrated in Figure 2-1. Sometimes the drug substance is depleted in the smaller granules and super-potent in the larger granules (Figure 2-1a). However, also different distribution profiles have been observed. The occurrence of the inhomogeneity phenomena has been observed in fluid bed, drum and high shear granulation. This may be also one of the reasons that over the years many different explanations for the granule inhomogeneity have been proposed. Most of these are related to solubility or particle size differences. Table 2-1 lists an overview of the different equipment and formulations that have been used to study the inhomogeneity phenomena.

Ojile et al. [1982] argued that the depletion of the drug substance in the smallest granules was related to the relative solubility of the drug and the filler. The smallest granules consisted of ungranulated material. A high solubility of the drug resulted in a lower presence of the drug in the ungranulated material. Miyamato et al. [1998] reported an opposite effect of the solubility. A factorial design study showed that a high solubility of the drug improved the distribution. Whitaker and Spring [1977] granulated a drug with a high solubility (sulphanilamide sodium) or a low solubility (sulphacetamide) at three different concentrations (0.02%, 1% and 2%). The results showed no influence of the drug solubility on the distribution. For both drugs it was found that the fines were drug enriched for the lowest concentration (0.02%) and were drug depleted for the 1% and 2% drug concentrations. An explanation for the effect of the concentration was not given. A study of Wan et al. [1992] showed also a depletion of the drug substance in the fines. However, dissolving the drug substance beforehand in the 5% PVP binder leads to an improvement of the granule homogeneity.

Also other mechanisms can contribute to the inhomogeneity, including the migration of the drug substance. Selkirk [1976] reported that solute migration during drying could also contribute to the variation in drug distribution in the granules. Migration of the solute to the outer surface of the granules and abrasion of the solute-enriched crust results in a higher presence of the solute in the smallest granules. On the one hand, when the solute is a drug substance the smallest granules were super-potent. On the other hand, the smallest granules were depleted with the drug substance when the solute is a filler. Warren and Price [1977] showed that migration of a drug substance depends on the viscosity of the binder. Migration was eliminated when the viscosity of the binder exceeded the 0.09 Pa.s. This indicates that the viscosity of the binder may counteract the influence of the solubility on drug distribution.

Besides solubility also the particle size or particle size difference between drug substance and filler material is important. Egermann and Reiss [1988] showed that the smallest particles accumulated in the larger granules. A smaller particle size of the drug resulted in fines (<100 µm) that were sub-potent and granules (>100 µm) that were super-potent. The opposite was observed if the drug particles are coarser than the filler particles. They argued that granules consisting of fine particles are stronger than granules made from coarse particles, thus the finer particles are favoured to become granulated. These results were confirmed by Vromans et al. [1999] and Hapgood et al. [2002], both showing that the fine particles accumulate in the larger granules. Moreover, Vromans et al. suggested a direct relationship between granule breakage and inhomogeneity. If there is a large extent of breakage only the strongest granules will survive the shear forces. The strongest granules consist of the finest (drug) particles causing the accumulation of these finest particles in the larger granules.

Several researchers have shown that homogeneous granules are obtained when powders with equal particle sizes are granulated. This strengthens the notion that the primary particle size is an important parameter [Opakunle and Spring, 1977, Egermann and Reiss, 1988, Vromans et al., 1999]. The influence of the particle size becomes even more obvious when a powder mixture with only one component is granulated. Even in this case the larger granules consisted of the smallest primary particles of the powder particle size distribution [Kapur et al., 1993, Scott et al., 2000].

An extensive literature overview on the inhomogeneity phenomena clearly indicates that the formation of inhomogeneous granules is a complex process. In some cases it is suggested that the inhomogeneity phenomena are related to the granule growth mechanisms. The growth mechanisms will be influenced by process, formulation and equipment variables. Consequently, these conditions will also influence the drug distribution. The next section gives an overview on the current understanding of these granule growth mechanisms in the high shear mixer.

Table 2-1 Overview of the studies focused on the inhomogeneity phenomena.

Authors	Equipment	Drug substance				Filler material		Binder	
		Type	Conc.	Solubility	Particle size [µm]	Type	Particle size [µm]	Type	Viscosity [Pa.s]
Wan, 1992	Fluid bed	Chlorpheniramine maleate	1%	>200 mg/ml	65	Lactose	50	5% PVP	NA
Lachmann, 1964	Rotary processor	NA	5%	Poor	NA	NA	NA	NA	NA
Warren, 1977	Planetary mixer	Propoxyphene HCl	6.4%		NA	Lactose, cornstarch	NA	PVP	0.001-1.0
						Calcium phosphate, cornstarch	NA		
Selkirk, 1976	Planetary mixer	Borax	2%	100 mg/ml	15.3	Lactose	5	Water	0.001
Opakunle, 1976	Planetary mixer	Borax	10-90%	100 mg/ml	14.8	Lactose	29.4	5% PVP	NA
		Citric acid		600 mg/ml	22.7				
		Sulphanilamide			10.4				
Miyamoto, 1998	High shear	Ascorbic acid	28%	High	NA	Lactose, cornstarch, cellulose	NA	0.07-5.7% HPC	NA
		Ethenzamide		Low	NA				
Oijle, 1982	Planetary mixer	Borax	2%	100 mg/ml	10	Lactose	13.5	Water	0.001
		Sodium Salicylate		1000 mg/ml	8.7				
		Sulphadimidine		0.5 mg/ml	8.6				
Whitaker, 1977	Oscillating granulator	Sulphanilamide Sodium	0.02, 1, 2%	High	NA	Lactose	NA	5% PVP	NA
		Sulphacetamide		Low	NA		NA		
Thiel, 1982	Fluid bed	Salicylic acid	0.1%	NA	3.5	Lactose	0-150	5% PVP	NA
						Lactose	75-350 µm		
de Vegt, 2001	High-shear mixer	None				Lactose, cornstarch	50, 15	7-27% HPC	0.3-10

Table 2-1 Continued

Authors	Equipment	Drug substance				Filler material		Binder	
		Type	Conc.	Solubility	Particle size [µm]	Type	Particle size [µm]	Type	Viscosity [Pa.s]
Oostra, 2002	High shear mixer	None				Lactose cornstarch	50, 15	7-27% HPC	0.3-10
Egermann, 1988	Planetary mixer	Salicylic acid	0.5%	NA	13.6 , 6.7	Lactose	5.0, 13.1	Water	0.001
		Sulfamethoxydiazine			5.0				
		Sulfamethoxazole			5.0				
Hapgood, 2002	High shear mixer	Hydrophobic crystals	1%	~0 mg/ml	<10, 15, 225	Lactose, cellulose	80, 40, 50	12-16% HPC	NA
Vromans, 1999	High shear mixer	Steroid	0.01%	Poor	15, 40	Lactose, Cornstarch	50, 8, 15	±17% HPC	±3
Scott, 2000	High shear mixer	None				Calcium carbonate	38	PEG	NA
Kapur, 1993	Drum	None				Iron ore	NA	Water	0.001

NA= data not available, PVP= polyvinylpyrrolidone, HPC= hydroxypropyl cellulose, PEG= polyethylene glycol

2.2 Current knowledge on granule growth mechanisms in the high shear mixer

Two different research strategies have been applied to elucidate the mechanisms of granule growth. The in-situ strategy is focused on the influence of process and formulation variables on one or more of the granule properties (after high shear granulation). The influence of these parameters can provide information about the growth mechanisms. The other method examines the influence of process and formulation variables on the properties of granules outside the granulator and attempts to translate this information to the situation in the high shear mixer (ex-situ method).

Both approaches have provided a certain level of understanding about the granule growth mechanisms. In the early years of granulation research the process was described by many different mechanisms, like nucleation, coating, layering, crushing, coalescence and abrasion. Currently, these mechanisms have been replaced by three main mechanisms namely, *I Wetting and nucleation, II Consolidation and coalescence* and *III Attrition and breakage*. In theory the granule growth in the high shear mixer is a combination of these three processes. In practice it is still difficult to identify these mechanisms in the high shear mixer.

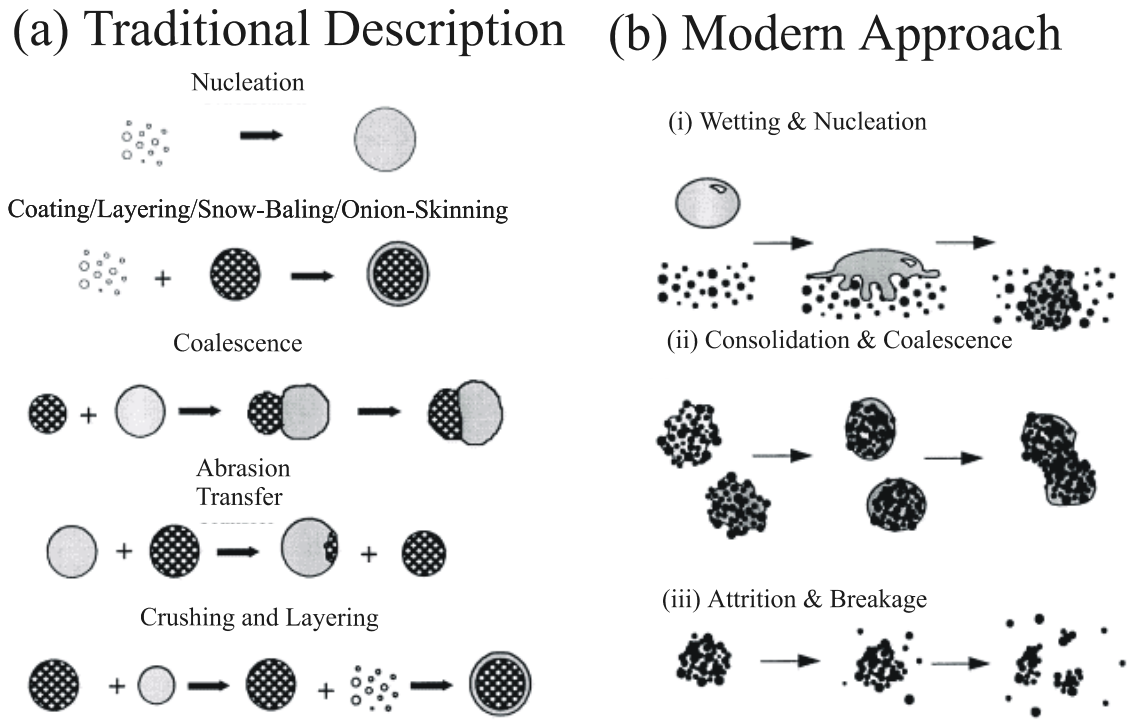


Figure 2-2 *Schematic of granulation processes* ***(a)*** *traditional view [Sastry and Fuerstenau, 1973],* ***(b)*** *modern approach [Ennis and Litster, 1997].*

2.3 Ex-situ approach

2.3.1 Nucleation

Nucleation is the initial stage of granule formation. The initial mixing of the liquid with the solid is an important parameter in nucleation. Litster et al. [2001] showed with experiments performed outside the granulator that spraying a binder solution on a moving powder bed can result in nuclei, which size is determined by the size of the sprayed droplets. The conclusion from this study was that nucleation could be droplet controlled. However, similar experiments performed in the high shear mixer showed that the conditions for droplet-controlled nucleation could not be met [Litster et al., 2002, Hapgood, 2000]. In addition, the binder is often added by pouring instead of by spraying. It was argued that in these cases nucleation is controlled by the mechanical dispersion of the binder [Litster et al., 2002, Hapgood, 2000].

In-situ experiments performed by Carstensen et al. [1976] and Knight et al. [1998] showed that the binder is not dispersed instantaneously in the high shear mixer. This means that instead of a homogeneous distribution, locally overwetted and dry regions are obtained. They argued that this causes the bimodal granule size distribution that was observed at the initial time points. Based on the binder distribution data Schæfer and Mathiesen [1996b] proposed two different mechanisms for nucleation (see Figure 2-3).

- Distribution mechanism; the binder droplets are too small to assemble several primary particles. Instead, the primary particles are coated with binder liquid. These wetted particles coalesce to form the initial granules, leading to a homogeneous distribution of the binder. A low viscosity and high impeller speed promotes this mechanism.
- Immersion mechanism; primary particles are engulfed by binder droplets, which possess a larger size than the primary particles. This results in a poor distribution of the binder, associated with accumulation of the binder in the larger granules. A high viscosity of the binder and a low impeller speed promote this mechanism.

A variation of the immersion mechanism was put forward by Vonk et al. [1999]. Experiments with coloured nuclei showed that the initial nuclei were fragmented. These fragments coalesced again to form secondary nuclei. The extent of fragmentation was strongly influenced by the impeller speed. At a low rotation speed, the fragmentation was minimal, whereas a high impeller speed led to the complete fragmentation of the nuclei. This nucleation mechanism was described as the destructive nucleation growth mechanism.

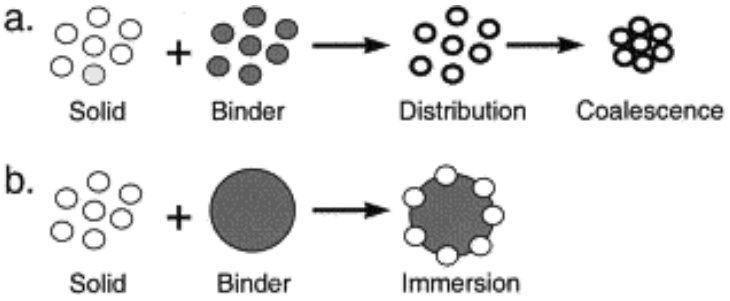


Figure 2-3 *Nuclei formation mechanisms **(A)** distribution mechanisms, **(B)** immersion mechanisms [Schæfer and Mathiesen, 1996b]*

2.3.2 Attrition and breakage of wet granules

The destructive nucleation growth mechanism signifies an important aspect in granulation, namely wet granule strength. Almost all the granule growth mechanisms that have been proposed are more or less related to the granule strength. The general opinion is that forces originating from the liquid bridges between primary particles determine the strength of a wet granule [Schubert, 1981]. Other forces however, like frictional forces may also contribute to the granule strength. Capillary and viscous forces determine the total force of a liquid bridge. The strength of a capillary bridge is determined by two components [Hotta et al., 1974, Lian et al., 1993]. There is a capillary suction pressure caused by the curvature of the liquid interface and a force due to the interfacial surface tension acting around the perimeter of the bridge cross-section. With ex-situ experiments (tensile test or uniaxial compression tests) the influence of capillary forces on the granule strength was evaluated [Rumpf, 1958, Newitt and Conway-Jones, 1958, Schubert, 1975, Schubert et al., 1975, Rumpf, 1962, Kristensen et al., 1985a,b]. Rumpf et al. [1958, 1962] has developed the following model to calculate the strength (σ) of moist granules.

$$\sigma = 6S\frac{1-\varepsilon}{\varepsilon}\frac{\gamma\cos\theta}{d} \qquad \textbf{Equation 2-1}$$

in which S is the saturation, ε the granule porosity, γ the surface tension of the liquid, θ the contact angle and d the primary particle diameter. The model clearly indicates which parameters are important for the granule strength. The strength of the granule increases with a decrease in particle size and porosity and an increase in saturation and wetting abilities. Although the model of Rumpf is widely used to describe the granulation process in the high shear mixer [Leuenberger et al., 1979; Ritala et al., 1988; Vonk et al., 1997; Vromans et al., 1999], there is one major deficiency. The model describes the strength of a granule under relatively low strain rates. A low strain rate means that the rate of granule deformation is low after granule impact. This situation can be valid for low intensity mixers, like drum granulators. Mazonne et al. [1987] and Ennis et al. [1990] however

showed that at relatively high velocities of the particles a viscous force determines the strength of a liquid bridge. In their studies the strength of a liquid bridge between two moving particles was measured. The results indicated that at certain velocities the viscous force exceeds the capillary force of a liquid bridge by several orders of magnitude. In this case the viscous force determines the strength of a liquid bridge according to,

$$F_v = \frac{3\pi\mu r^2}{2h}\frac{dh}{dt} \qquad \textbf{Equation 2-2}$$

in which μ is the viscosity, r the radius of the primary particles, h the separation distance between the particles and dh/dt the velocity of the moving particles. Uniaxial compression tests of granules under high strain rates confirmed that the influence of the viscosity is more important than the capillary forces [Iveson et al, 2002]. In the high shear mixer, where the tip velocity of the mixer arms is typically between the 1-10 m/s, impact velocities of the granules may be high. Therefore, it is likely that also the viscous force will contribute to the strength of the granules in the high shear mixer.

2.3.3 Consolidation and Coalescence

Although the influence of the binder viscosity on granule strength looks straightforward, the influence of the viscosity on granule growth is rather complex. Based on the force of a viscous liquid bridge Ennis [1991] proposed a model to describe the influence of viscosity on granule growth. According to this model, growth occurs by coalescence of surface wet granules. When two granules collide, a viscous liquid layer surrounding the granules dissipates the impact energy. If the impact energy is high and the viscous liquid layer cannot dissipate all the energy, rebound of the granules occurs. In contrast, if all the energy is absorbed the granules will stick together. The Stokes number describes the ratio of the impact energy and the energy dissipated by the viscous liquid bridge according to

$$St_v = \frac{2m\upsilon_0}{3\pi\mu a^2} \qquad \textbf{Equation 2-3}$$

in which μ is the viscosity, m is the mass and a the radius of the granules and υ_0 is the collision velocity of the granules. At a certain point the impact energy exactly equals the maximum energy that can be dissipated by the liquid bridge. This stokes number is called the critical Stokes (St_v^*) number and is given by

$$St_v^* = \left(1+\frac{1}{e}\right)\ln\frac{h}{h_a}$$ **Equation 2-4**

in which h is the thickness of the surrounding liquid layer, h_a is a measure for the surface asperities and e is the coefficient of restitution. When the Stokes number exceeds the critical Stokes number ($St_v >> St_v^*$) rebound of the granules will occur, while if the it is lower than the critical Stokes number ($St_v << St_v^*$) granules will coalesce.

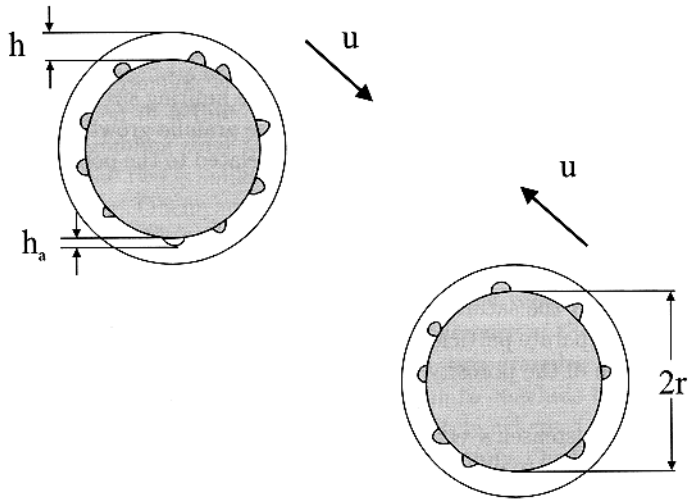


Figure 2-4 *Schematic representation of the coalescence model [Ennis, 1991]. The viscous liquid layer (h) dissipates the kinetic energy of the approaching granules. (u is the velocity of the moving granules, r the radius of the granule and h_a is a measure for the surface asperities).*

The usefullness of Ennis' collision model in the high shear mixer is limited. First of all, it is difficult to obtain an estimate for the collision velocity and the liquid-layer thickness. Secondly, the model assumes that the granules are non-deformable during a collision. However, impact experiments with granules showed that granules are certainly deformable. The deformation can also be responsible for energy dissipation during granule collisions [Iveson and Litster, 1998a,b]. A higher viscosity counteracts deformation. In contrast, according to the model of Ennis [1991] a higher viscosity promotes growth. This illustrates the twofold influence of the viscosity on granulation and the complexity of predicting growth behaviour with ex-situ experiments.

The result of granule deformation is that granules densify after impact, indicating that the porosity of the granules decreases [Iveson and Litster, 1996, 1998a]. This process is also called consolidation. As the porosity of the granules decreases, the liquid saturation increases and liquid can be squeezed to the outer surface of the granule, hereby stimulating further granule growth. Based on this assumption and the extent of granule deformation Iveson and Litster developed the growth regime map for granulation [Iveson and Litster, 1998b].

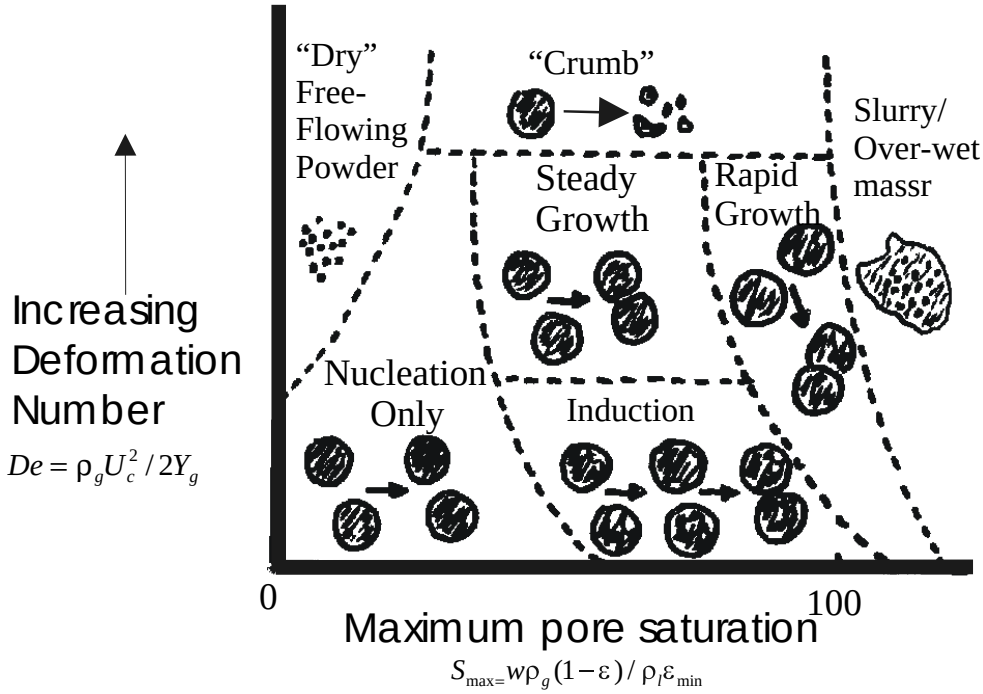


Figure 2-5 *Granule growth regime map [Iveson and Litster, 1998b]*

Figure 2-5 illustrates that the growth behaviour of granules is a function of the deformation number and the pore saturation. The Stokes deformation number is defined as the ratio between the kinetic energy of impact and the dynamic granule strength. Weak granules can deform more than strong granules and possesses a higher Stokes deformation number. Consequently, weaker granules can dissipate more energy, because these granules can deform to a larger degree. A higher value of the Stokes deformation number will promote granule growth. Another consequence of the deformation is that granules will condense resulting in a decrease in porosity and an increase in saturation.

The relation between the Stokes deformation number and the maximum pore saturation will determine the growth behaviour (Figure 2-5).

- ***"Dry" free flowing powder:*** The liquid content is so low that no nuclei are formed.
- ***Nucleation only:*** there is insufficient binder liquid to assure further growth of the nuclei.
- ***Crumb:*** The granules are too weak to resist the shear forces and are consequently broken down.
- ***Steady growth:*** The degree of deformation and liquid saturation is sufficient to induce the coalescence of granules.
- ***Induction:*** no granule growth takes place during the induction stage, because the granules are too strong to deform sufficiently to cause growth. Moreover, the saturation is too low to compensate this.

- ***Rapid growth:*** Every collision between granules results in coalescence.
- ***Slurry/Over-wet mass:*** The saturation becomes too high and a wet paste is formed.

An attempt has been made by Iveson to validate the growth regime map for the high shear mixer [Iveson et al., 2001]. Owing to difficulties in estimating the granule strength and the impact velocity the growth regime map unfortunately failed to predict the growth behaviour in the high shear mixer. Although it was possible to define growth behaviours with the ex-situ experiments, translation of these behaviours to the high shear mixer is still troublesome. This discrepancy between the ex-situ experiments and the in-situ results is typical for these types of experiments. However, ex-situ experiments did provide qualitative information about the influence of certain process and formulation variables on granule properties. This information can be used to explain the growth phenomena observed with the in-situ experiments.

2.4 In-situ approach

As was stated earlier the in-situ experiments usually measure the influence of process and formulation conditions on the properties of the granules. These properties are often determined after drying and sometimes after milling, which may obscure the results. Moreover, in most studies the variables are often investigated at different levels, which makes comparison of the results difficult. Nevertheless, this empirical approach provided some general influences of process and formulation variables on granule growth.

2.4.1 Impeller and chopper speed

Besides a mixing function the impeller and chopper are also responsible for the energy input in the process. The influence of the impeller and chopper speed therefore depends on how the granules respond to this energy input. If the increase in impact energy results in more deformation of the granules, both the granule size and growth rate increase. Various authors reported this observation [Knight, 1993, Knight et al., 2000, Holm et al., 1984, Kokubo and Sunada, 1996]. When the energy input became too high and granule deformation led to granule breakage, an increase in impeller speed caused a decrease in granule size. This explains why sometimes a decrease in granule size is observed when the impeller speed is increased [Schæfer et al., 1990a, 1990b, Ramaker et al., 1998, Knight et al., 2000].

The influence of the energy input on granule growth was examined by Knight et al. [2000]. Figure 2-6 indicates that for impeller speeds of 450 rpm and 800 rpm the growth rate is proportional with the energy input. The influence of the energy input on granule size is identical. At an impeller speed of 1500 rpm the effect of the energy input is less pronounced. The authors argued that this was caused by an increased degree of breakage at this speed.

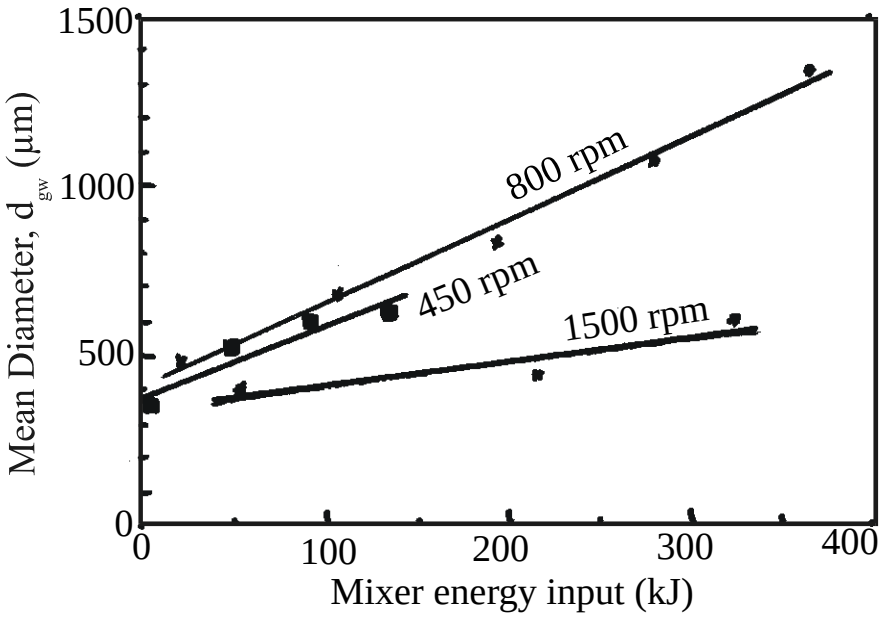


Figure 2-6 *Dependence of mean diameter on mixer energy input at impeller speeds of 450, 800 and 1500 min^{-1}. Adapted from Knight et al. [2000].*

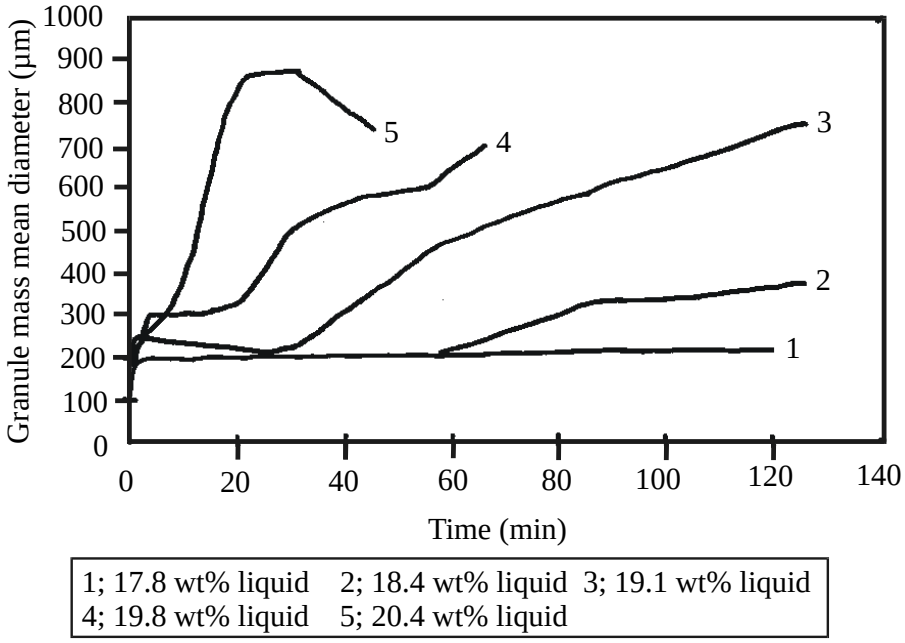
The chopper is supposed to function as a breaking device. However, Knight [1993] showed that turning off the chopper did not influence the average granule size. Hoornaert et al. [1998] showed that no growth phase was observed after the induction period if the chopper was not operated. This growth phase did occur when the chopper was functioning. They argued that the chopper has a densifying effect.

2.4.2 Process time

Obviously, the general influence of a prolonged process time is granule growth. Another influence of the process time is that the granule size distribution usually becomes more narrow [Knight et al., 1998, Schæfer and Mathiesen, 1996, Knight et al., 2000, Vonk et al., 1999]. However, not always an increase of the granule size in time is found. Hoornaert et al. [1998] observed a time period of no granule growth, sometimes followed by a sudden granule growth phase. This is shown in Figure 2-7. It was argued that during the no growth period granules become more condense (consolidation)

due to the repeated impacts, while the saturation is still too low to cause granule growth. This period would last until the saturation is sufficient to assure granule coalescence.

A logical consequence of the repeated impacts of the mixer arms on the granules is that the granules will densify. That is also the reason that usually a decrease in porosity is observed as a function of process time [Scott et al, 2000, Knight et al., 1998, Schæfer and Mathiesen, 1996]. Especially during the initial time points the decrease in porosity is pronounced, whereas almost no change in porosity is observed at prolonged process times.



1; 17.8 wt% liquid	2; 18.4 wt% liquid	3; 19.1 wt% liquid
4; 19.8 wt% liquid	5; 20.4 wt% liquid	

Figure 2-7 *Evolution of the mass mean granule diameter for different amounts of binder (µ = 3.9 mPa.s for all experiments). (1) 17.8 wt.% liquid (2) 18.4 wt.% liquid, (3) 19.1 wt.% liquid, (4) 19.8 wt.% liquid and (5) 20.4 wt.% liquid.*

2.4.3 Liquid/solid ratio

Since granulation is induced by a liquid phase, a logical consequence is that a higher concentration of the liquid results in a larger degree of granulation. An increased growth rate is also observed when the liquid/solid ratio increases [Knight, 1993, Bardin et al., 2001, Schæfer et al., 1990]. A phenomenon, called overwetting, may occur when the liquid/solid ratio becomes too high. In this case, granulation results in the formation of a paste [Keningley et al., 1997]. It is clear that this situation has to be avoided, because further processing (e.g. tableting) becomes difficult. The saturation of the granules increases when more liquid is added, which is the reason that a higher growth rate is observed. A higher saturation is directly related to a larger average granule size [Holm et al, 1985, Ritala et al., 1988, Schæfer et al, 1990b, Kristensen et al., 1984]. Alternatively, if the saturation is too low no granule growth is observed. This implies that granules must exceed a

critical saturation level in order to grow. This observation also explains the decreased period of no growth (consolidation) when the liquid content is increased, which was observed by Hoornaert et al. [1998] (see Figure 2-7). Owing to densification the porosity of the granules decreases resulting in an increase in saturation. If the saturation remains below the critical saturation no further growth will be observed. However, if the densification is sufficient to exceed this critical saturation growth will continue. This shift from no-growth to growth will be observed at an earlier process time for higher liquid concentration.

There is large influence of the material properties on the required liquid amount for granulation. For lactose liquid saturation levels between 20-50% were sufficient for granule formation [Holm et al., 1985, Kristensen et al., 1984]. A liquid saturation above 70% was necessary for the granulation of dicalcium phosphate [Holm et al., 1985, Kristensen et al., 1984]. Also the particle size of the powder influenced the effect of liquid concentration on granule growth. Keningley et al. [1997] showed that the minimum amount of liquid needed for granulation increased when the size of the constituent particles decreased. The same observation holds for the maximum amount of liquid that could be used for granulation.
Knight et al. [1998] showed that also the rate of liquid addition is of importance. They observed a larger average granule size for the pour-on experiments compared to the spray-on experiments. If liquid was added very fast (i.e. pour-on) regions in the powder bed existed where the liquid concentration is high, resulting in overwetting. This led to the local formation of large granules or lumps, whereas a gradual liquid addition (i.e. spraying) led to a more uniform distribution of the binder. In this case the changes of over wetting were reduced, although the same amount of liquid was used.

2.4.4 Viscosity

The viscosity of a liquid is a measure for the resistance of the liquid to shear. It is therefore not surprising that in high shear granulation dispersion of the binder becomes more difficult when the viscosity increases [Schæfer and Mathiesen, 1996a, 1996b]. Since the mixing of the liquid with the solid is retarded when the binder dispersion becomes more difficult, a smaller initial granule size is observed at high viscosity. However, once the granules have been formed the growth rate of the granules is higher for a more viscous binder [Schæfer and Mathiesen, 1996a, Ritala et al., 1986]. Granule growth can even become uncontrollable, when the viscosity becomes too high [Schæfer and Mathiesen, 1996b]. The general explanation for this observed growth behaviour is that a higher

viscosity promotes coalescence of granules. According to the theory of Ennis [1991] a viscous liquid layer surrounding the granules can absorb the impact energy, resulting in coalescence (see page 13). An increase in viscosity however also implies less deformation of the granules, since the dynamic granule strength increases. This explained the extensions of the induction period with an increase in viscosity that was observed by Hoornaert et al. [1998]. The higher resistance to deformation will retard the consolidation of the granules. Hence, the moment those granules become sufficiently wet to assure growth will occur at a later stage of the process.

Johansen and Schæfer [2001] and Keningley et al. [1997] showed that, depending on the primary particle size, a certain viscosity must be exceeded in order to obtain granule growth. When large primary particles were granulated with a low-viscosity binder, granule growth was limited. It was shown that the critical viscosity to assure granule growth decreased with a decrease in primary particle size. They argued that this observation was related to the granule strength. The shear forces broke down weak granules, obtained with a low viscosity binder and a large primary particle size. This minimises granule growth.

Table 2-2 *Relationship between primary particle size and liquid requirement.*

Material	Mean particle size	PEG % m/v	Reference
Lactose monohydrate	19 µm	35.6	Schæfer and Mathiesen, 1996a
Lactose monohydrate	22 µm	33.9-37.0	Schæfer et al., 1992
Lactose monohydrate	23 µm	17.1-29.3	Kinget and Kemel, 1985
Lactose monohydrate	32 µm	21.0-25.0	Kinget and Kemel, 1985
Lactose monohydrate	34 µm	30.8-33.9	Schæfer et al., 1992
Lactose monohydrate	44 µm	28.5-30.0	Schæfer et al., 1992
Lactose monohydrate	68 µm	23.1-27.7	Schæfer et al., 1990

2.4.5 Primary particle size

The influence of the primary lactose size on the amount of PEG required for granulation is shown in Table 2-2. Direct comparison between the results is difficult, since the average granule sizes obtained with these experiments were not the same. However, there is a general trend that more liquid is used when the particle size decreases. Schæfer et al. [1992] also showed that less liquid is required to obtain an identical average granule size when a larger lactose size is used for granulation. It is logical that the liquid requirement is related to the primary particle size. Granules exist due to the presence of liquid bridges between primary particles. More liquid is required to wet

the primary particles, when the size is smaller, since the surface area is larger. However, the liquid requirement is also influenced by other factors like the porosity or the material properties.
As was stated earlier, the primary particle size also influences the critical viscosity that is needed to assure granule growth [Johansen and Schæfer, 2001, Keningley et al., 1997]. To prevent complete breakage, a higher binder viscosity is necessary when the primary particle size of the feed material is larger.

2.5 Research Strategy

Based on this literature survey a schematic picture of the granulation process is proposed (Figure 2-8). The process and formulation conditions influence the granulation mechanism to some degree. In the end, the combination of these three mechanisms determine the overall granule properties. In this thesis we are highlighting one particular property; ***the drug distribution in the granules***.

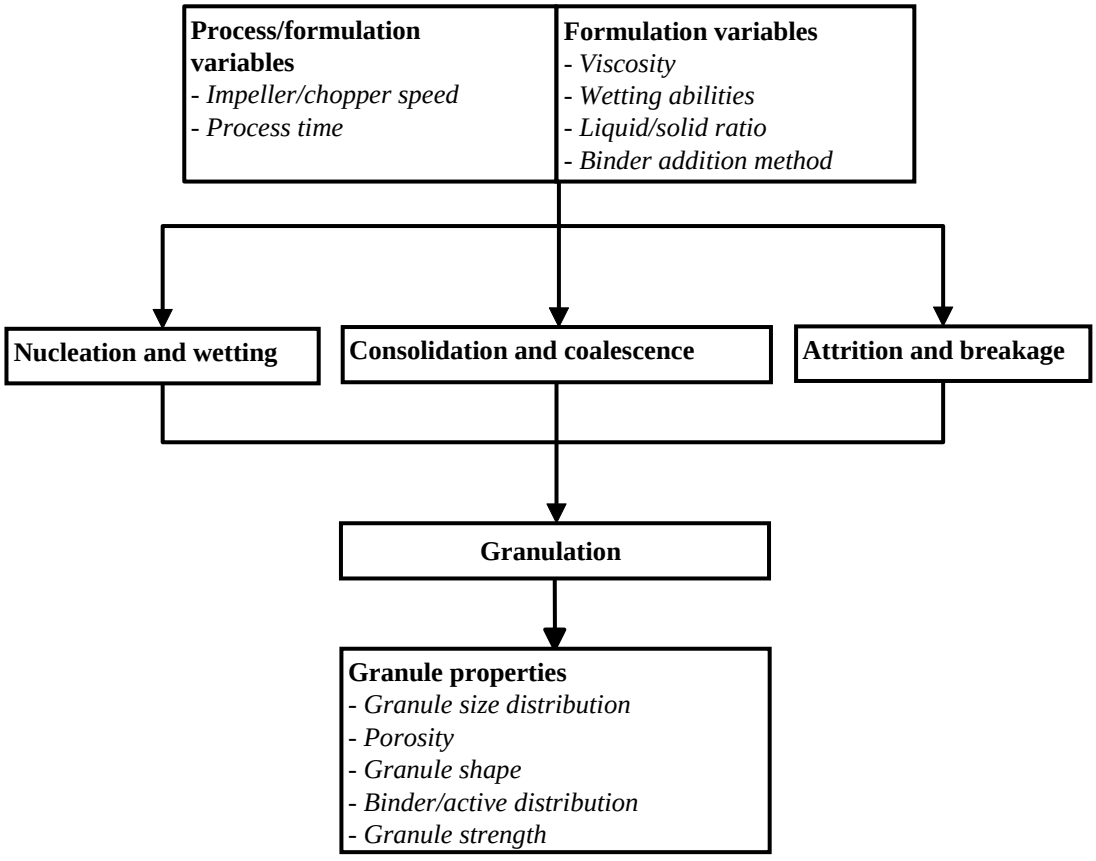


Figure 2-8 *Schematic representation of the high shear granulation process.*

The literature review made clear that the above representation is an idealised representation. The ex-situ experiments do provide extensive knowledge about the influence of various parameters on

the individual granulation mechanisms. However, translation of this information to the actual high shear granulation process is still troublesome. Hence, it is difficult to describe which influence these mechanisms have on the ultimate granule properties.

In contrast, with the in-situ experiments the influence of process and formulation variables on the ultimate granule properties are thoroughly described without knowledge of actual mechanisms of granulation. This makes the results often difficult to interpret and to compare, because different mechanism may eventually result in similar granule properties.

Combination of the knowledge obtained with both approaches leads to Figure 2-8, which signifies that the information obtained with the in- and ex-situ experiments has to be merged. In order to accomplish this the missing link between both approaches, the granulation mechanisms in the high shear mixer, must be elucidated. The solution for the granule inhomogeneity phenomena lies in the unravelling of the granulation mechanisms.

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3

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

Abstract

A poorly understood phenomenon observed during high shear granulation is the poor distribution of a drug in the granules. To investigate the causes of this inhomogeneity, lactose of three different particle sizes was granulated with 0.1% micronised estradiol (5 µm) in a 10L high shear mixer. An aqueous solution of HPC was used as binder. Granulation with the largest lactose particles (170 µm) yielded homogeneous granules. 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, while little demixing was observed for the smallest lactose grade. It was concluded that granulation with the largest particles resulted in breakage behaviour of the granules, thereby preventing demixing. However, once granules are strong enough (promoted by a smaller particle size and prolonged process time) to withstand 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 behaviour. It was argued that once granules survive, preferential growth of the small estradiol particles in favour of the larger lactose particles causes the demixing. The extent of demixing depends on the particle size difference.

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hij zit
als een kleine boedha
op het strand
hij en zijn vlieger
ver achter hem
de zee.

3.1 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 size enlargement by formation of liquid bridges between primary particles. A mixer arm that rotates at high speed in a bowl agitates the powder mix. 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 observed in various studies [Selkirk, 1976; Warren and Price, 1977; Oijle et al., 1982; Egermann and Reiss, 1988; Vromans et al. 1999]. Often the larger granule-size fractions exhibited the highest drug concentration. However the opposite, where the highest content was found in the smallest granule-size fractions, has also been observed [Oijle et al., 1982]. The unequal distribution of the drug in the granules may eventually affect the content uniformity of the drug product. However not only the drug substance is susceptible to demixing, also pharmaceutical filler materials (e.g. corn starch) show tendency for demixing [Vegt 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. However, despite the fact that there is an increasingly 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 literature. These mechanisms may also play a role during high shear granulation. The literature study in **chapter** 2 showed that 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 granules. 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 granules.

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

Egermann and Vromans et al. were the first who related demixing of the drug substance with granule growth mechanisms [Egermann and Reiss, 1988, Vromans et al., 1999]. Inhomogeneity of the granules 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 smaller 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 and the demixing of the drug substance and to establish whether there is an interrelationship between granule growth mechanisms and the demixing of a drug substance in the granules. 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 micronised 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 behaviour.

3.2 Theoretical considerations

The influence of the (primary) particle size on the granule growth in a high shear mixer is complex. 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 occurs [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 these granules. Moreover, the rate of densification depends on the deformation of the granules, which is also a function of granule strength.

Rumpf 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 [Rumpf, 1962]

$$\sigma = \frac{9}{8}\frac{(1-\varepsilon)}{\varepsilon}\frac{F_{bond}}{d_{3,2}^2} \qquad \textbf{Equation 3-1}$$

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].

$$\sigma_c = 6S\frac{(1-\varepsilon)}{\varepsilon}\frac{\gamma}{d_{3,2}} \qquad \textbf{Equation 3-2}$$

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 leads to deformation of the granules, are resulting in a rapid relative displacement of the associated particles. The viscous force of a liquid bridge is given by Reynolds' lubrication equation;

$$F_v = \frac{3\pi\mu d_{3,2}^2 v_p}{8h} \qquad \textbf{Equation 3-3}$$

in which μ is the viscosity, v_p the relative velocity of the moving particles and h is the interparticle gap distance. Incorporation of the viscous force (F_v) into equation 3-1 leads to the following description of the strength of a granule under dynamic conditions,

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

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.

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

By substituting *h* in equation 3-4, the model for the tensile strength of a granule under dynamic conditions becomes;

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

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 observations done for the force of a single viscous liquid bridge between two moving particles. Ennis has shown that above a certain liquid bridge volume the viscous force is independent of the liquid bridge volume [Ennis et al., 1990]. In this case, the strength of a dynamic liquid bridge can be attributed to the viscous force at the contact point corresponding 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).

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,

$$\sigma_{impact} = \frac{2}{3}\rho_g v_i^{\,2}$$ **Equation 3-7**

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}).

$$St_{def} = \frac{\rho_g v_c^{\,2}}{2\sigma_v}$$ **Equation 3-8**

In which v_c is the representative collision velocity and σ_v the dynamic granule strength, which is calculated with equation 3-6. It is assumed that the collision velocity equals the tip speed of the chopper [Iveson, 2001b]. The differences between both models are that the second model takes into account the dynamic conditions in a granulator and recognizes that the applied impact energy can be absorbed by deformation of the granules.

3.3 Experimental

3.3.1 Materials

Micronised 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, USA) and lactose 100M, 200M and 450M was supplied by DMV (Veghel, The Netherlands). Some powder characteristics of the excipients are shown in Table 3-1.

Table 3-1 *Particle sizes and density characteristics of the excipients.*

Materials	Weight mean diameter [$d_{4,3}$]	Surface mean diameter [$d_{3,2}$]	Tapped density	Tapped bed porosity
Lactose 100M	170 µm	60 µm	0.90 g/cm^3	0.42
Lactose 200M	50 µm	10 µm	0.85 g/cm^3	0.45
Lactose 450M	23 µm	6 µm	0.77 g/cm^3	0.50
Estradiol	5 µm	1.5 µm		

3.3.2 Granule preparation

For all the granulation experiments the same composition of the binder solution was used, 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 differences between lactose 100M, 200M and 450M the optimum amount of binder solution necessary to obtain acceptable granules varied with the granulation of each lactose grade, leading to different percentages of binder in the formulation (Table 3-2).

Table 3-2 *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[1]	8.0 %	10.0 %	14.0 %

[1]Percentage of dry powder

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 kilogram dry matter. The lactose and estradiol were dry-mixed in the Gral 10 for 5 minutes (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 a 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 minutes) a different batch was produced to prevent influences of sampling. The granules were dried on plates at 40°C at reduced pressure (Elbanton, The Netherlands) for 4 hours.

3.3.3 Granule characterization.

The granule size distribution was determined by sieve analysis of the dry granules with a series of 16 ASTM standard sieves in the range of 75-4750 µm. A sample of about 100 gram was sieved for 10 minutes on a vibrating sieve-shaker (Retsch, Haan, Germany) at an amplitude of 1.5 millimetre. 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 analysed for estradiol content. Measurements were done in duplicate. The distribution of estradiol in the granules is expressed as the demixing potential [Thiel and Nguyen, 1982],

$$DP(\%) = \frac{100}{\bar{p}} \sqrt{\Sigma \frac{w(p-\bar{p})^2}{100}} \qquad \textbf{Equation 3-9}$$

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

3.4 Results and discussion

3.4.1 Drug distribution

Figure 3-1a shows the (in)homogeneity of the estradiol granules 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 granules (Figure 3-1b). On basis of the results of Egermann and Vromans it was expected that the large particle size difference between lactose 100M (~170 µm) and estradiol (~5 µm) would lead to a poor distribution of estradiol [Egermann and Reiss, 1988; Vromans et al., 1999]. However, the distribution of estradiol is remarkably good. Only at a granulation time of 15 minutes there is a

sudden increase in inhomogeneity. At this point the drug accumulates in the larger granule-size fractions.

A decrease in primary particle size of lactose to 50 µm (lactose 200M) has a dramatic effect on the demixing behaviour of estradiol in the granules. 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 granules is in most cases better than that of the lactose 450M granules.

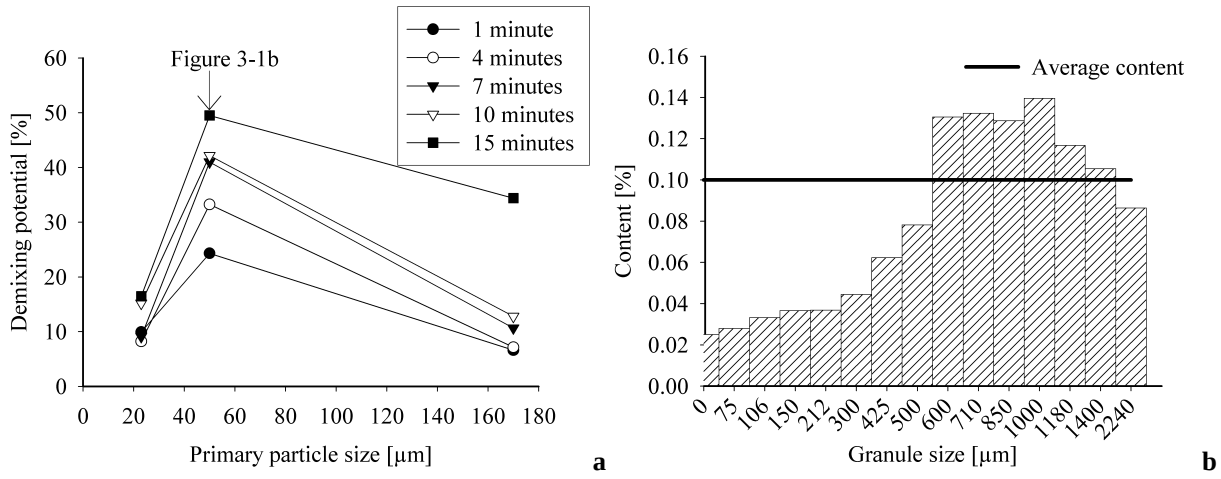

Figure 3-1(a) *The influence of the primary particle size of lactose on the drug distribution in the granules for different process times (process conditions: impeller 430 rpm; chopper 3000 rpm).* ***(b)*** *A typical example of a poor distribution of estradiol (lactose 200M, process time 15 minutes, process conditions impeller 430 rpm; chopper 3000 rpm).*

The influence of the impeller and chopper speed on the demixing potential and granule growth profiles for the different lactose grades is shown in Figure 3-2. 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 granules homogeneity. When a smaller particle size of lactose is used a completely different demixing behaviour is observed. Variations in impeller and chopper speed have almost no effect on the distribution of estradiol in the lactose 200M/450M granules. There is a large contrast in demixing behaviour between lactose

100M and lactose 200M/450M. This contrast, although less pronounced, is also observed for the growth curves. In first instance, a very rapid growth is observed for all the lactose's in the very first minute. Furthermore, it is noticed that further growth does not occur for lactose 100M. While a steady growth phase is observed for the other two lactoses until a plateau phase is reached after approximately 10 minutes. During the lactose 100M granulation experiments some wall adhesion of the granules was observed. Keningley et al. [1997] associated this wall adhesion with the formation of loose aggregates. This so-called crumb behaviour occurs when the granules are too weak to form permanent granules, but instead are constantly broken down and reforming [Keningley et al., 1997]. The wall adhesion was almost not observed with the lactose 200M and 450M experiments, suggesting that stronger permanent granules are formed. Clearly, lactose 100M exhibits a deviating behaviour with respect to granule growth and especially demixing, when compared to lactose 200M/450M.

Figure 3-2 also shows the influence of variation in impeller and chopper rate on the granule growth 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 one minute for the lactose 100M granules. 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. The chopper breaks down initial lumps, which originate from the direct method of binder addition. 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 behaviour between lactose 100M and lactose 200M/450M suggest a difference in growth mechanism between lactose 100M and lactose 200M/450M.

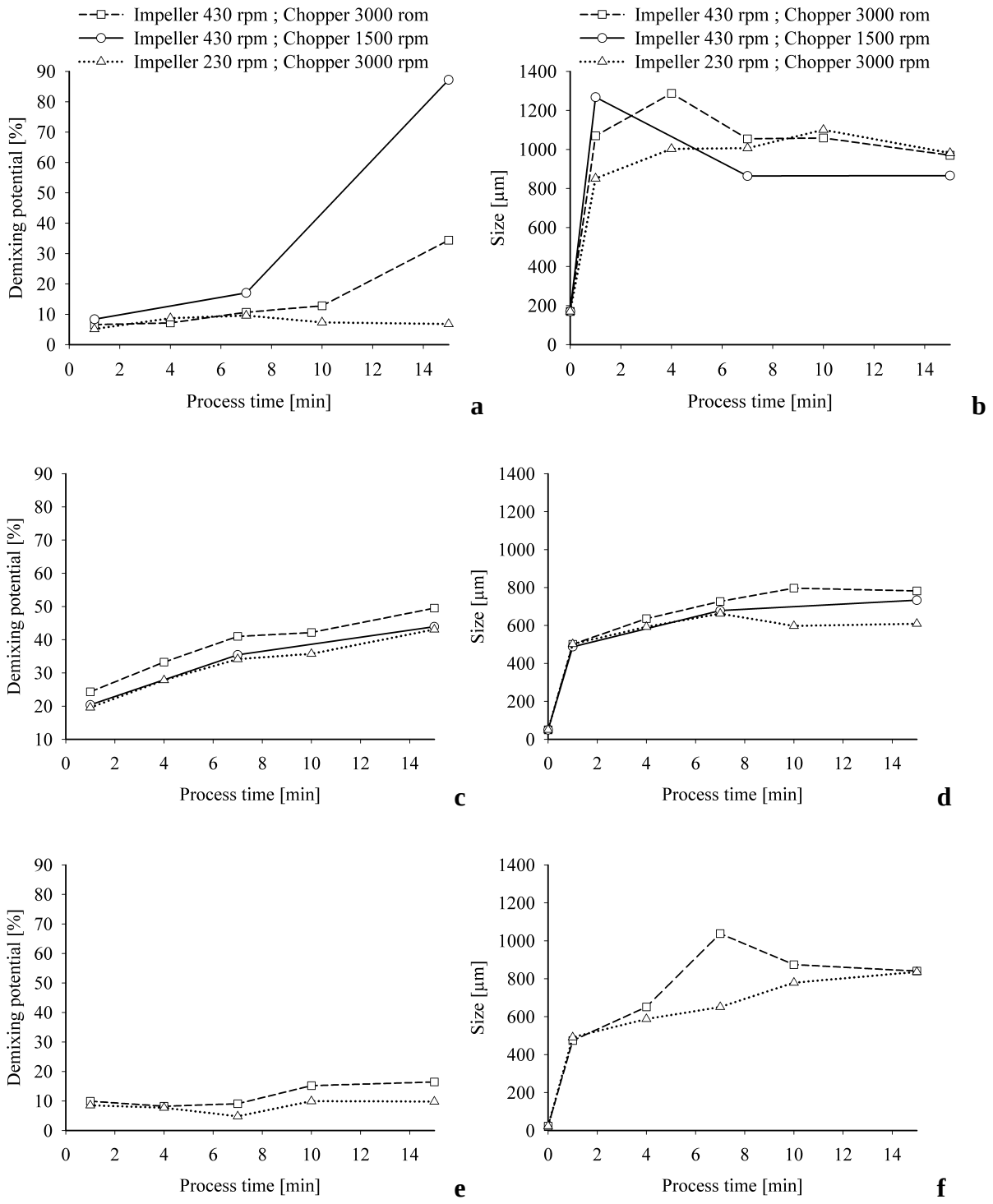

Figure 3-2 *The distribution of estradiol, expressed as Demixing Potential (DP) and the granule growth curves for lactose 100M* ***(a,b)****, 200M* ***(c,d)*** *and 450M* ***(e,f)*** *granules as a function of both the impeller and chopper speed.*

3.4.2 Porosity

The porosity of the granules was measured with mercury porosimetry. To increase the distinction between intergranular and intragranular porosity the large size fraction of the granules (between 1000 µm 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 8-0.1 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 granules 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 measurements. Therefore, changes in total porosity can be attributed to a change in intragranular porosity. This derived porosity of the lactose 100M granules, 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 granules is already decreased to approximately 0.15, after only 1 minute mixing (Figure 3-3). The fast densification corresponds with the rapid growth phase of the granules (Figure 3-2). 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, compared to 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.

3.4.3 Theoretical growth behaviour and homogeneity

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

3-4 shows the results of the calculations of the static granule strength (equation 3-2) as a function of porosity. The impact pressure of the chopper and the impeller are given by equation 3-7. When the

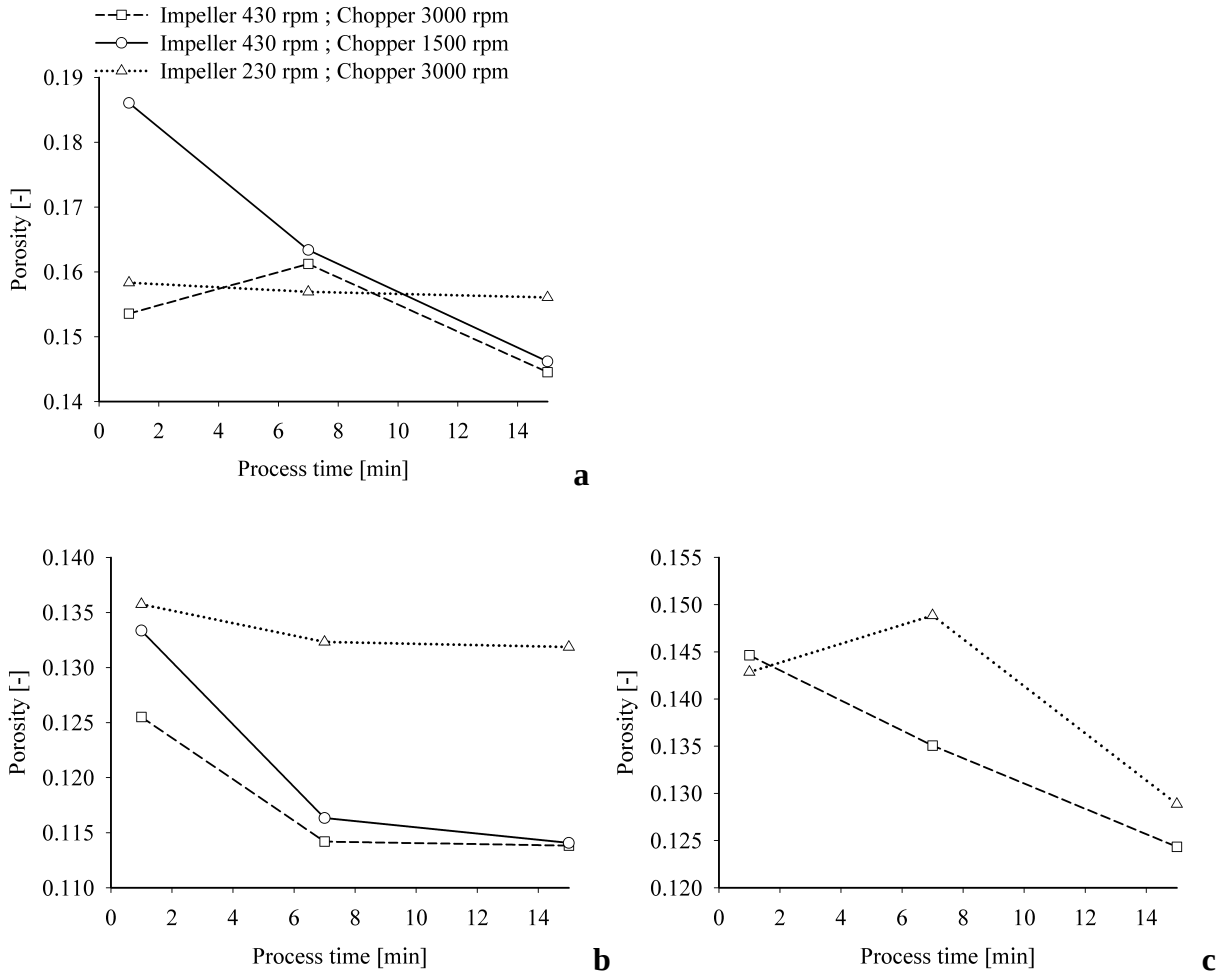

Figure 3-3 *The porosity for lactose 100M (a), 200M (b) and 450M (c) granules as a function of the process time at different impeller and chopper rates. For clarity reasons the porosities at t=0 min are not shown, because the values are much higher.*

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 behaviour of the granules. The experimentally observed crumb behaviour of lactose 100M granules, which indicate continuous breakage of the granules occurs, is indeed to be expected from Figure 3-4 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 behaviour. Prolonged mixing results in further densification and hence in stronger granules.

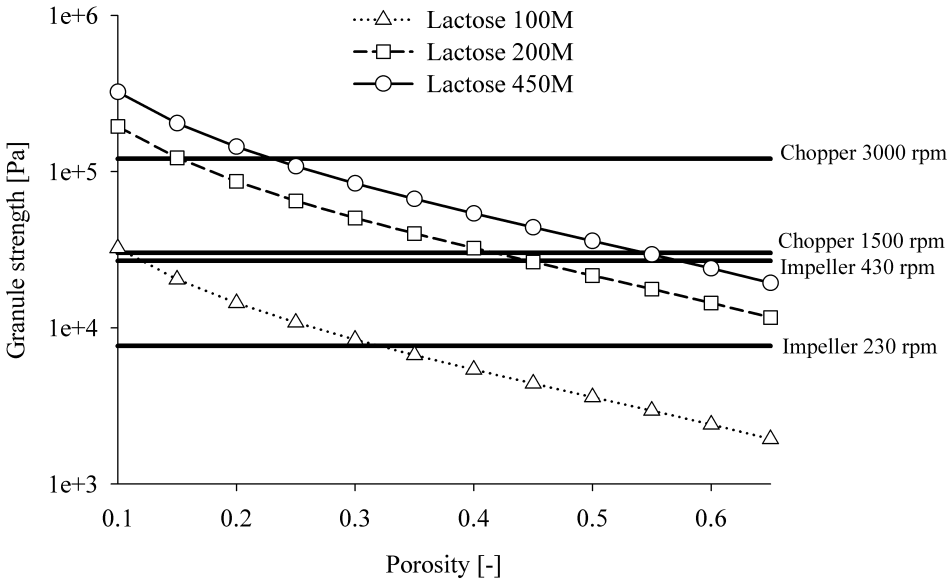

Figure 3-4 *The influence of the porosity on the static strength of the granules for lactose 100M, 200M and 450M. The impact pressure of the impeller and chopper was also calculated (horizontal lines). Impeller speed 430/230~5/3 m/s ; chopper speed 3000/1500 rpm ~11/5 m/s. Values used for calculations: saturation=90%, $d_{3,2}$=60, 10, 6 μm; ρ=1500 kg/m^3; γ=0.04 N/m.*

The restriction of the static model is 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 article an attempt is made. For that purpose, a model that describes the different granule growth behaviours 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 behaviour of the granules. In addition this map can also be used to predict breakage or no breakage behaviour of the granules under dynamic conditions. According to the growth regime map an increase in dynamic granule strength, resulting in a decreasing Stokes deformation number (equation 3-8), can lead to a shift from crumb behaviour (breakage) to steady/induction growth (no breakage). The theoretical calculation of the wet granule strength as a function of porosity and particle size (equation 3-6) was used to calculate the Stokes deformation number (St_{def}). The boundary between breakage behaviour and no breakage behaviour (Stdef~0.04) was experimentally established by Iveson et al. (2001b). Figure 3-5 shows that the order of magnitude calculation predicts a similar impact of primary particle size on growth behaviour as

earlier obtained with the static approach. Crumb behaviour for lactose 100M is expected at a high porosity and, as the process proceeds, densification of granules can lead to a shift no breakage behaviour. A decrease in chopper speed shows a shift for the lactose 100M curve, so a transition to no breakage behaviour can be expected at a higher porosity. Both lactose 200M and 450M immediately exhibit no breakage behaviour. 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 different growth behaviour of the granules, depending on porosity and impact forces.

Now the question arises what the relationship is between granule growth behaviour and demixing. The crumb behaviour of the lactose 100M granules, 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.

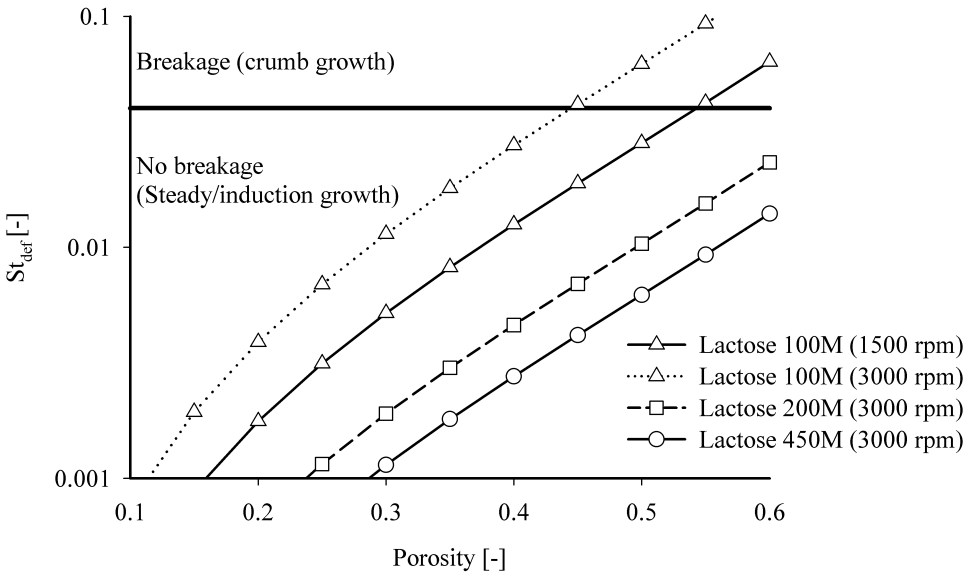

Figure 3-5 *The influence of the porosity on the stokes deformation number (St_{def}) calculated for a chopper rate of 3000 rpm (11 m/s) for lactose 100M, 200M and 450M and calculated for a chopper rate of 1500 rpm (5 m/s) for lactose 100M. Values used for calculations: μ=3.2 Pa.s; $d_{3,2}$=60, 10, 6 μm; ρ=1500 kg/m^3; v=chopper speed (chopper speed is used for calculations, because it exhibits the highest tip velocity).*

One important parameter that influences the drug distribution in the granules is wet granule strength. Another parameter that is important for the demixing of estradiol in the granules 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 0.01-0.05%, will influence granule strength to an extent that it can influence the breakage behaviour 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 determines the degree 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, so granule breakage will prevent demixing.

For lactose 200M/450M no breakage behaviour is expected, so preferential growth of the estradiol causes the demixing. The observed demixing of the estradiol in the lactose 200M granules is larger than for the lactose 450M granules, 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 granules, 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 granules the sudden increase in DP at a process time of 15 minutes 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.

3.5 Conclusion

The experiments show a relationship between granule growth mechanisms and demixing, in which the primary particle size plays an essential role. First, differences in primary particle size influence the wet granule strength. Breakage or crumb behaviour 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 demixing 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 the further observed demixing phenomena. A difference in primary particle size between lactose and estradiol results in demixing of estradiol. Preferential growth of the micronised estradiol particles in favour of the lactose particles explains the demixing behaviour of estradiol in the varying lactose granules.

3.6 List of symbols

ε	Porosity [-]
$d_{3,2}$	Surface mean diameter [µm]
F_{bond}	Bonding force [N]
F_v	Viscous force of a liquid bridge [N]
σ_c	Static granule strength [Pa]
σ_v	Dynamic granule strength [Pa]
γ	Surface tension [N/m]
S	Liquid saturation [-]
v_i	Tip velocity [m/s]
v_p	Relative velocity of the moving particles [m/s]
v_c	Collision velocity [m/s]
h	Interparticle gap distance [µm]
μ	Viscosity [Pa.s]
ρ_g	Granular density [kg/m^3]
σ_{impact}	Impact pressure [Pa]
St_{def}	Stokes deformation number [-]

DP Demixing Potential [%]

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4

Granule breakage phenomena in a high shear mixer; influence of process and formulation variables and consequences on granule homogeneity.

Abstract

Wet granulation is a process intended for size enlargement. A logical consequence is that many studies are focused on granule growth. However, next to built-up of granules granule breakage also occurs. The aim of this study is to investigate the wet granule breakage process in a high shear mixer. For that purpose, tracer experiments were conducted to investigate the influence of the particle size of lactose and the viscosity of the hydroxypropyl cellulose (HPC) solution on the granule breakage. The relationship between granule breakage behaviour and granule homogeneity was also investigated. A model to predict granule breakage, based on the ratio of the impact energy and the dynamic granule strength, was proposed. The tracer experiments showed that an increase in viscosity and a decrease in particle size eventually lead to a transition from breakage to no breakage behaviour of the granules. The model predicts similar influences of these parameters on the breakage behaviour and showed a clear correlation with the experimental data. Moreover, an interrelationship between granule breakage and homogeneity was found. The dynamic situation of granule breakage was associated with a continuous exchange of particles, which resulted in homogeneous granules. When granule breakage was absent granules remain intact and the preferential layering of the smallest particles yielded inhomogeneous granules.

Powder Technology, 2003 (133), 228-236.

heb jij ook zo'n last
van wat je eigenlijk
hoort te weten

4.1 Introduction

Since the beginning of the eighties high shear granulation has been a commonly used method to produce granules. The introduction of the high shear granulation technique gave rise to a number of studies, intended to elucidate the growth mechanisms of granules. From these studies a certain degree of understanding has emerged of the factors determining the eventual granule size or other granule characteristics such as porosity. Knowledge about the growth mechanisms can also help to explain the influence of formulation variables (like changes in binder viscosity, primary particle size and liquid content). Some studies try to determine the individual processes of high shear granulation, like coalescence, densification and nucleation [Ennis et al., 1990, Iveson, 1997, Hapgood, 2000, Tardos et al., 1997]. These individual mechanisms are now reasonably well understood owing to these studies, which were performed outside the granulator. The next step, the implementation and combination of the individual mechanisms within the granulator, appears to be more difficult. Iveson and Litster have made an attempt by developing a growth regime map for granulation [Iveson and Litster, 1998a]. The map combines the knowledge of the individual mechanisms, obtained from studying these mechanisms outside the granulator, to predict the growth behaviour inside the granulator. Different growth behaviours are predicted, depending on the ratio of the impact energy and the dynamic granule strength on the one hand to the saturation level of the granules on the other hand. When granules are weak, continuous breakage and coalescence takes place. Once granules survive the shear forces and subsequent growth depends on the saturation and densification of the granules. When the experimental granule growth curves can be matched with the predictive growth regime map a better understanding can be obtained about the mechanisms of high shear granulation and the parameters influencing these mechanisms. However, it is still difficult to understand if and how the granule growth curves can be translated into the map [Iveson et al., 2001b]. Changes in granule size alone cannot provide sufficient information to determine the growth behaviour. Therefore more knowledge of the process is necessary to relate experiment with theory.

From above it is clear that granule breakage behaviour is a key parameter in the granule growth mechanism. This importance is also reflected in **chapter 3** in which it was argued that granule breakage behaviour is related to the homogeneity of various excipients in the granules. In **chapter 3** a mechanism was proposed for the observed inhomogeneity features. It was stated that granule breakage is determined by the (dynamic) granule strength and the shear forces within the

granulator. If the impact forces are larger than the granule strength, continuous breakage and immediate coalescence of the granule fragments takes place. The dynamic situation of continuous breakage and growth leads to a constant exchange of primary particles, which results in a homogeneous distribution of the ingredients. When the granule strength exceeds the impact forces, granules will not break. In that case granule growth is more static (i.e. the exchange of primary particles between granules is minimal) and granules predominantly grow by layering. It has been argued that smaller primary particles have a higher affinity for this layering than coarser primary particles. When ingredients exhibit different particle size distributions, this so-called preferential layering will lead to a poor excipients distribution. In this case the smallest particles accumulate in the granules. The objective of this study was to investigate the granule breakage and the parameters influencing granule breakage inside the high shear mixer in order to validate the relationship between breakage and excipients distribution.

Table 4-1 *Characteristics of the different grades of lactose.*

Materials	Weight mean diameter [$d_{4,3}$]	Surface mean diameter [$d_{3,2}$]
Lactose 100M	170 µm	60 µm
Lactose 200M	50 µm	10 µm
Lactose 450M	23 µm	6 µm

4.2 Experimental

4.2.1 Materials

Table 4-2 *Formulations used for the tracer experiments. The percentages are by mass.*

Excipient	Lactose	HPC	Erythrosine	Water[1]	Viscosity [Pa.s]
Lactose 100M	98.0%	1.7%	0.3%	8.0%	3.2
Lactose 200M	97.6%	2.1%	0.3%	10.0%	3.2
Lactose 450M	96.7%	3.0%	0.3%	14.0%	3.2
Lactose 200M	99.7%	0%	0.3%	12.0%	0.001
Lactose 200M	98.9%	0.8%	0.3%	12.0%	0.072
Lactose 200M	98.5%	1.2%	0.3%	12.0%	0.275
Lactose 200M	97.7%	2.0%	0.3%	12.0%	1.09
Lactose 200M	97.2%	2.5%	0.3%	12.0%	2.78
Lactose 200M	96.7%	3.0%	0.3%	12.0%	4.13

[1]percentage of dry powder

The three different grades of lactose, varying in primary particle size, that were used for the granulation experiments (Table 4-1) were obtained from DMV (Veghel, The Netherlands). The

tracer used was erythrosine, a water-soluble red dye (Colorcon Ltd., Dartford, England). An aqueous solution of hydroxypropyl cellulose (Klucel EP, Aqualon Ltd., Wilmington DE, United States) was used as a binder. The formulations used for the experiments are listed in Table 4-2.

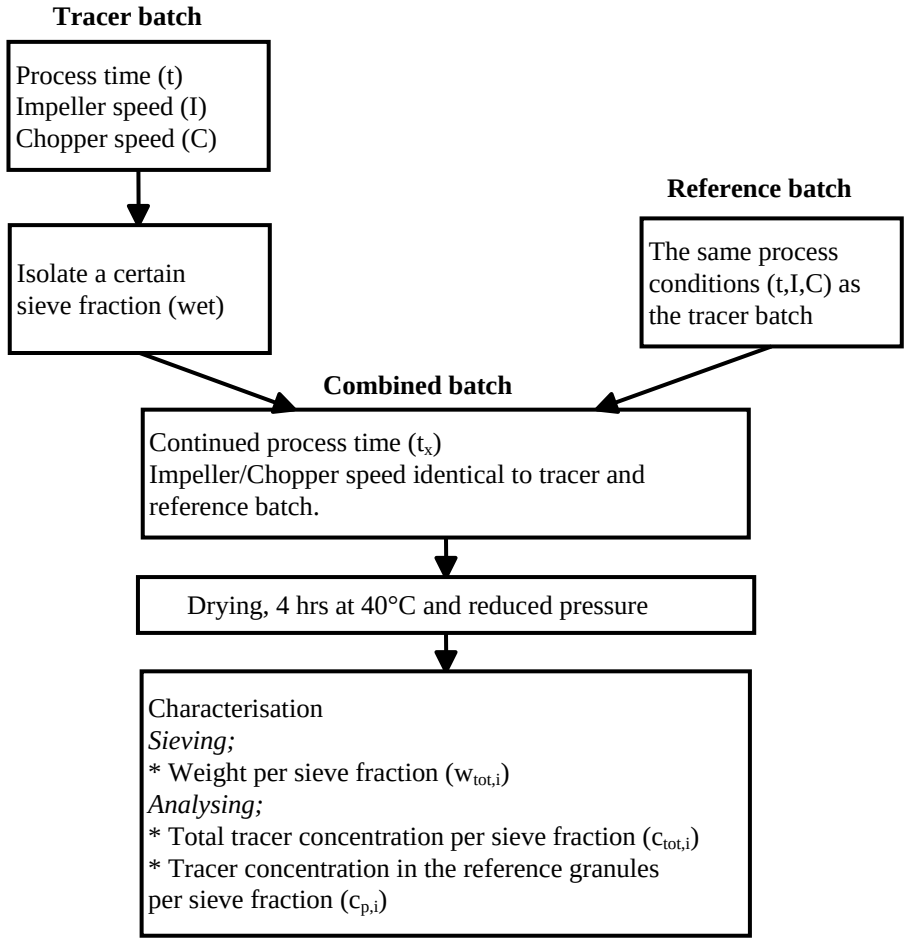

Figure 4-1 *Flow chart of the experimental set-up for the tracer experiments.*

4.2.2 Granulation

Figure 4-1 gives an overview of the experimental set-up of the tracer experiment. For production of the tracer granules erythrosine and the lactose were dry-mixed for 3 minutes in a 10-litre scale mixer granulator (Gral 10, Machines Collette, Wommelgem, Belgium). The binder was added by pouring the solution onto the rotating powder mass. The start of pouring was also the starting time for the granulation experiments. After a certain time the granulation process was stopped and the wet granules were stored on plates, which were covered with plastic to prevent water evaporation. The water content of the wet tracer batch was determined with a moisture balance (Sartorius, Goettingen, Germany) at 0, 20 and 40 minutes of storage. No significant water loss was observed during the 40 minutes, while the maximum time of storage after the production of the tracer batch was 20 minutes. The machine was cleaned and the reference batch (without the erythrosine) was

prepared. The process settings and times of the tracer batch and the corresponding reference batch were identical. Meanwhile, the tracer batch was wet sieved to isolate the correct fraction of tracer granules. After the granulation of the reference batch was completed the process was stopped. The wet tracer granules were mixed with the reference batch and the process was continued for a certain time period.

Table 4-3 *Experimental setup for the tracer experiments to investigate the influence of lactose size, process time and rotation speed.*

	Process time			**Rotation speed**	**Viscosity [Pa.s]**	**Size [µm]**	**Mass tracer granules [g]**
	1 min	**7 min**	**15 min**				
Lactose 100M Gral 10	1 min	1 min	1 min	I: 430 C:3000	3.2	1000-1400	40
	1 min	1 min	1 min	I: 430 C:1500		1400-2240	50
	1 min	1 min	1 min	I: 230 C:3000		1000-1400	40
Lactose 200M Gral 10	1 min	1 min	1 min	I: 430 C:3000	3.2	710-850	20
	1 min	1 min	1 min	I: 430 C:1500			20
	1 min	1 min	1 min	I: 230 C:3000			20
Lactose 450M Gral 10	1 min	1 min	1 min	I:430 C:3000	3.2	710-850	20
	1 min	1 min	1 min	I:430 C:1500			20

I=Impeller speed ; C=Chopper speed [rpm]

Table 4-4 *Experimental setup for the tracer experiments to investigate the influence of the viscosity.*

	Process time	**Rotation speed**	**Viscosity [Pa.s]**	**Size [µm]**	**Mass tracer granules [g]**
	7 min				
Lactose 200M Gral 10	3 min	I:430 C:1500	0.001	710-850	20
	3 min		0.072		20
	3 min		0.275		20
	3 min		1.09		20
	3 min		2.78		20
	3 min		4.13		20

I=Impeller speed ; C=Chopper speed [rpm]

At the end of the complete process the granules were plate-dried at 40°C and reduced pressure (Elbanton, Kerkdriel, The Netherlands). The experiments were performed at different process and formulation conditions. An overview of the conditions is given in Table 4-3 and Table 4-4.

4.2.3 Granule characterization

A sample of approximately 100 gram of dry granules, which was obtained by a rotating sample divider (Retsch PT100, Haan, Germany), was used for further analysis. The granules were sieved with a series of 14 ASTM sieves in the range of 150-3150 µm on a vibrating sieve shaker (Retsch, Haan, Germany). The concentration of erythrosine ($c_{tot,i}$) in sieve fraction i (i is the number of the sieve fraction) was determined with a chemical assay. For that purpose approximately 1 gram of granules was dissolved in 10 ml water and the erythrosine concentration was determined with UV spectroscopy. A certain sieve fraction contains granules that originate from either the tracer batch or the reference batch and the reference granules contain also some erythrosine due to tracer transfer. Therefore, erythrosine-rich particles (which are considered as tracer granules and have an intense colour) were separated manually from the other ones (reference granules, which are much paler than the tracer granules) and the erythrosine content in the remaining reference granules ($c_{p,i}$) was determined with the same chemical assay as described above. This procedure was repeated for all the sieve fractions. To determine the extent of breakage a breakage number is introduced. The breakage number equals the fraction of broken tracer granules, which is 100% minus the ratio of the total amount of erythrosine present in the tracer granules (A_{tracer}) divided by the total amount of erythrosine in all the granules (A_{total}):

$$\text{Breakage number (\%)} = \left(1 - \frac{A_{tracer}}{A_{total}}\right) * 100\% \qquad \textbf{Equation 4-1}$$

The amount of erythrosine in the tracer granules per sieve fraction equals the total amount of erythrosine in sieve fraction i ($A_{ts,i}$) minus the amount of erythrosine present in the reference granules in that fraction ($A_{ps,i}$). Tracer granules may be distributed over several sieve fractions because of growth, meaning that the amount of erythrosine present in the tracer granules is the sum of the amount of erythrosine in the tracer granules in each sieve fraction:

$$A_{tracer} = \sum_{i=1}^{14} (A_{ts,i} - A_{ps,i}) \qquad \textbf{Equation 4-2}$$

in which i is the number of the sieve fraction. The amount of erythrosine present in the reference granules per sieve fraction is given by:

$$A_{ps,i} = w_{p,i} c_{p,i} \qquad \textbf{Equation 4-3}$$

in which $c_{p,i}$ is the measured erythrosine concentration in the reference granules and $w_{p,i}$ is the total weight of the reference granules in the sieve fraction. A simple mass balance is used to calculate $w_{p,i}$ with the following equation:

$$w_{p,i} = \frac{(w_{tot,i}c_{tot,i} - c_{t,i}w_{tot,i})}{(c_{p,i} - c_{t,i})}$$ **Equation 4-4**

$w_{tot,i}$ is the total weight of the sieve fraction and $c_{t,i}$ is the concentration of erythrosine in the tracer granules.

Theoretically $c_{t,\mathrm{i}}$ equals 3 mg/g, $c_{p,\mathrm{i}}$ and $c_{tot,i}$ are measured with UV-spectroscopy, while $w_{tot,i}$ is determined by sieve analysis. Substituting equation 4-4 and 4-3 into equation 4-2 leads to the following equation to determine the total amount of erythrosine present inside the unbroken tracer granules.

$$A_{tracer} = \sum_{i=1}^{14}\left(w_{tot,i}c_{tot,i} - \frac{(w_{tot,i}c_{tot,i} - w_{tot,i}c_{t,i})}{(c_{p,i} - c_{t,i})}c_{p,i} \right)$$ **Equation 4-5**

The total amount of erythrosine in the granules (A_{total}) is given by

$$A_{total} = \sum_{i=1}^{14} w_{tot,i}c_{tot,i}$$ **Equation 4-6**

With these equations it is possible to calculate the degree of breakage (equation 4-1).

4.3 Results and discussion

4.3.1 Influence of formulation variables

The influence of the primary particle size of lactose on granule breakage is shown in Figure 4-2. The breakage numbers for lactose 100M ($d_{4,3}$~170 µm) after 1 and 7 minutes granulation are 98% and 100%, respectively. This means that complete breakage of the tracer fraction occurs within 1 minute. The erythrosine was distributed homogeneously all over the granule size fractions indicating complete fragmentation of the granules. At a process time of 15 minutes there is a small decrease in the breakage number to 90%, which still indicates a large amount of breakage. For lactose 200M and lactose 450M a completely different breakage behaviour is observed. Here only 40% of the tracer granules were broken. Strikingly, granules survive the shear forces after one minute of granulation. Apparently, the process of nucleation and granule formation occurs within one minute and within this first minute granules already possess the proper characteristics to withstand the shear forces. The broken fraction remains approximately the same at process times of 7 and 15 minutes. Overall, Figure 4-2 indicates that a decrease in particle size of the starting material leads to a decrease in breakage.

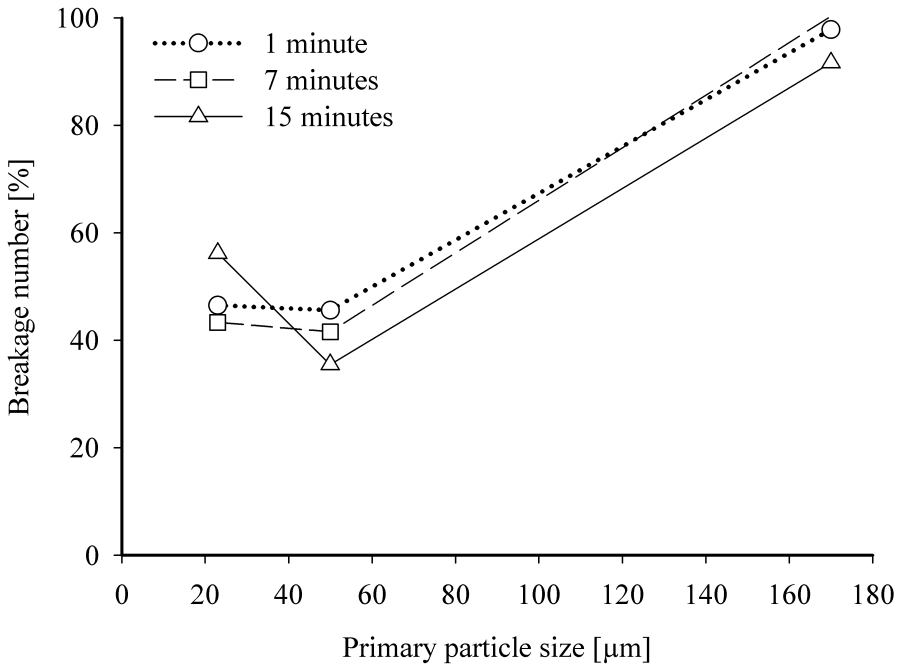

Figure 4-2 *The breakage numbers for lactose 100M ($d_{4,3}$ ~170 µm), lactose 200M ($d_{4,3}$ ~50 µm) and lactose 450M ($d_{4,3}$ ~23 µm) at an impeller and chopper speed of 430 rpm and 3000 rpm, respectively. The tracer granules and the reference granules were granulated separately for 1, 7 and 15 minutes, while the combined batch (tracer fraction plus reference batch) was granulated for another minute.*

Figure 4-3 shows the influence of the binder viscosity on the granule breakage behaviour. At low viscosity considerable granule breakage is observed. When using a more viscous binder solution, the degree of granule fragmentation decreases. At higher viscosities the percentage of breakage remains 40%. It is remarkable that the breakage number always seems to reach the same value of approximately 40%, even at a very high viscosity or a small particle size. It is unlikely that this is caused by migration of erythrosine with the binder, although erythrosine is water-soluble. Warren and Price showed that migration of water-soluble compounds is insignificant at a viscosity above 0.1 Pa.s [Warren and Price, 1976]. Apparently there always seems to be some granule breakage. Further examination revealed that in fact no complete fragmentation of the granules occurred anymore, but that surface attrition leads to the measured transfer of dye to the reference granules.

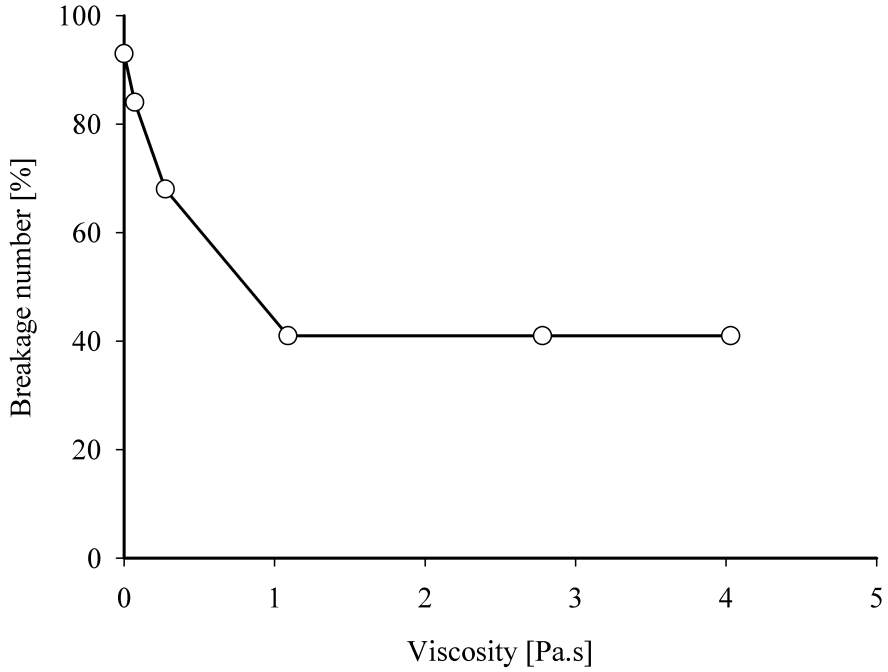

Figure 4-3 *Influence of the binder viscosity on the granule breakage behaviour of lactose 200M granules. Process conditions: impeller 430 rpm, chopper 1500 rpm, process time 7 minutes, continued time 3 minutes.*

The conclusion that primary particle size is important for granule strength was already recognised in the late 1950s. Rumpf developed a general model to calculate the influence of the primary particle size on granule strength [Rumpf, 1958]:

$$\sigma = \frac{9}{8}\frac{(1-\varepsilon)}{\varepsilon}\frac{F_{bond}}{d_{3,2}^2} \qquad \textbf{Equation 4-7}$$

in which ε is the intragranular porosity, F_{bond} is the bonding force between particles and $d_{3,2}$ is the surface mean diameter of the primary particles. In wet granulation the most important binding forces are the liquid bridges between primary particles. In the classical model by Rumpf the surface tension of the liquid gives rise to the primary binding force (F_{bond}) between particles. Several studies used this model to calculate the granule strength and predict the breakage behaviour in the granulator [Leuenberger et al., 1979, Ritala et al., 1988, Vonk et al., 1997, Vromans et al., 1999]. However, Figure 4-3 shows that in a high shear mixer the viscosity is also an important factor for breakage to occur. This is consistent with the theory that at high impact velocities the viscous force of a liquid bridge is order of magnitudes higher than the capillary forces [Kenningley et al., 1997, Franks and Lange, 1999, Iveson and Litster, 1998b]. It is therefore better to use viscous forces to calculate granule strength instead of the static capillary forces as used in the model of Rumpf.

Granule breakage occurs by shear or impact. It is likely that both forces will exert on the granules in a high shear mixer. However, the general perception in literature is that granules are more likely to break on impact, rather than shear [Iveson et al., 2001a], which is illustrated by the fact that almost all the work considering granule breakage is focused on granule behaviour after impact [Kenningley et al., 1997, Thornton et al., 1999, Iveson et al., 2002, Salman et al., 2002].

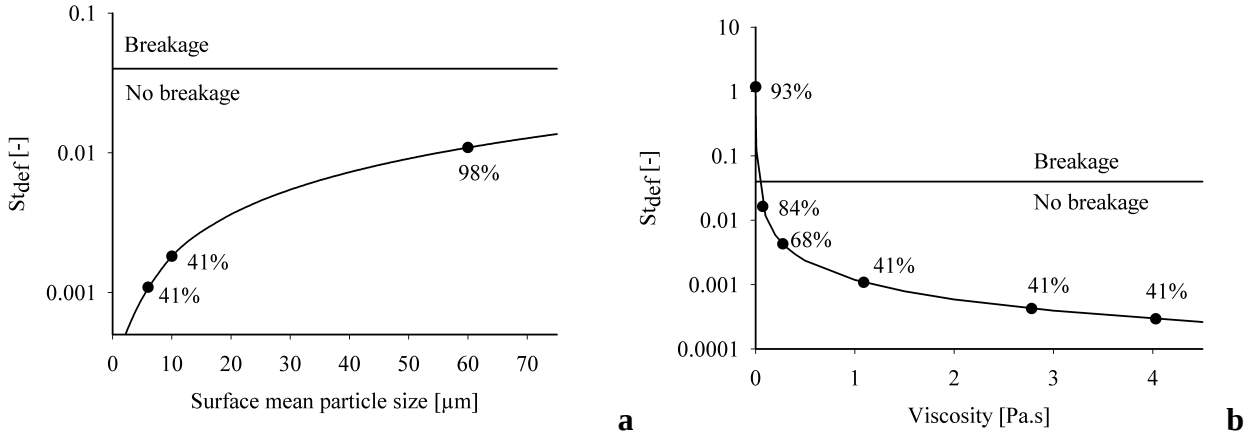

Figure 4-4 (a) *Relationship between the surface mean particle size of lactose 100M (60 µm), 200M (10 µm) and 450M (6 µm) and the Stokes deformation number. (b) The relationship between the Stokes deformation number and the binder viscosity calculated for 200M. The labels represent the determined breakage numbers. (Values used for the calculations; porosity (ε) 0.3 and impact velocity (v_c) 10 m/s for 4(a) and 5 m/s for 4(b) (v equals the chopper speed)).*

In **chapter 3** a modified model of Rumpf was proposed to predict the breakage behaviour of granules after impact under dynamic conditions. The granule strength is related to the viscous force of a liquid bridge with the following equation;

$$\sigma_v = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\pi\mu v_p}{16 d_{3,2}} \qquad \textbf{Equation 4-8}$$

in which μ is the liquid viscosity and v_p is the relative velocity of the moving particles inside a granule after impact. Because it is impossible to derive this velocity, it is assumed that this velocity equals the impact velocity of the mixer arm (v_c). The Stokes deformation number (St_{def}) , which is the ratio of the impact energy and the granule strength (σ_v), is used to predict granule breakage.

$$St_{def} = \frac{\rho_g v_c^{\,2}}{2\sigma_v} \qquad \textbf{Equation 4-9}$$

If the Stokes deformation number exceeds a critical value of 0.04 then granule breakage will occur, while a lower value indicates that granules remain intact [Iveson et al., 2001b]. Figure 4-4 shows

the calculated Stokes deformation numbers as a function of the viscosity and the primary particle sizes. It is clear that a decrease in the primary particle size or an increase in the viscosity results in stronger granules and a decreasing Stokes deformation number. At a certain particle size and viscosity the critical Stokes number will be reached and a shift in breakage behaviour is expected.

Figure 4-5 shows the relationship between the calculated Stokes deformation numbers for the experiments described in this study and the corresponding breakage numbers. A high Stokes deformation number is related to a large degree of breakage, while a low Stokes deformation number is associated with little breakage. The boundary between breakage and no breakage is observed at approximately 0.01, which is substantially lower than the value found by Iveson (0.04) or Tardos (0.2) [Iveson et al., 2001b, Tardos et al., 1997]. One of the reasons for this difference can be the rough estimate of the velocity of the moving particles (v_p) inside the granules, which is assumed to equal the impact velocity (v_c). This may be an overestimate, leading to an overestimate of the theoretical granule strength (see equation 4-8).

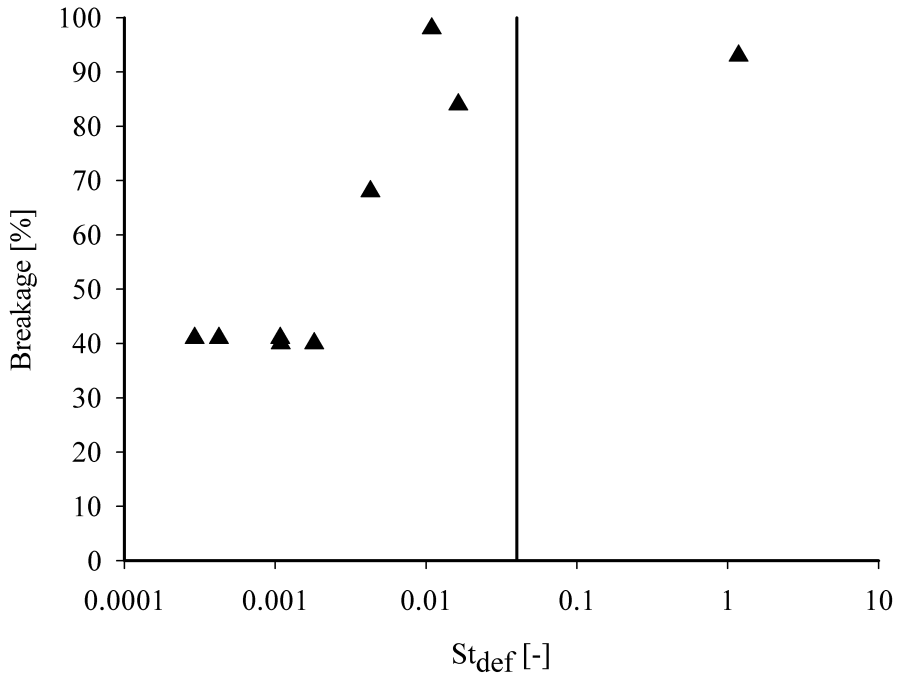

Figure 4-5 *The relationship between the Stokes deformation number and the determined breakage numbers. The vertical line represents the experimentally determined boundary between breakage and no breakage.*

4.3.2 Influence of process conditions

The previous results showed that the formulation parameters viscosity and particle size determine the eventual granule strength. The impact forces are opposing the granule strength. The balance between granule strength and impact forces determines whether breakage or no breakage behaviour of the granules will be observed. Figure 4-6 shows the breakage numbers as a function of both process times and impeller/chopper speed.

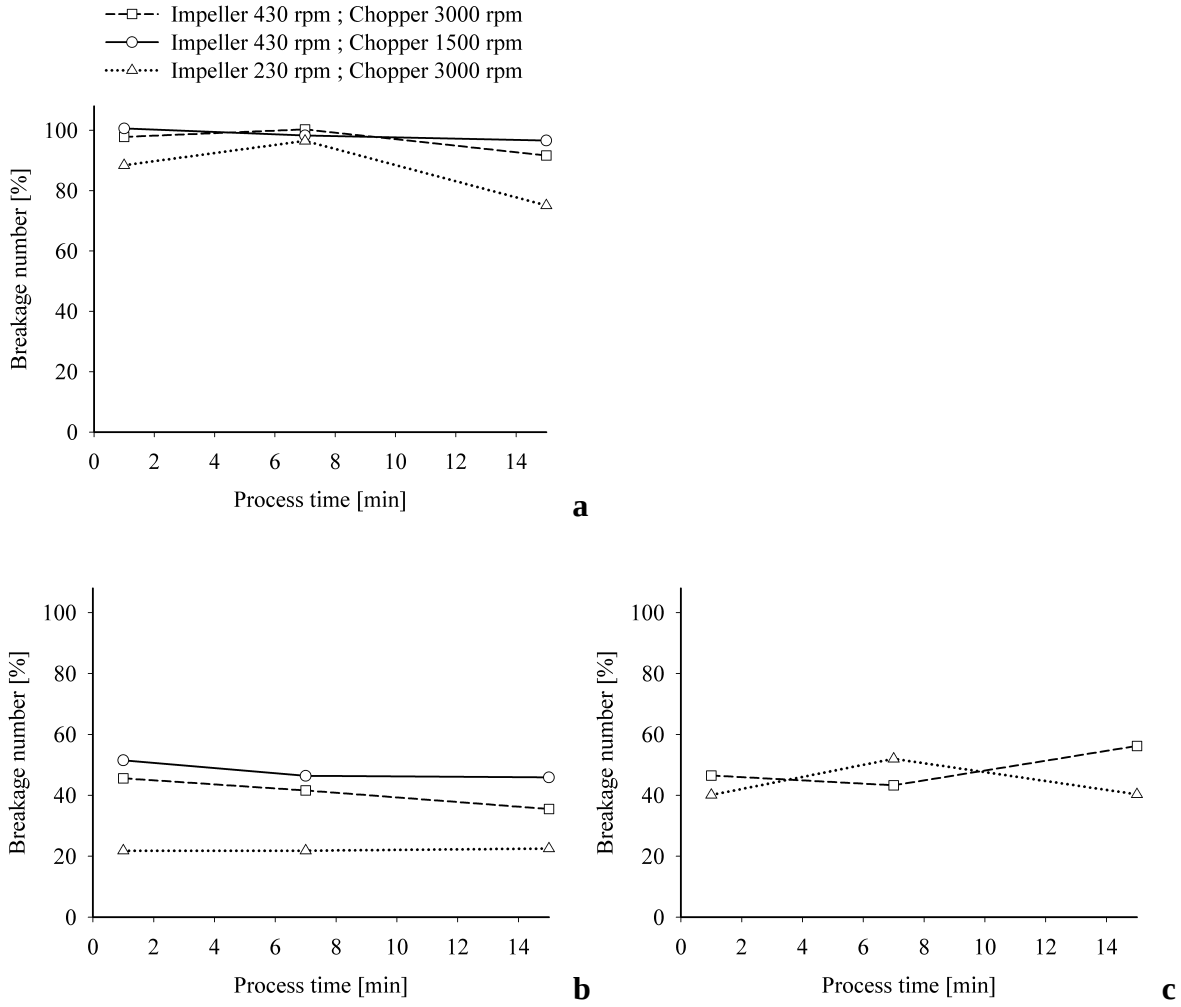

Figure 4-6 *The influence of process conditions on the breakage numbers of the lactose 100M, 200M and 450M granules.*

The figure shows that the effects of the rotation speed on breakage are small. The process time and rotation speed have little effect on the breakage behaviour. This means that the lactose 100M is in a clear breakage regime, while lactose 200M and lactose 450M exhibit significantly less breakage. In other words, the lactose 100M granules are too weak to resist the shear forces, whereas the lactose 200M/450M granules are too strong to be broken. This conclusion holds for all the process conditions investigated in this study. Only on the boundary between breakage and no breakage, a

change of the impact speed will influence the breakage behaviour. This conclusion is of importance for the growth of granules. In the no-breakage regime granules grow due to densification, so an increase of the impact speed will hasten the densification and the growth. When situated in the breakage regime, an increase in the impact speed can result in a higher extent of breakage and a decrease in growth in the breakage regime. This is probably also one of the reasons why no unambiguous influence of the impeller and chopper speed has been found in the literature. Most authors found an increasing growth rate with a higher impeller speed [Holm et al., 1984, Schæfer et al., 1992, Knight et al., 2000]. However, the opposite effect has also been found in a few experiments [Schæfer et al., 1990a, Schæfer et al., 1990b]. The same discrepancy is found for the influence of the chopper speed. Knight has found no influence of the chopper speed on the granule growth rate [Knight, 1993]. However, Hoornaert et al. showed that turning off the chopper led to a stop of granule growth [Hoornaert et al., 1998]. These examples indicate that knowledge about the granule breakage can be helpful to explain the influence of rotation speed on granule growth.

4.3.3 Relationship between breakage and homogeneity

A well-known problem of (high-shear) granulation is poor homogeneity of the granules, which is illustrated in **chapter 3**. Some granule size fractions contain consistently more drug than the average concentration, while other size fractions contain less than the average [Vromans et al., 1999]. In **chapter 3** it has been argued that granule breakage plays an important role in this phenomenon. Intensive granule breakage during growth results in a continuous exchange of primary particles between granules, resulting in homogeneous granules. If there is on the other hand no granule breakage the granules remain intact and the granules are more susceptible to a poor distribution of the ingredients. According to the preferential layering mechanism, a prolonged mixing process would result in a deterioration of the homogeneity. To test this idea the excipients distributions of some formulations (Table 4-5) were compared to the breakage behaviour of the same formulations.

Table 4-5 *Overview of the formulations used to determine the excipient homogeneity in the granulated material.*

Formulation	Binder	DP-values	Reference
1.0% Estradiol / Lactose 100M	HPC	Estradiol	[chapter 3]
1.0% Estradiol / Lactose 200M	HPC	Estradiol	[chapter 3]
1.0% Estradiol / Lactose 450M	HPC	Estradiol	[chapter 3]
Corn Starch / Lactose 200M	HPC	Corn Starch, HPC	[Oostra, 2002, de Vegt, 2001]

The ingredient distribution is expressed as the demixing potential (DP) of the excipient concentration in the sieve fractions. The demixing potential is a commonly used measure to express the (in)homogeneity of granule [Thiel and Nguyen, 1982, Vromans et al., 1999]. A higher DP indicates a poorer distribution. These DP-values of the excipients were adopted from **chapter 3** and other studies [Oostra et al., 2002, de Vegt et al., 2001], while the breakage numbers were determined by adding a tracer (erythrosine) to these formulations and performing the tracer experiments similarly to the method described above.

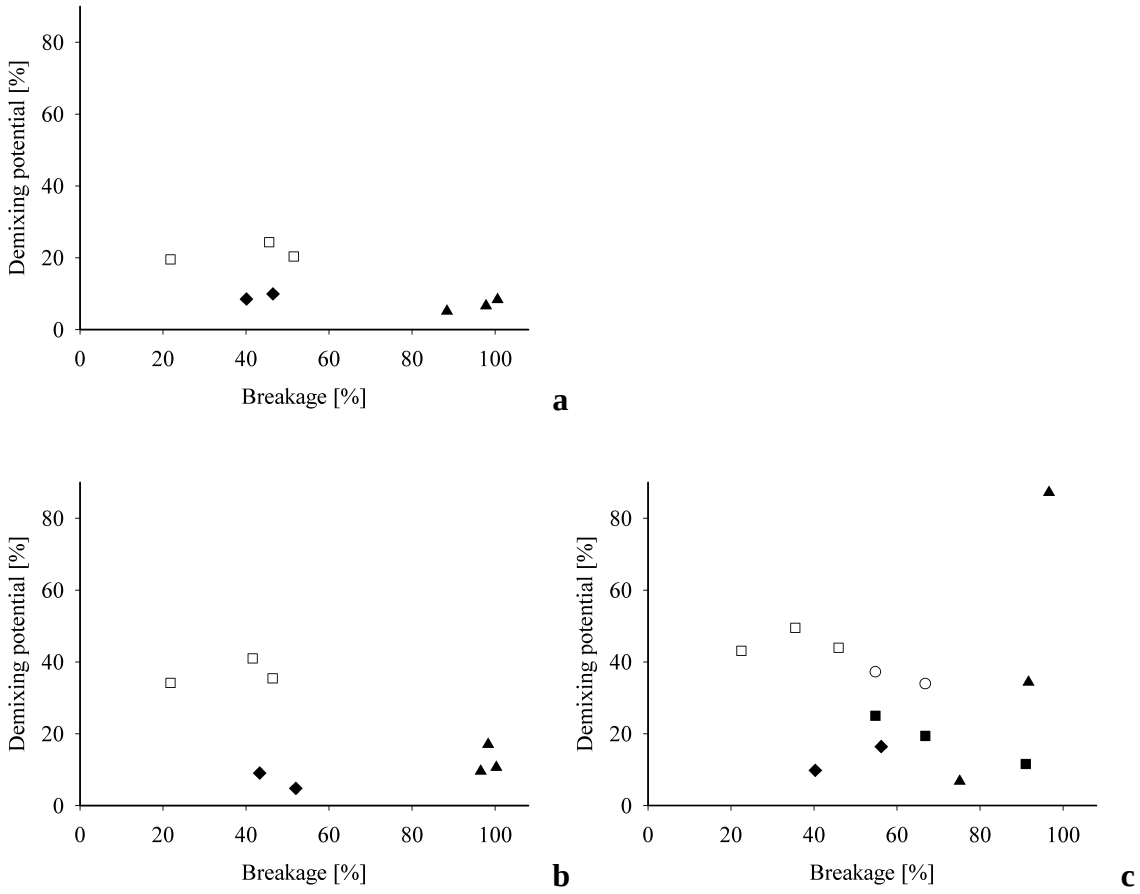

Figure 4-7 *Relationship between percentage of breakage and the distribution of various excipients (o corn starch/lactose 200M; ◆ estradiol/lactose 450M; ■ HPC/lactose 200M; □ estradiol/lactose 200M; ▲ estradiol/lactose 100M) The distribution is expressed as the demixing potential. All components were added as powder, except for HPC, which was added as an aqueous solution. (a) Process time of 1 minute, (b) 7 minutes and (c) 10,15 minutes.*

Figure 4-7 shows the relationship between the DP and breakage number after various process times. It can be seen that high breakage numbers generally result in low DP values, i.e. in a good homogeneity. When breakage is low or absent, higher values for the DP were obtained. This

tendency is enforced at prolonged mixing. However, the degree of inhomogeneity depends not only on the breakage. The particle size difference between the different excipients is also an important factor. When there is little to no breakage, granule growth occurs mainly by layering. As mentioned earlier, smaller particles have a higher affinity for layering than large particles (preferential layering). It can be concluded that a larger particle size difference between excipients results in a more extensive preferential layering. For example, the estradiol ($d_{4,3}$ ~5 µm) distribution in the lactose 200M granules is worse than for the lactose 450M granules, because of the larger particle size difference. Though, based on the particle size difference an even higher DP is expected for lactose 100M. However, the complete fragmentation of the granules prevents a poor homogeneity. Only at a process time of 15 minutes a deviating inhomogeneity behaviour is observed for lactose 100M. Despite the complete breakage inhomogeneous granules are formed. The reason for this unexpected increase in inhomogeneity is unclear. Perhaps that a changing balance between the rate of breakage and of preferential layering underlies this deviating behaviour. It is also interesting to observe the influence of breakage on the distribution of the binder (HPC). Also here a better distribution is observed with an increasing extent of breakage.

4.4 Conclusion

This study shows that the binder viscosity and primary particle size have a very large influence on granule breakage behaviour inside a high shear mixer. An higher viscosity and a smaller particle size increase the granule strength, which eventually leads to clear reduction of the breakage behaviour. Although there is still some breakage due to surface attrition, no complete fragmentation of the granules is observed. A model to predict the granule breakage behaviour shows the same influences of viscosity and particle size on breakage as was observed experimentally. There is a clear relationship between the predicted and the measured breakage behaviour, although the transition in breakage behaviour is observed at a lower Stokes deformation number than reported in literature. One of the reasons for this difference is the rough estimate of the impact velocity of the impeller/chopper blades with the granules. Measurements of the flow patterns of the granules will perhaps provide more information of the characteristic velocities inside the mixer in the future.
Granule breakage behaviour is an important factor for the granule growth mechanism. The demonstrated breakage behaviour of the lactose 100M granules leads to a growth mechanism of constant breakage and coalescence. This dynamic growth mechanism yields homogeneous granules due to rapid exchange of the primary particles during growth. Lactose 200M and 450M exhibit a

low degree of granule fragmentation upon shear. The granules that survive the shear forces remain intact and grow by densification. It is shown that this type of growth behaviour is associated with a poor distribution of the ingredients. The data seem to confirm that preferential layering is responsible for the deterioration of homogeneity in time.

4.5 List of symbols

A_{total} total amount of erythrosine in the granules [mg]
A_{tracer} total amount of erythrosine in the tracer granules [mg]
$A_{ts,i}$ total amount of erythrosine in sieve fraction *i* [mg]
$A_{ps,i}$ total amount of erythrosine in the reference granules in sieve fraction *i* [mg]
$c_{p,i}$ concentration erythrosine in the reference granules in sieve fraction *i* [mg/g]
$c_{tot,i}$ concentration erythrosine in the granules in sieve fraction *i* [mg/g]
$c_{t,i}$ concentration erythrosine in the tracer granules in sieve fraction *i* [mg/g]
$d_{3,2}$ surface mean primary particle size [µm]
$d_{4,3}$ weight mean primary particle size [µm]
F_{bond} bonding force [N]
St_{def} Stokes deformation number [-]
v_c impact velocity [m/s]
v_p relative velocity of the moving particles inside a granule [m/s]
$w_{p,i}$ mass of the reference granules in sieve fraction *i* [g]
$w_{tot,i}$ total mass of sieve fraction *i* [g]
ε porosity [-]
ρ_g granular density [kg/m^3]
μ viscosity [Pa.s]
σ granule strength [Pa]
σ_v dynamic granule strength [Pa]

4.6 References

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5

Experimental and modelistic approach to explain granule inhomogeneity through preferential growth

Abstract

Wet granulation of a powder mixture often leads to accumulation of the smallest particles in the large granules. The preferential uptake of these particles results in an inhomogeneous granules. The aim of this study was to investigate the mechanism of preferential growth. For that purpose the growth of one single granule was followed by adding a droplet of binder liquid to a rotating powder mixture of paracetamol and lactose. The particle sizes of both components were varied. At various time points mass and paracetamol content of the granule was determined. The results showed in all cases that the fine particles have a relatively higher presence in the granule than the coarse particles. These observations were independent of the fact whether the fine particles consist of lactose or paracetamol. During layering growth of the granule, caused by radial penetration of the liquid, fine particles appear to have a higher affinity for growth than coarse particles. It was argued that small particles penetrate the pores of the granule more easily than large particles, leading to the preferential adsorption of the fine constituents. A model based on this growth mechanism was able to predict the experimental results. It was concluded that this non-random growth process underlies the formation of inhomogeneous granules.

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5.1 Introduction

Wet granulation is a process intended to enlarge the particle size of powder. Primary particles are bound together by a binder liquid, resulting in the formation of granules. The powder mixture often consists of several different ingredients, which vary, amongst others, in primary particle size. It is obvious that every granule should contain the same proportion of excipients as the originating powder mixture. However, this is not always the case. Several studies have shown an inhomogeneous distribution of the excipients in the granules [Egermann and Reiss, 1988, Hapgood et al., 2002, Kapur et al., 1993, Oijle et al., 1982, Oostra et al., 2002, Plank et al., 2001, Scott et al., 2000, de Vegt et al., 2001, Vromans et al., 1999]. The inhomogeneity phenomena are also illustrated in **chapter 3**. For the pharmaceutical industry, where wet granulation is a frequently used process step, a poor distribution of the drug may lead to problems with the content uniformity of the ultimate dosage form (capsule, tablet). Understanding of the mechanisms underlying the formation of inhomogeneous granules is essential for an adequate development of a formulation, which meets the quality specifications.

In literature three distinct profiles of drug distribution in the granules have been reported, depending on the particle size of the drug and excipients. When the drug substance possesses the smallest particle size, often accumulation in the larger granules is observed [**Chapter 3**, Egermann and Reiss, 1988, Vromans et al., 1999]. On the other hand, when the excipients have a smaller particle size than the drug substance, accumulation of these particles in the large granules occurs, leading to depletion of the drug in those granules [Egermann and Reiss, 1988, Hapgood et al., 2002]. Both cases lead to inhomogeneous granules. Homogeneous granules are obtained when the drug substance and excipients have equal particle sizes [**Chapter 3**, Egermann and Reiss, 1988, Vromans et al., 1999]. The accumulation of small particles in the larger granules is not only observed for a multi-component powder mixture. Scott et al. and Kapur et al. showed that granules consisting of one single powder, the smaller primary particles accumulate in the larger granules [Scott et al., 2000, Kapur et al., 1993]. Remarkably, a particle size difference between drug substance and excipients does not always yield inhomogeneous granules. In **chapter 3** was shown that wet granulation of coarse lactose particles (170 µm) with fine estradiol particles (5 µm) yielded homogeneous granules in many cases.

In **chapter 3** two distinct mechanisms responsible for the formation of (in)homogeneous granules were proposed, namely granule breakage and preferential layering. The relationship between granule breakage behaviour and (in)homogeneity has already extensively been investigated in **chapter 4**. It was shown that granule breakage, causing a continuous exchange of primary particles, yielded homogeneous granules, despite the existence of a considerable particle size difference between the various components. On the other hand, once granule breakage is minimal the smaller particles accumulate in the larger granules resulting in inhomogeneous granules. If granule breakage is minimal, granules predominately grow by layering. Layering growth has already been identified as a general granule growth mechanism in the seventies [Sastry and Fuerstenau, 1973]. In **chapter 3** and **4** it has been argued that during layering growth, smaller primary particles have a higher affinity for layering than the larger particles. In other words there is preferential growth of the smaller particles. However, the mechanism of the preferential growth is poorly understood. The aim of this study is to elucidate the mechanism of the preferential growth. Moreover, a mechanistic model is proposed to predict the preferential growth.

5.2 Experimental

5.2.1 Materials

Table 5-1 *Overview of the mixtures used for the single granule growth experiments.*

Powder mixture	Concentration Paracetamol	Lactose		Paracetamol	
		$d_{4,3}$ [µm]	Span	$d_{4,3}$ [µm]	Span
Lactose 100M / paracetamol 45	1-80 mg/g	170	1.17	8 µm	2.33
[2]Lactose 75-106 µm / paracetamol 45	1-30 mg/g	115	1.05	8 µm	2.33
[2]Lactose 106-150 µm / paracetamol 45	1-30 mg/g	168	0.91	8 µm	2.33
[2]Lactose 150-212 µm / paracetamol 45	1-30 mg/g	230	0.87	8 µm	2.33
Lactose 100M / paracetamol 90-500	10 mg/g	170	1.17	166 µm	2.11
[2]Lactose 75-106 µm/ paracetamol >212 µm	10 mg/g	115	1.05	326 µm	0.66
Lactose 100M / [1]x mg/g lactose 450M / paracetamol 45	10 mg/g	170, 19	1.17, 2.35	8 µm	2.33

[1]x varies from 1-50 mg/g
[2]fractions were obtained by sieving lactose 100M; the size interval indicates the sieves that were used

Mixtures of paracetamol (BuFa, Uitgeest, The Netherlands) and lactose monohydrate (DMV, Veghel, The Netherlands) were used for the experiments. The particle size and the concentration of paracetamol and lactose were varied. The characteristics of powder mixtures that were used for the single granule growth experiments are listed in Table 5-1. The particle size of the constituents was measured with laser diffraction (Malvern Mastersizer S). A 1.5% (w/w) aqueous solution of

hydroxypropyl cellulose (HPC, Klucel EP, Aqualon, Wilmington, USA) with a viscosity of 13 mPa.s (Brookfield Rheometer, Model DV-III) was used as the binder solution.

5.2.2 Methods

To investigate the mechanism of preferential growth, the growth and homogeneity of one single granule was followed in time. For this purpose, approximately 10 gram of a binary mixture of paracetamol and lactose was weighed into a conical flask of 100 ml. The powder mixture was premixed for 30 minutes (Turbula T2C, Willy A. Bachofen AG machinefabrik, Switzerland). A volume of 100 µl binder solution was added to this powder mixture, which results in the formation of one single granule. Radial penetration of the binder liquid into the powder results in growth of the granule by layering. The granule remains intact during the process. The conical flask rotated slowly (16 rpm) to assure continuous refreshment of the primary particles in the vicinity of the (wet) granule. At various time points (60, 180, 300 and 600 seconds) the granule was isolated from the powder mixture and dried in a vacuum oven at 40°C for 2 hours. For each time point five different granules were produced. The mass of the granule was determined and the paracetamol content was analysed with UV spectroscopy. The porosity of the dried granule was measured with mercury intrusion porosimetry (Autopore II 9220, Micromeretics, USA). The porosity data were used to calculate the saturation in the granule at the different time points using the following equation,

$$S = \frac{V_{liquid}}{V_{air}} = \frac{V_{liquid}\,\rho(1-\varepsilon)}{w_a \varepsilon} \qquad \textbf{Equation 5-1}$$

In which w_a is the mass of the granules, ε is the porosity, ρ the density of the powder mixture, V_{liquid} the volume of the added binder liquid (100 µl) and V_{air} the volume of air in the dry granule. There is a small discrepancy between the calculated saturation level and the real saturation level. The calculation is based on porosity measurements of dry granules. In the wet state some lactose will dissolve, which crystallises when the granules are dried. Hence, the calculated saturation will be slightly higher than the real saturation.

5.3 Results and discussion

Figure 5-1 shows the mass of the granules at different time points and their corresponding paracetamol concentrations for the 10 mg/g paracetamol 45/lactose 100M mixture. In the growth curve (Figure 5-1a), two different growth phases can be distinguished. The mass increase during the first 60 seconds is very rapid, while after 60 seconds a clear decrease in growth rate is observed.

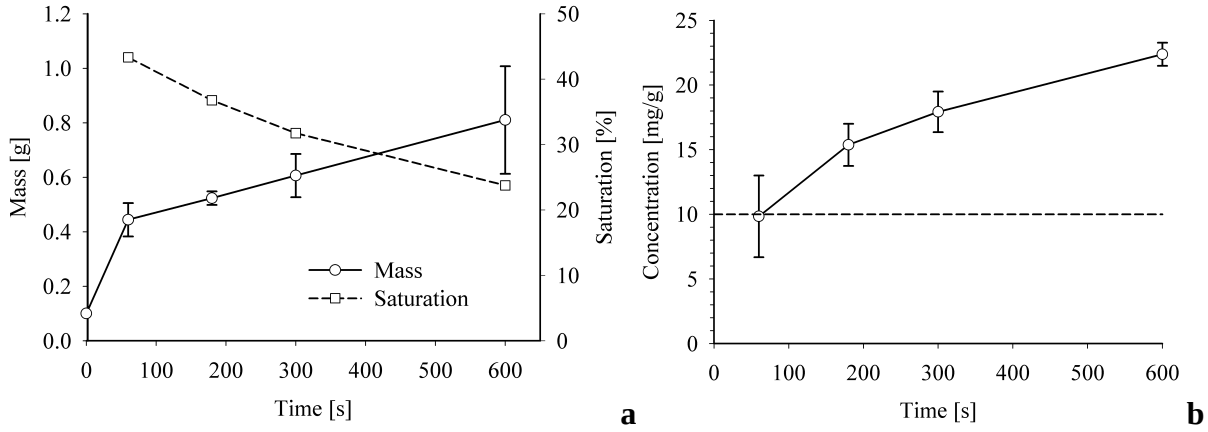

Figure 5-1 *The influence of process time on;* ***(a)*** *The mass increase and the saturation level of the granules and* ***(b)*** *the concentration of paracetamol in the corresponding granules originating from the 10 mg/g paracetamol 45/lactose 100M mixture ($d_{4,3}$~ 170 µm/8 µm). The error bars indicate the 95% confidence interval (n=5).*

The two stages of growth have been identified in many other processes in which the capillary penetration of liquid into porous media is involved [Danino and Marmur, 1994, Gillespie, 1958, Hapgood, 2002, Schaafsma et al., 1998]. The first (rapid) growth phase is caused by the penetration of the binder liquid in the powder bed [Denesuk et al., 1993, Hapgood, 2000, Middleman, 1995, Washburn, 1921]. After liquid penetration, drainage of the liquid to the outer surface of the granule and the subsequent adherence of primary powder particles to the newly wetted surface is responsible for the second layering growth, phase [Butensky and Hyman, 1971, Danino and Marmur, 1994, Gillespie, 1958, Schaafsma et al., 1998]. During this phase the saturation is well below the 100%, indicating that the pores are only partly filled with binder liquid (Figure 5-1a). Figure 5-1b shows that the two phases of growth also have a clear effect on the paracetamol content of the granule. In the first phase, the concentration of the granule equals the paracetamol concentration in the powder mixture, while further granule growth is associated with an increase in

the concentration. Apparently, the small paracetamol particles have a higher affinity for granule growth than lactose.

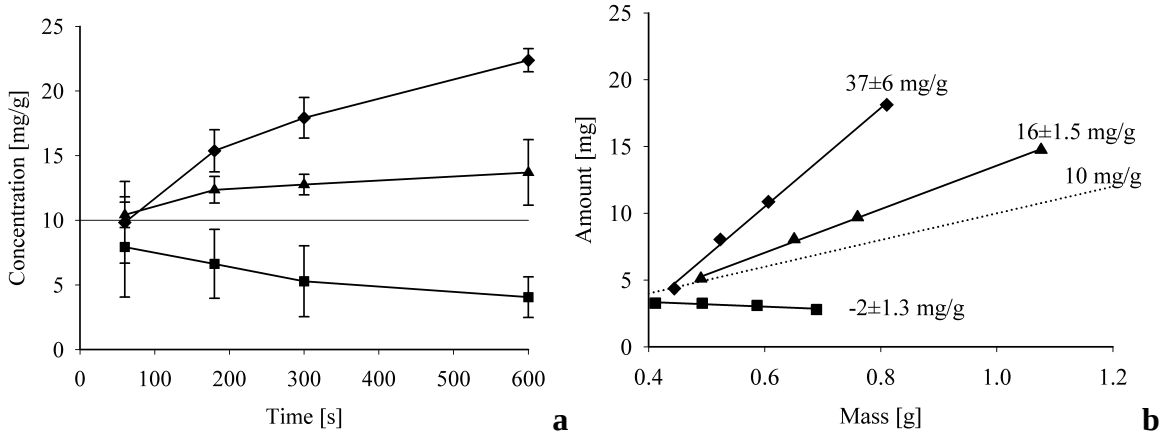

Figure 5-2 ***(a)*** *Influence of process time on the paracetamol concentration in the granules.* ***(b)*** *Relationship between granule mass and the amount of paracetamol in the corresponding granules. The slope of the lines (± 95% C.I.) equals the paracetamol increase during growth. The dashed lines correspond with the powder bed concentration of paracetamol. ◆ 10 mg/g paracetamol 45/lactose 100M($d_{4,3}$~8 µm/170 µm). ■ 10 mg/g paracetamol >212 µm/lactose 75-106 µm ($d_{4,3}$~326 µm/115 µm). ▲ 10 mg/g paracetamol 90-500/lactose 100M ($d_{4,3}$~166 µm/170 µm). The error bars indicate the 95% confidence interval (n=5).*

In Figure 5-2a, the particle sizes of the two constituents are varied. Obviously, the particle size has a significant effect on the outcome. When the particle size of paracetamol is smaller than that of lactose, an increase in paracetamol concentration is observed. In contrast, an inversion of the particle sizes difference results in a decrease in the paracetamol concentration in the granule during growth. A plot of the granule mass against the amount of paracetamol in the corresponding granules shows a linear relationship (Figure 5-2b). The slope of this line represents the concentration increase of paracetamol during granule growth. Theoretically, the slope should equal 10 mg/g, if the granule grows proportionally to the paracetamol/lactose ratio in the powder mixture. Hence, a larger slope than 10 mg/g means that paracetamol particles adhere preferentially to the granules, whereas a smaller slope than 10 mg/g is associated with preferential growth of lactose. The difference between the theoretical slope and the determined slope is a value for the affinity of paracetamol for growth. This value is used throughout the remainder of this article as a measure for the preferential growth. The values for preferential growth can be derived from Figure 5-2b. The preferential growth for the paracetamol 45/lactose 100M mixture is 27 mg/g (37 mg/g minus 10 mg/g). An increase in the particle size of paracetamol leads to a preferential growth of 6 mg/g. Hence, an equal particle size

of paracetamol and lactose obviously results in the reduction of the preferential growth. A further increase in paracetamol size results in a value of –12 mg/g. The negative value for preferential growth signifies that predominantly lactose is bound to the granule. These results indicate that a higher affinity of primary particles for growth depends on the particle size. The constituent with the smallest particle size exhibits the highest affinity.

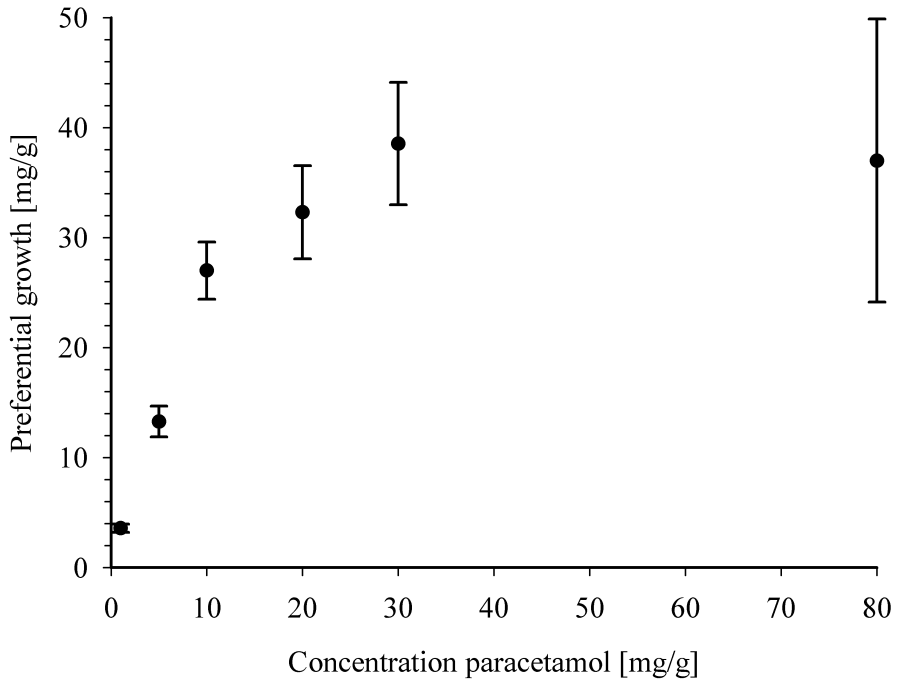

Figure 5-3 *Influence of paracetamol concentration in the lactose 100M/paracetamol 45 mixture ($d_{4,3}$~230 µm/8 µm) on the preferential growth of paracetamol. The error bars indicate the 95% confidence interval.*

It is likely that the affinity for growth will also depend on the concentration of both constituents in the powder mixture. For that reason the influence of the paracetamol concentration on the growth was investigated. The results are shown in Figure 5-3. In first instance, the value for preferential growth increases with an increasing proportion of paracetamol in the powder bed. Beyond a paracetamol concentration of 30 mg/g no further increase is observed. It can be argued that the extent of preferential growth is determined by an equilibrium between the kinetics of granule growth (growth rate) and the availability of free paracetamol particles in the vicinity of the granule surface (rate of refreshment). The maximum value for preferential growth in Figure 5-3 seems to indicate that at a certain paracetamol concentration, the refreshment rate of the paracetamol

particles exceeds the growth rate, leading to saturation of the system and a maximum of preferential growth.

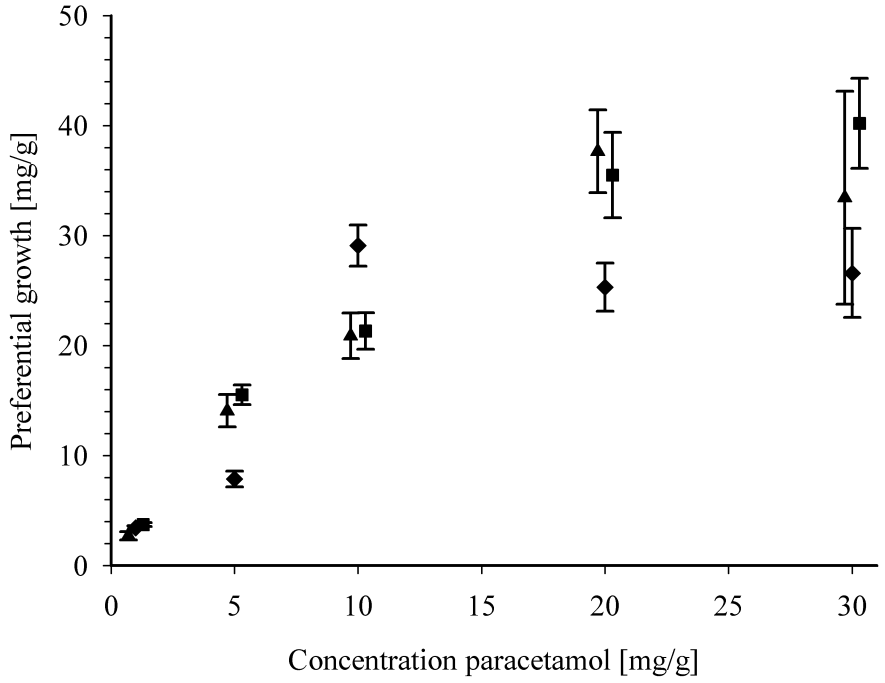

Figure 5-4 *Influence of the particle size of lactose on the preferential growth of paracetamol at different concentrations of paracetamol. ◆ Lactose 75-106 µm/paracetamol 45 ($d_{4,3}$~115 µm/8 µm) ■ Lactose 106-150 µm/paracetamol 45 ($d_{4,3}$~168 µm/8 µm) ▲ Lactose 150-212 µm/ paracetamol 45 ($d_{4,3}$~230 µm/8 µm). The error bars indicate the 95% confidence interval.*

Figure 5-2 and Figure 5-3 show that both the particle size and the concentration of paracetamol have a large influence on the extent of preferential growth. Of course also the particle size of the bulk material (i.e. lactose) can be varied. This will have an effect on the granule pore structure, which is very much less the case when the minor components' particle size is changed. The influence of the lactose particle size on the extent of preferential growth of paracetamol is shown in Figure 5-4. It shows that although the particle size difference between the various lactose grades is substantial, the influence on preferential growth is minimal. Only for the lactose 75-106 µm mixture a small decrease in the preferential growth of paracetamol is observed compared to the other mixtures, whereas no difference is observed between the lactose 106-150 µm and lactose 150-212 µm mixtures An additional experiment was performed where a part of the coarse lactose 100M ($d_{4,3}$~170 µm) was replaced by an equal amount of the fine lactose 450M ($d_{4,3}$~19 µm). Lactose 450M has approximately the same particle size as paracetamol 45. Figure 5-5 shows that an

increasing amount of fine lactose in the powder mixture results in a decrease in the preferential growth of paracetamol. At a concentration of 50 mg/g lactose 450M preferential uptake of paracetamol does not take place any more, but is obviously displaced by the fine lactose.

Table 5-2 *Primary particle size of the powder mixtures and pore size, porosity data of the resulting granules.*

Mixture	Particle size [$d_{4,3}$]	Average Pore size	Porosity
Lactose 75-106 µm	115 µm	32 µm	46%
Lactose 106-150 µm	168 µm	44 µm	44%
Lactose 150-212 µm	230 µm	62 µm	44%
Lactose 100M	170 µm	36 µm	43%
Lactose 100M/10 mg/g lactose 450M	163 µm	37 µm	44%
Lactose 100M/30 mg/g lactose 450M	166 µm	35 µm	43%
Lactose 100M/50 mg/g lactose 450M	156 µm	33 µm	43%

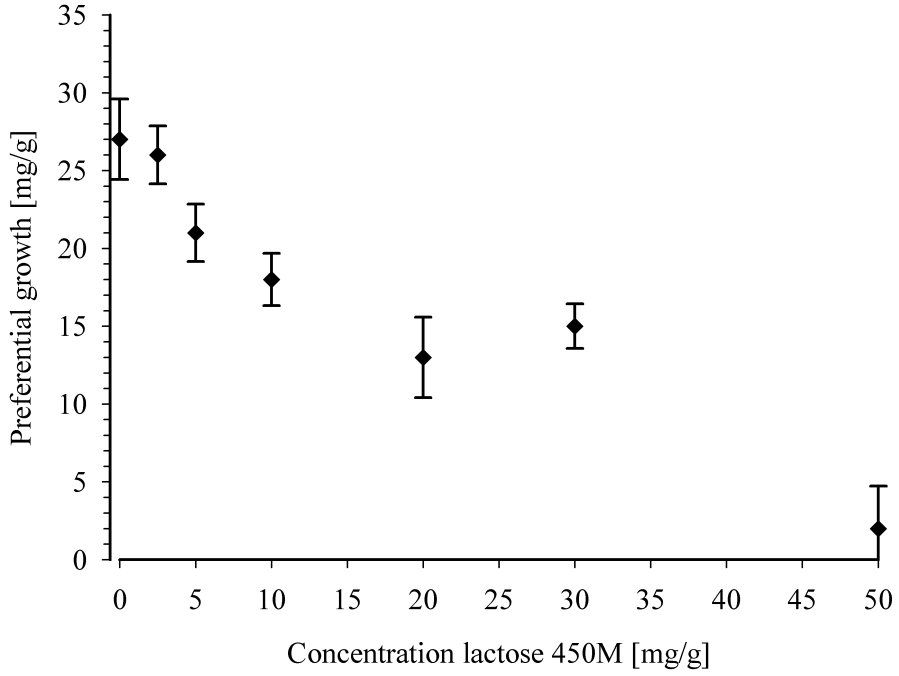

Figure 5-5 *The preferential growth of paracetamol as a function of the concentration of lactose 450M in the mixture of 10 mg/g paracetamol 45/lactose 450M/lactose 100M ($d_{4,3}$~8 µm/19 µm/170 µm). The error bars indicate the 95% confidence interval.*

Figure 5-4 shows that a change in lactose particle size only has a minor effect on the extent of preferential growth, while the addition of fine lactose to the mixture leads to a clear reduction (Figure 5-5). Table 5-2 shows that the effect of both variations on granule pore size is the reverse. A

decrease in lactose particle size results in a decrease in pore size, while the porosity remains constant. Although the pore structure of these granules changes, a decrease in lactose size appears to have only a minor effect on the preferential growth of paracetamol. On the other hand, addition of fine lactose does not influences the granule pore size, while the effect on preferential growth is large. Based on these observations it is argued that although a particle size difference between lactose and paracetamol underlies the preferential growth, it does not determine the degree of the preferential growth. Instead, the results suggest that the particle size overlap between lactose and paracetamol is an important factor for the extent of preferential growth. The significance of this observation becomes clear in the remainder of this article.

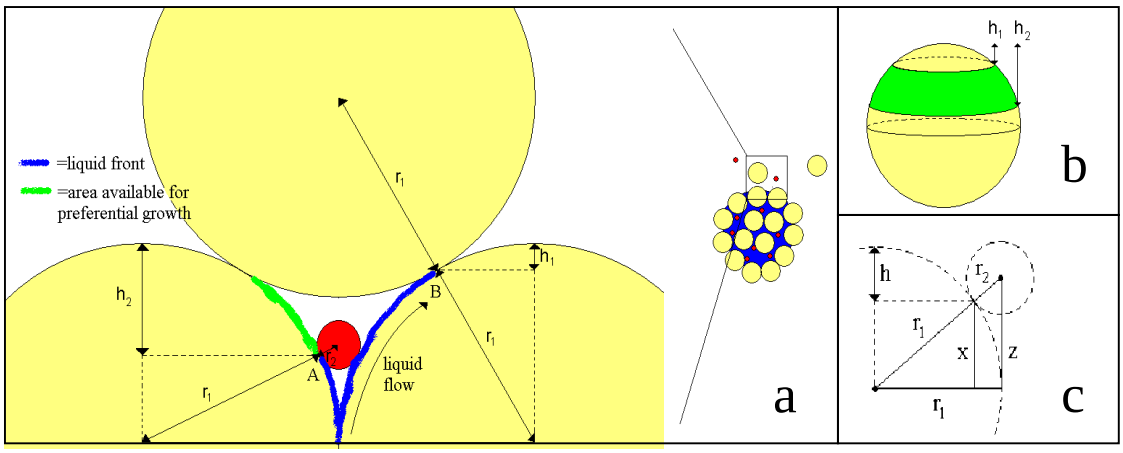

Figure 5-6 ***(a)*** *overview of the proposed mechanism of preferential growth.* ***(b)*** *3-Dimensional depiction of the area available for preferential growth. Equation 5-4 can be used to calculate this area for a sphere (see text for further explanation).* ***(c)*** *Trigonometric picture of the preferential growth model.*

The results of the single granule growth experiments show that;

- A particle size difference between lactose and paracetamol results in preferential growth of the smallest particles (Figure 5-1, Figure 5-2).
- An increase in paracetamol concentration in the mixture results in an increase in preferential growth until a maximum value is reached (Figure 5-3, Figure 5-4).
- A change in granular structure, caused by a change in lactose size, does not lead to a substantial change in the degree of preferential growth (Figure 5-4).
- Replacement of a small part of the coarse lactose particles in the mixture by fine lactose particles leads to a significant decrease in preferential growth (Figure 5-5).

In the remainder of this article a model for the preferential growth is proposed in an attempt to explain these results. A schematic picture of the model is shown in Figure 5-6. The model is based

on a powder mixture, consisting of two components, with different particle sizes. It is assumed that the particle sizes of these components are mono-sized and that the particles are spherical. The coarse particles represent the major component (lactose) and the fine particles the minor component (paracetamol) in the mixture

When the binder solution is added, liquid flow is responsible for the growth of the granule. The capillary pressure difference existing between the pores inside and pores at the boundary of the granule is the driving force for liquid flow to the outer surface of the granule. Gradually the pores will be filled with liquid [Schaafsma et al., 1998]. The pores in the granules are not completely filled with liquid, because the saturation is much smaller than 100%. Therefore, only a layer of liquid is indicated in Figure 5-6. At a certain point the level of the liquid front is far enough to assure binding of the fine particles, which have penetrated the pores (point A in Figure 5-6). Particles that are still too large to enter the pores will encounter a dry surface and will hence not be bound. In this stage the surface of the granule seems dry for coarse particles, while it is wet for fine particles leading predominantly to growth of the fine component. The distance (h_2) of the liquid front at point A to the outer surface of the granule can be calculated for perfectly round particles

$$h_2 = r_1\left(1-\frac{\sqrt{2r_1r_2+r_2^2}}{r_1+r_2}\right) \qquad \textbf{Equation 5-2}$$

In which r_1 is the radius of the coarse particle and r_2 the radius of the fine particle. A complete derivation of equation 5-2 is given in the appendix. The preferential growth of the small particles will stop if the liquid front has reached the point when also the large particles can adhere (point B in Figure 5-6). Again, this distance of the liquid front at point B to the outer surface (h_1) can be calculated with equation 5-2. In this case r_2 equals r_1, so equation 5-2 will become,

$$h_1 = (1-\tfrac{1}{2}\sqrt{3})r_1 \qquad \textbf{Equation 5-3}$$

The surface area on the particle between h_1 and h_2 is only available for the adherence of the fine particles leading to the preferential growth. When the liquid front reaches point B all particles can adhere independent of their size.

The preferential growth model comprises in fact a two-step process. First of all only the fine particles are adhered. When also the coarse particles encounter a wet surface a new layer of particles will be formed around the granule. The composition of this layer is equal to the proportion (concentration) of the coarse and fine particles in the mixture. The two-step process, preferential

growth followed by the formation of a new layer, is repeated as long as the saturation in the granule is sufficiently high to assure further growth.

The model can be extended to a 3-dimensional structure of the granule by calculating the surface area that is available for preferential growth on a spherical particle (Figure 5-6b). This surface area (the area between h_1 and h_2) for a spherical particle is,

$$A = 2\pi r_1 (h_2 - h_1) = 2\pi r_1^2 \left(\tfrac{1}{2}\sqrt{3} - \frac{\sqrt{2r_1 r_2 + r_2^2}}{r_1 + r_2} \right) \qquad \textbf{Equation 5-4}$$

An assumption is that the total area A is available for preferential growth of the fine particles. The projected area of a fine particle is πr_2^2. Hence, the maximum number of particles (N_2) that can adhere to the surface area A is,

$$N_2 = \frac{A}{\pi r_2^2} = \frac{2r_1^2}{r_2^2} \left(\tfrac{1}{2}\sqrt{3} - \frac{\sqrt{2r_1 r_2 + r_2^2}}{r_1 + r_2} \right) \qquad \textbf{Equation 5-5}$$

In this equation it is assumed that only a monolayer of small particles adheres to the surface of the large particle. The total volume of these adhered particles is,

$$V_2 = \tfrac{4}{3}\pi r_2^3 N_2 = \tfrac{8}{3}\pi r_1^2 r_2 \left(\tfrac{1}{2}\sqrt{3} - \frac{\sqrt{2r_1 r_2 + r_2^2}}{r_1 + r_2} \right) \qquad \textbf{Equation 5-6}$$

The volume of one coarse particle is,

$$V_1 = \tfrac{4}{3}\pi r_1^3 \qquad \textbf{Equation 5-7}$$

It is possible to calculate the mass ratio of the large particle to the small particles with the densities of both components. This mass ratio is a measure for the preferential growth of the fine particles. The maximum value for preferential growth (i.e. complete surface available is covered with a mono-layer of fine particles) is given by

$$P_{\max} = \frac{V_2 \rho_2}{V_1 \rho_1} = \frac{2r_2 \rho_2}{r_1 \rho_1} \left(\tfrac{1}{2}\sqrt{3} - \frac{\sqrt{2r_1 r_2 + r_2^2}}{r_1 + r_2} \right) \qquad \textbf{Equation 5-8}$$

This value for preferential growth indicates that a certain mass percentage of fine particles adhere on a large particle. The values for $P_{max,}$ which have been calculated with equation 5-8, for the different lactose/paracetamol mixtures are shown in Table 5-3. Whether the complete surface will

be covered and whether the maximum value for preferential growth is reached, depends on the availability of the fine particles and on the growth rate of the granule.

Figure 5-3 and Figure 5-4 actually show maximum values at higher concentrations of paracetamol. To compare the predicted maximum preferential growth values with the experimental values, the curves in Figure 5-3 and Figure 5-4 are fitted with the following function;

$$P_c = P_{\max,\,fit}(1 - e^{-kC_p}) \qquad \textbf{Equation 5-9}$$

In which C_p is the concentration of paracetamol in the mixture and P_c is the preferential growth at concentration C_p and *k is* an overall constant, which is a term for the growth and mixing kinetics. The curves in Figure 5-3 and Figure 5-4 are fitted with equation 5-9 for $P_{max,fit}$ and *k*. These values are listed in Table 5-3. Combination of equation 5-8 and 5-9 leads to a term to calculate the preferential growth at various concentrations of paracetamol.

$$P_c = \frac{2r_2\rho_2}{r_1\rho_1}\left(\tfrac{1}{2}\sqrt{3} - \frac{\sqrt{2r_1r_2 + r_2^2}}{r_1 + r_2}\right) * (1 - e^{-kC_p}) \qquad \textbf{Equation 5-10}$$

The predicted values and the measured values for the preferential growth of paracetamol in the different lactose mixtures are listed in Table 5-3. Despite the fact that the paracetamol and lactose particles are neither spherical nor mono-sized, the data in Table 5-3 show a good correspondence between the two values. Only the paracetamol 45/lactose 75-106 µm mixtures show a relatively large difference between experimental and predicted values.

The experimental results show that, once there is a particle size difference between paracetamol and lactose, a change in the particle size of lactose and granule pore structure has only a minor effect on the preferential growth of paracetamol (Figure 5-4). The model can help to explain this observation. A decrease in the particle size of lactose (r_1) results in a decrease of the area available for preferential growth per particle (equation 5-4). However, the weight of the lactose particle (r_1) also decreases with a decreasing particle size. The net effect is an increase in the predicted preferential growth. Although the predicted increase is not observed in the experiments, the model largely supports the observation that a decrease in particle size difference between lactose and paracetamol only results in a small change of the preferential growth.

Moreover, the experiments showed that addition of fine lactose to the powder mixture does result in a reduction of preferential growth (Figure 5-5). Only lactose particles small enough to penetrate the pores can compete with the paracetamol particles for adherence on the surface area available for the preferential growth of paracetamol. This will lead to dilution of the paracetamol on the surface of

the granule. The amount of paracetamol on the surface will now depend on the ratio of paracetamol compared to the total concentration of fine particles (lactose 450M plus paracetamol). This ratio is expressed as,

$$\frac{Conc.\ paracetamol}{Total\ conc.\ fine\ particles} = \frac{C_p}{C_p + 0.45C_{450M}} \qquad \textbf{Equation 5-11}$$

In which C_p is the concentration of paracetamol, C_{450M} the concentration lactose 450M in the powder mixture. The lactose 450M particles are slightly larger than the paracetamol particles, so there is no complete overlap in particle size for lactose and paracetamol. The actual particle size overlap between lactose and paracetamol is approximately 45%. This value of 0.45 is used as a correction factor for the lactose 450M concentration in equation 5-11. With the help of this ratio the preferential growth at different concentration of the fine lactose ($P_{c,450M}$) can be calculated with

$$P_{c,450M} = \frac{P_c C_p}{C_p + 0.45C_{450M}} \qquad \textbf{Equation 5-12}$$

In which P_c is the value for preferential growth in absence of the fine lactose (equation 5-10). The results of the calculations are shown in Table 5-4. The good correspondence between the experimental and the predicted preferential growth indicate that the proposed mechanisms for preferential growth are plausible.

From the single granule growth experiments it can be concluded that a particle size difference between lactose and paracetamol leads to preferential growth of the smallest particles in the mixture. The results of the single granule growth experiments correspond with the phenomena observed for granule (in)homogeneity in the high shear granulator [**chapter 3**]. In both cases the particles with the smallest size accumulate in the granules during growth, resulting in inhomogeneity. The single granule growth experiments showed that when the smallest particle is a drug substance an increased concentration of the drug substance in the granule is observed, while if the drug substance is the largest particle a decreased drug concentration is observed. Moreover, both the single granule growth and the granulation process show that granulation with excipients with equal particle sizes results in more homogeneous granules [Vromans et al., 1999]. Similar behaviour of a drug substance has been observed inside the granulator [**Chapter 3**, Egermann and Reiss, 1988, Hapgood et al., 2002, Vromans et al., 1999]. However, the granules in the single granule growth experiments remain intact during the process of granule growth, but also for the

granulator holds that inhomogeneous granules are formed when the granules are not broken during the granulation process, while breakage prevents the formation of inhomogeneous granules [**chapter 4**].

Table 5-3 *Comparisons of the predicted and the experimental values for preferential growth of paracetamol for different lactose/paracetamol mixtures. The predicted values were calculated with equation 5-11. The values for k, r_1 and r_2, which were used for the calculation, are also shown. Lactose density 1.54 g/cm^3 (ρ_1), paracetamol density 1.29 g/cm^3 (ρ_2).*

Experiment	**Lactose 100M / paracetamol 45**		
k=81	[1]P(max,fit)=40 mg/g	[2]P(max)=45 mg/g	
r_1=170 µm	r_2=8 µm		
Concentration	Preferential growth [mg/g]		
paracetamol	Prediction	Experimental	Difference
1.0 mg/g	3.5	3.6	0.1
5.0 mg/g	15.0	13.3	-1.7
10.0 mg/g	25.0	27.0	2.0
20.0 mg/g	36.1	32.3	-3.8
30.0 mg/g	41.0	38.5	-2.5
80.0 mg/g	44.9	37.0	-7.9

Experiment	**Lactose 106-150 µm / paracetamol 45**		
k=72	[1]P(max,fit)=43 mg/g	[2]P(max)=45 mg/g	
r_1=168 µm	r_2=8 µm		
Concentration	Preferential growth [mg/g]		
paracetamol	Prediction	Experimental	Difference
1.0 mg/g	3.1	3.7	0.6
5.0 mg/g	13.7	15.5	1.9
10.0 mg/g	23.2	21.3	-1.9
20.0 mg/g	34.6	35.5	0.9
30.0 mg/g	40.1	40.2	0.1

Experiment	**Lactose 75-106 µm / paracetamol 45**		
k=143	[1]P(max,fit)=28 mg/g	[2]P(max)=60 mg/g	
r_1=115 µm	r_2=8 µm		
Concentration	Preferential growth [mg/g]		
paracetamol	Prediction	Experimental	Difference
1.0 mg/g	8.0	3.4	-4.5
5.0 mg/g	30.5	7.9	-22.6
10.0 mg/g	45.4	29.1	-16.4
20.0 mg/g	56.3	25.3	-31.0
30.0 mg/g	58.9	26.6	-32.3

Experiment	**Lactose 150-212 µm / paracetamol 45**		
k=91	[1]P(max,fit)=39 mg/g	[2]P(max)=36 mg/g	
r_1=230 µm	r_2=8 µm		
Concentration	Preferential growth [mg/g]		
paracetamol	Prediction	Experimental	Difference
1.0 mg/g	3.1	2.7	-0.4
5.0 mg/g	13.0	14.1	1.0
10.0 mg/g	21.3	20.9	-0.4
20.0 mg/g	29.9	37.7	7.8
30.0 mg/g	33.3	33.4	0.2

[1]*Fitted with equation 5-9*
[2]*Calculated with equation 5-8*

Table 5-4 *Comparisons of the predicted and the experimental values for preferential growth of paracetamol for different concentrations of lactose 450M in the lactose/paracetamol mixtures. The predicted values were calculated with equation 5-12. The values for k, r_1 and r_2, which were used for the calculation, are also shown. Lactose density 1.54 g/cm^3 (ρ_1), paracetamol density 1.29 g/cm^3 (ρ_2).*

Experiment	**Lactose 100M/ Lactose 450M/ Paracetamol 45**		
k=81	[1]P(max,fit)=40 mg/g	[2]P(max)=45 mg/g	
r_1=170 µm	r_2=8 µm		
Concentration	Preferential growth [mg/g]		
lactose 450M	Prediction	Experimental	Difference
0 mg/g	25.0	27.0	2.0
2.5 mg/g	22.4	26.0	3.6
5.0 mg/g	20.4	21.0	0.6
10.0 mg/g	17.2	18.0	0.8
20.0 mg/g	13.1	13.0	-0.1
30.0 mg/g	10.6	15.0	4.4
50.0 mg/g	7.7	2.0	-5.7

[1]*Fitted with equation 5-9*
[2]*Calculated with equation 5-8*

A difference between the single granule growth mechanisms and granule growth in the high shear mixer is the mechanism of growth. The granules in the conical flask only exhibit layering growth. In the high shear mixer also coalescence of granules contributes to the growth. In **chapter 3** it was shown that the largest degree of inhomogeneity was observed during the initial minutes of the high shear granulation process. At this initial stage the fraction of ungranulated primary particles is large, hereby enhancing the layering growth. Hence, layering will be the predominant growth mechanism in the beginning of the granulation process. If these layered and non-homogeneous granules remain intact after coalescence, the inhomogeneity is enduring. In this case the non-homogeneous granules will only shift to a larger granule size fraction. Breakage of the coalesced granules will neutralise the inhomogeneity. In **chapter 3** was shown that once inhomogeneous granules have been formed the inhomogeneity is permanent. This indicates that although coalescence might be an additional mechanism of granule growth in the high shear mixer, it does not prevent the demixing. Hence, there is a strong analogy between granule inhomogeneity phenomena in the single granule growth experiments and in the high shear mixer. The mechanisms of preferential growth described in this study are also involved in the formation of inhomogeneous granules in the high shear mixer.

5.4 Conclusion

Wet granulation of a powder mixture with various components leads to accumulation of the smallest particles in the granule, resulting in inhomogeneous granules. It can be concluded that a non-random growth process, called preferential growth, underlies these inhomogeneity phenomena.

5.5 Appendix

With some trigonometry it is possible to derive Equation 5-2 (see Figure 5-6c). According to Pythagoras' Theorem the length of line *z* in Figure 5-6c can be calculated with.

$$(r_1 + r_2)^2 = r_1^2 + z^2 \qquad \textbf{Equation 5-13}$$

Thus,

$$z = \sqrt{2r_1r_2 + r_2^2} \qquad \textbf{Equation 5-14}$$

The ratio between line *x* and line *z* equals the ratio between line r_1 and line r_1 plus r_2 according to,

$$\frac{x}{z} = \frac{r_1}{r_1 + r_2} \qquad \textbf{Equation 5-15}$$

Combination of equation 5-14 and 5-15 leads to a term to calculate *x*,

$$x = \frac{r_1\sqrt{2r_1r_2 + r_2^2}}{r_1 + r_2}$$ **Equation 5-16**

Now *h* can be calculated with the following equation,

$$h = r_1 - x = r_1\left(1 - \frac{\sqrt{2r_1r_2 + r_2^2}}{r_1 + r_2}\right)$$ **Equation 5-17**

5.6 References

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6

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

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 100M ($d_{4,3}$~170 µm),* ***(2)*** *lactose 200M ($d_{4,3}$~50 µm) and* ***(3,4)*** *10% magnesium-stearate/lactose 100M or 200M. Between 1 and 15 seconds 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 both fractions was determined. The observed binder distribution behaviour reveals that three different nucleation mechanisms can occur:* ***(I)*** *For lactose 100M holds that all the binder is initially located in the granules. These granules are subsequently broken again.* ***(II)*** *The lactose 200M granules also contain 100% of the added liquid. Contrary to lactose 100M the lactose 200M 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. Consequently, the binder is completely dispersed in the non-granular material.*

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op stelten staan
hoog boven jezelf
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6.1 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 [Vromans et al., 1999]. 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 [Egermann and Reiss, 1988, Hapgood et al, 2002, Oostra et al., 2002, de Vegt et al., 2001, Vromans et al., 1999]. 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.

In this thesis the mechanisms involved in the formation of non-homogeneous granules are investigated. In **chapter 4** it was shown that breakage behaviour of the granules prevented a poor distribution of the drug substance. Once granule breakage is minimal, granules grow by layering. During layering preferential adherence of the smallest (drug) particles on the granules causes the inhomogeneity [**Chapter 5**]. 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 one minute of granulation and also the largest extent of growth occurs during this first minute [**Chapter 3**]. Unfortunately, there is still lack of detailed information about this initial stage of the granulation process (i.e. 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 (Figure 6-1). 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* [Schæfer and Mathiesen, 1996] or the *mechanical dispersion mechanism* [Hapgood, 2000]. When liquid volumes

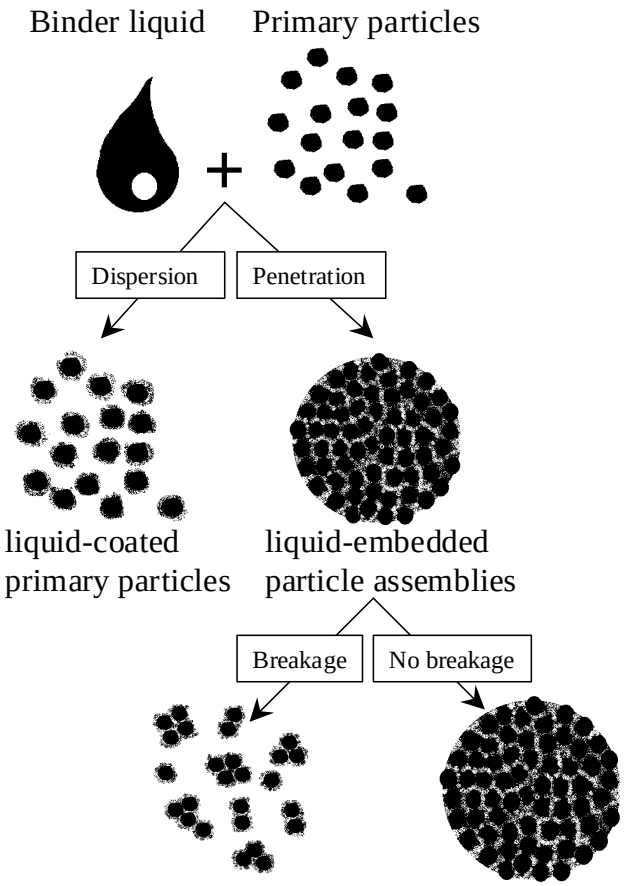

Figure 6-1 *Schematic overview of the possible nucleation mechanisms in the high shear mixer proposed in literature. See text[1] for explanation of the different mechanisms.*

[1]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.

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 [Schæfer and Mathiesen, 1996, Vonk et al., 1997]. Depending on the strength of these freshly formed granules; granules break or remain intact during the process. It should be noted that the proposed mechanisms are based on measurements done at least one minute after the start of liquid addition. This means that there is no information about the early

seconds of the process. In **chapter 3** it is shown that after one minute the process is 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 Figure 6-1 are valid. The aim of this study is to investigate both theoretically and experimentally, how granules are formed during the initial seconds of the high shear granulation process and which mechanisms are involved.

6.2 Experimental

6.2.1 Materials

For the experiments four different powder mixtures were used; (1) lactose 100M with a weight mean particle size of 170 µm, (2) lactose 200M with a weight mean particle size of 50 µm, (3) a mixture of 10% magnesium stearate and lactose 100M and (4) a mixture of 10% magnesium stearate and lactose 200M. The mixture of magnesium stearate and lactose were dry-mixed for 10 minutes 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)

6.2.2 Methods

To evaluate the nucleation behaviour, approximately 15 gram binder solution was added to 1000 gram of a powder mixture. Hence, the percentage of binder liquid is only 1.5% which is approximately a tenth 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. 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 with 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 rpm and 1500 rpm, respectively. This corresponds with a tip velocity of 5 m/s for both the impeller and the chopper. The mixer was stopped at different time points after the binder was added and 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 material 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 x 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 can be calculated with the following equation;

$$Percentage\ of\ binder\ (\%) = \frac{f_g C_g (1000 + M_b)}{M_b (C_b + C_g)} \qquad \textbf{Equation 6-1}$$

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 (gram) in equation 6-1 equals the filling grade of the bowl. The liquid/solid ratio of the fraction larger than 280 µm was also determined, which is expressed as,

$$Liquid\ /\ Solid\ ratio = \frac{C_g}{C_b} \qquad \textbf{Equation 6-2}$$

The experiments were done in triplicate.

6.3 Results

In **chapter 3** and **4** it was shown that lactose 100M forms granules, which cannot survive the shear forces in the process. Figure 6-2a indicates what happens during the first seconds after liquid addition for lactose 100M. The amount of binder in the fraction >280 µm rapidly decreases in the first 15 seconds. After 15 seconds 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 Figure 6-2b. The value of approximately 0.1 indicates that a relatively large fraction of the material larger than 280 µm is solid. Hence, granules are formed already 5 seconds 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 seconds practically no granules are present anymore and the binder is homogeneously distributed over the lactose 100M particles.

The insert in Figure 6-2a, which is deduced from Figure 6-1, schematically shows the nucleation behaviour of lactose 100M. 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.

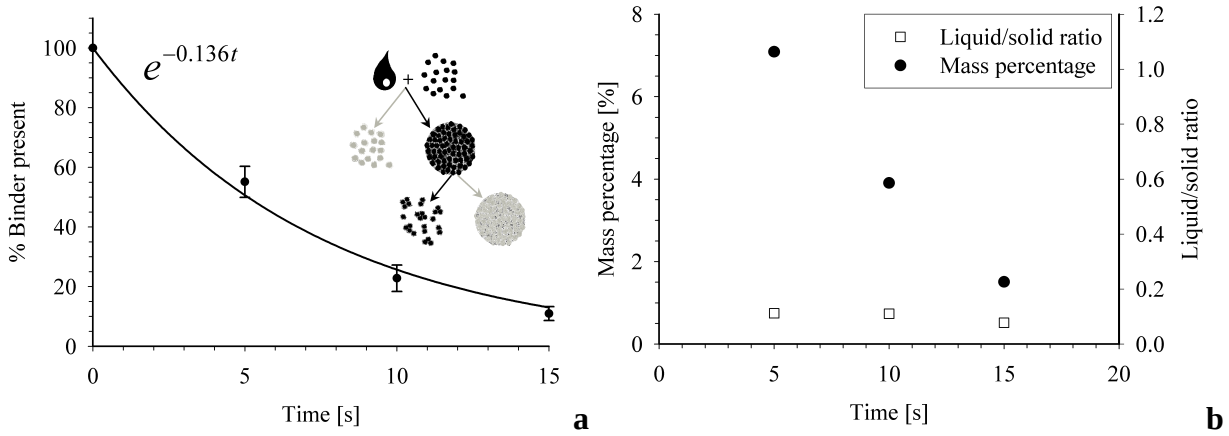

Figure 6-2 ***(a)*** *Influence of process time on the binder percentage that is present in the fraction >280 µm for the lactose 100M mixture. The insert depicts a schematic representation of the nucleation mechanism.* ***(b)*** *The mass percentage of powder that is larger than 280 µm and liquid/solid ratio of the material present in this fraction.*

Addition of the same amount of binder to lactose 200M clearly leads to completely different binder distribution behaviour than observed for lactose 100M. Figure 6-3a shows that after 5 seconds the complete amount of binder is present in the fraction larger than 280 µm. Contrary to the results of lactose 100M, even after 300 seconds still 75% of the total amount of binder is located in this fraction. Figure 6-3b shows that the mass percentage of the material larger than 280 µm varies between the 9-12%. 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.

Figure 6-3b shows that the liquid/solid ratio of the lactose 200M 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. In **chapter 5** it was shown 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. Hence, it is possible that this type of nucleation mechanism is correlated with the inhomogeneity phenomena.

The insert in Figure 6-3a schematically illustrates the observed nucleation behaviour of lactose 200M. Similar to the granule formation of lactose 100M, granules are formed in the early seconds by liquid penetration. The difference however is that the lactose 200M granules are not broken down, whereas the lactose 100M granules were susceptible for breakage. Hence, a change of lactose 100M to lactose 200M has a dramatic effect on the nucleation behaviour. The only difference between lactose 100M and 200M 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.

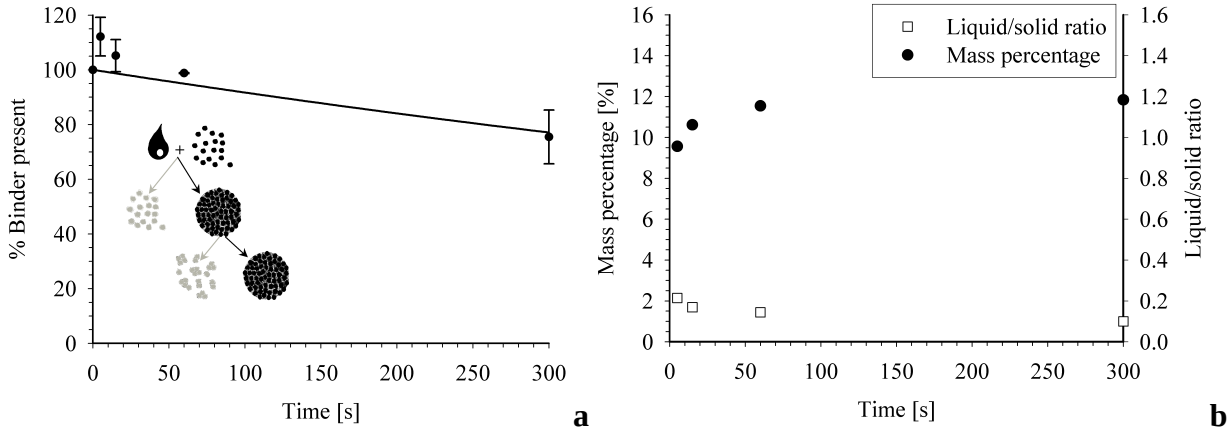

Figure 6-3 ***(a)*** *Influence of process time on the binder percentage that is present in the fraction >280 µm for the lactose 200M mixture. The insert depicts a schematic representation of the nucleation mechanism.* ***(b)*** *The mass percentage of powder that is larger than 280 µm and liquid/solid ratio of the material present in this fraction.*

To confirm the role of penetration in the granule formation, magnesium stearate was premixed with lactose to coat the lactose 100M and 200M 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. The results for the binder distribution in the powder mixture of 10% magnesium stearate/lactose 100M is shown in Figure 6-4a. Compared to the lactose 100M experiments, addition of 10% magnesium stearate to lactose 100M 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 100M experiment. However, the influence of magnesium stearate on the liquid/solid ratio is pronounced. A L/S ratio of 0.1 was observed for the lactose 100M experiment, while addition of magnesium stearate results in an L/S ratio between 1.0-0.5. This indicates that the material largely consists of binder liquid. A L/S ratio of approximately 0.2 for a standard granulation process of lactose will result in over-wetted granules. Hence, a L/S ratio between 1.0-0.5 points to a wet paste.

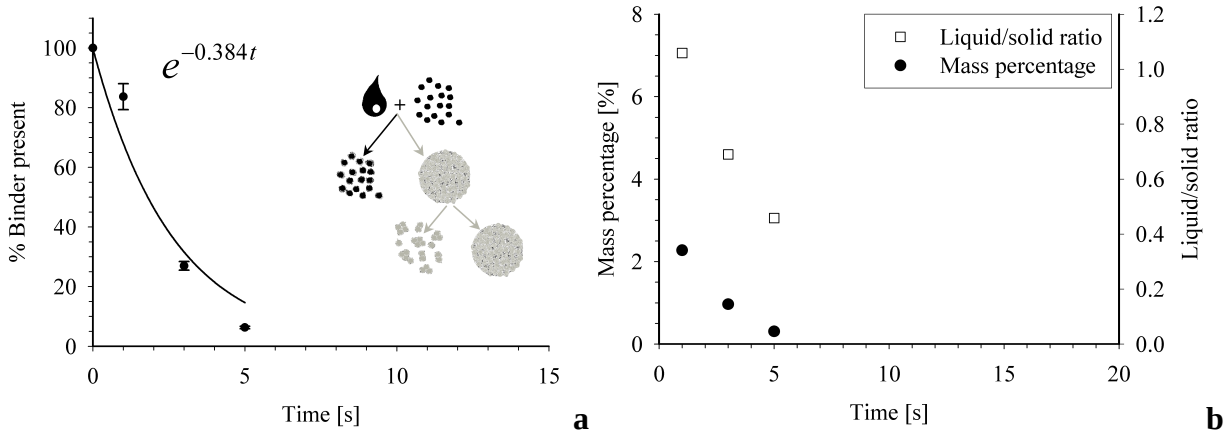

Figure 6-4 ***(a)*** *Influence of process time on the binder percentage that is present in the fraction >280 µm for the 10% magnesium stearate/lactose 100M mixture. The insert depicts a schematic representation of the nucleation mechanism.* ***(b)*** *The mass percentage of powder that is larger than 280 µm and liquid/solid ratio of the material present in this fraction.*

The influence of magnesium stearate is even more pronounced for lactose 200M. Figure 6-5a shows that after 15 seconds almost no binder is present anymore and the L/S ratio is enormously increased. The inserts in Figure 6-4a and Figure 6-5a show that the nucleation mechanism for the magnesium stearate/lactose mixtures is controlled by complete dispersion of the binder. It is clear that the ultimate results of this nucleation mechanism, i.e. distribution of the binder liquid to the ungranulated material, is the same as observed for the penetration involved nucleation and breakage mechanism (lactose 100M experiment). However, it is noted that there is a paramount difference between both nucleation mechanisms. The high L/S ratios observed for the magnesium stearate/lactose mixtures suggest that the binder is present as almost pure liquid 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 100M holds that the distribution of the binder is induced by the breakage of the granules.

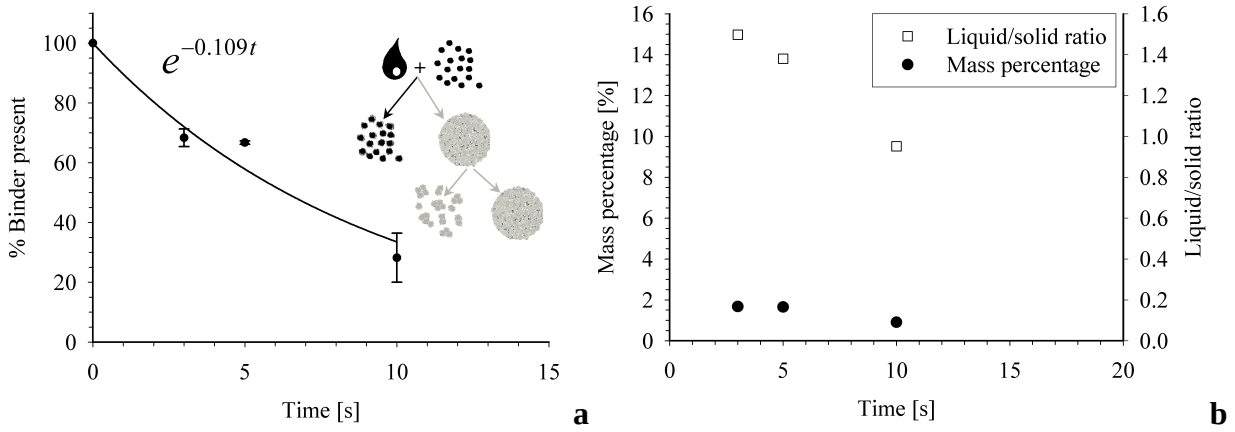

Figure 6-5 ***(a)*** *Influence of process time on the binder percentage that is present in the fraction >280 µm for the 10% magnesium stearate/lactose 200M mixture. The insert depicts a schematic representation of the nucleation mechanism.* ***(b)*** *The mass percentage of powder that is larger than 280 µm and liquid/solid ratio of the material present in this fraction.*

6.4 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 [Gluba, 2002, Schaafsma, 2000]. Even in the high shear mixer this correlation was found when spraying a low viscosity binder (<100 mPa.s) under special conditions [Hapgood, 2000]. 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 [Knight et al., 1998]. The mechanical agitation of the powder mixture by the impeller and chopper blades is responsible 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 100M and 200M experiments actually showed (see Figure 6-2 and Figure

6-3) that granules can be formed by penetration. The penetration time for a droplet into a porous substrate is determined by [Denesuk, 1993, Middleman, 1995];

$$t = 3.55 \frac{r_d^2}{\varepsilon_p^2 R_{pore}} \frac{\mu}{\gamma \cos\Theta} \qquad \textbf{Equation 6-3}$$

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 [Denesuk, 1993, Middleman, 1995, Hapgood, 2000, Popovich, 1999]. 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)

$$V_g = \frac{V_l}{\varepsilon_g} \qquad \textbf{Equation 6-4}$$

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 equation 6-5.

$$V_g = \frac{1}{6}\pi d_g^3 \qquad \textbf{Equation 6-5}$$

And the volume of the liquid is described by equation 6-6.

$$V_l = \frac{4}{3}\pi r_d^3 \qquad \textbf{Equation 6-6}$$

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 equation 6-4, 6-5 and 6-6.

$$d_g = \frac{2r_d}{\varepsilon_g^{1/3}}$$ **Equation 6-7**

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 lead to densification). For that reason different values are used for the powder bed porosity (ε_p) and the granule porosity (ε_g). Combination of equation 6-3 and 6-7 leads to the following equation to calculate the granule size after liquid penetration

$$d_g = 1.06\left(\frac{\varepsilon_p^2 R_{pore}\gamma\cos\Theta}{\mu\varepsilon_g^{2/3}}t\right)^{\frac{1}{2}}$$ **Equation 6-8**

In order to obtain an indication of the characteristic penetration time necessary to get a granule with a size of 280 µm, equation 6-8 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

$$t_{280} = 6.97*10^{-8}\frac{\mu\varepsilon_g^{2/3}}{\varepsilon_p^2 R_{pore}\gamma\cos\Theta}$$ **Equation 6-9**

Figure 6-6 shows the predicted granule size as a function of the available penetration time for the indicated conditions. It can be calculated that a penetration time of 0.17 seconds 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.

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 instantaneously 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 argued that this instantaneous distribution of the binder is impossible [Carstensen et al., 1976,

Butensky and Hyman, 1971, Holm et al., 1983, Holm et al., 1984, Knight et al., 1998]. On the other hand, when the binder dispersion is not instantaneous and droplet volumes persist, large enough to

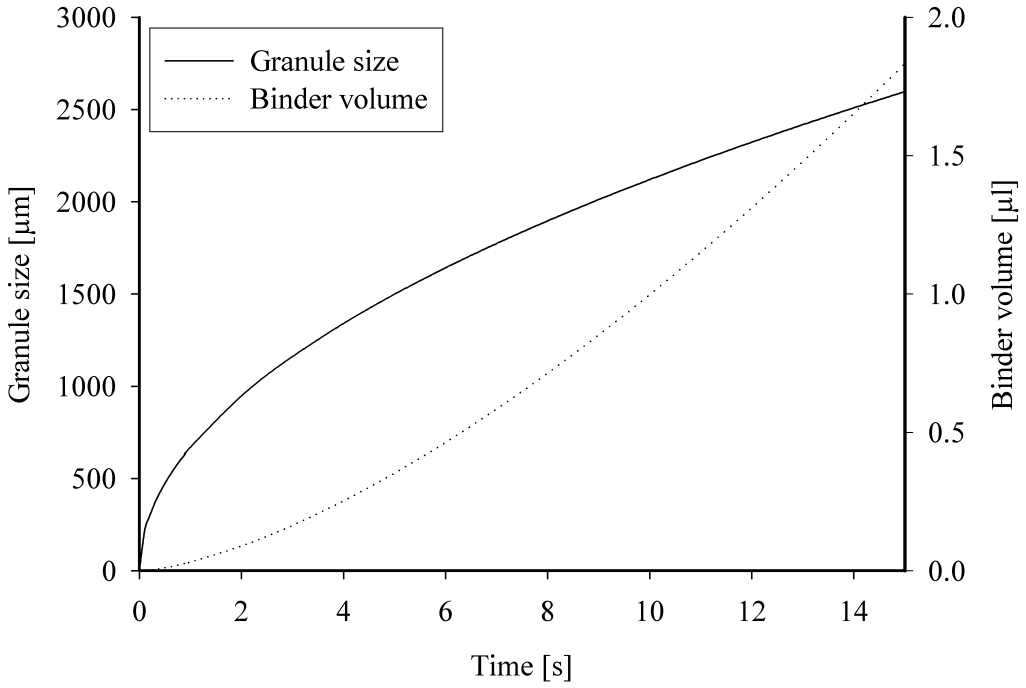

Figure 6-6 *The influence of the available penetration time on the size of the granules and the binder volumes necessary to form these granules. The granule size was calculated with equation 6-8. The values used for the calculations are; viscosity (μ), 1 Pa.s; pore radius (R_{pore}), 15 μm; porosity 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 [Danjo et al., 1992].*

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 Figure 6-7. The figure shows the percentage of the binder that is still available in sufficiently large volumes (theoretically >0.0023 µl) to form nuclei. However, the binder distribution behaviour observed for the magnesium stearate/lactose experiments (Figure 6-4a and Figure 6-5a) can be interpreted as indications for the binder dispersion rate, since the binder was present as almost pure liquid fragments. This suggests that the values for the theoretical first-order binder dispersion rates shown in Figure 6-7 are realistic.

In the high shear mixer the binder dispersion and the penetration are not separate processes, but occur simultaneously. In fact, 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 Figure 6-7a that for the lowest binder dispersion rate 37% of the binder is still present after 5 seconds. According to Figure 6-6 the nuclei size after a penetration time of 5 seconds is 1500 µm. Hence, assuming that the total volume has penetrated during these 5 seconds, 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 seconds, 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 seconds. 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 equation 6-5, while the percentage undersize of the nuclei at this time point is determined by the dispersion rate,

$$\%\ undersize = (1 - e^{-kt}) * 100\% \qquad \textbf{Equation 6-10}$$

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 200M after 60 seconds 100% of the binder is still located in the fraction larger than 280 µm implies that this assumption seems realistic (Figure 6-3). 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 Figure 6-7b. It 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 ability of the binder, liquid penetration is involved in the formation of the granules. This conclusion is also experimentally observed for lactose 100M and 200M. 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 100M and no granule breakage for lactose 200M, respectively.

It is clear that in case of no wetting of the binder (contact angle exceeding 90°), absence of 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.

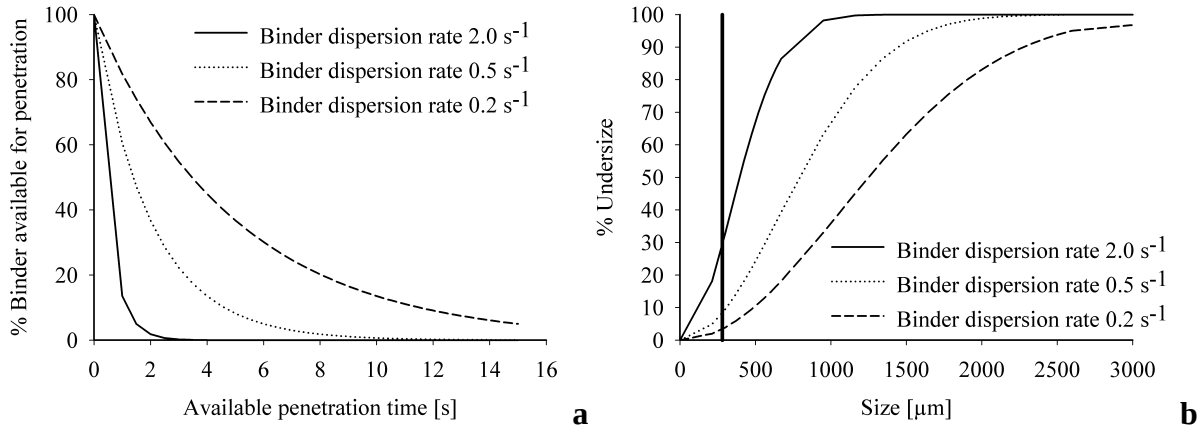

Figure 6-7 ***(a)*** *first-order binder dispersion curves expressed as the percentage of binder that is still available for penetration in sufficiently large volume to form granules,* ***(b)*** *influence of the binder dispersion and penetration rate on the nuclei size distributions after the penetration process is completed. The vertical line represents the cut-off size (280 µm) between granular and non-granular material (see text for explanation).*

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 predominant 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.

6.5 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 100M)
- Penetration-involved nucleation and no granule breakage (lactose 200M)
- Dispersion-only 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, respectively.

6.6 List of Symbols

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 [sec]
μ	Viscosity [Pa.s]
ε_g	Porosity granule [-]
ε_p	Porosity powder bed [-]
γ	Surface tension [N/m]
Θ	Contact angle [-]

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7

Quantitative proof of liquid penetration-involved granule formation in a high shear mixer.

Abstract

Chapter 6 *revealed that the granule formation in a high shear mixer depends on a balance between the rate of liquid penetration and binder dispersion. Three distinct nucleation mechanisms could be qualified;* ***(I)*** *granule formation by liquid penetration followed by granule breakage or* ***(II)*** *absence of granule breakage and* ***(III)*** *complete dispersion of the binder liquid. The aim of this study was to quantify the mechanisms of granule formation. A substandard amount (1.5% w/w) of binder liquid was added to a lactose mixture, while the mixer was operating. The powder mixture was frozen with liquid nitrogen after 15 seconds and analysed by sieving. The results show that, despite the minimal liquid amount, granules are formed under most conditions. It is argued granules are being formed by a liquid penetration process. These freshly formed granules are broken down at low viscosity (<1 Pa.s) and remain intact at higher viscosity (>1 Pa.s). Only at extreme conditions (viscosity>30 Pa.s) hardly any granules are formed. In this case penetration of the liquid becomes practically impossible and the binder is completely dispersed. A model based on the processes of liquid penetration, binder dispersion and granule breakage, confirms the observed nucleation behaviour. It is conclusively shown that an increase in viscosity results in a transition from nucleation mechanism* ***I→II→III****.*

onkwetsbaar
met je nagels diep
in de palm van je hand

7.1 Introduction

In the pharmaceutical industry granules are often used as intermediates for the production of tablets or capsules. A problem sometimes introduced by high shear granulation is a poor distribution of the active in the granules [Miyamoto et al., 1998, Egermann and Reiss, 1988, Vromans et al., 1999, Hapgood et al., 2002]. It is clear that the tablets or capsules must meet the content uniformity specifications set by the authorities. However, not only drug products should comply with these quality guidelines. The current code of federal regulations specified by the FDA contains the following guideline (CFR-21 §211.110): *"To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."*

It is clear that manufacturing of inhomogeneous granules can cause the variability of the drug product, which emphasises the importance of producing homogeneous granules. However, in order to produce these homogeneous granules the mechanisms involved in the formation of inhomogeneous granules must be clarified. This was the reason that a research project was started on this subject.

Chapter 4 and **5** showed that granulation mechanisms like granule breakage and preferential layering are important factors that determine granule (in)homogeneity. Besides, **Chapter 3** showed that the poor distribution of the active was already expressed at the initial stage of the granulation process. Hence, the nucleation process, which is defined as the process of initial granule formation, seems to play an eminent role in the inhomogeneity phenomena.

Investigation of the early seconds of the high shear granulation process revealed that three different processes determine the granule formation: binder dispersion, liquid penetration and granule breakage [**Chapter 6**]. This is schematically illustrated in Figure 7-1.

The figure indicates that the process starts with two separate phases; a solid and a liquid phase. When liquid comes into contact with the powder bed, penetration of the liquid into the powder bed can result in the formation of granules [Schæfer and Mathiesen, 1996]. However, impacts of the mixer arm will disperse the binder liquid, which counteracts the penetration. The balance between

the penetration and the dispersion determines the ultimate mechanism of granule formation. Real-time measurements of the initial seconds of the granulation process showed that in case of good

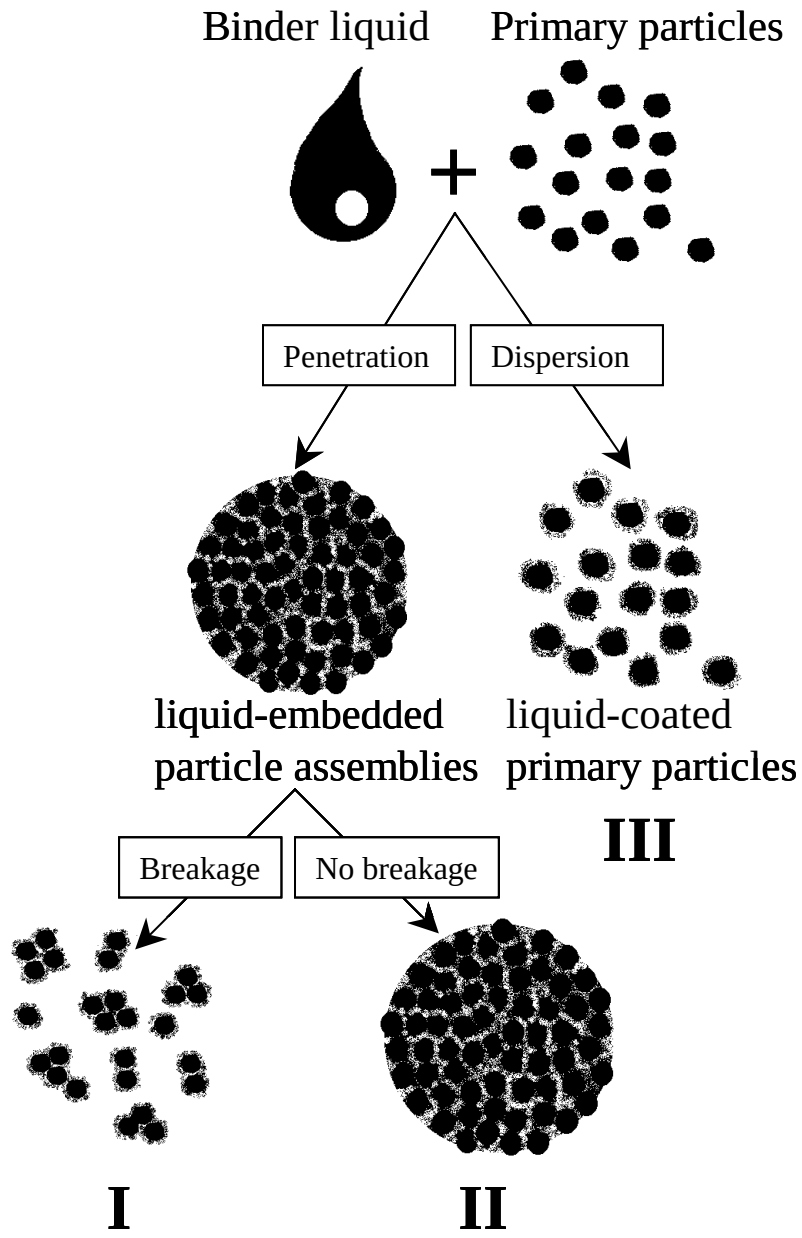

Figure 7-1 *Schematic overview of the possible nucleation mechanisms in the high shear mixer. Three different nucleation mechanisms can be distinguished;* ***(I)*** *penetration involved nucleation and granule breakage,* ***(II)*** *penetration involved nucleation and absence of granule breakage and* ***(III)*** *dispersion-only nucleation, See text*[1] *for further explanation of these mechanisms.*

[1]*In order to prevent confusion it is necessary to use an unequivocal 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 fragmentation process of pure binder liquid volumes into smaller volumes. Breakage is a term for the fragmentation of the granular material.*

wetting abilities of the binder, penetration is the predominant process. This liquid penetration leads to the formation of granules according to mechanism I and II in Figure 7-1. Once these granules have been formed the strength of the granules determines whether they are broken down by or survive the shear forces. If the penetration becomes too slow with respect to the binder dispersion (high viscosity or poor wetting) complete binder dispersion will occur (mechanism III).

The mechanisms illustrated in Figure 7-1 are *qualitative* representations of the nucleation behaviour. This implies that it is not completely clear at which conditions these mechanisms play a role. It has been shown that the relative importance of the different processes (breakage, penetration and dispersion) is determined by the process and formulation variables. The processes of liquid penetration and granule breakage were already extensively investigated in **Chapter 4** and **6**. It is however unclear to what extent the binder dispersion is influenced by process and formulation variables. In this study the information on the aforementioned rate processes is coupled to obtain a quantitative description of the nucleation behaviour. Hence, the aim is to *quantify* the granule formation behaviour in the high shear mixer.

7.2 Description of the nucleation model

The basis of the nucleation behaviour in the high shear mixer is the process of capillary liquid penetration into a porous powder bed. When liquid penetrates into a powder bed an agglomerate is formed. In a static situation this process of liquid penetration is well investigated and described. Models are available that can predict the penetration rate [Denesuk et al., 1993, Middleman, 1995, Hapgood, 2000, Popovich et al., 1999]. Based on these references a model was proposed to calculate the ultimate granule size (d_g) after liquid penetration [**Chapter 6**].

$$d_g = 1.06\sqrt{\frac{t}{\mu a}} \qquad \textbf{Equation 7-1}$$

in which

$$a = \frac{\varepsilon_g^{2/3}}{\varepsilon_p^2 R_{pore}\gamma\cos\Theta} \qquad \textbf{Equation 7-2}$$

R_{pore} is the pore radius, ε_p the porosity of the powder bed, ε_g the porosity of the granule, γ the surface tension of the binder liquid, θ the contact angle of the liquid, μ the viscosity of the binder liquid and t is the time that is available for penetration. In the dynamic situation existing in the high shear mixer this available time is limited, because the binder is rapidly dispersed by the mechanical

agitation. In order to obtain granules by liquid penetration two prerequisites must be met. Firstly, binder liquid must be available long enough to enable penetration. Secondly, this binder liquid must be present in volumes large enough to assemble several primary particles. Whether these conditions are met depends on the balance between the binder dispersion rate and liquid penetration rate. The minimal time period that binder liquid must be present in sufficiently large volumes is given by the $t_{280\ \mu m}$[**Chapter 6**].

$$t_{280\ \mu m} = 6.97 * 10^{-8} a\mu \qquad \textbf{Equation 7-3}$$

The $t_{280\ \mu m}$ is defined as the theoretical penetration time that is necessary to form a granule with a size of 280 µm. A granule size of 280 µm has arbitrarily been chosen as the boundary between granular and non-granular material (primary particles). This cut-off size is also used in the experiments.

Chapter 6 showed that a first-order process could describe the dispersion of the binder. This indicates that liquid is dispersed gradually from relatively large volumes into smaller volumes. Penetration of the large volumes will yield larger granules than penetration of the smaller volumes. Consequently, the gradual dispersion results in a size distribution of the granules. In the previous chapter it was argued that the granule size distribution after liquid penetration is determined by

$$\%\ undersize = (1 - e^{-kt}) * 100\% \qquad \textbf{Equation 7-4}$$

in which k is the dispersion rate constant. The ultimate size of the granules depends on the penetration rate and is determined by equation 7-1.

Once the granules have been formed, granule breakage may destruct these freshly formed granules. Several other studies have shown that granular material can be subjected to breakage in the high shear mixer [Vonk et al., 1997, Ramaker et al., 1998, Pearson et al., 2001]. Under the dynamic conditions of the high shear, the binder viscosity and the primary particle size of the constituents particularly determine the granule strength [Keningley et al., 1997, Franks, 1999, Iveson, 1998]. A model used as an estimate for granule breakage behaviour in the high shear mixer was proposed in **Chapter 3** and **4**. The strength of a granule under dynamic condition (σ_v) is given by;

$$\sigma_v = \frac{9}{8}\frac{(1-\varepsilon)^2}{\varepsilon^2}\frac{9\mu\pi v_p}{16 d_{3,2}} \qquad \textbf{Equation 7-5}$$

in which $d_{3,2}$ is the surface mean primary particle size and v_p the tip velocity of the mixer arms. Breakage behaviour can be predicted by comparing the granule strength with the impact energy.

The ratio between the kinetic energy of impact and the dynamic granule strength, is given by the Stokes deformation number (St_{def})

$$St_{def} = \frac{\rho_g v_p^{\ 2}}{2\sigma_v} \qquad \textbf{Equation 7-6}$$

in which ρ_g is the granular density. Tardos et al. and Iveson et al. established that the boundary between breakage and no breakage behaviour of the granules was observed at a St_{def} of approximately 0.1 [Tardos et al., 1997, Iveson et al., 2001]. The critical viscosity (μ^*) at which the transition between breakage and no breakage behaviour is observed is then given by combination of equation 7-5 and 7-6,

$$\mu^* = 2.24\frac{\rho_g v_p \varepsilon^2 d_{3,2}}{(1-\varepsilon)^2} \qquad \textbf{Equation 7-7}$$

Table 7-1 *Particle sizes and bulk density characteristics of the lactose grades.*

Materials	Weight mean diameter [$d_{4,3}$]	Surface mean diameter [$d_{3,2}$]	Bulk density
Lactose 100M	170 µm	60 µm	0.75 g/cm^3
Lactose 200M	50 µm	10 µm	0.55 g/cm^3
Lactose 450M	23 µm	6 µm	0.47 g/cm^3

7.3 Experimental

7.3.1 Materials

Lactose 100M, lactose 200M and lactose 450M (DMV, Veghel, The Netherlands) were used as starting materials. Some characteristics of the different lactose grades are shown in Table 7-1. Aqueous solutions of hydroxypropyl cellulose (HPC, Klucel EF, Aqualon, Wilmington, USA) and polyvinyl pyrrolidone (PVP, Plasdone K-29/32, ISP global technologies, Köln, Germany) were used a binder liquid. Table 7-2 lists the data of the binder solutions that were used for the experiments.

7.3.2 Nucleation experiments

The nucleation experiments were performed in a 10-liter high shear mixer with a top driven impeller and chopper (Gral 10, Machines Collette, Wommelgem, Belgium). The filling grade of the bowl was 1000 gram. To investigate the nucleation behaviour a substandard amount of 15 gram binder liquid was added by a syringe in one go to a rotating powder mixture (impeller speed 430

rpm, chopper speed 1500 rpm). This amount is approximately a tenth of the amount that is normally used to granulate 1000 gram lactose [**Chapter 3**]. The amount of 15 gram was chosen, because in case the binder would distribute homogeneously over the primary particles, binder-coated primary particles contain insufficient binder to coalesce and form granules again [**Chapter 6**]. This means that granules obtained in the experiments, are solely formed by liquid penetration. A sample of approximately 80 gram was taken from the powder mixture 15 seconds after binder addition. This sample was immediately poured into the liquid nitrogen to freeze penetration process. The process was frozen to stop the liquid penetration. The frozen powder mixture was sieved by hand with a series of 7 ASTM sieves (280 µm, 425 µm, 600 µm, 850 µm, 1000 µm, 1400 µm, 2360 µm). The sieve size of 280 µm was arbitrarily chosen as the boundary between granular (>280 µm) and non-granular (<280 µm) material. With the sieve analysis the mass fraction of granular material in the complete powder bed (yield) and the average size of the granular material was determined. This means that the non-granular fraction was not used in the average granule size calculations. The process of sampling and sieving was repeated at 1 minute and 5 minutes after binder addition. These samples were not poured into the liquid nitrogen, because liquid penetration is completed at these time points. The data were analysed by analysis of variance (ANOVA).

7.3.3 Bed porosity measurements

Equation 7-2 shows that the porosity of the powder bed is an important parameter for penetration. In order to predict the nucleation behaviour with the model a value for the bed porosity and pore size should be known. It is impossible however to determine the porosity and the pore size of the powder bed in the high shear mixer. To obtain a reasonable estimate of the powder bed porosity, the porosity of lactose agglomerates was measured with mercury intrusion porosimetry (Autopore II 9220, Micromeretics, USA). These agglomerates were prepared by adding 100 µl water to a bulk powder bed in a Petri-dish. Penetration of this volume into the powder results in an agglomerate of approximately 1 gram.

Table 7-2 *Overview of the binder solutions used for the nucleation experiments***.**

Hydroxypropyl cellulose [w/w %]	Viscosity	Polyvinyl-pyrrolidone [w/w %]	Viscosity
10%	0.3 Pa.s	55%	0.3 Pa.s
20%	4.1 Pa.s	100%	4.6 Pa.s
27%	8.2 Pa.s	120%	12.8 Pa.s
31%	18.8 Pa.s	140%	27.9 Pa.s
35%	31.6 Pa.s		

7.4 Results

In **chapter 6** an experiment was performed that gave a reasonable indication of the binder dispersion rate in the high shear mixer. In this experiment the binder dispersion rate (*k*) for a HPC-solution with a viscosity of 1 Pa.s was estimated to be 0.11 s^{-1} (see Figure 6-5). This vaue was determined for a mixture of lactose 200M. The contact angle of an aqueous solution of HPC on lactose is 34° and the surface tension of this solution is 0.044 Nm^{-1} [Danjo et al., 1992]. Table 7-3 indicates that the pore radius wthin a lactose 200M agglomerate is 5 µm and the corresponding porosity is 40%. These values were used as estimates for the bed porosity (ε_p in equation 7-2) in the high shear mixer. With the help of this information the size and size distribution of the nuclei were calculated with equation 7-1 and 7-4, respectively. In Figure 7-2a these size distributions are shown for the nucleation experiment with lactose 200M. The values are calculated for the time point $t\sim\infty$. Theoretically, at this time point the penetration and dispersion processes are completed.

It is not expected that granule breakage plays a crucial role at the viscosities shown in Figure 7-2a, because it is estimated with equation 7-7 that no breakage occurs if the viscosity exceeds 0.08 Pa.s.

It is clear that the model predicts a decrease in granule size with an increase in viscosity. A higher viscosity lowers the penetration rate, resulting in smaller granules. Figure 7-2a also shows that the yield of granules diminishes. In fact, a relatively larger contribution of dispersion is involved. Hence, not only the granule size decreases but also the percentage of granular material decreases. This is also illustrated in Figure 7-2b. Moreover, the figure shows that below the viscosity of 0.08 Pa.s no granules are present owing to the expected breakage. Granules formed by liquid penetration are subsequently broken down by the shear forces (mechanism I in Figure 7-1). Above a viscosity of 0.08 Pa.s there is no breakage predicted. This is expressed as the sharp rise of the dashed line in Figure 7-2b. Mechanism II in Figure 7-1 now becomes the most important nucleation mechanism. A further increase in viscosity results in a gradual decrease of the percentage granular material. This means that an increasing part of the binder is completely dispersed over the primary particles without forming granules. Hence, the nucleation mechanism shifts to dispersion-only nucleation at higher viscosity (mechanism III in Figure 7-1). These data illustrate how the viscosity can influence the nucleation behaviour in the high shear mixer.

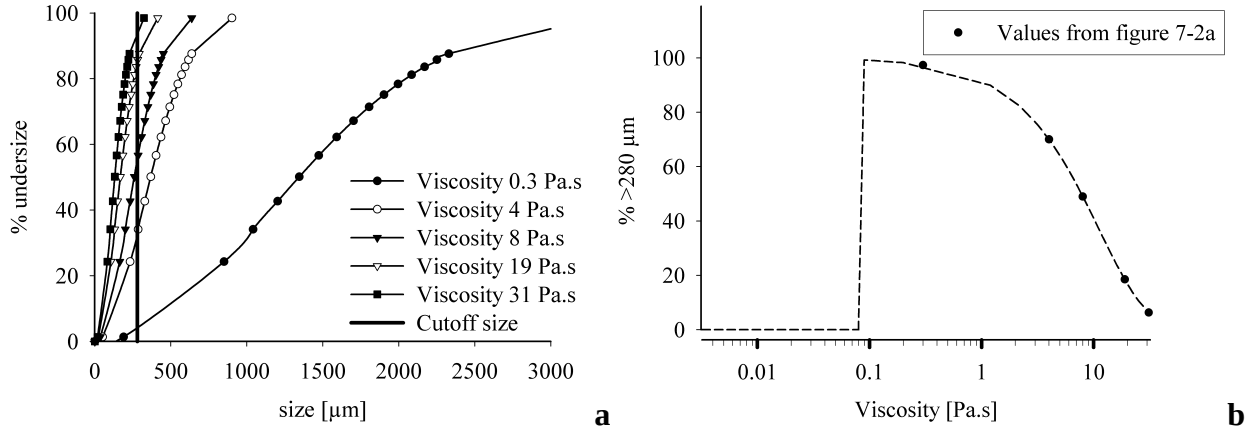

Figure 7-2 (a) *Predictions[1] of the quantitative nucleation model (equation 7-4) for the influence of the viscosity on the granule size distribution of lactose 200M. The vertical line represents the arbitrarily cut-off size between granular (>280 µm) and non-granular (<280 µm) material.* ***(b)*** *The percentage granules larger than 280 µm. The data points are adapted from figure 7-2a, while the dashed line is calculated with equation 7-12 (see appendix).*

[1]It can be calculated with equation 7-7 that the critical viscosity (μ^*) for granule breakage is 0.08 Pa.s for lactose 200M (data used for the calculation; v_p~5 m/s (equals the impeller tip velocity for 430 rpm), ε~0.4, $d_{3,2}$~10 µm and ρ_g~1500 kg/m^3).

Table 7-3 *The influence of the lactose grade on the measured pore size and porosity of the fixed powder bed. These values were used to estimate the pore size and porosity of a rotating powder bed in the high shear mixer.*

	Pore radius (R_{pore})	**Porosity (ε_p)**
Lactose 100M	17.9 µm	0.43
Lactose 200M	5.3 µm	0.40
Lactose 450M	2.3 µm	0.37

Figure 7-3 shows the experimental granule size distributions of lactose 200M, determined 15 seconds after binder addition. When comparing Figure 7-2 and Figure 7-3 it is clear that in both cases the granule size distribution shifts to a smaller size upon an increasing viscosity. This means that the predicted influence of the viscosity corresponds qualitatively with the experimental results.

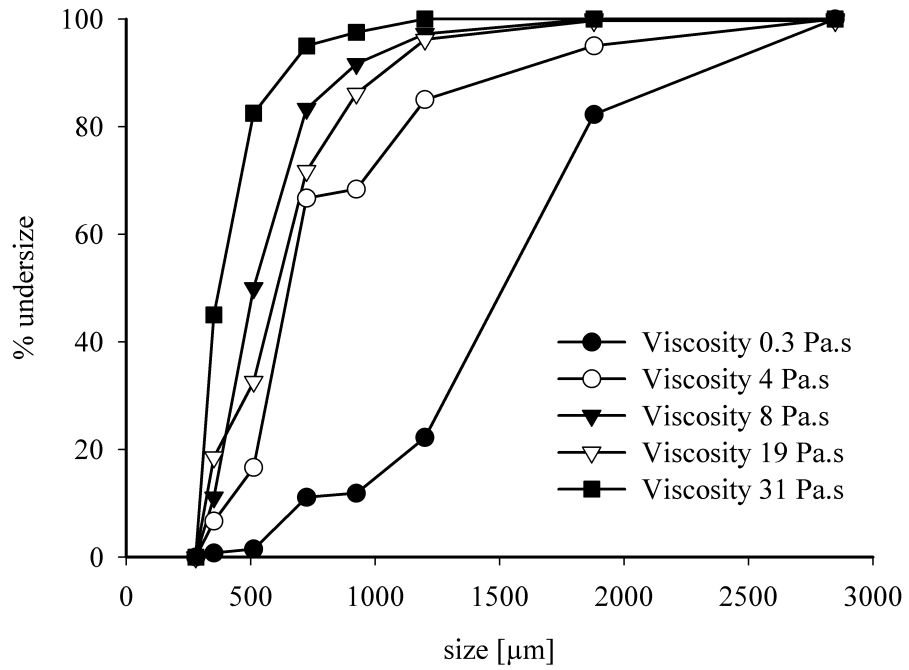

Figure 7-3 *Influence of the viscosity of the HPC solution on the experimental granule size distributions of lactose 200M (impeller speed 430 rpm, chopper speed 1500 rpm). The size distributions start at a value of 280 µm, since this was the cut-off size between granular and non-granular material.*

Figure 7-4a and Figure 7-4b depict the size and mass percentage of the nuclei (fraction >280 µm) for lactose 200M at different time points after liquid addition. With the aid of this figure the influence of process time on the nucleation behaviour can be evaluated. At viscosities of 0.001 and 0.3 Pa.s granules are formed after 15 seconds. However, at prolonged process times a decrease in yield and size is observed, indicating that granule breakage occurs. Although not all the granules are broken within 5 minutes, the results clearly indicate that mechanism I is the predominant nucleation mechanism at low viscosity. In contrast, if the viscosity exceeds 4 Pa.s almost no decrease in size and yield in time is observed. Granules are stronger at higher viscosity and breakage plays no longer a role (mechanism II in Figure 7-1). A further increase in viscosity reduced the granule yield and size. At a viscosity of 4 Pa.s the average granule size and yield are 1000 µm and 8%, respectively. When a binder solution with a viscosity of 32 Pa.s is used, an average granule size of 500 µm and 3% yield is obtained, which means that an increasing part of the binder liquid is completely dispersed without forming granules. This decrease in size and yield illustrates the transition from penetration-involved nucleation to dispersion-only nucleation (mechanism II→III).

Figure 7-4c and Figure 7-4d show the nucleation results for lactose 450M. Lactose 450M possesses a smaller primary particle size than lactose 200M. The results show that over the complete viscosity range, granules are formed after a process time of 15 seconds. Hence, also for lactose 450M holds that liquid penetration is involved in the formation of granules. The yield and size curves of lactose 450M are very similar to the curves of lactose 200M. Also for lactose 450M the nucleation mechanism shifts from I→II→III upon an increasing viscosity. Nevertheless, the change in primary particle size from lactose 200M to 450M has a relatively small effect on the results. First of all, it is noticed that the breakage at a viscosity of 0.001 and 0.3 Pa.s is less pronounced for lactose 450M. Equation 7-7 predicts that the boundary between breakage and no breakage occurs at a viscosity of 0.04 Pa.s, i.e. at a lower value than that calculated for lactose 200M. This indicates that lactose 450M granules are stronger than lactose 200M granules. Also in other studies it has been reported that a smaller primary particle size yield stronger granules [Keningley et al., 1997, Johansen and Schæfer, 2001].

Another influence of the primary particle size is shown in Table 7-3. The table shows that a decrease in pore size and porosity at smaller particle sizes. According to equation 7-1, this leads to a smaller average granule size, because liquid penetration retards when the porosity and the pore size decreases. ANOVA-analysis of the lactose 200M and 450M data reveals however no significant difference ($p=0.2$) in granule size between both grades. In contrast, the yield of the lactose 450M granules is significantly lower ($p<0.001$) than the yield of the lactose 200M granules. Apparently, the yield is more sensitive to changes in e.g. the primary particle size than the average granule size.

Figure 7-4e and Figure 7-4f show the nucleation results of lactose 100M. The figure indicates that at a viscosity of 0.001 Pa.s no granules are obtained, not even at a process time of 15 seconds. This is caused by the complete breakage of the granules within 15 seconds. At a viscosity of 4 Pa.s even after 5 minutes granules are present. Remarkably, the yield at this viscosity varies between the 2-4%, which is significantly ($p<0.001$) lower than the yield at the same viscosity for the other lactose grades. Moreover, a further increase in viscosity does not lead to the previously observed decrease in yield. This indicates that the yield profile of lactose 100M is deviating from the profiles of lactose 200M and 450M. It is likely that granule breakage causes the lower yield values for lactose 100M, although the model does not predict this breakage at a viscosity higher than 0.7 Pa.s. Nevertheless, the increase in yield, which is associated with an increase in viscosity, signifies that the granules strengthen. This reduces the degree of breakage. Apparently, the gradual transition between breakage and no breakage for lactose 100M occurs within the viscosity range of 4-32 Pa.s.

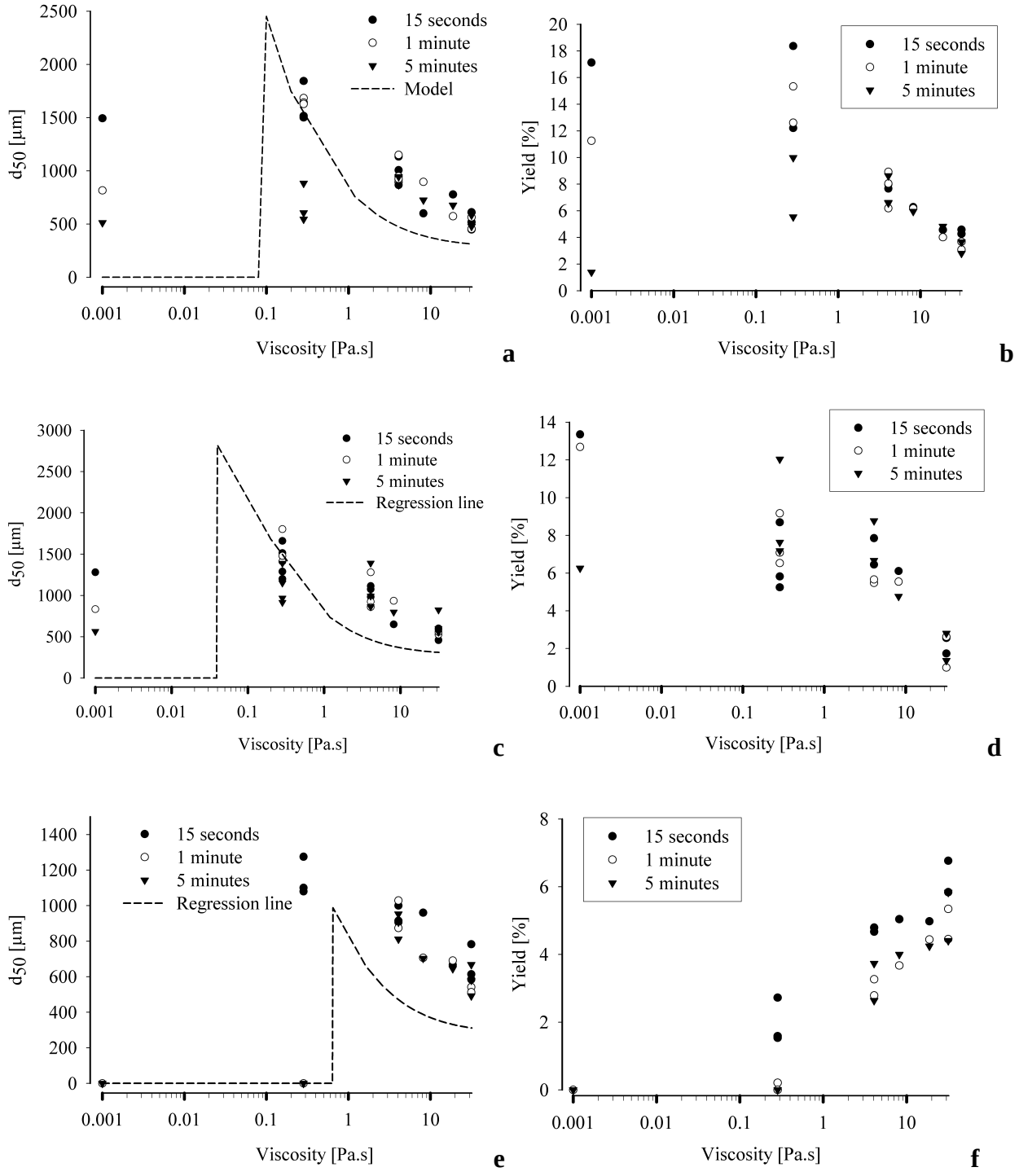

Figure 7-4 *Influence of the process time and viscosity of the HPC solution on the d_{50} and the yield of the granular material only. The symbols represent the experimental data.* ***Lactose 200M; (a,b)*** *The dashed line illustrates the predicted average granule size by equation 7-8 (k is assumed to be 0.11 s^{-1}).* ***Lactose 450 M; (c,d)*** *The dashed line illustrates the best fit of the model determined with equation 7-8 (k is 0.0472±0.0161 s^{-1} (95% C.I.)).* ***Lactose 100M; (e,f)*** *The dashed line illustrates the best fit of the model determined with equation 7-8 (k is 0.469±0.275 s^{-1} (95% C.I.)).*

For lactose 200M and 450M this transition from mechanism I→II is observed within a viscosity range of 0.001-4 Pa.s. In contrast to the other types of lactose, no transition from mechanism II→III is observed for lactose 100M within the investigated viscosity range.

With equation 7-1 it is possible to predict the granule size after liquid penetration. However, these size calculations also incorporates the fraction smaller than 280 µm, while this fraction is omitted in the experimentally determined granule size. In order to compare both sizes equation 7-1 has to be rewritten. This eventually results in the following set of equations to predict the average granule size. In the appendix a complete derivation is given.

$$d_{50} = \begin{cases} 0 & ;\mu < \mu^* \\ 1.06\sqrt{6.97*10^{-8} + \dfrac{0.69}{\mu a k}} & ;\mu \geq \mu^* \end{cases}$$

Equation 7-8

Obviously, the model only predicts that granules are present when the viscosity exceeds the critical viscosity for breakage. Below this viscosity it is assumed that all the granules are broken. Consequently, the average granule size is then 0 µm.

In Figure 7-4a the results of these calculations are shown for lactose 200M (dashed line). First of all, it is noticed that there are some discrepancies between the predicted and experimental results. At low viscosity no granules are predicted due to breakage. The experimental results reveal that there are granules present, although the size of the granules decreases in time. This emphasises that breakage is a kinetic process and that the model is not able to describe this situation. Of course, it is unlikely that the sharp transition between breakage and no breakage occurs in reality. Instead, a gradual transition seems to be more logical.

It should be noted that for the calculations, a dispersion rate constant of 0.11 s^{-1} has been used. This dispersion rate constant was determined at a binder viscosity of 1 Pa.s and assumed to be constant over the complete viscosity range. This is probably a too rough assumption, since it is more likely that liquid dispersion will retard with an increase in viscosity. This may also explain why the model underestimates the average granule sizes at higher viscosity, although it can be concluded at the same time that viscosity obviously has no predominant influence on the dispersion rate constant.

Despite these differences between the calculated and experimental results, the model can still give a quantitative prediction of the nucleation behaviour. Penetration-involved nucleation and granule breakage is estimated at a viscosity between 0.001-0.08 Pa.s, while absence of breakage is predicted at higher viscosity. Also the transition from penetration-involved to dispersion-only nucleation is

calculated. In fact, the experimentally observed transition form nucleation mechanisms I→II→III is fairly well predicted by the model.

For the nucleation model knowledge of the binder dispersion rate is essential. Two different methods can be used to estimate the dispersion rate. Firstly, the dispersion was experimentally determined in **Chapter 6**. This rate constant is used for the predictions in Figure 7-2 and Figure 7-4a (dashed line). An alternative method to determine this rate is by deducing it with non-linear regression analysis. The equation that predicts the average granule size as a function of the viscosity (equation 7-8) was used for the non-linear regression analysis of the experimentally determined average granule sizes (Figure 7-4a, c and e). When this is done for the experimental data shown in Figure 7-4a, a dispersion rate of 0.12±0.05 s^{-1} is obtained. This value corresponds well with the value of 0.11 s^{-1} determined with the experimental method. For lactose 100M a binder dispersion rate of 0.384 s^{-1} was determined with the experimental method [**Chapter 6**], while the non-linear regression method yields a dispersion rate of 0.469 s^{-1} (see Figure 7-4e). No value was measured with the experimental method for lactose 450M. However, the binder dispersion rate extracted with the regression analysis is 0.0472 s^{-1}.

Table 7-4 *Overview of the binder dispersion rates that were extracted from the experimental data through non-linear regression analysis.*

Lactose	Impeller [rpm]	Chopper [rpm]	Binder liquid	a [equation 7-2]	k* [s^{-1}]	95% C.I. [s^{-1}]
100M	430	1500	HPC	2.65E+06	0.469	±0.275
200M	430	1500	HPC	1.03E+07	0.121	±0.0454
450M	430	1500	HPC	2.79E+07	0.0472	±0.0160
100M	430	1500	PVP	3.67E+06	0.597	±0.397
200M	430	1500	PVP	1.43E+07	0.0821	±0.0205
450M	430	1500	PVP	3.86E+07	0.0281	±0.00633

* k=binder dispersion rate, which is fitted with equation 7-8.

In addition to the experiments performed with a hydroxypropyl cellulose solution, the experiments were also done with polyvinyl pyrrolidone as binder. The contact angle of an aqueous solution of PVP on lactose is 62°, while the surface tension of the solution is 0.06 Nm^{-1} [Pepin et al., 2001]. This means that slightly poorer wetting properties are obtained with the PVP solutions. The fitted binder dispersion rates of the HPC and PVP solutions are listed in Table 7-4. The yield and size data of these experiments are not shown in a graph, because the yield and size profiles strongly resemble the previously described results of lactose 100M, 200M and 450M. This means that independent of the impeller speed or the used binder the following is observed:

- Transition from nucleation mechanism I→II→III for lactose 200M and 450M within the viscosity range 0-32 Pa.s.
- Transition from nucleation mechanism I→II for lactose 100M within the viscosity range 0-32 Pa.s.

The influence of the primary lactose size on the binder dispersion is shown in Figure 7-5. The figure shows that an increase in primary particle size results in an increase in binder dispersion rate for both HPC and PVP. This is most probably due to the increase in cohesion and friction upon decreasing particle size. This reduces the flowability of the powder, hereby influencing the binder dispersion rate constant. There is no difference in dispersion rates between the HPC and PVP binder, which is logical since the viscosity range of the binders and the added binder amounts were similar.

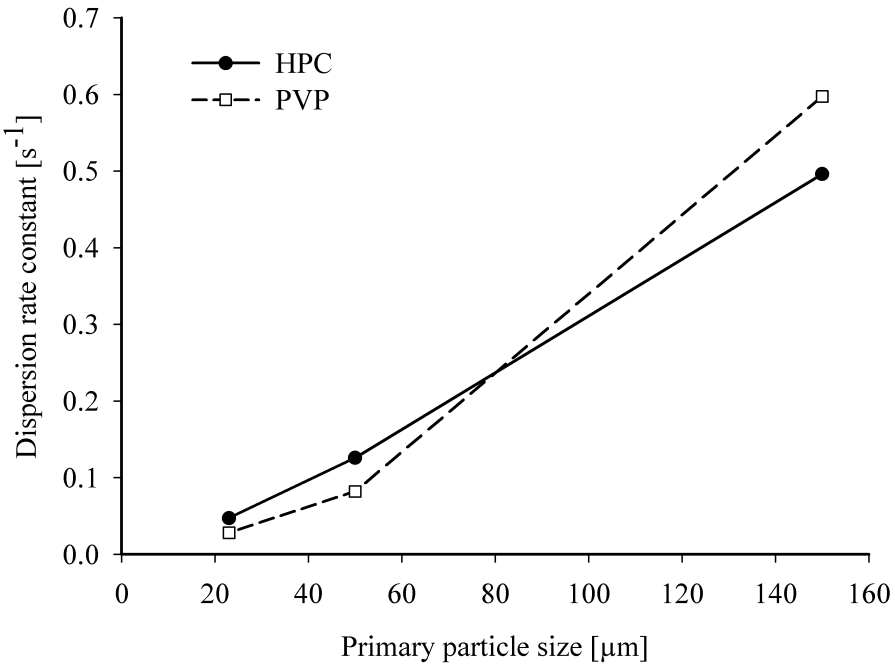

Figure 7-5 *Influence of the primary lactose size on the binder dispersion rates of the HPC and PVP binder liquid.*

7.5 Conclusion

The results show that at most conditions, granules were formed by liquid penetration. Only at very extreme viscosity, liquid penetration is not involved in the nucleation process. Hence, within the operating-window at which high shear granulation is commonly performed (particle size 10-100

µm, viscosity 0.001-5 Pa.s and good wetting abilities of the binder) penetration-involved nucleation is the predominant nucleation process. The strength of these freshly formed granules determines the subsequent behaviour; breakage or no breakage.

7.6 Appendix

The size distribution in Figure 7-2 was calculated with equation 7-4. The average size (d_{50}) can be extrapolated from this figure. The penetration time that corresponds with the 50% undersize (d_{50}) is given by

$$t_{50} = \frac{\ln(0.5)}{k} \qquad \textbf{Equation 7-9}$$

The average granule size (d_{50}) is then given by combining equation 7-9 with equation 7-1.

$$d_{50} = 1.06\sqrt{\frac{0.69}{\mu a k}} \qquad \textbf{Equation 7-10}$$

In this d_{50}-calculation the size fraction of 0-280 µm is also used. However, in the experiments this size fraction is regarded as non-granular material and only powder material with a size larger than 280 µm were designed as granules. Hence, in order to compare the calculated d_{50} with the experimental d_{50} the nuclei sizes smaller than 280 µm must be omitted from the average nuclei size calculations. Hence, equation 7-10 has to be rewritten. The % undersize at 280 µm is given by

$$\%\ undersize_{280\mu m} = (1 - e^{-kt_{280\mu m}}) * 100\% \qquad \textbf{Equation 7-11}$$

The $t_{280\ \mu m}$ is defined as the penetration time that corresponds with a nuclei size of 280 µm (equation 7-3). The percentage of granules that are formed by liquid penetration is then given by

$$\%\ granules\ > 280\ \mu m = 100\% - \%\ undersize_{280\ \mu m} = e^{-6.97*10^{-8}\mu a k} * 100\% \qquad \textbf{Equation 7-12}$$

which means that the 50% undersize for the granular material (>280 µm) becomes

$$\frac{100\% - \%\ undersize_{280\mu m}}{2} + \%\ undersize_{280\mu m} = (1 - 0.5e^{-kt_{280\mu m}}) * 100\% \qquad \textbf{Equation 7-13}$$

If equation 7-13 is equated with equation 7-4 than it is possible to calculate the time that corresponds with the 50% undersize. In this case the t_{50} is described by equation 7-14

$$t_{50} = t_{280\mu m} + \frac{0.69}{k} \qquad \textbf{Equation 7-14}$$

Incorporation of equation 7-14 into equation 7-1 leads to the following equation to calculate the average nuclei size (d_{50}) of the nuclei larger than 280 µm.

$$d_{50} = 1.06\sqrt{6.97*10^{-8} + \frac{0.69}{\mu a k}}$$ **Equation 7-15**

Hence, now it is possible to compare the experimental data with the predicted data for the average nuclei size.

7.7 List of symbols

k	Binder dispersion rate [s^{-1}]
$t_{280\mu m}$	Theoretical penetration time necessary for a granule of 280 µm [s]
d_g	Granule diameter [m]
d_{50}	Average granule diameter [m]
$d_{3,2}$	Surface mean primary particle size [m]
$d_{4,3}$	Weight mean primary particle size [m]
R_{pore}	Pore radius [m]
v_p	Impact velocity [m/s]
μ	Viscosity [Pa.s]
μ^*	Critical viscosity for granule breakage [Pa.s]
ε	Porosity [-]
ε_g	Porosity granule [-]
ε_p	Porosity powder bed [-]
γ	Surface tension [N/m]
θ	Contact angle [-]
ρ_g	Granule density [kg/m^3]

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8

Influence of the liquid quantity on the nucleation mechanism in high shear granulation.

Abstract

Although liquid is intensively mixed with solid material in high shear granulation, often a poor distribution of the liquid in the granules is observed. Often, the poor distribution is already observed in the initial stage of granulation, the nucleation phase. A previous chapter showed that liquid penetration is responsible for the formation of the granules. However, in order to investigate only the nucleation mechanisms a substandard amount of binder liquid was used. The aim of this paper was to examine the influence of liquid concentration on the mechanisms of granule formation and to relate these mechanisms to granule inhomogeneity. Granulation experiments with lactose 200M were performed with varying amounts of an aqueous solution of 20% hydroxypropyl cellulose (1.5%, 5.0%, 7.5%, 11.0% and 14.5%). Subsequently, the binder liquid and granule size distribution were determined. The results showed that for the low liquid concentrations (1.5% and 5.0%) the largest mass fraction of the powder, the ungranulated material, contains no binder, while almost 100% of the binder was located in the granular mass. This is the consequence of the liquid penetration-involved nucleation. The binder distribution gradually improved when the liquid concentration is further increased to 7.5%, 11.0% and 14.5%. For all the liquid amounts holds that the granules remained intact as the process proceeds. It was argued that although the granules are formed by liquid penetration, less free powder is available for this penetration when more liquid is added. Consequently, more liquid is dispersed over the primary particles, which results in the improved distribution. It was conclusively shown that the penetration-involved mechanism of granule formation could introduce a poor distribution of the solids and the liquid.

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8.1 Introduction

Literature reports several examples of the formation of non-homogeneous granules in a high shear mixer [Miyamoto et al., 1998, Egermann and Reiss, 1988, Vromans et al., 1999, Hapgood et al., 2002, Scott et al., 2000]. In the pharmaceutical industry the formation of these inhomogeneous granules has to be prevented to assure quality of the drug product. Hence, for an optimal product development it is of paramount importance to understand which mechanisms are involved. Some aspects of granule inhomogeneity have been unravelled. It was shown that the particle size of the starting materials is one of the critical parameters [**Chapter 3**, Egermann and Reiss, 1988, Vromans et al., 1999, Hapgood et al., 2002]. Granules consisting of coarse primary particles are susceptible to breakage, resulting in a continuous exchange of primary particles between granules [**Chapter 4**]. This dynamic situation leads to the formation of homogeneous granules. In contrast, granule breakage was minimal when fine primary particles were used as starting material. In this case granules remain intact during the process, leading to a less dynamic growth mechanism of layering. Ex-situ experiments showed that during layering the smallest (drug) particles have the highest affinity for growth, resulting in accumulation of these particles in the granules [**Chapter 5**]. This mechanism, so-called preferential layering, is responsible for the actual inhomogeneity. Hence, the *size* of the primary particles determines the breakage behaviour, whereas the particle *size difference* determines the degree of the granule inhomogeneity.

Strikingly, a poor drug distribution already existed during the first minute of the granulation process. Moreover, also the largest extent of granule growth and inhomogeneity occurred during this initial stage. This indicates that nucleation plays an eminent role. However, the mechanisms of granule formation and its impact on drug distribution remained unclear.

Strictly spoken, granulation starts at the moment binder liquid is added to the powder bed. The liquid is dispersed through the powder and binds the primary particles together to form granules. When liquid comes into contact with a porous powder bed, penetration of the liquid into the capillaries of the powder can occur. Schæfer and Mathiesen and Hapgood et al. [Schæfer and Mathiesen, 1996, Hapgood, 2000] argued that granules are formed by this mechanism of liquid penetration. Actual measurements in the early seconds of the high shear granulation demonstrated process that liquid penetration is involved in the formation of the granules [**Chapter 6**]. It was shown that the balance between penetration rate and binder dispersion rate determines the ultimate

size of the granules [**Chapter 7**]. Depending on the granule strength, these freshly formed granules may be broken. However, in most cases the granules remained intact during the process. These nucleation experiments were performed with a substandard amount of binder liquid (1.5%) compared to the normally used amount (8-14%). Nevertheless, it provided a fundamental understanding of the early seconds of the high shear granulation process. The addition of a substandard amount of binder is a commonly used method [Litster et al., 2001, Litster et al., 2002, Hapgood, 2002]. This method is applied to assure that only nucleation is investigated. In order to extrapolate the understanding of granule formation to a 'full-scale' process with respect to liquid content the experiments have to be extended to a standard level of the binder liquid. The aim of this study is to investigate the influence of an increasing liquid quantity on the mechanisms of granule formation and to relate these mechanisms to the inhomogeneity phenomena.

8.2 Experimental

8.2.1 Materials

The material used for the granulation experiments was lactose 200M (DMV international, Veghel, The Netherlands). The weight mean primary particle size of lactose 200M is approximately 50 µm. An aqueous solution of hydroxypropyl cellulose (Klucel EP, Aqualon, Wilmington, USA) was used as binder liquid. Paracetamol was obtained from BuFa (Uitgeest, The Netherlands) and erythrosine, a water-soluble red dye, from Colorcon (Dartford, England).

8.2.2 Granulation

The granulation experiments were performed in a 10-litre high shear mixer (Gral 10, Machines Colette, Wommelgem, Belgium). The mixer was operated with an impeller speed of 430 rpm and a chopper speed of 1500 rpm. The filling grade of the bowl was 1000 gram lactose 200M. An aqueous solution of 20% (w/w) hydroxypropyl cellulose (HPC) and 1% (w/w) paracetamol was used as the binder liquid. The paracetamol was dissolved in the binder liquid to trace the location of the binder liquid. This was done because there are no conventional techniques to analyse hydroxypropyl cellulose quantitatively. The viscosity of the binder solution (4.0 Pa.s) was measured with a cone and plate viscometer (Brookfield rheometer DV-III). The binder solution was added to the powder bed by a syringe within one second. Already during the liquid addition phase the mixer blades were rotating. The high shear mixer was stopped one minute after liquid addition and a sample of approximately 80 gram was taken. The mixer was started again immediately after sampling and after 4 minutes the process was stopped (total process time of 5 minutes). Again a

sample was taken. Both samples were plate-dried at 40°C and reduced pressure (Elbaton, Kerkdriel, The Netherlands) for 4 hours. This experiment was repeated for five different liquid amounts, namely 15, 50, 75, 110 and 145 gram of binder solution. The filling grade, binder viscosity and paracetamol concentration in the binder were kept constant during these experiments.

An additional experiment was done for the binder liquid amount of 110 gram. In this experiment the binder liquid was added in two phases. At first, 95 gram of a 20% (w/w) HPC solution was added. A second quantity of 15 gram, consisting of the same binder solution plus 0.1% (w/w) erythrosine, was added immediately after the first phase. At a process time of 15 seconds the process was stopped and the granules were plate dried for 4 hours. The experiment was repeated for process times of 1 minute and 5 minutes, respectively.

8.2.3 Granule characterisation.

The dried granules were sieved on a vibrating sieve shaker (Retsch, Haan, Germany) with a series of 7 ASTM sieves (280 µm, 425 µm, 600 µm, 850 µm, 1000 µm, 1400 µm and 2360 µm) into 8 sieve fractions. The mass of each sieve fraction was weighed to determine the granule size distribution. The sieve fraction <280 µm (indicated as sieve fraction i=1) was designated as the non-granular material, whereas the sieve fractions >280 µm (fractions i=2-8) were designated as the granular material. This division was made to make a distinction between properties of the granular and non-granular material. The concentration of paracetamol in the original binder solution and in the different sieve fractions was analysed with a HPLC method with UV detection at 254 nm (column; Nucleosil 100 C18, 5 µm, 250 x 4.6 mm (Chrompack, The Netherlands). The concentration of paracetamol is a measure for the total amount of binder liquid in the sieve fraction. The original amount of binder liquid in a sieve fraction can be calculated with

$$\textit{Amount of binder liquid in sieve fraction } i = \left(c_{g,i} w_{g,i} / c_b\right) \qquad \textbf{Equation 8-1}$$

in which $c_{g,i}$ is the concentration of paracetamol in the sieve fraction, c_b is the paracetamol concentration in the original binder liquid and $w_{g,i}$ is the mass of the sieve fraction. The total amount of binder liquid in the eight sieve fractions is

$$\textit{Total amount of binder liquid} = \sum_{i=1}^{8} \left(c_{g,i} w_{g,i} / c_b\right) \qquad \textbf{Equation 8-2}$$

The percentage of the binder liquid in the granular material (sieve fractions >280 µm) is then given by

$$\textit{Percentage of binder liquid in granular material} = \frac{\sum_{i=2}^{8}\left(c_{g,i} w_{g,i} / c_b\right)}{\sum_{i=1}^{8}\left(c_{g,i} w_{g,i} / c_b\right)} \qquad \textbf{Equation 8-3}$$

The granules originating from the granulation experiment where part of the binder was coloured with a red-dye were characterised by image analysis. Microscopic pictures were taken form the sieve fractions 280 µm, 425 µm, 600 µm and 850 µm. The clear red granules and the rest of the granules were counted on these pictures to determine the percentage of red granules. This was done for each time point (15 seconds, 1 minute and 5 minutes).

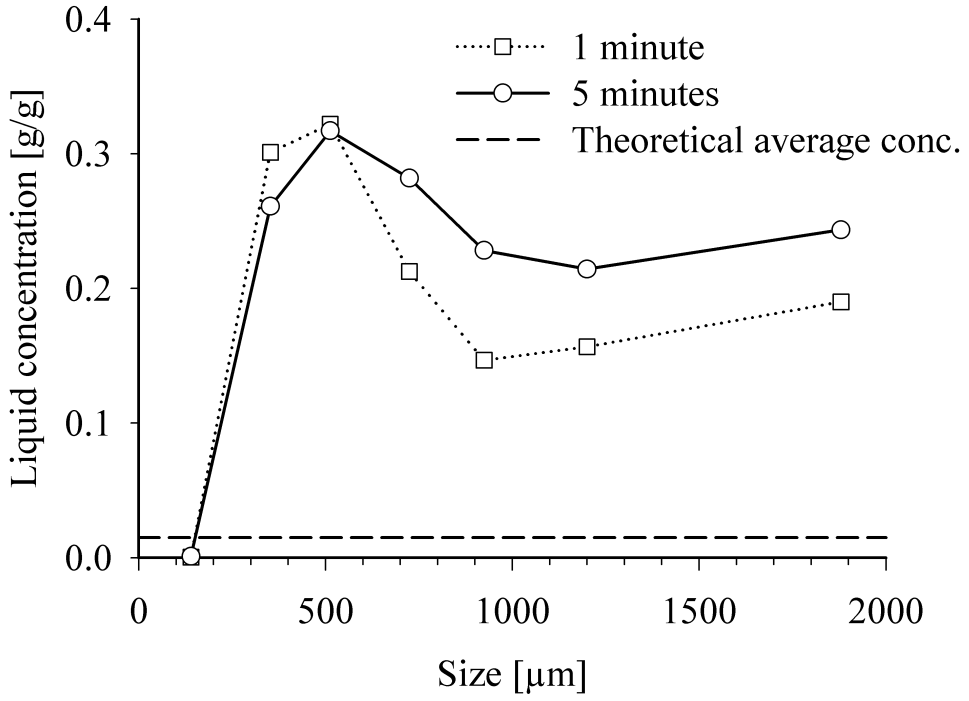

Figure 8-1 *The binder concentration in the different sieve fractions after a process time of 1 and 5 minutes, respectively. A binder amount of 15 gram was added. The horizontal dashed line illustrates the theoretical average concentration of 0.015 g/g.*

8.3 Results

Figure 8-1 shows the concentration of the binder in the different granule size fractions for the binder liquid amount of 15 gram. This amount is approximately a tenth of the amount normally used to granulate lactose 200M. Despite of this fact granules were formed. The powder mass consisted of a fraction of 10% granules and 90% ungranulated powder. Figure 8-1 shows that almost all the binder liquid is located in these granules, whereas the largest mass fraction, the non-granular material,

contained practically no binder. In case of a homogeneous distribution the theoretical average concentration of the binder liquid should be 0.015 g/g. These results showed that the concentration in the granules much higher than this average concentration, while the concentration in the ungranulated powder mass is below average. This indicated that the binder liquid is poorly distributed over the powder mass.

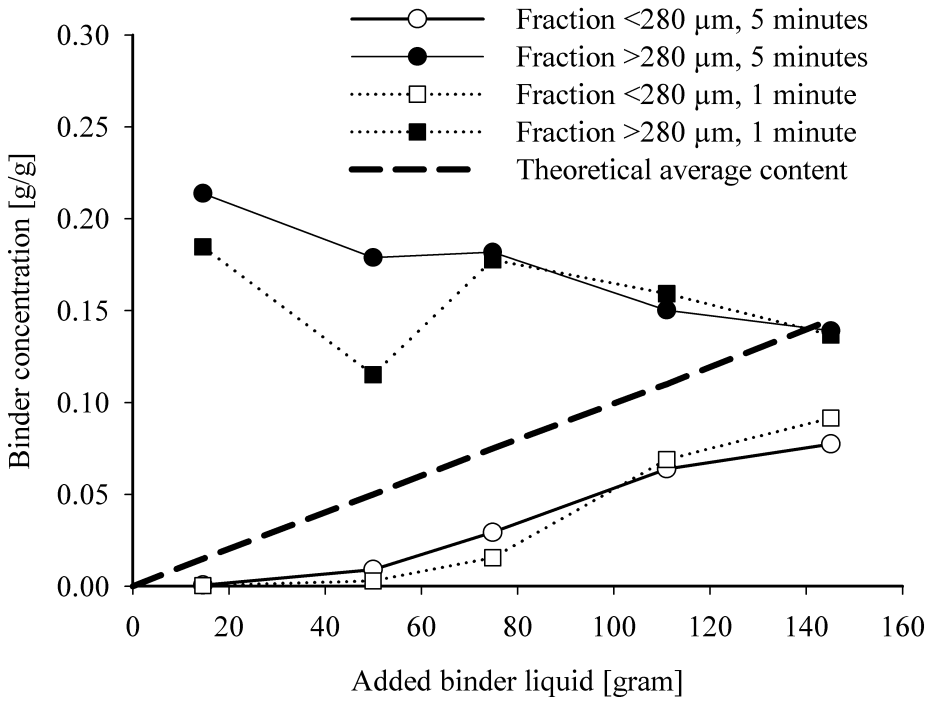

Figure 8-2 *The binder liquid concentration in the granulated and ungranulated powder mass after a process time of 1 minutes and 5 minutes, respectively. The dashed line illustrates the theoretical average concentration in case of a homogeneous binder distribution.*

Chapter 6 showed that the inhomogeneous distribution of the binder could be attributed to the mechanisms of granule formation. When the binder liquid is poured into the high shear mixer, the mechanical agitation is responsible for the dispersion of the liquid into droplets. These droplets become smaller as the process proceeds. Parallel to the binder dispersion process, penetration of these binder droplets into the porous powder bed results in granule formation. On the one hand, when the binder dispersion is the dominant process complete dispersion of the binder will occur. This results in a homogeneous distribution of the binder over the (primary) particles. On the other hand, when the penetration is faster than the binder dispersion granules are formed. Hardly any binder will then distribute over the primary particles, because the penetration prevents complete binder dispersion. In this case the binder is mainly present in the granules. A homogeneous

distribution is only obtained when these freshly formed granules are broken down again. Obviously, this homogeneity is not observed for lactose 200M. In fact, the inhomogeneous distribution shown in Figure 8-1 demonstrates that in case of lactose 200M granules are directly formed by liquid penetration. The homogeneity did not improve as the process proceeds, because the granules remain intact and keep their integrity.

Figure 8-2 shows the influence of the liquid amount on the binder distribution. In this figure the binder concentration in the granulated and ungranulated powder mass is compared to the theoretical average concentration. It is clear that the concentration in the granules exceeded this average concentration, while the opposite is observed for the ungranulated material. This poor binder distribution is observed for all the liquid amounts, although the situation improves when more liquid is added. The inhomogeneity suggested that liquid penetration was also involved when standard amounts of binder liquid are added.

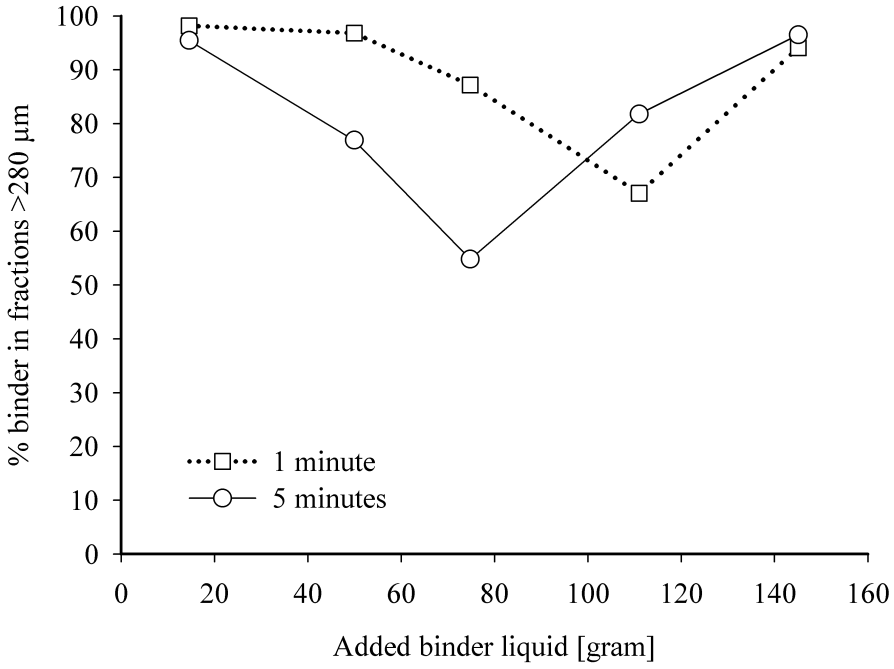

Figure 8-3 *Overview of the influence of binder liquid amount on the total percentage of binder in the granular material after a process time of 1 minute and 5 minutes, respectively. The sieve fractions >280 µm were designated as the granular material.*

Figure 8-3 shows the impact of an increase in liquid content on the amount of binder in the granules. The granules contain 100% of the binder when 15 gram binder solution is added. In this case there was an excess of dry powder with respect to the liquid available for penetration. This

explained why almost 100% of the added binder could penetrate the powder bed and form granules. The same conclusion was valid when 50 gram of binder liquid is added. Again all the binder was present in the granules at a process time of 1 minute. This percentage decreased as the process proceeds, probably owing to some breakage and/or attrition. If the amount of binder liquid is further increased, the percentage of binder liquid in the granules decreased. Apparently, an increasing amount of the binder liquid was dispersed over the primary particles. The consequence of this behaviour was that the concentration of the binder liquid in the ungranulated powder increased. This is also illustrated in Figure 8-2. When more liquid was added relatively less free powder is available for penetration. This caused the increased binder dispersion upon an incremental liquid amount. Figure 8-3 also shows that a minimum is obtained. This minimum is observed at 110 gram and 75 gram for a process time of 1 minute and 5 minutes, respectively.

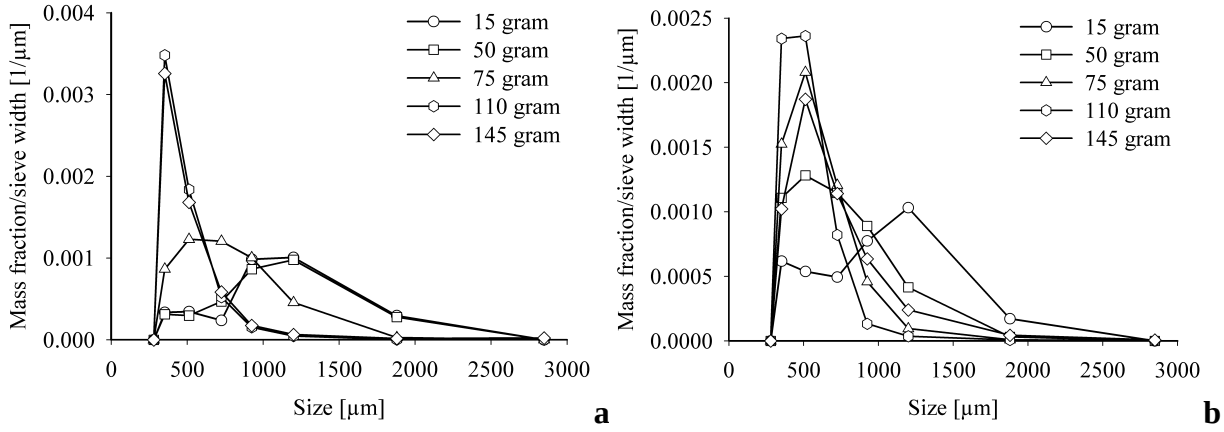

Figure 8-4 *Influence of binder liquid amount on the size distribution of the granular material (>280 µm) after a process time of (a) 1 minute and (b) 5 minutes.*

If the liquid content exceeded these amounts an increase in the presence of liquid in the granules was observed. Besides, there is also an increase in liquid content as the process proceeds from 1 minute to 5 minutes, which indicate that there is granule growth. This growth was not observed for at the lower liquid amounts. Obviously, more granules were present when an increased amount of binder liquid is added. Hence, the chance that granules coalesced became greater. The fact that liquid was also present in the ungranulated powder also promoted the coalescence of the primary particles. This means that at higher liquid amounts also coalescence contributed to the granule growth and granule growth was not only induced by liquid penetration.

Figure 8-4 shows that an increase in liquid amount results in a shift of the granule size distribution to a smaller size. The fact that there is relatively less powder available when the liquid content increases influences the ultimate granule size. Hence, the limited availability of the powder formed a restriction for the penetration process and granules became smaller. However, the experiments where 110 gram of binder liquid was added in two phases (coloured and colourless phase) revealed that penetration is still the prevalent mechanism of granule growth. The microscopic pictures of the granules showed that the two liquid phases were also separately present in the granules, because a large fraction of white granules and a small fraction of red granules were observed.

The theoretical ratio between the colour phase (15 gram) and the total amount of binder (110 gram) is 13.6%. Image analysis of the microscopic pictures demonstrated that after 15 seconds the percentage of red granules in the sieve fractions is 13.4% (see Table 5). Hence, this percentage almost equalled the theoretical percentage of the tracer phase. Although this percentage decreased in time, probably owing to some breakage, even after 5 minutes 10% of the granules consisted of red granules. The majority of the granules remained intact during the process. This confirmed that liquid penetration was responsible for the formation of these granules. In contrast, if the granules were formed by coalescence of binder-coated primary particles, the reference and colour binder liquid would be homogeneously mixed, which would result in pink granules.

Table 5 *Overview of the counted number of red and rest granules in the various sieve fractions and the total percentage of red granules in the powder mass. The original percentage of coloured binder liquid was 13.6%.*

Sieve	15 seconds		1 minute		5 minutes	
	red	**rest**	**red**	**rest**	**red**	**rest**
280 µm	423	3320	308	2785	212	2155
425 µm	501	2395	403	2832	419	2625
600 µm	250	1516	181	1551	164	1462
850 µm	80	864	77	637	65	760
Total	1254	8095	969	7805	860	7002
Percentage	**13.41%**		**11.04%**		**10.94%**	

8.4 Discussion

The results of this study conclusively showed that, independent of the liquid content, granules are formed by liquid penetration. Moreover, once these granules have been formed they keep their integrity, because there is hardly any granule breakage. This is an important conclusion, because now it is possible to relate the early stage of granulation with phenomena observed during the granulation process. One of those phenomena is the inhomogeneous distribution of the binder liquid, which is observed in many studies concerning high shear granulation [Knight et al., 1998, Schæfer and Mathiesen, 1996, Oostra et al., 2002, de Vegt et al., 2001, Carstensen et al., 1976]. The inhomogeneity is expressed as an accumulation of the binder in the granules, while the ungranulated powder is sub potent in binder content. The results of this study actually showed that the mechanism of nucleation is responsible for this occurrence.

Another aspect of the conclusion, the fact that granules keep their integrity, is also a significant notice. One of the properties that is important in this context is the poor distribution of the drug substance over the granules. It is most likely that also this inhomogeneity event is induced by the penetration-involved nucleation mechanism. Indeed, the outcome of this nucleation behaviour is that two distinct fractions are formed, a granulated and an ungranulated powder fraction. Consequently, the coalescence of the primary particles with the granules is an obvious growth mechanism. In other words, this type of nucleation promotes layering growth.

In a previous study it was shown that during layering there is preferential growth of the smallest primary particles in a powder mixture [**Chapter 5**]. This results in accumulation of these smaller primary particles in the granules. Since granules remain intact, this inhomogeneity problem persists during the whole process. Granulation of lactose 200M with micronised estradiol ($d_{4,3}$~5 µm) also yielded accumulation of estradiol in the larger granules [**Chapter 3**]. Hence, the mechanism of granule formation and subsequent growth observed for lactose 200M promotes the formation of inhomogeneous granules with respect to the solids and the liquid.

8.5 List of symbols

$c_{g,i}$ Concentration or paracetamol in the sieve fraction i [mg/g]

c_b Concentration or paracetamol in the binder solution [mg/g]

$w_{g,i}$ Mass of sieve fraction i [g]

8.6 References

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9

Results of this thesis results in the context of current literature.

In the production process of solid formulations wet granulation in a high shear mixer is a commonly used process-step. Important granule properties with respect to the optimisation are granule size and uniformity. A too large granule size compared to the weight of the dosage units or an inhomogeneous distribution of the dug substance in the granules can eventually result in a poor content uniformity of the end product. Hence, in order to produce granules with optimal properties it is important to have control over the wet granulation process. It is remarkable that this control is often based on trial-and-error experience. In order to prevent this time- and drug-consuming approach more fundamental knowledge about the high shear granulation process is necessary. For that purpose a research project was started, which is described in this thesis. The aim of the project was to elucidate the mechanisms involved in the formation of non-homogeneous granules in a high shear mixer.

The drug distribution in the granules is just one granule property. However, also other granule characteristics (e.g. size, size distribution, porosity) can be of importance. In many industries it is important to have a notion how certain changes in the process and formulation conditions influence the granulation behaviour. A commonly applied research approach is to evaluate the influence of these conditions by monitoring their effect on the granule properties, attempting to establish empirical rules for granulation. This empirical approach is used because there is lack of information about the mechanisms of granulation in the high shear mixer. Consequently, it remains often unclear why certain phenomena occur.

In the introduction was stated, "*The solution for the granule inhomogeneity lies in the unravelling of the granulation mechanisms in a high shear mixer*". In this context a schematic picture of the high shear granulation process was proposed based on an extensive literature survey. Figure 9-1 shows that the granulation process can be described by three individual mechanisms acting simultaneously in the high shear mixer [Iveson et al., 2001]. These three mechanisms are all influenced by process and formulation variables. The balance between these granulation mechanisms determines the ultimate granule properties.

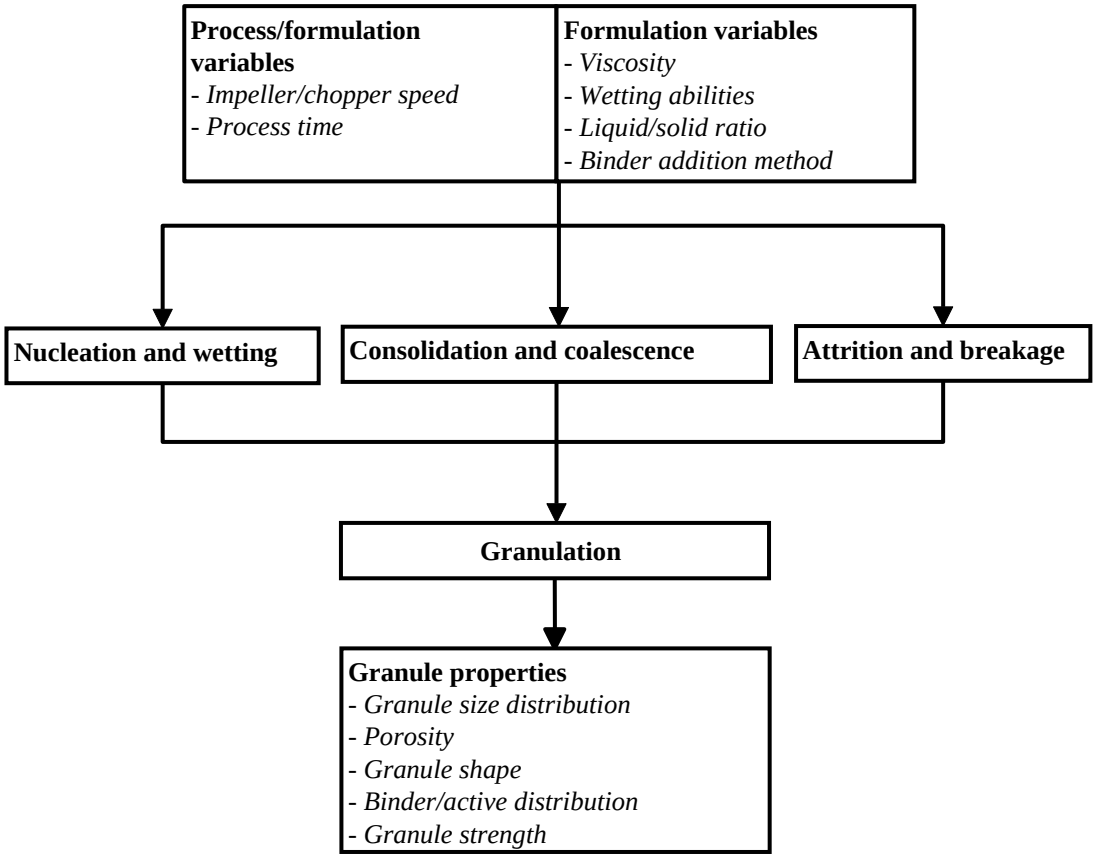

Figure 9-1 *Schematic representation of the high shear granulation process.*

When it is possible to describe the process like is illustrated in Figure 9-1, a more fundamental basis is given to explain and predict the influence of the different variables on granulation behaviour, resulting in a control of the granulation process and the granule properties. In current practice this situation is not yet achieved, because of the indistinct granulation mechanisms. This research project provided additional understanding about the granulation mechanisms in the high shear mixer.

In this chapter the conclusions from this thesis concerning the granulation mechanisms are discussed in a broader perspective. Table 9-1 lists an overview of the studies that investigated high shear granulation. The ranges of the process and formulation variables that were examined are also indicated.

Table 9-1 *Overview of the process and formulation conditions for various high shear granulation studies.*

	Author	Impeller [rpm]	Chopper [rpm]	Scale	Particle size [µm]	Viscosity [mPa.s]	L/S ratio [%]	Process time [min]	Binder	Filler	Contact angle
1	Hoornaert, 1998	200 (5 m/s)	3000 (25 m/s)	50-L	80	1-22	18.8-20.4	0-13	PVP	Sodium sulphate, cellulose	NVG
2	Bardin, 2001	No value	0	NVG	15	1	175-220	0-60	water	Silica powder	NVG
3	Knight, 2000	450-1500 (5-17 ms/s)	0	8-L	23	81	12	0-25	PEG 1500	Calcium carbonate	60°
4	Knight, 1993	300 (9.4 m/s)	3000 (17 m/s)	30-L	24	81	20-26	0-25	PEG 1500	Sodium phosphate	NVG
5	Keningley, 1997	1000 (10 m/s)	0	1.5-L	12-248	1-56,000	40-110	0-20	Silicon oil	Calcium carbonate	NVG
6	Kokubo, 1993	300	3000	25-L	50	3-16	20	10	HPC, HPMC, MC	Lactose/ cellulose	NVG
7	Knight, 1998	150 (5 m/s)	3000 (17 m/s)	30-L	4-23	81	12-19	0-22	PEG 1500	Calcium carbonate	60°
8	Ritala, 1988	400	3000	25-L	21	1-120	20-35	0-6	PVP, PVP-PVA, HPMC	Dicalcium phosphate	0°
9	Holm, 1983	250-500	0-3000	25-L	52	8	1.8-10.1	0-15	PVP-PVA	Lactose	NVG
					14	14	6.8-18.3	0-14		Dicalcium phosphate	NVG
10	Holm, 1984	250-500	0-3000	25-L	52	8	8	5-11	PVP-PVA	Lactose	NVG
					19	14	15.7-17			Dicalcium phosphate	NVG
11	Johansen, 2001a	800	0	8-L	5-214	50-100,000	4-15	10	PEG	Calcium carbonate	60°
12	Ramaker, 1998	400 (5 m/s)	0	10-L	50	1	50	20	water	Lactose/ cellulose	NVG
13	Johansen, 2001b	500-1100 (6-13 m/s)	0	8-L	5	150; 15,000; 20,000	15-35	0-10	PEG 3000, PEG 20000	Calcium carbonate	60°

	Author	Impeller [rpm]	Chopper [rpm]	Scale	Particle size [µm]	Viscosity [mPa.s]	L/S ratio [%]	Process time [min]	Binder	Filler	Contact angle
14	Scott, 2000	300 (4 m/s)	1400 (3 m/s)	10-L	38	81	13	0-15	PEG 1500	Calcium carbonate	60°
15	Schæfer, 1996a	1200 (14 m/s)	0	8-L	19	100-1,200	23	0-17	PEG 3000, PEG 6000	Lactose	NVG
		900 (10 m/s)			7		30	0-17		Anhydrous lactose	NVG
		800 (9 m/s)			17		11	0-16		Calcium phosphate	NVG
16	Eliasen, 1998	1000-1500 (11-17 m/s)	0	8-L	23	30-400	23	0-20	PEG 3000, Gelucire, Stearate	Lactose	NVG
17	Schæfer, 1996c	1500 (17 m/s)	0	8-L	19	130-27,000	23	0-15	PEG 3000, 6000, 8000, 10000, 20000	Lactose	NVG
18	Schæfer, 1996b	1500 (17 m/s)	0	8-L	20	60-27,000	23	0-15	PEG 2000, 3000, 6000, 8000, 10000, 20000	Lactose	NVG
					34	60-4,700	22	12	PEG 2000, 3000, 6000, 8000, 10000	Anhydrous lactose	NVG
19	Pearson, 2001	150 (5 m/s)	3000 (17 m/s)	30-L	13	81	14	0-20	PEG 1500	Calcium carbonate	NVG
20	Vonk, 1997	430 (5 m/s)	3000 (10 m/s)	10-L	45, 63	1	50	0-16	water	Lactose/ cellulose	NVG
		15-276 (0.4-5 m/s)	3000	25-L				0-30			NVG
21	Kokubo, 1996	300	3000	25-L	50	3	20	10	HPMC	Lactose/corn-starch/cellulose	NVG
22	Schæfer, 1990b	500-800-1400	3000	10-L	23	280-1,100	17-20	0-30	PEG 3000, PEG 6000	Calcium phosphate	NVG
		1400			68		15-18			Lactose	NVG
23	Schæfer, 1990a	200-1200	0-3000	10-L	30- 70	NVG	0-16.8	10	PVP-PVA	Lactose	NVG
					20					Calcium phosphate	

	Author	Impeller [rpm]	Chopper [rpm]	Scale	Particle size [µm]	Viscosity [mPa.s]	L/S ratio [%]	Process time [min]	Binder	Filler	Contact angle
24	Schæfer, 1992	500-700 (13-18 m/s)	1500	50-L	44	280	19-20	0-8	PEG 3000	Lactose	NVG
					34		20-22				NVG
					22		22-24				NVG
25	Vromans, 1999	430 (5 m/s)	NVG	10-L	70, 17	4,000	16	12 min	HPC	Lactose/ cornstarch	NVG
		75-250 (2-6 m/s)	NVG	75-L							NVG

Abbreviations; **PEG,** polyethylene glycol, **PVP,** polyvinylpyrollidone; **PVP-PVA,** polyvinylpyrrolidone-ploy vinylacetate; **HPMC,** hydroxypropyl methyl cellulose; **HPC,** hydroxypropyl cellulose; **MC,** methyl cellulose; **NVG,** no value given

9.1 Nucleation

The results of the nucleation experiments (**chapter 6** and **7**) made clear that the balance between two rate processes, *binder dispersion and liquid penetration*, determines the nucleation behaviour in the high shear mixer. This is illustrated in Figure 9-2. Additionally, the experiments in **chapter 7** showed that under most conditions the process of liquid penetration is faster than the binder dispersion, which means granules are formed by liquid penetration. Only at extreme conditions (viscosity above 30,000 mPa.s or no wetting of the liquid) liquid penetration becomes practically impossible, resulting in complete dispersion of the binder. In most studies listed in Table 9-1 the investigated viscosity varies between 1 and 5,000 mPa.s. Based on these values it is likely that also in these studies liquid penetration is responsible for the granule formation. Regarding the wetting ability of the binder, unfortunately in these studies almost no information is given. However, realising that most binders are based on solutions of hydrophilic polymers, it may be assumed that these binders will spread over the used filler materials. With this information and the conclusion that granule formation is induced by liquid penetration, some empirical phenomena observed in the literature can be explained;

- *Bimodal granule size distribution*; Penetration-involved nucleation results in the formation of granules. However, primary particles that are not embedded by the binder liquid remain largely ungranulated, especially at the initial stage of granulation. This leads to the observed bi-modality. [Scott et al., 2000, Knight et al., 1998, Knight et al., 2000, Schæfer and Mathiesen, 1996b]
- *Accumulation of the binder in the larger granules*; due to penetration the binder liquid is mainly located in the granules, while a minor part of the binder is located in the ungranulated material. [Knight, 1998, Schæfer and Mathiesen, 1996b, Oostra et al., 2002, de Vegt et al., 2001]
- *Smaller initial granule size at increasing viscosity*; a higher viscosity retards the penetration rate, hence smaller granules are formed by liquid penetration. [Ritala et al., 1986, Schæfer and Mathiesen, 1996a]

These examples emphasise the substantial influence of the nucleation mechanism on the ultimate granule properties. For a more quantitative prediction it is necessary to obtain an indication of the binder dispersion rate. The values for the dispersion rates are however unclear in the different mixers. Therefore, it is important that in the future more effort is made to investigate the binder

dispersion phenomena, so that the formation of the granules can be described quantitatively. Knowledge about the binder dispersion rate might also be a powerful tool for up scaling purposes. One of the starting points of upscaling is the similarity principle. When the dispersion rate is identified as one of the critical parameters, up scaling should be performed on the basis of similar dispersion effects.

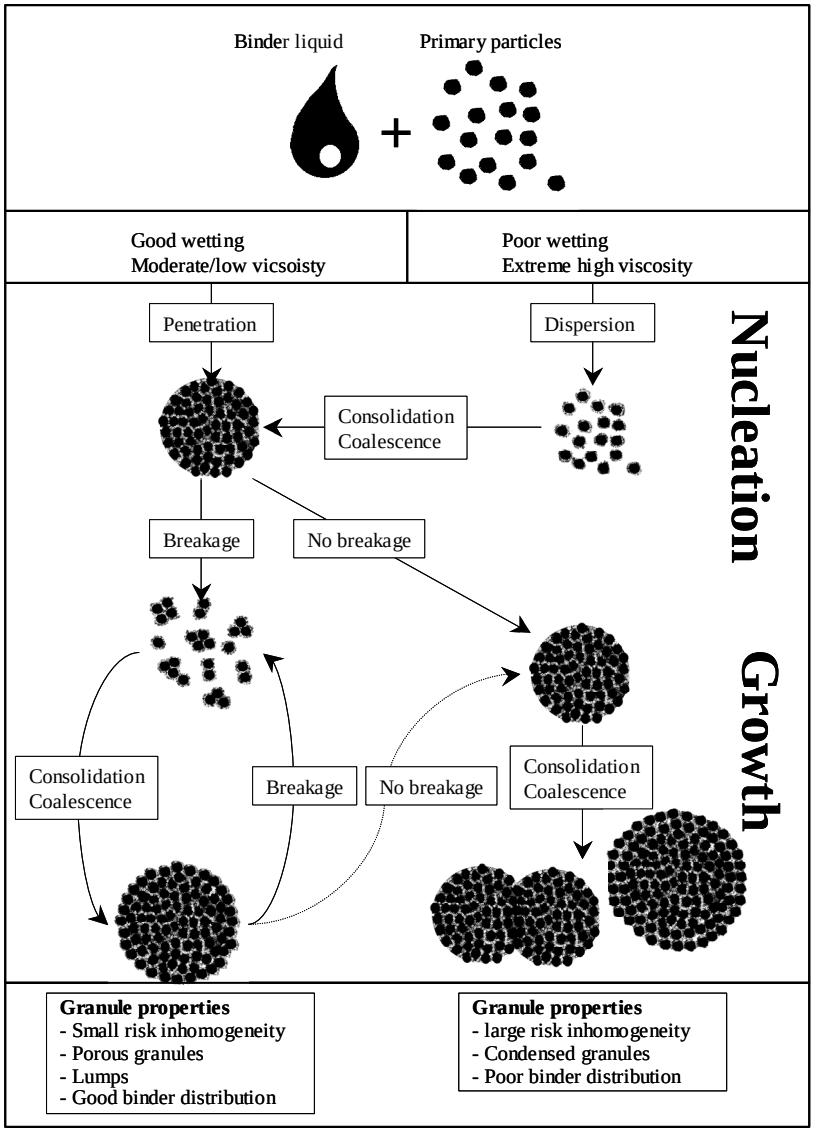

Figure 9-2 *Schematic of high shear granulation (see text for further explanation).*

9.2 Granule breakage

Figure 9-2 shows that another aspect of the granulation process is the granule breakage behaviour. Granule breakage behaviour is often used as a generic term for both complete fragmentation and attrition. In case of attrition granules retain their integrity, however there is wear of the outer surface

of the granule. Consequently, the decrease in mass and size is minimal. Fragmentation, which means a complete destruction of the granule, results in a major decrease in size and mass of the original granule.

In this thesis three different ways to determine the breakage inside the high shear mixer have been applied. Different values of breakage are obtained with the different methods. The values for the breakage behaviour of lactose 200M are listed in Table 9-2.

- In **chapter 4** breakage was measured by monitoring a sieve fraction of tracer granules. The breakage was quantified by comparing the tracer content in the tracer granules with the tracer content in the rest of the granules. The tracer experiments measure the mass transfer from one granule size fraction to other size fractions. By measuring the tracer quantitatively in each size fraction also small transfers of granule mass can be determined. Hence, the value of 40% breakage is a measure for both breakage and attrition.
- In **chapter 6** and **7** the breakage was determined with the nucleation experiments. The granule size and yield were followed in time. If these values remain approximately constant in time there is little/no breakage. Clearly, a reduction of these values means breakage. For lactose 200M 3% breakage is determined with this method. Obviously, this is a less sensitive measure for breakage than obtained with the tracer experiments, because mass transfer between granules does not lead to a change of the overall granule mass. Hence, it is unlikely that the mass change caused by attrition is measured, indicating that merely fragmentation is measured.
- In **chapter** 8 microscopic pictures of the granule sieve fractions were made after addition of the binder in two separate phases (coloured phase and colourless phase). Counting the number of coloured and colourless granules at different time points gives an indication of the breakage behaviour. Also in this case fragmentation is measured, since only the intact coloured granules are counted.

Table 9-2 *The percentage of granule breakage determined with the different methods for lactose 200M granulated with a hydroxypropyl cellulose solution having a viscosity of 4 Pa.s.*

	Tracer experiments ***(Chapter 4)***	**Nucleation experiment** ***(Chapter 6 and 7)***	**Microscopic pictures** ***(Chapter 8)***
Granule breakage Lactose 200M	40%	3%	20%

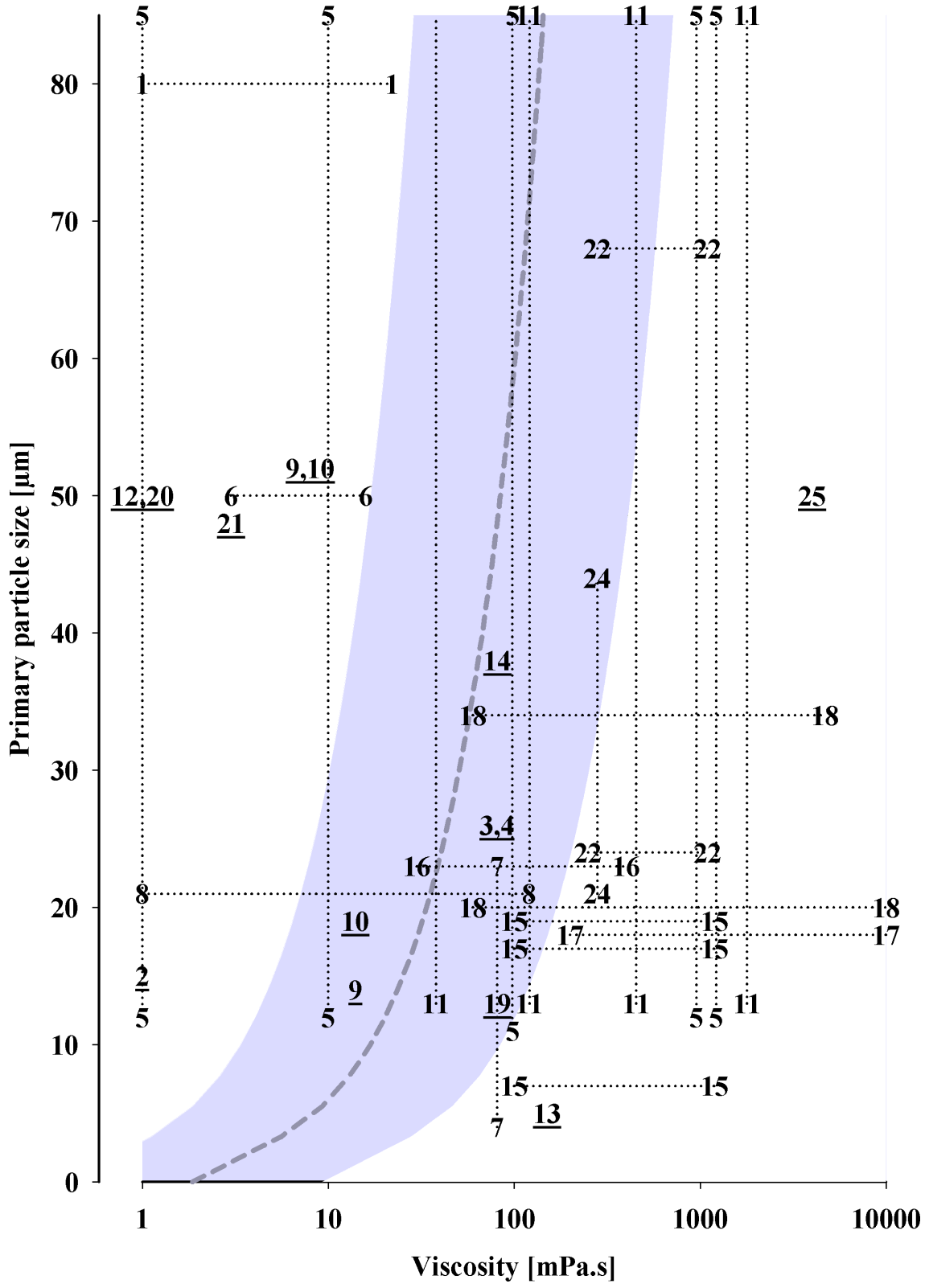

Figure 9-3 *See next page for caption text.*

Figure 9-3 *Overview of the particle size and viscosity ranges used for the different high shear granulation studies[1]. The dashed grey line refers to the estimated boundary between breakage (left side) and no breakage (right side) behaviour determined in this thesis. The line is calculated with equation 7-7 (see* ***chapter 7****). The grey area represents a bandwidth for the boundary between breakage and no breakage behaviour of +/-500% (Values used for the calculations;* ε*~40%,* ρ_g*~1500 kg/m*^{3} *and* v_p*~5 m/s).*

[1]*The numbered labels refer to the studies indicated in Table 9-1; an underlined number represents a single value for the particle size and viscosity, while numbers that are not underlined refer to a particle size or viscosity range. In this case the investigated range is depicted by the thin dotted lines between two identical labels.*

It is important to make a distinction between attrition and breakage. If granules remain intact during the process they will keep their original properties. It has been shown that the properties of the granules (e.g. binder distribution, granule size) are already determined for a large degree during the initial stage of granulation. Moreover, intact granules can function as kernels for preferential growth, stimulating the formation of non-homogeneous granules. Attrition or mass transfer between these granules will not lead to major changes of these properties, while breakage results in a complete loss of the integrity and properties of the original granule. Once granules are formed, granule breakage behaviour determines the further granule growth mechanisms and also the granule properties. This is schematically illustrated in Figure 9-2.

Although it is clear that breakage is an important mechanism for granulation, the breakage behaviour is rarely investigated in studies concerning high shear granulation. Only the studies 5, 12 and 19 in Table 9-1 actually measured the breakage behaviour. However, in the next part an attempt is made to estimate the breakage behaviour for the remaining studies. Figure 9-3 shows the regions of granule breakage and no breakage behaviour that were determined in this thesis as a function of the primary particle size and the viscosity. The values for the primary particle size and the viscosity of the studies listed in Table 9-1 are also indicated in this figure. Combination of this information leads to an estimate for the granule breakage behaviour in the other studies. It should be noted that of course also other properties like impeller speed, mixer type, particle shape and size distribution will have an influence. This is also the reason why a bandwidth of 1000% is applied for the boundary between breakage and no breakage behaviour.

In order to validate these predictions a comparison is made between the estimates and the actual breakage results of the studies that investigated breakage [studies no. 5,12 and 19 in Table 9-1]. In

study no. 12 [Ramaker et al., 1998] complete breakage of the granules was observed, while in study no. 19 [Pearson et al., 2001] only a small degree of breakage was measured. The results of study no. 5 [Keningley et al., 1997] revealed that breakage is observed at low viscosity (1 and 10 mPa.s) and no breakage behaviour at higher viscosity (>100 mPa.s). It is clear that these experimental results are in good agreement with the predicted breakage behaviour shown in Figure 9-3.

An indication of the breakage behaviour can help to explain some phenomena observed in literature. In literature a contradictory influence of the impeller speed on growth is reported. In many cases an increased growth rate is observed at higher impeller speeds [Knight, 1993, Knight et al., 2000, Holm et al., 1984, Kokubo and Sunada, 1996]. In some cases however the opposite is observed, [Schæfer et al., 1990a, 1990b, Ramaker et al., 1998, Knight et al., 2000]. It is likely that this behaviour is caused by the difference in breakage behaviour. If breakage is predominant an increase in impeller speed will result in a larger degree of breakage and a smaller granule size. If there is little breakage a higher impeller speed leads to more collisions and more granule deformation, which leads to an increase in the ultimate granule size.

Johansen and Schæfer (2001) and Keningley et al. (1997) showed that, depending on the primary particle size, a certain viscosity must be exceeded in order to obtain granule growth. It was shown that the critical viscosity to assure granule growth decreased with a decrease in primary particle size. It is likely that this observation is also correlated with the breakage behaviour. Granules consisting of large primary particles are more susceptible for breakage hereby counteracting the growth. Hence, a higher viscosity is needed to prevent the breakage of these granules.

These examples signify the possible influence of granule breakage behaviour on the granule properties. Hence, it is of paramount importance that high shear granulation studies should not only focus on granule growth. Without knowledge about the granule breakage behaviour it is impossible to determine the growth mechanisms.

9.3 Consolidation and coalescence

Although the consolidation and coalescence is not really investigated in this thesis, the granulation results still provided some information about these mechanisms. Figure 9-2 illustrates that independent of the breakage behaviour consolidation and coalescence are the mechanisms of granule growth. However, it is important to realize that the extent of the consolidation and coalescence depends on the breakage behaviour.

In case of breakage a granule is shattered into small fragments and primary particles. Coalescence of these particles and fragments will result in built-up of granules, while the shear forces will break these granules again. In this case the granule properties will depend on the balance between the rate of breakage and the rate of the other processes (see Figure 9-2). This is illustrated with the following granule properties:

- **Size**; In case of breakage the balance between the rate of breakage and of coalescence determines the ultimate granule size.
- **Homogeneity;** Breakage results in a continuous exchange of primary particles between granules. This behaviour stimulates the formation of homogeneous granules. However, preferential layering promotes the accumulation of fine particles in the granules, which results in inhomogeneity. Again, the rates of these processes determine the ultimate distribution of the primary particles. In **chapter 3** and **4** was shown that the breakage behaviour of lactose 100M granules usually yielded homogeneous granules (see **Chapter 3** Figure 3-2b). Nevertheless, in some cases inhomogeneity was observed despite the breakage behaviour. Perhaps, a change in the balance between the rate of breakage and of preferential growth causes this inhomogeneity.
- **Porosity;** the rates of the granule breakage and consolidation will also determine whether densification occurs during granulation. Generally, very porous granules will be obtained when breakage is a predominant granulation mechanism, because consolidation is counteracted by breakage. However, densification results in strengthening of the granules, which may eventually lead to a transition from breakage to no breakage behaviour during the granulation process. The transition in breakage behaviour is illustrated in Figure 9-2 (dashed arrow). Although this shift in breakage behaviour during the process is not observed in this study, it might be feasible in other circumstances. This is determined by the balance between the rate of breakage and the rate of densification.

Granule breakage makes the granulation in the high shear mixer more complex to understand. The reason for the complexity is that a subtle balance between the rates of breakage, coalescence, consolidation and preferential growth determine the ultimate result of granulation. Therefore, the determination of these rates deserves more attention in future research.

However, also when breakage is absent the growth behaviour is complex. Since usually a very broad size distribution is obtained, coalescence of many different size classes may contribute to growth. **Chapter 8** showed that the penetration-involved nucleation mechanism leads to the

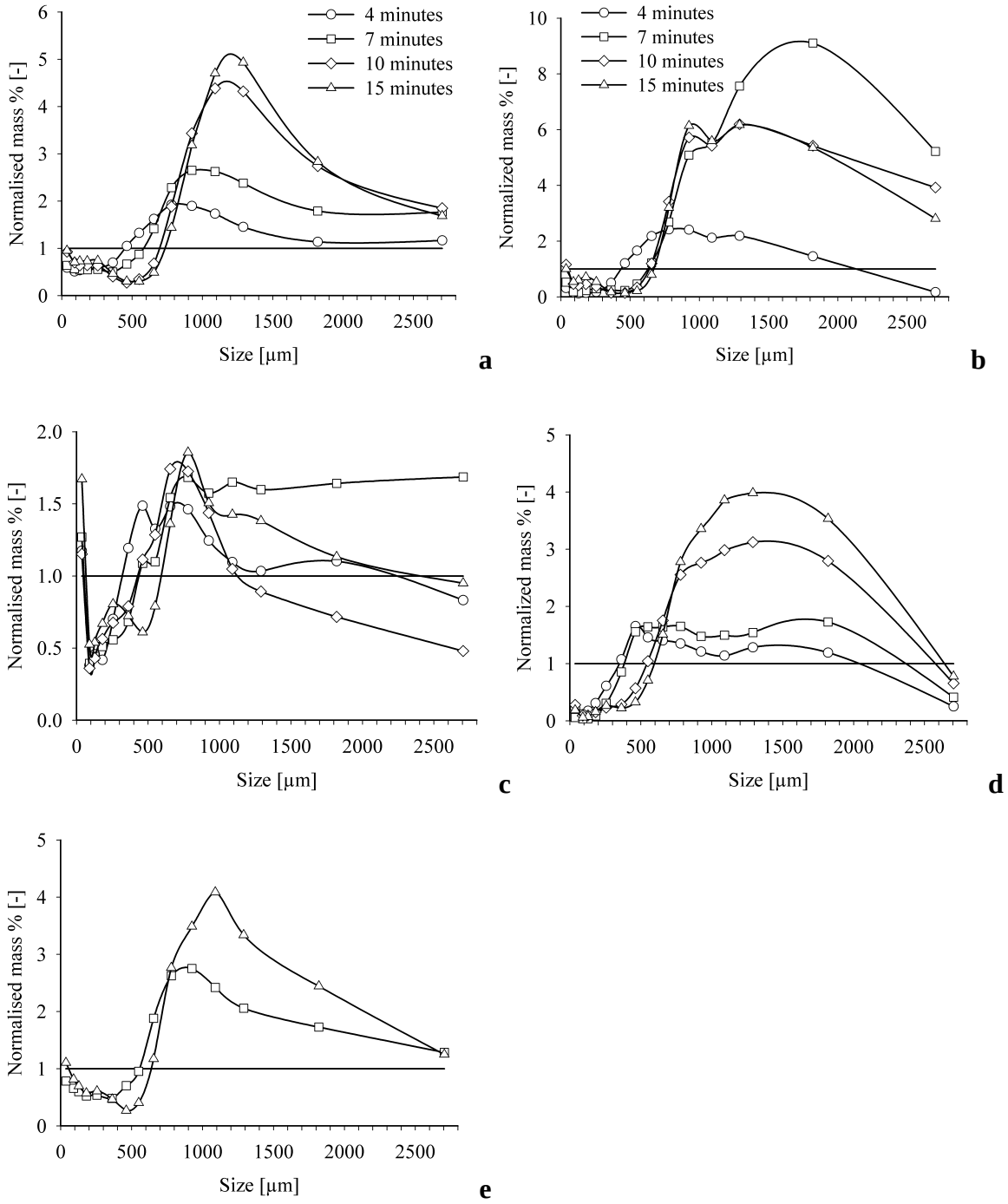

Figure 9-4 *The normalised size distributions for the 0.1% estradiol/lactose 200M and lactose 450M granules at different mixer speeds and process times. The mass fractions were normalised for the size distribution obtained after a process time of 1 minute. (a) Lactose 200M, impeller 430 rpm, chopper 3000 rpm, (b) lactose 450M, impeller 430 rpm, chopper 3000 rpm, (c) lactose 200M, impeller 230 rpm, chopper 3000 rpm, (d) lactose 450M, impeller 230 rpm, chopper 3000 rpm, (e) lactose 200M, impeller 430 rpm, chopper 1500 rpm. (Adapted from figure 3-2.)*

formation of two distinct fractions, a granulated (coarse particles) and an ungranulated (fine particles) fraction. Obviously, this is a very rough distinction. However, based on the properties of these fractions the following can be stated about the mechanisms of coalescence:

- **Granule coalescence (Coarse-coarse); C**oalescence of very coarse granules will play no important role in growth, since the high kinetic energy of the coarse granules will not favour that these granule stick together after collision [Ennis, 1990]. The coalescence of small granules will be more likely, because their kinetic energy is lower.
- **Layering (Coarse-fine);** The low kinetic energy of the fine particles and the high binder content of the coarse granules will stimulate this growth behaviour.
- **Primary particle coalescence (Fine-fine);** Owing to the penetration-involved nucleation mechanism (**chapter 6,7** and **8**) the primary particles contain almost no binder liquid, which is necessary for coalescence. This means that coalescence of primary particles is of minor importance for growth.

In Figure 9-4 the normalized growth curves for lactose 200M and lactose 450M are shown. These growth curves are adapted from figure 3-2 (**chapter 3**). The figure shows that the large particles grow at the cost of the small/primary particles (layering). During layering preferential growth of the smallest primary particles introduces the granule inhomogeneity (**chapter 5**). Figure 9-5 also shows a clear relationship between the granule size of lactose 200M and lactose 450M and the demixing of estradiol in these granules. The inhomogeneity of the lactose 450M granules is less pronounced compared to lactose 200M, because the particle size difference between estradiol and lactose 450M is smaller. These observations seem to confirm that layering is an important growth mechanism.

9.4 Conclusion

In the different chapters of this thesis the individual granulation mechanisms, like breakage, granule formation and preferential layering, were unravelled and investigated. Models based on physical processes were proposed, which are able to describe these mechanisms at different process and formulation conditions. These individual mechanisms provided the building blocks for the framework of high shear granulation that is shown in Figure 9-3. The balance between these mechanisms, which is influenced by the process and formulation variables, determines the ultimate granule properties. One of those properties is the poor distribution the solid constituents in the

granules. This chapter illustrated that understanding of the granulation mechanisms provides a fundamental basis to explain the phenomena of high shear granulation.

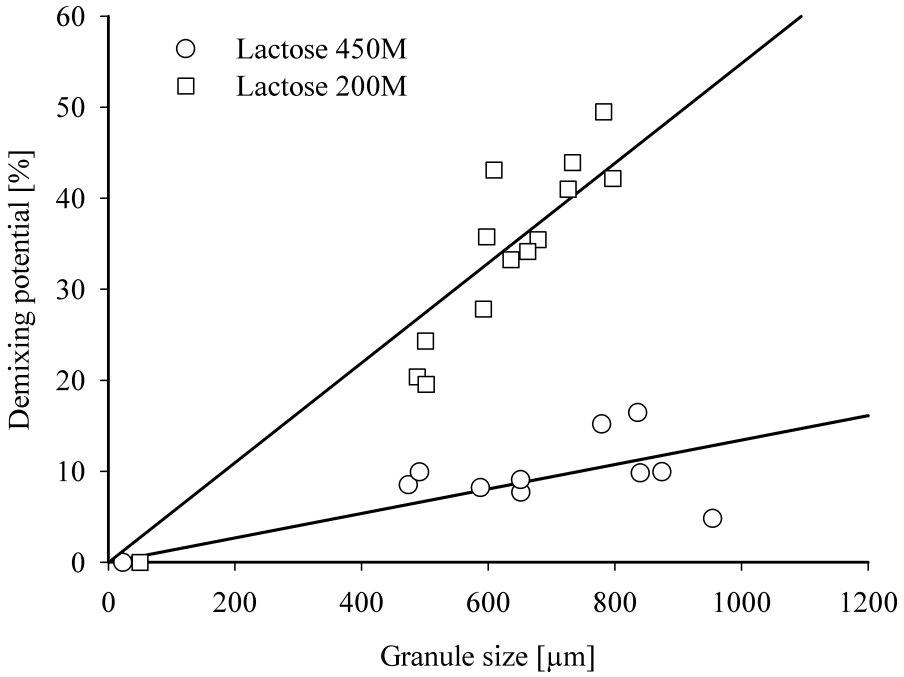

Figure 9-5 *Relationships between the weight mean granule size and demixing potential of the 0.1% estradiol/lactose 200M and lactose 450M formulation. The figure is adapted from figure 3-2.*

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Summary

General

In this thesis the granulation mechanisms that are involved in the formation of non-homogeneous granules in a high shear mixer are elucidated. The inhomogeneity is expressed as a granule size-dependent variation in composition of the granules. This granule property is of special interest for the pharmaceutical industry. Problems with the homogeneity of the granules might introduce a poor content uniformity of the ultimate drug product. The relevance of the investigation of these mechanisms is emphasised by the current initiative of the authorities concerning quality assurance. This initiative is focused on quality testing throughout the process, which implies that testing at the final stage is inadequate. High shear granulation is commonly used as an intermediate step in the production process of a solid formulation. Consequently, quality control of high shear granulation with respect to granule uniformity is essential. Unfortunately, there is limited information about the mechanisms underlying the inhomogeneity of the granules. This means that the control is often based on trial-and-error experiments instead of science. This thesis provides new scientific insights into these mechanisms, namely;

- Granule breakage behaviour, which results in a continuous exchange of primary particles, has a positive influence on granule homogeneity (**chapter 3 and 4**). In contrast, absence of granule breakage means that heterogeneous granules can be formed.
- During layering small primary particles have a higher affinity for growth than large particles. This mechanism, called preferential growth, is responsible for the inhomogeneity (**chapter 5**).
- Penetration of binder liquid into the porous powder bed results in the immediate formation of granules already in the early seconds of the granulation process. If these freshly formed granules are strong enough to withstand the shear forces, these granules can function as kernels for preferential growth. Consequently, this nucleation mechanism can induce the granule inhomogeneity (**chapter 6,7 and 8**).

Furthermore, the effects of changes in process and formulation parameters on these mechanisms are determined. In the different chapters mechanistic models are proposed. Firstly, these model are

intended to describe these mechanisms. Secondly, the theoretical calculations are used to evaluate the influence of the process condition.

The enumerated mechanisms are not only of importance for the granule inhomogeneity phenomena. In fact, these mechanisms will influence the general granulation behaviour in the high shear mixer. This is reflected in **chapter** 9, which discusses the content of this thesis in the perspective of current knowledge of high shear granulation. This discussion points out that comprehension of the rate processes of high shear granulation is a general interest. The understanding of the mechanisms provides a fundamental basis to prevent costly trial-and-error experiments to assure control of the high shear granulation process. For the pharmaceutical industry this control is mainly focused on homogeneity, while other granule properties will be of importance in a different industrial environment.

Summary of chapters

In **chapter 2** a general overview is given of the studies focused on the granule inhomogeneity phenomena. Moreover, the current knowledge on the granulation mechanisms in the high shear mixer is summarised.

In **chapter 3** the influence of the primary lactose size of lactose on the distribution of micronised estradiol in the granules is investigated. The most homogeneous distribution is obtained with the coarsest (lactose 100M) and the finest lactose grade (lactose 450M), while the largest degree of granule inhomogeneity is observed for the intermediate lactose grade (lactose 200M). The poor distribution is associate with an accumulation of the finest particles (estradiol) in the larger granules. Based on these observations, it is hypothesized that two distinct mechanisms are important for the granule (in)homogeneity; *granule breakage* and *preferential growth*.

In **chapter 4** the breakage behaviour of the granules inside the high shear mixer is determined. The fate of a coloured granular fraction is monitored to measure the breakage. These tracer experiments show that the lactose 100M granules are completely broken, while little breakage is observed for lactose 200M and lactose 450M granules. The decrease in the primary lactose size yields stronger granules, which causes the observed transition from breakage to no breakage behaviour. Besides, the experiments show that also an incremental viscosity can induce the transition from breakage to no breakage behaviour. A model, which is based on the granule strength under dynamic conditions,

is proposed to predict breakage behaviour. The model is able to estimate the observed influence of the primary particle size and the viscosity on granule breakage.
The mechanism of preferential growth is investigated in **chapter 5** with ex-situ experiments. Addition of a droplet to a powder mixture of lactose and paracetamol produces a single granule. Radial liquid penetration is responsible for the layering growth of the granule. Chemical assay of this granule at different time points reveals that during layering there is accumulation of the finest particles in the granules. This implies that the finest primary particles have the highest affinity for growth. This observation is independent of the fact whether these particles are drug or filler particles. During layering growth liquid flows from the inner pores to the outer pores of the granule, hereby wetting the outer surface of the granule. Fine particles can enter the surface pores and encounter a wet surface at an earlier stage than the coarse particles, which are excluded by the pores. Consequently, the porous structure of the outer surface of the granules is responsible for the preferential growth. A mechanistic model, which is based on this assumption, describes the preferential growth quantitatively.

The mechanism of granule breakage and preferential growth can explain the observed inhomogeneity phenomena of **chapter 3.** Granule breakage leads to a continuous exchange of (primary) particles between granules, hereby assuring homogeneity. This behaviour is observed for lactose 100M. If breakage is absent, the finest particles have the highest affinity for granule growth, indicated by the term ‘preferential growth’. Moreover, preferential growth is more pronounced when the particle size difference between filler and drug substance is larger. This explained why the homogeneity of the lactose 200M granules is poorer compared to the lactose 450M granules.

Another aspect of granule inhomogeneity is the fact that the phenomena are already observed in the first minute of the granulation process. This initial stage is investigated in **chapter 6** and **chapter 7**. In **chapter 6** experiments are performed where a substandard amount of binder liquid was added to four different powder mixtures; **(1)** lactose 100M **(2)** lactose 200M and **(3,4)** 10% magnesium-stearate/lactose 100M or 200M. The process is frozen with liquid nitrogen after a few seconds in order to investigate this early stage of the process. The frozen sample is sieved into granular and non-granular material and the liquid distribution in both fractions is determined. For lactose 100M all the binder is initially located in the granules, while the largest mass fraction (ungranulated powder) contains no liquid. The lactose 100M granules are subsequently broken again, which is

consistent with the observation in **chapter 4**. In addition, for lactose 200M also 100% of the binder liquid accumulates in the granules. In contrast to lactose 100M, lactose 200M granules withstand the shear forces. It is argued that in both cases liquid penetration is the key mechanism of granule formation. A theoretical evaluation also confirms that liquid penetration leads to the immediate formation of the primary granules. This means that the initial granule formation is not a stepwise process of wetting and subsequent coalescence of primary particles. Instead, the binder liquid immerses several primary particles to form a granule. The hydrophobicity of the magnesium-stearate/lactose mixture prevents the liquid penetration. Consequently, complete binder dispersion to the non-granular material occurs.

When the binder liquid is poured into the high shear mixer, the mechanical agitation is responsible for the dispersion of the liquid into droplets. These droplets become smaller as the process proceeds. Parallel to the binder dispersion process, penetration of these binder droplets into the porous powder bed results in granule formation. Two regions can be identified. Firstly, if the binder dispersion is the dominant process complete dispersion of the binder will occur. This results in distribution of the binder over the (primary) particles. Secondly, if the penetration is faster than the binder dispersion granules are formed. Hardly any binder will then distribute over the primary particles, because the penetration prevents complete binder dispersion. In this case the binder is mainly present in the granules. A distribution over the primary particles is only obtained when these granules are broken down again. These results indicated that the three mechanisms of granule formation that can be qualified; **(I)** penetration-involved granule formation and breakage, **(II)** penetration-involved granule formation and absence of granule breakage and **(III)** dispersion-only nucleation.

The influence of several process and formulation conditions (e.g. particle size, viscosity, binder type and process time) on the nucleation mechanism is investigated in **chapter 7**. The results show that at a low viscosity, granules are formed by liquid penetration and are subsequently broken down by the shear forces (**mechanism I**). When the viscosity exceeds a certain critical value, the formed granules are no longer broken down (**mechanism II**). A further increase of the viscosity leads to a gradual transition from the penetration-involved to the dispersion-involved mechanism. At extreme high viscosity values (>30 Pa.s) liquid penetration becomes almost impossible. In this case the dispersion-only nucleation is predominant (**mechanism III**). These observed transitions in

nucleation behaviour as a function of the viscosity are proven valid for the complete range of the investigated process and formulation conditions.
These nucleation experiments point out that granule formation is controlled by three different rate processes; *granule breakage*, *binder dispersion* and *liquid penetration*. These rate processes are combined in a model, which predicts the nucleation behaviour in the high shear mixer. The model can describe the occurrence of each nucleation mechanism as a function of the viscosity and primary particle size.

The experiments described in **chapter 6** and **chapter 7** are performed with a reduced amount of binder liquid in order to investigate the nucleation only. The added amount is approximately a tenth of the amount normally used to granulate lactose. To extrapolate the findings of **chapter 6** and **7** to a full-scale process, granulation experiments are performed where the liquid quantity is gradually increased to a standard amount. The effect of this increase on the binder distribution over the granules is determined. In **chapter 8** it is conclusively shown that liquid penetration is also the main mechanism of granule formation in case a standard amount of liquid is added.
In **chapter 9** the mechanisms of preferential growth, granule breakage and granule formation are discussed in the context of current literature. The findings of this thesis are extrapolated to other studies concerning high shear granulation to obtain a general overview of the granulation mechanisms and to explain various granulation phenomena.

Samenvatting

Algemeen

In dit proefschrift worden de granulatie mechanismen die leiden tot de vorming van niet homogene granules tijdens het snelkneed proces opgehelderd. Deze inhomogeniteit komt tot uitdrukking als een variatie in de samenstelling van de granules die afhankelijk is van de granule grootte. Deze granule eigenschap is vooral van belang in de farmaceutische industrie. Problemen met de inhomogeniteit van de granules kunnen namelijk een slechte uniformiteit van het eindproduct veroorzaken. Het belang van dit onderzoek wordt onderschreven door huidige initiatieven van de verschillende overheden betreffende de kwaliteitscontrole van geneesmiddelen. Dit initiatief is gericht op het meten van de productkwaliteit gedurende het gehele proces. Daarbij is het dus niet langer voldoende om alleen een acceptabele kwaliteit van het eindproduct aan de tonen.

Het granuleren in een hogesnelheidsmenger is een veel gebruikte processtap tijdens de productie van een vaste toedieningsvorm (capsule of tablet). Het is dan ook van essentieel belang om het proces zo te sturen dat homogene granules gevormd worden. Er is echter weinig kennis over de mechanismen die ten grondslag liggen aan de granule inhomogeniteit. Dit houdt in dat de sturing van het proces vaak gebaseerd is op empirie in plaats van op wetenschappelijk gronden. Dit proefschrift verschaft nieuwe wetenschappelijke inzichten in deze mechanismen, namelijk;

- Het breken van granules, wat leidt tot een continue uitwisseling van primaire poederdeeltjes, heeft een positief effect op de granule homogeniteit (**hoofdstuk 3 en 4**). Echter, heterogene granules kunnen worden gevormd wanneer de granules niet breken.
- De kleinere primaire poederdeeltjes hebben een grote affiniteit voor granule groei dan de grotere deeltjes. Dit mechanisme, genaamd preferentiële groei, is verantwoordelijke voor de inhomogeniteit (**hoofdstuk 5**).
- Vloeistof penetratie in een poreus poeder bed leidt tot de onmiddellijke vorming van granules tijdens de eerste secondes van het granuleer proces. Als deze granules sterk genoeg zijn om de afschuifkrachten in de menger te weerstaan dan kunnen deze granules functioneren als kernen voor de preferentiële groei. Dit mechanisme van granule vorming kan dus een heterogeniteit van het granulaat veroorzaken (**hoofdstuk 7,8 en 9**).

Bovendien worden de effecten van verschillende proces- en formuleringsparameters op de mechanismen bepaald. In de verschillende hoofdstukken worden modellen geïntroduceerd die deze effecten kunnen beschrijven.

Uiteraard zijn de veronderstelde mechanismen niet alleen van belang voor de inhomogeniteit fenomenen. In feiten zullen de mechanismen het algehele granuleer gedrag in de hogesnelheidsmenger beïnvloeden. Dit wordt beschreven in **hoofdstuk 9**, waar de inhoud van dit proefschrift wordt bediscussieerd in de context van de huidige kennis op het gebied van granulatie. Deze discussie wijst uit dat begrip van de granuleer processen een fundamentele basis vormt om te voorkomen dat vele experimenten nodig zijn om de productkwaliteit te kunnen garanderen. In de farmaceutische industrie is deze kwaliteit vooral gefocust op homogeniteit, maar andere granulaat eigenschappen zijn waarschijnlijk van belang voor andersoortige industrieën. Ook deze eigenschappen zullen beïnvloed worden door de beschreven granulatie mechanismen.

Samenvatting van de hoofdstukken

In **hoofdstuk 2** wordt een algemeen overzicht gegeven van de studies die zijn gericht op de granule heterogeniteit. Bovendien wordt een samenvatting gegeven van de huidige kennis betreffende de granuleer mechanismen in een hogesnelheidskneder.

In **hoofdstuk 3** wordt de invloed van de primaire deeltjesgrootte van lactose op de verdeling van gemicroniseerd estradiol in de granules onderzocht. De meest homogene verdeling van estradiol wordt verkregen met de grofste (lactose 100M) en de fijnste lactose kwaliteit (lactose 450M), terwijl de slechtste verdeling wordt waargenomen voor de lactose kwaliteit met de tussenliggende deeltjesgrootte (lactose 200M). De slechte verdeling manifesteerd zich als een ophoping van estradiol in de grotere granules. Op basis van deze bevindingen wordt verondersteld dat twee verschillende mechanismen van belang zijn voor de granule (in)homogeniteit, namelijk *het breken van de granules* en *de preferentiële groei*.

In **hoofdstuk 4** wordt het breekgedrag van de granules in de snelkneder bepaald. De (her)verdeling van een gekleurde zeeffractie wordt gevolgd om het breekgedrag te meten. Deze tracer experimenten laten zien dat de lactose 100M granules volledig worden gebroken, terwijl er nauwlijks breekgedrag wordt waargenomen voor de lactose 200M en 450M granules. De afname in deeltjesgrootte van de lactose leidt tot sterkere granules wat uiteindelijk dus resulteert in de overgang van breek naar niet breekgedrag. Bovendien laten de experimenten zien dat ook een toenemende viscositeit deze overgang in breekgedrag kan veroorzaken. Een model wat gebaseerd is

op de granule strekte onder dynamische omstandigheden wordt voorgesteld om het breekgedrag te kunnen afschatten. Het model is in staat om de invloed van de primaire deeltjesgrootte en de viscositeit op het breekgedrag te kunnen voorspellen.

Het mechanisme van de preferentiële groei wordt bestudeerd in **hoofdstuk 5** met ex-situ experimenten. Hierbij wordt één enkele granule gevormd door een druppel bindervloeistof toe te voegen aan een poedermengsel van lactose en paracetamol. Radiale vloeistof penetratie leidt vervolgens tot een groei door de vorming van lagen rondom de granule. Chemische analyse van granule op verschillende tijdspunten laat zien dat de fijnste poederdeeltjes zich ophopen in de granule tijdens de groei. Dit houdt in dat de fijnste deeltjes de hoogste affiniteit hebben voor granule groei. Deze waarneming is onafhankelijk van het feit of de fijnste deeltjes nu lactose of paracetamol deeltjes zijn. Tijdens de groei stroomt er vloeistof vanuit de binnenste poriën naar buitenste poriën wat uiteindelijk leidt tot de bevochtiging van de buitenkant van de granule. Fijne deeltjes kunnen deze poriën binnendringen en komen in een eerder stadium een vochtig oppervlak tegen als de grofste deeltjes, die deze poriën niet kunnen binnendringen. De poreuze structuur van de granules is dus aanleiding voor de preferentiële groei. Een mechanistisch model, wat gebaseerd is op deze aanname, kan deze preferentiële groei beschrijven.

De breek en preferentiële groei mechanismen kunnen de inhomogeniteit fenomenen die zijn waargenomen in **hoofdstuk 3** verklaren. Het breken van de granules leidt tot een continue uitwisseling van primaire deeltjes, wat resulteert in een homogene verdeling. Dit gedrag is van toepassing op de lactose 100M granules. Als er nauwlijks breekgedrag optreedt dan hebben de fijnste deeltjes de hoogste affiniteit voor granule groei. Deze preferentiële groei speelt een grotere rol naarmate het deeltjesgrootte verschil tussen de verschillende bestandsdelen groter is. Dit verklaart waarom de homogeniteit van de lactose 200M granules slechter is dan van de lactose 450M granules.

Een ander aspect wat van belang is, is dat heterogeniteit al tot uitdrukking komt in de eerste minuut van het granuleerproces. Deze initiële fase van het proces wordt bestudeerd in **hoofdstuk 6 en 7**. In **hoofdstuk 6** worden experimenten uitgevoerd waarbij een minimale hoeveelheid binder vloeistof wordt toegevoegd aan vier verschillende poedermengsels; **(1)** lactose 100M, **(2)** lactose 200M en **(3,4)** 10% magnesium stearaat en lactose 100M/200M. Een paar seconden na de toevoeging van de binder wordt het proces bevroren met vloeibare stikstof. Dit bevroren monster wordt gezeefd in twee fracties; een gegranuleerde en een niet gegranuleerde poederfractie. De vloeistof verdeling in beide fracties wordt vervolgens bepaald. Voor lactose 100M geldt dat in eerste instantie alle

vloeistof zich bevindt in de gegranuleerde fractie, terwijl de grootste massafractie (het niet gegranuleerde materiaal) geen vloeistof bevat. De lactose 100M granules worden echter gebroken, wat overeenkomt met de waarnemingen in **hoofdstuk 4**. Ook voor lactose 200M geldt dat alle vloeistof zich ophoopt in de gegranuleerde fractie. In tegenstelling tot lactose 100M granules kunnen de lactose 200M granules wel de krachten in de snelkneder weerstaan. Er wordt geargumenteerd dat in beide gevallen vloeistof penetratie verantwoordelijk is voor de initiële vorming van de granules. Deze argumentatie wordt ondersteund door een theoretische berekening. Concreet betekent dit dat granules niet worden gevormd door een stapsgewijs proces van bevochtiging en vervolgens plakken van primaire poederdeeltjes. In plaats daarvan worden verscheidene poederdeeltjes tegelijkertijd omvangen door vloeistof en een granule wordt gevormd. De hydrofobiciteit van het magnesium stearaat voorkomt de bevochtiging van het poeder en dus is er geen vloeistof penetratie mogelijk. Het gevolg is dat de vloeistof volledig wordt gedispergeerd over het niet gegranuleerde materiaal.

Wanneer vloeistof in de snelkneder wordt gegoten is de mechanische werking van de mixer verantwoordelijk voor de dispersie van de vloeistof in druppels. Deze druppels worden steeds kleiner gedurende het proces. Parallel aan deze vloeistof dispersie kan penetratie van deze vloeistof deeltjes in het poederbed leiden tot de vorming van granules. Als de vloeistof dispersie het dominante proces is dan zal de vloeistof zich volledig verdelen voordat er überhaupt penetratie heeft plaatsgevonden. Als dit echter niet het geval is dan zullen granules ontstaan door de vloeistof penetratie. Omdat dit mechanisme voorkomt dat de vloeistof zich verdeeld over de primaire deeltjes zullen deze deeltjes ook nauwlijks vloeistof bevatten. In dit geval is bijna alle binder aanwezig in de granules. De vloeistof zal zich alleen verder verdelen als deze granules worden gebroken. De experimentele resultaten laten zien dat drie mechanisme van granule vorming kunnen worden gekwalificeerd, namelijk; **(I)** vorming van granules door penetratie en vervolgens worden deze granules weer gebroken (lactose 100M), **(II)** vorming van granules door penetratie en de granules blijven intact (lactose 200M) en **(III)** volledige dispersie van de binder vloeistof (10% magnesium stearaat en lactose 100M/200M).

In **hoofdstuk 7** wordt de invloed van verschillende proces- en formuleringsparameters (deeltjesgrootte, viscositeit, binder type en procestijd) op het vormingsmechanisme van granules onderzocht. De resultaten laten zien dat bij een lage viscositeit granules worden gevormd door vloeistof penetratie, maar dat deze granules vervolgens worden afgebroken (**mechanisme I**). Als de

viscositeit een kritische waarde overschrijdt dan worden de gevormde granules niet langer afgebroken (**mechanisme II**). Een verdere toename van de viscositeit leidt tot een geleidelijke overgang van vloeistof penetratie naar dispersie. Bij een extreem hoge viscositeit (>30 Pa.s) is vloeistof penetratie haast onmogelijk. In dit geval speelt alleen de volledige vloeistof dispersie nog een rol (**mechanisme III**). Deze verschuivingen van het mechanisme van granule vorming onder invloed van de viscositeit wordt waargenomen voor alle onderzochten parameters.
Deze experimenten wijzen bovendien uit dat granule vorming wordt bepaald door drie verschillende processen; *granule breken*, *vloeistof dispersie* en *vloeistof penetratie*. Deze drie processen zijn gecombineerd in een model, wat het mechanisme van de granule vorming in de snelkneder kan voorspellen als functie van o.a. de primaire deeltjesgrootte en de viscositeit.

De experimenten die zijn beschreven in **hoofdstuk 6** en **hoofdstuk 7** zijn uitgevoerd met een minimale hoeveelheid binder vloeistof om alleen de vorming van de granules te kunnen onderzoeken. De toegevoegde hoeveelheid binder is ongeveer een tiende van de hoeveelheid die normaal wordt toegevoegd. Om de bevindingen van **hoofdstuk 6** en **hoofdstuk 7** te extrapoleren naar een standaard proces worden experimenten uitgevoerd waarbij de binder hoeveelheid geleidelijk wordt verhoogd. Het effect van deze toename in vloeistof op de binder verdeling wordt gemeten. In **hoofdstuk 8** wordt afdoende bewezen dat vloeistof penetratie ook het belangrijkste mechanisme van granule vorming is wanneer er een standaard hoeveelheid binder wordt gebruikt.
In **hoofdstuk 9** worden de mechanisme van preferentiële groei, granule breekgedrag en granule vorming bediscussieerd in het perspectief van de huidige literatuur. De bevindingen van dit proefschrift worden geëxtrapoleerd naar andere studies op het gebied van granuleren in een snelkneder om een algemeen overzicht te krijgen van de mechanismen en hun invloed op verschillende granulatie fenomenen.

Samenvatting voor vrienden en familie

In dit proefschrift worden de resultaten beschreven van een onderzoek naar granuleren in een snelkneder. Maar voordat er wordt ingegaan op de details van het onderzoek moet eerst duidelijk worden wat granuleren is. In *Het Groot Woordenboek der Nederlandse Taal* wordt de volgende omschrijving van granuleren gegeven;

granuleren *(granuleerde, h. gegranuleerd) [1823 <Fr. granuler>]* ***I*** *(overg.)* ***1*** *in een korrelig poeder veranderen, syn. korrelen (1): om gietijzer te granuleren smelt men het, en giet het daarna uit in water dat in beweging is; gegranuleerd slakkenzand* ***2*** *(graf.) greineren* ***3*** *(farm.) (m.betr.t. stoffen) zodanig mengen dat men er tabletten van kan maken* ***II*** *(onoverg.), (med.) (van de oppervlakte van een wond) granulaties (2) vormen.*

Granuleren in de farmaceutische industrie kan dus worden gedefinieerd als het veranderen van een poeder in een korrelig poeder, zodanig dat men er tabletten van kan maken. Een meer plastische omschrijving van granuleren is het aan elkaar plakken van primaire poeder deeltjes, dat leidt tot de vorming van grotere deeltjes. Eén granule is dus samengesteld uit een heleboel kleinere deeltjes. Als de kristalsuiker de primaire poederdeeltjes zijn dan is een suikerklontje de granule.

In de farmaceutische industrie wordt het granuleren eigenlijk altijd gebruikt als een tussenstap tijdens de productie van tabletten of capsules. Een belangrijke reden deze extra stap in een proces te introduceren is dat eigenschappen van granules vele voordelen bieden ten opzichte van de eigenschappen van de uitgangsmaterialen, zoals;

- De stroming van grotere deeltjes (granules) is vaak veel beter dan de stroming van kleine deeltjes. Dit kun je illustreren door wat kristalsuiker en wat poedersuiker in twee identieke glazen te doen en dan langzaam de glazen omkeren. Je zult zien dat de kristalsuiker eerder uit het glas glijdt dan de poedersuiker. Een voordeel van een betere stroming is dat het materiaal nu makkelijker in gebruik is bij de vervolg stappen, zoals het tableteren of het capsuleren.
- Door primaire deeltjes aan elkaar te plakken voorkom je stofvorming. Dit is van belang omdat er in de farmaceutische industrie vaak met zeer actieve stoffen wordt gewerkt en een blootsteling aan deze stoffen gedurende een lange tijd kan schadelijk zijn voor de werknemers. Deze blootstelling kun je minimaliseren door het stofgedrag te verminderen.

De meest gebruikte manier te granuleren is door vloeistof aan het poedermengsel toe te voegen. Vaak is deze vloeistof een oplossing van een bindmiddel in water. Je kunt deze oplossing vergelijken met behangplaksel. De vloeistof zorgt voor de initiële binding tussen de deeltjes. Vervolgens worden de granules gedroogd en zorgt het bindmiddel voor een permanente binding van de deeltjes. Om ervoor te zorgen dat de vloeistof goed met het poeder vermengd wordt moet het geheel goed geroerd worden. Dit roeren kan op vele verschillende manieren gebeuren, wat ook geleidt heeft tot een grote diversiteit van granuleer apparaten. In dit onderzoek is gekeken naar de werking van de zogenaamde snelkneder (Eng. high shear mixer). Een snelkneder is eigenlijk niets meer dan een veredelde keukenmixer, dus door een snelle rotatie van de mengbladen in een kom wordt het poedermengsel met het vocht gemengd.
Het produceren van de granules is dus een simpel proces. Het complexe van het granuleren zit hem ook niet in het produceren, maar in het begrijpen waarom de granules gevormd worden. Er is namelijk nog veel onbekend over het de mechanismen van de granule vorming. Een vraag die terecht gesteld kan worden is; waarom is het belangrijk om het proces te begrijpen als je zonder begrip ook al granules kan maken? Om deze vraag te beantwoorden is het van belang om wat inzicht te hebben in het ontwikkelingstraject van een tablet of capsule.

Als er in de research afdelingen van een farmaceutisch bedrijf een potentiële geneeskrachtige stof ontdekt wordt dan moet deze stof worden verwerkt in een toedieningsvorm die gemakkelijk te gebruiken is door de patiënten. In de meeste gevallen zal dit een tablet of een capsule zijn. De geneeskrachtige stof hoeft vaak in zeer kleine hoeveelheden toegediend te worden, dus om de toedieningsvorm enigszins hanteerbaar te maken worden er vaak vulmiddelen gebruikt. Deze vulmiddelen hebben geen biologische werking, ze kunnen echter wel de functionaliteit van de toedieningsvorm beïnvloeden. In eerste instantie is het belangrijk dat de vulmiddelen zo gekozen worden dat de geneeskrachtige stof gedurende enkele jaren stabiel is. Als de geneeskrachtige stof verdwijnt en wordt omgezet in andere stoffen dan zal het zijn werking verliezen en kunnen de andere stoffen misschien bijwerkingen veroorzaken. De keuze van de juiste vulmiddelen is dus sterk afhankelijk van de eigenschappen van de geneeskrachtige stof. Van dit mengsel van vulmiddelen en geneeskrachtige stof(fen) moeten een toedieningsvorm gemaakt worden door bijvoorbeeld te granuleren en te tableteren. Daarbij moet in ogenschouw worden genomen dat er in de vroege fase van de ontwikkeling van een tablet maar een zeer geringe hoeveelheid

geneeskrachtige stof beschikbaar is (enkele tientallen grammen). Er is dus nauwlijks ruimte om veel dingen uit te proberen en eigenlijk moet het proces de eerste keer al goed zijn.

Zoals al blijkt uit kunnen de bestanddelen van de mengsels van de geneeskrachtige stof en de vulmiddelen sterk variëren, waarmee ook de eigenschappen van de mengsels sterk verschillend kunnen zijn. Hierdoor is het praktisch onmogelijk is om één standaard 'recept' te maken voor het granuleerproces. In plaats daarvan moet per combinatie van geneeskrachtige stof en vulmiddelen het granuleer proces opnieuw bekeken en ontwikkeld worden. Hiervoor is echter maar een beperkte hoeveelheid geneeskrachtige stof beschikbaar, waardoor je erg afhankelijk bent van de ervaring van de operators om een goed granuleerproces te ontwikkelen. Als er meer kennis over het granuleerproces is, dan wordt het in de toekomst eenvoudiger om een proces te ontwikkelen.
Dat het nog niet zo eenvoudig is om een goed granuleerproces te ontwikkelen blijkt wel uit het feit dat er vele voorbeelden bestaan, waarbij er geen optimaal granulaat geproduceerd is. Vaak komt dit tot uitdrukking als een niet-homogene samenstelling van de granules. Deze inhomogene verdeling kan uiteindelijk zelfs resulteren in een ongelijkmatige verdeling van de geneeskrachtige stof over de tabletten, waardoor sommige tabletten meer geneeskrachtige stof bevatten dan wenselijk is en andere weer minder. Uiteraard zullen deze tabletten worden afgekeurd tijdens de routinematige controles. Om deze uitval te voorkomen is het van belang om deze inhomogene verdeling van de geneeskrachtige stof te voorkomen. Om dit doel te bereiken zul je eerst moeten begrijpen hoe de granules nu gevormd worden. Dit was het doel van dit onderzoeksproject.

In het vervolg van deze samenvatting zal een korte beschrijving worden gegeven van de bevindingen van dit onderzoek per hoofdstuk. Hoofdstukken 1 en 2 worden hierbij niet behandeld, omdat dit een algemene samenvatting is van wat er tot nu toe bekend is over het granuleren in een snelkneder en over de inhomogene verdeling van de stoffen tijdens het granuleren.

Hoofdstuk 3

In hoofdstuk 3 worden experimenten beschreven, waarbij een vulmiddel (lactose) met een geneeskrachtige stof (estradiol) wordt gegranuleerd in de snelkneder. De experimenten worden uitgevoerd met drie verschillende deeltjesgroottes van het vulmiddel namelijk, 170 micrometer, 50 micrometer en 23 micrometer (één micrometer (µm) is één miljoenste meter). De deeltjesgrootte van de geneeskrachtige stof is constant gehouden (5 µm). Na het granuleren zijn er granules gevormd variërend in deeltjesgrootte van heel klein tot groot (0.075-2.5 millimeter in diameter).

Het gevormde granulaat wordt gedroogd en gesplitst in verschillende fracties door middel van 15 zeven. Elke zeef heeft daarbij een verschillende maaswijdte, zodat iedere fractie granules bevat van één bepaalde grootte. Vervolgens wordt de concentratie van de geneeskrachtige stof in iedere deeltjesgrootte fractie wordt bepaald. Met deze informatie kun je een verdeling van de geneeskrachtige stof over het gehele granulaat bepalen. In figuur 3-2b (zie blz. 36) is hiervan een voorbeeld gegeven. Uit deze figuur blijkt dat de kleine granules minder geneeskrachtige stof bevatten dan de grotere granules, terwijl het wenselijk is dat alle granules een zelfde hoeveelheid stof bevatten. In dit voorbeeld is de geneeskrachtige stof dus slecht verdeeld over het granulaat.

Een nadeel van de manier van weergeven zoals dat is gedaan in figuur 3-2b is dat je maar één verdeling per figuur kan tonen. Het is handiger om de verdeling uit figuur 3-2b te karakteriseren met één getal, de zogenaamde ontmengpotentiaal. Zo is het mogeloijk om met één figuur de homogenitiet van verschillende granulaten weer te geven, waardoor een vergelijk makkelijker is. Voor de ontmengpotentiaal geldt des hoger deze waarde, des te slechter is de verdeling over het granulaat. De verdeling van de geneeskrachtige stof over verschillende granulaten is weergegeven in figuur 3-2a (zie blz 36). In deze figuur staat op de horizontale as de deeltjesgrootte van het vulmiddel weergegeven en op de verticale as de bijbehorende ontmengpotentialen van het granulaat na verschillende procestijden. Elk punt stelt dus een verdeling voor, zoals is weergegeven in figuur 3-2b. Uit de figuur blijkt dat voor alle granuleertijden geldt dat de slechtste verdeling wordt verkregen met de deeltjesgrootte van het vulmiddel van 50 µm. Wanneer de kleinere of de grotere variant van het vulmiddel wordt gebruikt is de ontmengpotentiaal duidelijk lager.

In figuur 3-2a worden dus de resultaten van de experimenten getoond. Uit deze resultaten blijkt wel dat de deeltjesgrootte van het vulmiddel een belangrijke rol speelt bij de ontmenging, maar waarom? Een gangbare manier om dit soort vragen in de wetenschap te beantwoorden is het stellen van hypotheses (verklaringen). Van tevoren wordt er een (logische) verklaring bedacht voor de waarnemingen. Soms worden deze verklaringen onderbouwd door theoretische berekeningen (modellen). Dit is ook gedaan in hoofdstuk 3. Dus alle, op het oog ingewikkelde, wiskundige formules in hoofdstuk 3 zijn niets meer dan een poging om de waarnemingen van figuur 3-2a te verklaren via een model. In hoofdstuk 3 zijn twee volgende verklaringen bedacht voor de waarnemingen in figuur 3-2a namelijk;

1. Granules die zijn samengesteld uit grote deeltjes van het vulmiddel zijn minder sterk dan granules die bestaan uit kleine deeltjes. Aangezien de mengarmen van de mixer grote

krachten op de granules uitoefenen kunnen de granules breken, oftewel uiteenvallen in de oorspronkelijke deeltjes. Dit zal eerder het geval zijn voor de minder sterke granules. Gesteld wordt dat de granules die bestaan uit het vulmiddel met de grootste deeltjes (170 µm) worden gebroken in de snelkneder. De gebroken deeltjes plakken vervolgens weer aan elkaar om een granule te vormen. Deze granule zal vervolgens wederom gebroken worden. Door dit dynamische gedrag krijg je een continue uitwisseling van de deeltjes tussen de granules en deze uitwisseling heeft een positieve invloed op de verdeling van de geneeskrachtige stof. Vandaar ook de lage ontmengpotentialen voor het vulmiddel met een deeltjesgrootte van 170 µm.

2. Die granules die bestaan uit respectievelijk de deeltjes van 50 µm en 23 µm zullen niet gebroken worden in de snelkneder, omdat deze granules sterker zijn. Als de granules dus eenmaal gevormd zijn blijven ze gedurende het gehele proces intact. Op het moment dat ze intact blijven kunnen ze doorgroeien. Tijdens deze groeifase hebben de kleinere deeltjes een grotere affiniteit voor groei dan de grotere deeltjes. De kleinste deeltjes in het mengsel zijn de geneeskrachtige stof deeltjes en deze deeltjes zullen dus eerder groeien als de grotere vulmiddel deeltjes. Dit zou ook de ophoping van de geneeskrachtige stof in de granules kunnen verklaren. Hierbij geldt ook dat des te groter het verschil in deeltjesgrootte tussen de geneeskrachtige stof en het geneesmiddel des te erger zal de ophoping zijn in de granules. Dus volgens deze verklaring is de verdeling van de geneeskrachtige stof slechter als de 50 µm deeltjes gebruikt worden in plaats van de 23 µm deeltjes.

Natuurlijk is het bedenken van verklaringen alleen vaak niet voldoende. Om deze verklaringen te testen zullen er vernuftige experimenten bedacht en uitgevoerd moeten worden.

Hoofdstuk 4

Uit de voorgaande verklaringen komt duidelijk naar voren dat het al dan niet breken van granules een belangrijke rol speelt met betrekking tot de homogeniteit. Om dit breken van de granules werkelijk te meten zijn in hoofdstuk 4 zogenaamde tracer experimenten uitgevoerd. Tracer experimenten kunnen het best omschreven worden als experimenten, waarbij aan het (witte) granulaat een zeeffractie gekleurde (rode) granules wordt toegevoegd. Vervolgens wordt het granulaat met de tracer granules nog enige tijd gemengd in de snelkneder. Na afloop van het experiment wordt er gemeten wat er met de gekleurde granules gebeurd is door het gedroogde granulaat te zeven. Als alle tracer granules zich nog in precies dezelfde zeeffractie bevinden als

waaruit ze oorspronkelijk afkomstig waren dan zijn ze niet gebroken (oftewel 0% breuk). Zijn de tracer granules echter verdwenen en zijn alle granules nu licht roze gekleurd dan zijn ze helemaal gebroken (oftewel 100% breuk). Natuurlijk zijn er ook vele tussenliggende verdelingen van de tracer granules mogelijk. Dezelfde vulmiddelen die gebruikt zijn in hoofdstuk 3 zijn ook gebruikt in hoofdstuk 4 om het breken van de granules te meten. Dus wederom worden de experimenten uitgevoerd met drie verschillende deeltjesgroottes van het vulmiddel namelijk, 170 micrometer, 50 micrometer en 23 micrometer.

De resultaten van de breekexperimenten worden getoond in figuur 4-2 (zie blz 52). Op de horizontale as zijn de deeltjesgroottes van de gebruikte vulmiddelen weergegeven, terwijl op de verticale as het percentage breuk staat getoond. Uit de resultaten blijkt duidelijk dat granules die zijn samengesteld uit het vulmiddel met de grootste deeltjes (170 µm) volledig kapot geslagen worden in de snelkneder (100% breuk). Dit komt overeen met de verwachtingen die beschreven stonden in verklaring 1. De granules die bestaan uit de kleinere vulmiddel varianten (23 en 50 µm) laten duidelijk veel minder breuk zien (40%). Deze resultaten zijn in overeenstemming met het eerste gedeelte van verklaring 2.

Hoofdstuk 5

Met de experimenten uit hoofdstuk 4 is dus aangetoond dat breuk een positief effect heeft op de homogeniteit, zoals gesteld is in verklaring 1. Dit maakt echter nog niet duidelijk waarom geen tot weinig breuk juist een negatief effect kan hebben op de verdeling van de geneeskrachtige stof. Om dit te onderzoeken zijn experimenten uitgevoerd waarbij de groei van één enkele granule in een poedermengsel werd gevolgd. Hierbij werd ervoor gezorgd dat deze granule intact blijft gedurende het proces. Als basis voor de granule werd een poeder mengsel bestaand uit een vulmiddel en een geneeskrachtige stof gebruikt, waarbij zowel de deeltjesgrootte van het vulmiddel als van de geneeskrachtige stof werd gevarieerd. De volgende combinaties van het poedermengsel werden gebruikt (A, B en C);

- A; deeltjesgrootte vulmiddel groter dan deeltjesgrootte geneeskrachtige stof.
- B; deeltjesgrootte vulmiddel groter gelijk aan deeltjesgrootte geneeskrachtige stof.
- C; deeltjesgrootte vulmiddel kleiner dan deeltjesgrootte geneeskrachtige stof.

Door nu op verschillende tijdstippen de verhouding van de geneeskrachtige stof ten opzicht van het vulmiddel in de granule te meten kan de homogeniteit bepaald worden. Als de granule homogeen blijft dan is de verhouding van beide stoffen in de granule ten alle tijden gelijk. Als deze

verhouding gaat afwijken dan is dat een duidelijke aanwijzing dat de granule inhomogeen is. Het volgende voorbeeld illustreert dit. Stel je start met een mengsel bestaand uit een vulmiddel en een geneeskrachtige stof in de verhouding 10:1. Door één druppel vloeistof toe te voegen aan dit mengsel wordt er één granule gevormd en logischerwijs bestaat die granule uit vulmiddel en geneeskrachtige stof in de verhouding 10:1. Vervolgens zal deze granule groeien, waarbij dus poeder uit het mengsel aan de granule plakt. Als zowel de geneeskrachtige stof als het vulmiddel een gelijke 'plakkans' hebben dan zal de verhouding van de stoffen in de granule 10:1 blijven. Als echter de vulmiddeldeeltjes een grotere kans hebben om te plakken dan zal de hoeveelheid vulmiddel meer toenemen in de granule dan de hoeveelheid geneeskrachtige stof. De verhouding zal dan bijvoorbeeld veranderen van 10:1 naar 15:1. Hebben de geneeskrachtige stof deeltjes een grotere kans dan zal het omgekeerde gebeuren, dus de verhouding kan dan van 10:1 naar 10:3 gaan. Dat dit niet alleen een theoretisch verhaal is blijkt wel uit de resultaten van de verschillende poedermengsels (zie ook figuur 5-2a, blz 68);

- A; de verhouding van de geneeskrachtige stof en het vulmiddel in de granule verandert in de tijd, waarbij er relatief gezien meer geneeskrachtige stof door de granule wordt opgenomen. Er ontstaat dus een inhomogene granule (symbool ◆ in figuur 5-2a).
- B; de verhouding van de geneeskrachtige stof en het vulmiddel blijft gelijk, dus homogene granule (symbool ▲in figuur 5-2a).
- C; de verhouding van de geneeskrachtige stof en het vulmiddel in de granule verandert in de tijd, waarbij er relatief gezien meer vulmiddel door de granule wordt opgenomen. Er ontstaat dus een inhomogene granule (symbool ■ in figuur 5-2a).

Het enige verschil tussen de poedermengsel A, B en C is de deeltjesgrootte. Hieruit blijkt dus wel dat de deeltjesgrootte van de uitgangsmaterialen een grote invloed heeft op de homogeniteit van de granule. Is de deeltjesgrootte van het vulmiddel gelijk aan de deeltjesgrootte van de geneeskrachtige stof dan blijft de granule homogeen (poedermengsel B). Is er echter een deeltjesgrootte verschil (poedermengsel A en C) dan zullen de kleinste deeltjes zich ophopen in de granule. In het geval van poedermengsel A zijn de kleinste deeltjes de geneeskrachtige stof deeltjes, terwijl voor poedermengsel C geldt dat de vulmiddel deeltjes het kleinst zijn. Daarbij geldt bovendien dat de ophoping dramatischer is naarmate het deeltjesgrootte verschil tussen het vulmiddel en de geneeskrachtige stof groter is. Dus als je terugkijkt naar hoofdstuk 3 dan verwacht je op basis van deze resultaten inderdaad dat de granules die bestaan uit de 50 µm deeltjes inhomogener zijn dan de

granules die zijn samengesteld uit de 23 µm deeltjes, omdat het deeltjesgrootte verschil met de geneeskrachtige stof groter is.

De reden waarom kleine deeltjes eerder plakken aan een granule is eigenlijk vrij simpel. Het oppervlak van een granule is nooit helemaal vlak, maar bevat allerlei holtes en poriën. Kleine deeltjes kunnen deze holtes binnendringen, terwijl dit onmogelijk is voor grote deeltjes. Hierdoor is het oppervlak van een granule wat beschikbaar voor groei voor de kleine deeltjes (veel) groter dan voor de grote deeltjes (voor een schematische weergave zie figuur 5-6, blz 72). De kleine deeltjes hebben dus gewoon meer kans dat ze plakken aan de granule. Het is ook mogelijk om deze kans uit te rekenen, vandaar ook alle wiskundige formules in hoofdstuk 5.

Hoofdstuk 6,7 en 8

Uit de voorgaande hoofdstukken werd duidelijk hoe een inhomogene granule wordt gevormd. Echter, de vraag hoe een granule nu gevormd wordt is nog niet beantwoord. Dit is ook geen makkelijke vraag om te beantwoorden aangezien de vorming van de granules zich afspeelt in de eerste seconden van het granuleerproces. Om nu toch die eerste seconden van het proces te bekijken zijn er experimenten uitgevoerd waarbij het proces letterlijk na een paar seconden bevroren werd door vloeibare stikstof (-80°C) toe te voegen.

Uit de resultaten van deze experimenten bleek dat vooral de vloeistof verdeling een belangrijke apect is bij de vorming van granules. Voordat je begint met granuleren heb je een gescheiden systeem van vloeistof en vaste stof. Terwijl aan het eind van het proces granules gevormd zijn waarbij de vloeistof verdeeld is tussen de vaste stof. De vloeistof kan zich op twee manieren verdelen over het poederbed. Ten eerste zorgt de werking van de mixer voor een mechanische verdeling van de vloeistof. Daarnaast kan de vloeistof zich ook verdelen in een poeder bed door vloeistof penetratie. Het proces van vloeistof penetratie kan het best worden geïllustreerd door een suikerklontje net in de koffie of thee te hangen. De vloeistof zal het suikerklontje binnendringen en stijgen. Dit proces kan zich ook afspelen in de snelkneder, omdat hier ook poeder en vloeistof samenkomt. Natuurlijk is het wel een stuk moeilijker om deze vloeistof penetratie waar te nemen, omdat in tegenstelling tot het suikerkontje, de vloeistof en het poeder continu in beweging is.

Uiteindelijk bleek dat de vorming van granules een wisselwerking was tussen twee processen, namelijk de mechanische verdeling van de vloeistof en de vloeistof penetratie. De mechanische werking zorgt er namelijk voor dat de vloeistof wordt verdeeld in kleine druppeltjes. Deze druppeltjes penetreren in het poederbed en vormen direct granules. Natuurlijk bepaald de sterkte

van deze granules of ze al dan niet breken, zoals onderzocht is in hoofdstuk 4. Breken de granules niet dan zal het deeltjesgrootte verschil tussen vulmiddel en geneeskrachtige stof bepalen of de granules homogeen blijven tijdens de groei (hoofdstuk 5). Breken de granules dan zullen de fragmenten weer aan elkaar plakken en granules vormen, die vervolgens weer gebroken worden. Dit dynamische gedrag leidt tot homogene granules.

Uit de experimenten bleek dat in bijna alle gevallen granules gevormd worden door het mechanisme van vloeistof penetratie en mechanische verdeling. Alleen in extreme gevallen (bijvoorbeeld als de vloeistof zo stroperig is dat penetratie onmogelijk is) zal de vloeistof volledig verdeeld worden over de deeltjes en zullen deze deeltjes vervolgens aan elkaar plakken om granules te vormen. Een schematische tekening van al de hierboven beschreven mechanismen staat weergeven in figuur 7-1, blz 101.

Hoofdstuk 9

In dit proefschrift werden dus de mechanismen onderzocht die ten grondslag liggen aan de vorming van inhomogene granules. Naast dit onderzoek zijn er nog tientallen andere onderzoeken die kijken naar de verschillende aspecten van granuleren in een snelkneder. De homogeniteit van de granules is maar één van die aspecten. In hoofdstuk 9 wordt geprobeerd een verband te leggen tussen de resultaten van dit onderzoek en dat van andere onderzoeken. Het grote voordeel van het ontrafelen van mechanismen is namelijk dat deze mechanismen algemeen geldend zijn. Welke mechanismen de grootste rol spelen wordt alleen bepaald door de instelling van een apparaat of de samenstelling van de formulering. Dit maakt dat de bevindingen van dit proefschrift gebruikt kunnen worden om ook andere fenomenen dan de granule homogeniteit te verklaren. De mechanismen zijn als het waren de algemene regels voor het granuleren in de snelkneder.

Dankwoord

Het aardige van iets afronden zit hem volgens mij in het feit dat je op zo'n moment de tijd neemt om terug te kijken. Dit geldt zeker voor het afronden van dit proefschrift. Tijdens het experimenteren of het schrijven van de artikelen ga je helemaal op in de drukte van dat moment, nog niet wetend waar het allemaal toe zal leiden. Gaandeweg de promotie vormt zich wel een beeld, maar pas op het moment dat het proefschrift echt af is neem je de tijd om terug te kijken.

Terugkijkend, kan ik wel zeggen dat één persoon een speciale rol had in deze promotie, namelijk mijn promotor Herman Vromans. Of om in jouw woorden te spreken, jij was de belangrijke rode draad in mijn promotieonderzoek. Mijn dank hiervoor en dit is meer dan een formele dankbetuiging tegenover het feit dat jij de mogelijkheid hebt geboden om binnen Organon te promoveren. Je was er op de momenten dat dit nodig was, maar bovenal was je er niet op de momenten dat hier geen noodzaak voor bestond. Hierdoor kon ik mijn eigen plan trekken en in alle zelfstandigheid het onderzoek verrichten. Vooral de laatste jaren van mijn promotie zou ik je willen omschrijven als een sparringpartner en een klankbord. Deze samenwerking resulteerde uiteindelijk in een succesvolle promotie.
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Naast Fried wil ik ook graag alle andere (oud)collegae van de sectie solids bedanken voor de afgelopen tijd. Anton, Theo, Joost, Kees, Ad, Henny, Vincent, Peter, Onno, Mari, Fiona, Wim, Edwin, Joop en Monique bedankt voor alles en het is een klein wonder dat jullie mijn geouweneel zo goed doorstaan hebben. Het is ook niet voor niets dat jullie mijn kantoor klassificeerde als zijnde "lawaaihok". Mijn bewondering gaat vooral uit naar mijn voormalige kamergenoot. Jouw ruime

ervaring binnen de farmaceutische industrie vormde jou tot een uiterst geschikt aanspreekpunt voor een groentje zoals ik. Bovendien moet ik toegeven dat ik vooral veel geleerd heb van jouw Brabantse manier van leven. Onno, jou leerde ik kennen als nuchtere en rustige Fries ("Friezen, dat zijn van die dooien") die geëmigreerd was naar Brabant. Achteraf gezien waren denk ik juist deze karaktereigenschappen de reden dat wij vaak maalden over de wetenschap en andere zaken. Het is namelijk lekker om als zijnde een drukke persoon van gedachten te wisselen met een rustige persoon zoals jij. Ik hoop dat we deze gedachtewisseling kunnen voortzetten. Mari, onze fietstochten door de Limburgse heuvels en de Brabantse Kempen waren een welkome ontspanning naast het werk. Het was alleen wel jammer het tempo regelmatig stagneerde omdat jij weer eens een lekke band had (al gaf me dat wel de gelegenheid om uit te rusten als ik weer eens kramp had).
Daarnaast hebben ook drie stagiares een wezenlijke bijdrage geleverd aan het promotie onderzoek. Dankzij hun frisse kijk op het onderwerp kreeg ik weer nieuwe inzichten en inspiratie.

Een groot deel van de experimenten die beschreven zijn in dit proefschrift zijn uitgevoerd in het "GMP-gebied". Voor de mensen die niet bekend zijn met het GMP kunnen deze ruimtes het best worden omschreven als een cellencomplex met vrije in- en uitgang. Daarbij was het wel noodzakelijk dat je bij binnenkomst de plaatselijk witte klederdracht met bijpassende, in mij geval handgemaakte, schoenen (vanwege het feit dat ik schijnbaar op grote voet leefde) en een haarnetje. (De reden van het dragen van een haarnetje als zijnde een kalende man was mij niet geheel duidelijk.) De temperaturen in het GMP deden je vermoeden dat men zich bevond op een tropisch eiland. Dit kon echter niet verhullen dat het GMP-gebied geen Walhalla was. Gelukkig was Bas er altijd, die met zijn cassette speler de gangen van het gewelf opluisterde met muziek van The Doors, Nirvana, Soundgarden en The Beatles. Het was wel jammer dat de aanwezige apparatuur de muziek soms overstemde, maar desondanks was jouw muziek een welkome aanvulling en een begrip in het GMP.

De terugblik die ik net geschetst heb betrof eigenlijk een beschrijving van de mensen uit mijn directe werkomgeving. Deze mensen waren belangrijk, maar de mensen in mijn directe privé omgeving nog belangrijker. Ik ben ervan overtuigd dat ik zonder de hulp van deze mensen mijn promotieonderzoek niet succesvol had kunnen afronden. Dit klinkt onwaarschijnlijk, maar de reden dat deze mensen zo belangrijk zijn was dat de basisvoorwaarde voor een promotie of werk in het algemeen, namelijk een stabiel leven, bij aangetast was. Ruim 5 jaar geleden is er bij mij kanker

geconstateerd en ook al werd ik na enkele chemo's en operaties een jaar later genezen verklaren, toch lijken alle zekerheden na die tijd illusies. Het moeilijkste van deze periode was niet zozeer de kanker zelf, maar juist de weg terug die bij tijd en wijlen oneindig leek. Dit promotieonderzoek maakte een groot deel uit van die lange weg terug. De steun van mijn ouders, mijn broer, mijn schoonfamilie en mijn vrienden heeft mij de afgelopen jaren enorm geholpen vooral met zaken die veel belangrijker waren dan het promotieonderzoek (ook al vergat ik dat wel eens). Daarin heeft één persoon een onbeschrijfelijke rol gespeeld, daarbij zegt het woord onbeschrijfelijk voldoende. Astrid, ik ben klaar met de terugblik, want de toekomst is voor ons veel belangrijker.

Kaspar

hij slaapt nog niet
hij ligt gewoon
maar wat te denken

Curriculum vitae

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