Chapter 1
Introduction: The influence of process and powder parameters on granule size and shape in high shear granulation

1.1 Introduction
Granulation is a process to enlarge powder particles, which can be advantageous for many reasons. First of all, due to the size enlargement gravity forces are increased faster than Van der Waals forces, which results in improved flow properties. Secondly, the amount of dust generated by powder handling is reduced, resulting in improved safety, since dust can cause dust explosions, and respiration of dust may cause health problems. This is especially the case in pharmaceutical industries, where highly potent drugs are processed. Thirdly, due to granulation, segregation (demixing) can be minimized. Next to that, compression and dissolution characteristics of the granules are improved. Finally, product attractiveness may be improved, which may be of importance in for example the food or cosmetic industry [1-3].

To perform particle size enlargement, a number of primary particles are to be bound to form an agglomerate. This can be achieved using cohesive forces of the powder only (dry granulation) or using capillary and viscous forces by addition of a binder liquid (wet granulation).

1.1.1 Dry granulation
Dry granulation is a technique chosen, for instance, if the powder is sensitive to moisture [2]. In dry granulation powder particles have to come in close contact with each other, to have the Van der Waals forces create the agglomerate. Slugging, which means the compression of a powder, is mostly used to obtain bonding. This can be performed in a roller compacter, in which powder particles are fed between two large rolls and thereby compacted. Sometimes even the presence of adsorbed layers of moisture is enough to bind particles [2]. Another possible technique to achieve granulation without the use of a liquid is fluid bed granulation. In this process powder particles are aerated, which makes the powder behave like a fluid. As long as the primary particle size is below approximately 5 µm, the Van der
Waals forces are strong enough to create a granule [2]. For instance, when using milled lactose, spheres of approximately 1 mm in diameter were obtained [4].

1.1.2 Wet granulation
When liquid can be used, wet granulation is an option for particle enlargement. The process can be divided in several stages (Figure 1). After dry mixing of the primary powder particles the liquid is added to the powder mixture. This liquid can be sprayed or poured on the powder bed directly, or it can be added to the powder bed as a solid constituent which melts after heating the granulation vessel, thus forming a binder liquid (melt granulation). The wetted particles bind other particles to form nuclei. Due to contact with other nuclei, the wall of the granulator, or other parts of the granulator (for instance impeller, chopper, or baffles) the nucleus might deform or densify. Two nuclei can coalesce when the material is deformed. Densification enables liquid movement to the surface, which is then available for binding of other particles. The fundamental mechanisms occurring during melt granulation are not different from that occurring during wet granulation.

In wet granulation many techniques and different types of equipment can be used. Fluidisation is possible, this results in porous granules. This technique is a typical example of a low shear granulation process. A tumbling drum also applies low shear forces. Extrusion of the wet mass (followed by a spheronisation step) is also a quite commonly used technique. Finally, in high shear granulation high shear forces are exerted on the powder particles, leading to dense granules [5].

In wet granulation, the amount of binder liquid used is usually defined as the ratio of binder liquid mass to the powder mass [6]. However, prediction of the appropriate amount of water to obtain the desired granule size is difficult, due to the fact that this amount is affected by many variables. Examples of these variables are powder mixture properties, such as moisture content and particle size, and liquid characteristics, like viscosity [7].

1.1.3 High shear granulation
This thesis is focussed on high shear granulation. Basically, a high shear mixer consists of an impeller and a chopper (Figure 2). The impeller is used to exert high shear forces on the powder particles, which results in breakage, densification, and growth. Large lumps are chopped into smaller pieces by the chopper, resulting in a smaller granule size distribution [8]. The advantages of high shear granulation are the possibility to produce dense, spherical granules, the mixers are robust, and the mixers can easily handle cohesive powders. Next to that, processing time is short. However, the amount of liquid required is sensitive to the variations in the raw materials, complicating standardisation of the process. In this respect the high shear granulation process seems to be a successful candidate to be controlled by PAT (Process Analytical Technology). The enormous densification can also be a disadvantage, since problems with drug release can occur when inadequate excipients are chosen [9].
Introduction: The influence of process and powder parameters on granule size and shape in high shear granulation

Figure 1: Schematic presentation of the different stages occurring during the wet granulation process. First the wetting and nucleation stage, during which nuclei are formed. In the second stage, growth occurs due to plastic collisions of the nuclei. These collisions cause densification of the nuclei. Liquid is pushed out of the nuclei, enabling growth. If nuclei are not strong enough, parts may break off (attrition) or the agglomerate might break into pieces (breakage). These broken parts can be taken up again by other granules. The granulation process ends with an equilibrium between growth and breakage or attrition.

Although the process is called high shear granulation, the high shear forces are actually not always 'high'. The mixer has the potential to produce high shear forces, but these forces are transmitted to the powder mass only if the powder is sufficiently cohesive or becomes sticky due to binder addition. Shear forces in the granulator are strongly dependent on the properties of the wet mass and they increase rapidly as soon as a 'granulation limit' is achieved; i.e. at the point where granules start to form a shearing powder mass [9]. Therefore, high shear forces are only present from the moment when the powder is wetted and nuclei are formed [9].

To obtain good nucleation and liquid distribution, a toroidal roping flow regime is desired in the granulator (Figure 3) [10]. Impeller speed has to be high enough to ensure this roping flow regime, since too low an impeller speed leads to a bumping flow regime, which provides insufficient mixing. Powder surface velocity is highest.
in the roping regime, and the improved bed turnover continuously presents fresh powder to the spray zone [11]. The bed turnover is characterised by the Froude number, this variable may also be used to scale up the wet granulation process [11, 12].

A rotary processor (spheroniser) in which centrifugal and kinetic forces cause a rope-like motion of particles, can also be used to obtain spherical particles. This process resembles a high shear granulation process. However, there is no chopper present, and the kinetic forces are generated by a rotating plate instead of an impeller. Heng et al. describe their plate optimisation research to obtain spheres. Using studs improves shear, thereby improving sphericity, i.e., thus leading to more spherical granules [11].

![Figure 2: A Collette type high shear granulator. In this picture impeller and chopper are mounted on the lid, however, they can also be mounted on the bottom or on the side of the vessel.](image)

1.2 Nucleation mechanisms

Nucleation starts whenever the powder comes into contact with liquid. The way in which this first contact with liquid is established is important, since a non-uniform liquid distribution results in a broad granule size distribution [12-14]. If after nucleation growth hardly occurs (induction or nucleation phase, see section 1.3), the final granule size distribution is dependent on binder dispersion [15].

Schæfer and Mathiesen proposed two nucleation mechanisms; SMIH (Schæfer and Mathiesen’s Immersion Hypothesis) and SMDH (Schæfer and Mathiesen’s Distribution Hypothesis) [16, 17]. In the first mechanism particles are immersed in a binder droplet, where one droplet forms one nucleus; the nucleation mechanism is droplet controlled. In the second mechanism (SMDH) binder droplets are smaller than powder particles. The droplets are dispersed over the bed, coat the primary particles and nuclei are formed by coalescence of the wetted primary particles. In conclusion, droplet size in relation to the primary particle size determines which
Introduction: The influence of process and powder parameters on granule size and shape in high shear granulation

nucleation mechanism will occur. Abberger et al. [18] showed that the nucleation mechanism also determines granular structure. Distribution leads to a more open granule structure, whereas immersion leads to a more compact structure (see section 1.2).

Figure 3: Flow profile of granules in the high shear mixer. Particles flow in a rope-like motion, this is called the roping flow regime.

As shown above, the nucleation phase is regarded as very important. Therefore, Hapgood and Litster [19, 20] have investigated the parameters in nucleation. They showed the importance of drop penetration time versus bed renewal. When drops are penetrated very fast in the powder bed, but the upper surface of the bed is not cleared fast enough, the bed will become locally overwet, resulting in large nuclei. On the other hand, in case of a very slow penetration, but a very fast bed renewal, the liquid will be distributed well and the nuclei size distribution could even be small. This was visualized in a nucleation regime map in which the drop penetration time is used as a parameter. The drop penetration time $\tau_p$ is defined as:

$$\tau_p = 1.35 \frac{V_o^{\frac{2}{3}}}{\varepsilon_{\text{eff}} \cdot R_{\text{eff}}} \cdot \frac{\mu}{\gamma_{LV} \cdot \cos \theta}$$

Equation 1

$V_o$ (total drop volume), $\varepsilon_{\text{eff}}$ (effective bed porosity), and $R_{\text{eff}}$ (effective pore radius) describe the bed properties, whereas $\mu$ (liquid viscosity), $\gamma_{LV}$ (liquid surface tension), and $\theta$ (solid-liquid contact angle) describe the drop properties. The dimensionless spray flux $\Psi_A$ is defined as the ratio of the liquid area flux to the solid area flux:
\[ \Psi_A = \frac{3V}{2A \cdot d_d} \]  

Equation 2

In this equation the powder traverses the spray zone with a flux $A$ (m$^2$/s), $V$ is the volumetric spray rate and $d_d$ is the drop diameter. At a low dimensionless spray flux the wetted powder is quickly replaced by non-wetted powder. One droplet can form one nucleus, leading to a droplet controlled nucleation regime. If the liquid is only slowly absorbed by the powder bed or the wetted powder is not removed fast enough from the spray area, the liquid has to be dispersed mechanically to prevent local overwetting. In Figure 4 this nucleation regime map is shown in combination with the SMIH and SMDH. Although the latter two mechanisms originate from melt granulation, where the amount of liquid binder depends on the temperature and the size of the flakes, the nucleation regimes are comparable to those mentioned in the nucleation regime map of Haggood and Litster. In the drop controlled region, powder particles are immersed in a droplet, which forms the primary nucleus. When the droplets are uniform in size, a narrow nuclei size distribution can be obtained. On the other hand, in the mechanical dispersion region liquid has to be dispersed through the powder bed to allow primary particles to coalesce. There can be an excess liquid (slow liquid absorption or high spray flux) or primary particles that are too large to be immersed in the droplet. In that case, due to the poor liquid distribution, the nuclei size distribution will in general be broader [21]. However, using high shear granulation, and therefore a high mixing capacity, in some cases pouring in liquid might even improve variation of the granules [22].

1.3 Granule growth

The growth step in granulation has been described differently by different authors. Vonk et al., for example, describe a destructive nucleation growth mechanism, in which nuclei are broken down, densified, and further growth occurs [23]. They claim an equilibrium between growth and breakage, since abraded parts can be used to form new granules.

According to Scott et al. the granule growth mechanism depends on the nucleation mechanism [17]. The SMIH (immersion mechanism) leads to preferential nucleation, where nuclei do not grow much. This nucleation mechanism is promoted by pouring-on liquid; all water is immediately distributed over the powder bed. The SMDH (distribution mechanism), in which the liquid binder is distributed over the powder, leads to preferential growth. The nuclei formed grow by coalescence with primary particles and other granules. Since coalescence promotes growth of the large granules, a bimodal granule size distribution could be obtained. This nucleation mechanism is promoted by using a melt-in liquid addition method [17].
Ennis et al. describe the granule growth stage using a Stokes deformation number [24, 25]. This deformation number is defined as the ratio between the externally applied kinetic energy and the energy dissipated by the liquid bonds between the particles. The small size of the primary nuclei and consequently the relative thick binder layer results in a smaller viscous Stokes number than the critical viscous Stokes number. This means that all collisions may result in coalescence. Values higher than the critical Stokes number will result in breakage.

**Figure 4:** Nucleation regime map according to Hapgood and Litster, with the addition of Schæfer and Mathiesen’s Immersion and Distribution hypothesis. The dimensionless spray flux $\Psi_a$ is the ratio of the area flux of the droplets to the area flux of powder surface through the spray zone. The drop penetration time $\tau_p$ is predicted from the capillary pressure driven flow of liquid into pores in the powder bed [16, 17, 19, 20].

Based on all these considerations, Iveson and Litster clustered growth regimes, and introduced a growth regime map (Figure 5) [26]. In this map the maximum pore saturation, i.e. the amount of liquid present in the pores inside the granules as a fraction of the total pore volume, is shown on the X-axis, and granule deformation, given by Stokes deformation number, is shown on the Y-axis. When too little binder liquid is available to ensure growth or when nuclei are so weak that they break upon collision, the material is in the dry powder regime. The nucleation regime means that nuclei are formed, but there is insufficient binder liquid to promote further growth. Therefore, this regime is placed at low pore saturation. In induction growth there is a long period without growth due to the low deformability of the material. Once the material is compacted enough, a period of rapid growth occurs, often called ‘ball growth’. If the wet mass is highly deformable, rapid coalescence growth will occur, being in the steady growth regime [26]. The characteristic of this regime is that average granule size increases linearly with time. In crumb behaviour the material is too weak to form permanent granules. Instead granules are constantly crushed and reformed. At too high pore saturation,
the material will be overwetted, and a slurry is obtained. It is possible to switch growth regimes by adapting the properties of the wet mass. This can be done for example by changing viscosity of the binder (increasing binder viscosity means lower Stokes deformation number) or changing the amount of binder (increasing binder amount means increasing pore saturation and an increasing Stokes deformation number).

**Figure 5**: Growth regime map, as introduced by Iveson and Litster [26].

### 1.4 Wet granule strength

During granulation, wet granule strength determines whether a granule either survives the high shear forces and is able to grow or does not survive and is crushed into pieces. Rumpf was the first to calculate wet granule strength with the assumption that capillary forces in wet granules are dominant [27]. However, Ennis et al. showed that in a dynamic situation viscous forces are dominant [24]. Equation 3 describes wet granule strength for the dynamic situation. In this equation, \( \mu \) is the viscosity of the binder fluid, \( v_p \) is the relative velocity of the moving granules, and \( d \) is the primary particle size.

\[
\sigma = \frac{9}{8} \cdot \frac{(1 - \varepsilon)^2}{\varepsilon^2} \cdot \frac{9 \cdot \mu \cdot v_p}{16 \cdot d}
\]

Equation 3

This dynamic granule strength is generally used to calculate Stokes deformation number. Vonk et al. also tried to calculate wet granule strength, but they started at
Introduction: The influence of process and powder parameters on granule size and shape in high shear granulation

the site of the impeller. The impact force of the impeller can be calculated from its speed [23].

\[ \sigma_{impact} = \frac{1}{3} \cdot \frac{d_a}{d_p} \cdot \rho \cdot V_{tip}^2 \]  
Equation 4

Wet granule strength also determines granule size distribution. If wet strength is low, continuous breakage takes place, leading to crumb regime. In this way a wide size distribution, a high intragranular porosity and an irregular shape are obtained [30].

1.5 Granule shape

A spherical and smooth granule may be desired for several reasons; among these reasons are the flow properties and the desire to coat the granule. A spherical shape means a minimum surface area to volume ratio, which results in reduced cohesive forces, thereby resulting in a better flow of the powder [28]. Another reason for spheronisation is the use of the spherical granules as substrates for drug layering [29]. Spherical granules sized between 0.1 and 1.0 millimetre in diameter can be coated directly, in order to obtain for example a sustained release product [28].

In summary, spherical granules can be advantageous. However, after the granulation process spherical granules are not always obtained. The focus of this chapter is on the influence of process parameters and powder properties on granule shape.

1.5.1 Characterizing shape

The first question regarding granule shape that needs to be answered is how to define granule shape. Usually, shape has been described using shape factors [33-42], and a variety of shape factors has been proposed and tested [33-45]. However, it is not possible to define a shape factor which is suitable for all purposes. The shape factor of choice is dependent on its use. For instance, if a smooth surface is desired, using a two-dimensional shape factor in which the perimeter of the figure is used might be practical and provide sufficient information [30-42].

The shape factor circularity, defined as the ratio of the surface area of the two dimensional figure is compared to its perimeter, is mostly used in literature. Therefore, when the term 'spherical' is used in this section, it is referred to circularity.
1.5.2 How to influence shape

Describing the granule size distribution can also be an indication of granule shape, depending on the method of size measurement. A small granule size distribution indicates that granule shape will be spherical. Of course, it cannot indicate roughness. A broad granule size distribution might indicate an irregular shape, but this effect is less profound [43]. Therefore, granule shape is often given together with the granule size distribution.

The way granules are formed may be indicative for the resulting granule shape. Granules showing ‘crumb behaviour’ often exhibit a rough surface area, due to the continuous breakdown and build-up of granules [43]. On the other hand, granules in the ‘steady growth’ regime are often so deformable that spheres with a smooth surface are easily obtained. Finally, granules of the ‘induction type’ behaviour deform slowly, so an irregular surface area and granule shape can be expected, especially after the occurrence of ball growth. Since the parameters from the production process like impeller speed, binder liquid characteristics, primary particle size, vessel wall material, etc. affect the granulation behaviour, changing the production process will influence granule shape. The next sections describe the effects of these parameters.

The effects on the wet granulation process are mentioned above. However, after drying the granules are often further processed, during which the granules are susceptible to breakage and attrition as well, thus influencing shape again. Therefore, dry granule strength has to be high. Various factors affect the dry granule strength, the most important are: the nature of the powder, the amount and composition of the binder liquid and the shear used during the process [44].

1.5.3 Process related parameters involved in granule shape

Impeller and chopper speed

Usually it is stated that the impeller is used to impact on the powder and make granules, and the chopper is used to chop large granules into smaller ones. The shape of the chopper indeed can lead to breakage. Impeller and chopper are indeed designed for these purposes, however, both devices impact on the granules, so both devices can lead to densification and growth, or to breakage. Therefore, the described effects of impeller speed below can also be read as effects of chopper speed.

Changing impeller speed can have several effects. Ennis stated that, at prolonged granulation times, the granule diameter varies with the inverse square root of the impeller speed [45]. However, that is not necessarily true. There is a balance between growth and breakage, both induced by the impeller. By changing impeller speed, this balance is changed as well. Increasing impeller speed can be in favour of growth, thus leading to an increased granule size [46-49], or in favour of breakage, resulting in a decreased granule size [50].
Impeller speed has also an effect on the spheronisation behaviour. According to Seo and Schaefer, there is a minimum impeller speed needed to create spherical pellets [51]. On the other hand, Eliasen et al. found that a too high impeller speed leads to less spherical granules [47]. Heng et al. show in melt granulation that a higher impeller speed results in more spherical granules. However, after a certain time, dependent on impeller speed a plateau value was obtained, after which shape did not change anymore [28].

The above shows that process conditions determine sphericity. This is not only true in high shear granulation, but also in the extrusion-spheronisation process. According to Lövgren and Lundberg, extrusion speed does not affect granule sphericity, however, spheronisation speed does. Increased speed of the spheroniser leads to increased sphericity [52]. Again it is shown that a minimum speed of the spheroniser is necessary. Low speed means too little interactions, so no spheronisation is possible [53]. Not only speed, but also fill grade is influencing shape. For example, overloading the spheroniser requires longer process times to reach a spherical product [52, 53].

In conclusion, dependent on the powder material and binder used, increasing impeller speed can increase or decrease granule sphericity. This is also true in for the spheronisation speed in a spheroniser.

Massing time
Next to changing impeller speed, increasing massing time also has an effect on the granules produced. First of all, due to an increased number of collisions, porosity is lowered, as shown in a drum granulator [54]. But more importantly in this case, increasing massing time also leads to more spherical granules [28, 55, 56]. This is again also true for the spheroniser; the longer the material is on the spheronisation plate, the more spherical it becomes [57]. So, slowly deformable granules need time to spheronize. However, it has to be kept in mind that too long massing time can result in ball growth or change the granulation mechanism due to evaporation of the liquid. Changing impeller speed or changing the powder formulation can be an easier solution.

Equipment effects
The last major process related item which also has an effect on the granule obtained is the type of equipment. For instance, the type of mixing motion can differ significantly, leading to different granulation mechanisms. Vessel wall material also influences the granulation process. Wet mass wall adhesion in high shear granulation is described for a 250 ml vessel [14], and for 8 to 600 l vessels [58]. The smaller the granulation scale, the larger the wall effect will be. Not only the loss of material due to sticky material is a problem, but also granules will be slowed down by the vessel wall. The further away from the vessel wall, the higher the velocity of pellets will be [50]. In conclusion, vessel wall material affects wet mass wall adhesion, thereby influencing the granulation process [14].
1.5.4 Powder related parameters influencing granule shape

Although process parameters determine the granulation process for a great deal, the most important variable is of course the material to be granulated. In wet granulation, a powder and a binder solution are used.

**Effect of particle size**

In general, the effect of primary particle size on granule shape is simply that a decreasing primary particle size leads to an increasing value of circularity. This was found for lactose produced by melt granulation [18], and the same effect was found using microcrystalline cellulose formulations [29]. In case of small powder particles, an increasing impeller speed leads to a lower porosity, thus a lower friability. Also, the resulting granule size distribution is smaller [59].

Smaller primary particles need more binder liquid than larger primary particles to obtain similar sized granules. This shows that the amount of binder liquid needed is dependent on the surface area [60, 61]. So, small primary particles take up relatively more binder liquid than coarse primary particles.

When using smaller primary particles, wet granule strength is increasing [54]. If granules are too brittle, the granules may break upon impact, and they can end up in the crumb regime, leading to less spherical granules. However, this effect can be avoided by increasing binder viscosity, since this increases wet granule strength [62]. Using small primary particles (below approximately 10 µm) has traditionally been troublesome. Often the granulation procedure leads to uncontrollable growth, since a high liquid saturation level is needed to obtain a sufficient deformability to have granule growth. Due to the small primary particle size, cohesivity is high, leading to such strong granules that the material in itself is hard to deform. The addition of liquid makes the mass more deformable, due to the decreased particle-particle interactions. However, if too much liquid is added or if granulation times are too long, ball growth may occur [63].

In conclusion, granulation of powder particles below 10 µm is sensitive to the amount of liquid added. On the other hand, large primary particles can also cause problems in granulation. Large primary particles lead to low granule strength, where breakage will dominate, and in the worst case granulation cannot occur [63].

1.5.5 Binder related parameters influencing granule shape

**Amount of binder**

Apparently, there is an optimum amount of liquid binder to produce granules. To a certain extent, the more liquid used, the denser the granules will be [54, 64], leading to increased sphericity. Therefore, the amount of binder not only determines granule size, but also granule shape and dry granule strength [44]. However, when using MCC too much water results in water pockets within the granules, leading to more porous granules [48]. When these water pockets arise,
the granular material is weakened, breakage is likely to occur, and the coalescence of broken pieces of granules leads to more irregularly shaped granules [48].

In an extrusion process, the amount of liquid binder is also important. Extrusion is preferably performed at 100% liquid saturation; a higher liquid amount will also result in water pockets, thus a higher porosity. Upon increasing liquid amounts, particle-particle interactions are reduced. Therefore, less force is needed for the extrusion process [65]. So in the extrusion process higher liquid amounts lead to a more porous structure, but the extrudate is more easily obtained from the subsequent spheronisation process. In the high shear granulation process granule shape is also dependent on the liquid saturation. If water pockets arise, an irregular granule shape is expected, whereas if liquid is still to be absorbed in the powder bed, deformation is still possible, leading to more spherical granules.

In melt granulation it is known that next to the amount of binder, droplet size has an effect on granule shape. Larger droplets lead to an increasing value of circularity. This is explained by the higher liquid saturation at the agglomerate surface, making the surface more deformable [18].

Viscosity of the binder liquid

Binder liquid viscosity determines the granulation process to a significant extent. A high viscosity (> 1 Pa-s) affects the consolidation of the granule [66]. The higher viscosity, the less compacted the granule will be, due to the decreased mobility of the binder fluid [43, 45, 67]. The reduced mobility also leads to decreased binder distribution, leading to a broad granule size distribution. Another effect of a highly viscous binder liquid is the increased wet granule strength [43, 54]. This can result in a less deformable material, resulting in a less spherical shape [43].

When applying a high viscosity binder in melt granulation, the dominating granule formation mechanism is immersion. Therefore, the agglomerates formed resemble the original shape of the binder flakes. The high viscosity causes poor rounding of these agglomerates [63].

Addition of a lower viscosity binder (< 1 Pa-s) means that surface tension dominates [66]. A lower viscosity leads to more spherical granules [16]. On the other hand, if viscosity is too low, granule strength can become insufficient to resist the shearing forces of the impeller, which can result in breakage or chipping. This might lead to a more irregular shape [43].

Eliasen et al. worked with melt granulation, using a low viscosity binder (dependent on the temperature between 6 and 12 mPas). Increasing impeller speed led to increased temperature thus decreased viscosity. They found larger particles, but less spherical particles upon increasing impeller speed. Their conclusion was that the effect on shape and smoothness is dependent on the balance between the effects of liquid saturation, surface plasticity, and comminution (or breakage/shattering) [47].
1.5.6 **Wet powder mixture**
Within the wet powder mixture water can act as a plasticizer. In this case, the wet material is easily deformable [7], which is necessary for the spheronisation of the granules [68, 69]. However, sphericity is not only dependent on the plasticity of the wet mass. When for example various silicates were added to increase plasticity of the wet mass, the expected increased sphericity was not always found. The effect appeared to be mixture dependent, however, the physico-chemical background was not further investigated [68].

For the extrusion process, special requirements of the wet powder mixture are needed. The extrudate must be brittle enough to be able to break into cylinders, however, it must be strong enough to withstand the forces in the spheronizer. And finally, the wet mass must be plastic enough to be converted into spheres [70]. Sousa et al. discovered, that when extruding/spheronizing different materials (microcrystalline cellulose, glucose, mannitol, lactose, calcium phosphate, and barium sulphate) lactose was the only one tested not resulting in spherical particles [71].

Microcrystalline cellulose (MCC) is known for its ability to form spherical granules. Kleinebudde introduced the crystallite-gel model to account for the spheronisation behaviour of MCC. The crystallite-gel model implies that a gel is formed, since MCC will be broken down to smaller subunits. Single crystallites might be formed, which form a gel and in this way immobilize liquid [72]. As a reaction to this model, Ek and Newton claim that indeed cellulose particles hold water, as a sponge. MCC can adsorb 16-26% of water based on dry weight, and is able to immobilize even more (this is called structured water). During extrusion ‘sponges’ are compressed until water is squeezed out, in this way the extruder is lubricated [73]. In this way, MCC also is a spheronization enhancer, but the rheology of a wet mass containing MCC strongly depends on the water content. Therefore, MCC is regarded as a molecular sponge. However, the deformability of a wet MCC mass is also dependent on the liquid used. For instance, MCC-glycerol mass behaves more plastic than a MCC-water mass, resulting in a difference in porosity of the resulting granules [67].

1.5.7 **Conclusion**
The above shows that many variables influence granule shape. The granulation process can be optimized to generate spherical granules e.g., by changing impeller speed, massing time, and type of equipment. The equipment chosen has to ensure adequate mixing, and the vessel wall material chosen has to be optimal for the nucleation process. Next to these equipment settings, the material to be granulated determines granule shape. The smaller the powder particles, the more spherical the granules will be. The amount of binder and binder viscosity also determine granule shape by influencing the granulation process. Most important is the rheology of the wet mass. It must be strong enough to withstand the forces in the granulator, and deformable enough to form spherical granules.
Introduction: The influence of process and powder parameters on granule size and shape in high shear granulation

Although detailed knowledge exists on the effects of a certain change for a specified granulation process, it has still not been possible to derive rules that are generally applicable to all wet granulation processes. Therefore, more research should be performed to find the underlying relationship between the process parameters, the granulation process, and the eventual shape.

1.6 Aim of this thesis

The ultimate goal of research into wet granulation is to control granule size and granule shape. However, wet granulation is a complicated process, in which the result (granule size and granule shape) is dependent on the process parameters and the physico-chemical properties of the materials used. To be able to control granule size and granule shape, understanding of the high shear granulation process and the parameters in the process is necessary. The aim of the research described in this thesis was to investigate which material properties and apparatus settings are responsible for the shape of a granule in high shear granulation.

Several variables were investigated. First, in Chapter 2, different shape factors are compared to find the most suitable shape factor to describe granule shape. This investigation resulted in recipes to obtain the most spherical granules with the smallest granule size distribution for all components used in this thesis. Furthermore, it raised the idea that granule shape is determined by the growth mechanism. Therefore, granule growth was studied.

This was started with investigating some equipment effects. The effects of vessel wall material on the nucleation process and on the final granule size distribution is shown in Chapter 3. The effects of powder sticking to the lid of the granulator are described in Chapter 4. Then in Chapter 5 the relation between granule size, granule stickiness and torque are shown.

Finally, granule growth mechanisms were investigated. Chapter 6 describes a method to distinguish different growth mechanisms. In Chapter 7 the effect of the amount of binder fluid on the growth of MCC granules and their shape is shown, and in Chapter 8 measurements of deformability of wet compacts are shown.

1.7 Symbols

\[ A \] Powder flux through the spray zone
\[ d_s \] Granule size
\[ d_d \] Drop diameter
\[ d_p \] Primary particle size
\[ R_{eff} \] Effective pore radius
\[ V \] Volumetric spray rate
\[ V_0 \] Total drop volume
Relative velocity of the moving granules

Impeller tip speed

**Greek symbols**

- $\gamma_{lv}$: Liquid surface tension
- $\varepsilon_{\text{eff}}$: Effective bed porosity
- $\theta$: Solid-liquid contact angle
- $\mu$: Viscosity of the fluid
- $\rho_a$: Density of the granules
- $\sigma$: Dynamic wet granule strength
- $\sigma_{\text{impact}}$: Wet granule strength calculated from the impact force of the impeller
- $\tau_p$: Drop penetration time
- $\Psi_A$: Dimensionless spray flux

### 1.8 Literature

Introduction: The influence of process and powder parameters on granule size and shape in high shear granulation

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