Chapter 3
The effect of vessel material on granules produced in a high shear mixer

3.1 Summary
In this study the effect of different vessel wall materials on the granule size distributions obtained during high shear granulation of different materials is investigated. The distributions obtained in glass and stainless steel vessels differ from those obtained in PMMA (PolyMethylMethAcrylate) and PTFE (PolyTetraFluoroEthylene) vessels. The high contact angle of PMMA forces all liquid immediately into the more easily wetted powder bed. In this vessel a fast liquid absorbing powder nucleates in the droplet controlled regime, leading to a narrow particle size distribution. In a vessel with a low contact angle (glass or stainless steel) a liquid layer can be formed on the wall surface. This liquid causes an inhomogeneous distribution of liquid over the powder bed; a broader granule size distribution is the result. With a powder that slowly absorbs liquid, local overwet areas can be created, resulting in large granules. This results in broader granule size distributions as well. In conclusion; the contact angle of the vessel material and the wetting rate of the powder used determine the granule growth process and the resulting granule size distribution.

3.2 INTRODUCTION

3.2.1 Granulation process

High shear granulation is a commonly used unit operation to produce larger granules of primary particles [1]. The granulation process has been described to consist of different growth regimes. Several authors have described these regimes [2-5]. Roughly, the first stage is wetting and nucleation, followed by consolidation and coalescence, and finally attrition and breakage.

The initial growth stage is the nucleation regime, where wetted particles stick together and form primary nuclei. The second growth stage of granules is the consolidation or coalescence of nuclei. This second growth stage can be described using a Stokes deformation number [6, 7]. 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 result in coalescence.

At the end of the second growth stage, when the viscous Stokes number becomes equal to the critical viscous Stokes number, growth stops and compaction starts. Due to the collisions, the packing of the particles becomes denser and liquid moves to the granule surface. When enough binder liquid is present at the granule surface, further growth by coalescence occurs. After a successful collision, particle rearrangement to a sphere may occur. Coalescence promotes the growth of larger granules. At the end of the coalescence regime, crushing and layering will be the predominant process [2]. The last growth stage is now reached: granules become too large to withstand the high shear forces. Breakage and attrition takes place, the broken pieces can be layered around existing granules, or can coalesce. Vonk et al. showed that an equilibrium between growth and breakage is obtained [8].

3.2.2 Vessel wall material

Laboratory scale granulator vessels can be made from a variety of materials, whereas industrial (large) scale granulator vessels are generally made of stainless steel, which may however be coated to change the material properties. The aim of this study was to investigate whether different vessel wall materials affect the outcome of the granulation process. This is relevant for scale up since it will mean that the vessel wall properties of laboratory equipment need to match that of (future) production equipment. In this study, the granulation process is investigated in 250 mL vessels, using glass, PMMA, stainless steel, and PTFE as vessel wall materials. Glass and PMMA are often chosen for their transparency; the granulation process can be observed. Stainless steel is a logical choice since it is the material mostly used in large scale granulators, and PTFE was chosen for its low friction. This could prevent powder and granules sticking to the wall, thereby altering the granulation process.
3.3 Materials and Methods

Microcrystalline Cellulose (MCC) (Pharmacepl® 101, DMV International, Veghel, the Netherlands), Microfine Cellulose (MFC) (Elcema P100, Degussa AG., Frankfurt, Germany), and α-lactose 450M (Pharmatose® 450M, DMV International, Veghel, the Netherlands) are granulated using water as a binding agent. Liquid was added as a continuous flow through a tube with a 1 mm orifice by a computer controlled dosimat (765 Dosimat, Metrohm Ltd., Hensau, Switzerland). The process conditions for the granulation procedures are given in Table 1. To exclude production influences (e.g. increase in impeller speed might change granule size), we chose to change only the vessel material. The process conditions chosen, with respect to the amount of liquid, liquid addition rate, impeller speed, and chopper speed, were optimised per powder.

Table 1: Process conditions used for granulation of MCC, MFC, and α-lactose. Granulation time was 900 s in all cases.

<table>
<thead>
<tr>
<th></th>
<th>MCC</th>
<th>MFC</th>
<th>α-lactose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount of powder (g)</td>
<td>24</td>
<td>10</td>
<td>24</td>
</tr>
<tr>
<td>Amount of liquid (ml)</td>
<td>24</td>
<td>18</td>
<td>4.3</td>
</tr>
<tr>
<td>Liquid addition rate (ml/min)</td>
<td>48</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>Impeller speed (rpm)</td>
<td>1000</td>
<td>1000</td>
<td>750</td>
</tr>
<tr>
<td>Chopper speed (rpm)</td>
<td>1500</td>
<td>1500</td>
<td>750</td>
</tr>
</tbody>
</table>

Vessels of four different materials are used, all with similar size and shape and all polished; glass, PMMA (PolyMethylMethAcrylate), stainless steel, and PTFE (PolyTetraFluoroEthylene).

High-shear granulation is performed in a MI-PRO 250 (Pro-C-epT, Zelzate, Belgium). The produced granules are dried overnight at 50°C. Granule size distribution is determined by sieving the whole batch of granules using ASTM standard sieves. From the mass based distribution the $d_{50}$ is extracted. Primary particle size (as shown in Table 2) was measured by laser diffraction, type HELOS KA/LA, dispersed with dispersion system RODOS (Sympatex GmbH., Clausthal-Zellerfeld, Germany).

Water sorption measurements were carried out in the setup shown in Figure 1. This setup was previously used for measuring water uptake of tablets by van Kamp et al. [9]. Experiments are carried out five times, using 5 g of powder. The sorption of water by the powder bed takes place over a surface of 380 mm². During the high shear granulation process, powder in the wetting zone is continuously renewed, leading to non-wetted powder in the wetting zone. Therefore, we focus on the initial sorption rate of the powder; water sorption rate is calculated from the amount of water taken up during the first 50 s. It is found that sorption is linear during this period for the materials tested.
Table 2: Physicochemical characteristics of the primary powders used.

<table>
<thead>
<tr>
<th></th>
<th>$d_{50}$ (µm)</th>
<th>Bed porosity (-)</th>
<th>Sorption rate (g/s) ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC 101</td>
<td>58</td>
<td>0.78</td>
<td>0.149 ± 0.005</td>
</tr>
<tr>
<td>MFC P100</td>
<td>42</td>
<td>0.84</td>
<td>0.079 ± 0.007</td>
</tr>
<tr>
<td>α-lactose 450 M</td>
<td>16</td>
<td>0.70</td>
<td>0.019 ± 0.004</td>
</tr>
</tbody>
</table>

Figure 1: The sorption measurement setup. On the glass filter (1) a glass cylinder filled with powder (2) is placed. This column of powder is into contact with water in a beaker (3). The sorption rate of the powder is measured by the decrease of mass in the beaker, measured by a balance (4) and recorded by a computer. Water to fill the tubes can be taken from the storage (5).

3.4 Results

Figure 2 shows pictures of the different granules after drying. Clearly the size and size distribution is different when different vessels are used. Figure 3 shows that granulating MCC in different vessels leads to different granule size distributions. Glass (Fig. 3A) and stainless steel (Fig. 3C) result in similar granule size distributions. Granulation in PMMA (Fig. 3B) results in 6 out of 8 experiments in similar size distributions. However, granule size was smaller in two experiments. The batches giving the small granules are those in which all powder took part in the granulation process immediately from the start. The other batches are those in
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which the initial amount of powder taking part in the process was incomplete. When the remaining fraction enters the process later on, this will result in larger granules [10]. Finally, granulation in the PTFE vessel (Fig. 3D) gives irreproducible results. Two of the five distributions even show a large fraction of powder which is hardly granulated, in spite of the fact that it was observed that powder was taking part in the process. The poor reproducibility of the PTFE results is also reflected in the high average width and large difference between the highest and lowest \(d_{50}\) obtained (Table 3).

Figure 2: Granules produced in the different vessels. Bar represents 2 mm.
Table 3: The average granule size ($d_{50}$) ± the average distribution widths ($d_{90}$-$d_{10}$), the number of granulations (n), followed by the lowest and highest obtained $d_{50}$ of all granule size distributions in the four different vessels.

<table>
<thead>
<tr>
<th>Vessel material</th>
<th>Av. $d_{50}$ (mm)</th>
<th>Av. width ($d_{90}$ - $d_{10}$) (mm)</th>
<th>n</th>
<th>Lowest $d_{50}$ obtained (mm)</th>
<th>Highest $d_{50}$ obtained (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC glass</td>
<td>0.83</td>
<td>0.54</td>
<td>5</td>
<td>0.82</td>
<td>0.85</td>
</tr>
<tr>
<td>PMMA</td>
<td>0.69</td>
<td>0.25</td>
<td>8</td>
<td>0.58</td>
<td>0.74</td>
</tr>
<tr>
<td>steel</td>
<td>0.77</td>
<td>0.32</td>
<td>4</td>
<td>0.75</td>
<td>0.82</td>
</tr>
<tr>
<td>PTFE</td>
<td>0.57</td>
<td>0.36</td>
<td>5</td>
<td>0.36</td>
<td>0.74</td>
</tr>
<tr>
<td>MCC glass</td>
<td>0.78</td>
<td>0.95</td>
<td>3</td>
<td>0.75</td>
<td>0.80</td>
</tr>
<tr>
<td>PMMA</td>
<td>1.98</td>
<td>1.16</td>
<td>3</td>
<td>1.93</td>
<td>2.01</td>
</tr>
<tr>
<td>steel</td>
<td>0.84</td>
<td>0.84</td>
<td>4</td>
<td>0.82</td>
<td>0.86</td>
</tr>
<tr>
<td>PTFE</td>
<td>1.29</td>
<td>1.38</td>
<td>5</td>
<td>1.12</td>
<td>1.56</td>
</tr>
<tr>
<td>MFC glass</td>
<td>1.19</td>
<td>4.47</td>
<td>3</td>
<td>0.86</td>
<td>1.47</td>
</tr>
<tr>
<td>PMMA</td>
<td>1.57</td>
<td>2.17</td>
<td>3</td>
<td>1.51</td>
<td>1.56</td>
</tr>
<tr>
<td>steel</td>
<td>0.88</td>
<td>3.43</td>
<td>4</td>
<td>0.81</td>
<td>1.05</td>
</tr>
<tr>
<td>PTFE</td>
<td>1.72</td>
<td>3.26</td>
<td>5</td>
<td>0.47</td>
<td>3.79</td>
</tr>
</tbody>
</table>

Figure 3A: Five granule size distributions of MCC granulated in a glass vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions. The curve marked with * was observed 3 times.
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**Figure 3B**: Eight granule size distributions of MCC granulated in a PMMA vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions. The curve marked with * was observed 4 times.

**Figure 3C**: Four granule size distributions of MCC granulated in a stainless steel vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions.
Figure 3D: Five granule size distributions of MCC granulated in a PTFE vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions.

The size distributions obtained after granulating MFC in different vessels are shown in Figure 4. The last graph (Fig 4E) shows a comparison of MFC granule size distributions from the four different vessels. The distributions of lactose are shown in Figure 5. Again different vessels result in different size distributions. For MFC and lactose, granulation in the PMMA vessel (Figs. 4B & 5B) results in the largest granules, whereas granulation of MCC in PMMA (Fig. 3B) can give the smallest granules. This is even clearer in Table 3, in which the average $d_{50}$ of the granule size distributions made in the different vessels are listed. The different behaviour is also seen when the width of the size distribution (difference between $d_{90}$ and $d_{10}$) is taken into consideration. MCC has the narrowest size distribution, whereas the size distributions of lactose and MFC are wide.

In glass and steel vessels the granulation behaviour of MFC (Fig 4A & 4C, respectively) is similar and reproducible, which makes the granulation behaviour of MFC comparable to that of MCC in these vessels. The granulation of lactose in glass or stainless steel vessels (Fig 5A & 5C, respectively) is also reproducible but results in size distributions broader than for the comparable MFC or MCC granulations. In the size distributions of granules prepared in the glass or steel vessel two distinct peaks are visible. The second peak has about double the size of the first peak. This is an indication for the occurrence of preferential growth occurring for only a limited number of granules. Obviously, the growth occurs according to a mechanism in which one granule binds about 7 other granules (which results in a size increase of 2).
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Figure 4A: Three granule size distributions of MFC granulated in a glass vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions.

Figure 4B: Three granule size distributions of MFC granulated in a PMMA vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions. The curve marked with * was observed 2 times.
Figure 4C: Four granule size distributions of MFC granulated in a stainless steel vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions. The curve marked with * was observed 2 times.

Figure 4D: Five granule size distributions of MFC granulated in a PTFE vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions.
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In the PTFE vessel no reproducible size distributions could be obtained (Fig. 5D). Moreover, the size distributions of the granular materials produced in the PTFE vessel are irreproducible irrespective of the powder used.

Table 2 lists physicochemical characteristics of the primary powders used in this study. The MCC powder bed sorbs water almost twice as fast as the MFC powder bed, and 7 times faster than the lactose powder bed. The bed porosities are all
between 70 and 80%.

**Figure 5B**: Three granule size distributions of lactose granulated in a PMMA vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions.

**Figure 5C**: Four granule size distributions lactose granulated in a stainless steel vessel using the same process conditions. Different types of lines are used just to be able to distinguish between the different distributions.
A possible explanation for the variations seen in the size distributions of the granulations prepared in the different vessel materials may be found in differences in the contact angles of the vessel wall. The contact angles of the four vessels with water differ from each other. Table 4 lists the contact angles of the four materials. Glass and stainless steel show the lowest contact angles, indicating a hydrophilic behaviour. PMMA is just slightly hydrophilic, whereas PTFE is highly hydrophobic [11, 12].

<table>
<thead>
<tr>
<th>Vessel material</th>
<th>Contact angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>30</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>50</td>
</tr>
<tr>
<td>PMMA</td>
<td>72</td>
</tr>
<tr>
<td>PTFE</td>
<td>126</td>
</tr>
</tbody>
</table>

### 3.5 Discussion

We hypothesise that the granulation behaviour (especially the initial nucleation) is determined by the balance between the contact angle of the vessel wall and the sorption rate of the powder material. A low contact angle (for example glass and stainless steel) allows the formation of a layer of liquid on the wall. This liquid is not immediately taking part in the nucleation process. For a more slowly imbibing powder, nuclei swept against the wall take up the water, causing rapid coalescence growth of these nuclei. Due to the uneven liquid distribution over the powder,
nucleation takes place according to the distribution mechanism. The size distribution of the nuclei is broad, and the final granule size distribution will probably also be broad. Only those nuclei that are swept against the wall will take up water and show growth, which explains the bimodal distributions seen with lactose granulated in glass or steel.

When the vessel wall material possesses a high contact angle (PMMA and PTFE), water rather stays in the powder mixture, since the powder mixture is more easily wetted. If the liquid is absorbed in the powder bed quickly, nucleation starts immediately and all nuclei are approximately of the same size (droplet controlled nucleation). The following slow consolidation process is called preferential nucleation [4, 13]. In this case, the final granule size distribution is likely to be narrow.

However, with a low contact angle of the vessel wall (glass, stainless steel) and a fast imbibing powder (MCC), a minor fraction of the liquid will not immediately take part in the process. Therefore, in the second growth stage some nuclei are more wetted than others, leading to a somewhat broader granule size distribution. This is in agreement with the finding of Holm et al. [14], who concluded, that when moisture distribution is not optimal, larger aggregates are formed due to excessive wetting, resulting in a broader granule size distribution. Hoornaert et al. also have shown that a relatively small change in the amount of binder can significantly change the granule size distribution obtained by granulation [2].

A different situation arises when the powder cannot take up the liquid quickly (MFC, lactose), but a high contact angle of the wall (PMMA) still forces all water into the powder. Nuclei are formed, but due to the slow uptake of water in the powder bed there is still unbound liquid present. This results in a situation of local overwetting in the powder bed, leading to a relatively low number of nuclei with a high water content. Coalescence growth occurs, which results in larger granules [14]. This explains why large granules are formed from MFC and lactose granulated in a PMMA vessel.

When a powder cannot take up liquid quickly, a low contact angle of the vessel wall will slow down the liquid penetration into the powder bed. The liquid spreads better over the powder. Nuclei are wetted more evenly, which results in smaller granules.

In Figure 6 the different granulation mechanisms found for the different vessels and different materials are depicted schematically.

MCC and MFC are similar materials; both consisting of cellulose. However, due to a different treatment, they possess different material properties. MFC is more amorphous than MCC; therefore more binder fluid is necessary to saturate the water-powder mixture [15, 16]. The effects are visible in Table 1, which shows the process conditions used. For granulation of MCC the mass of powder equals the mass of water used, whereas for granulation of MFC the mass of water was almost twice the mass of powder.
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**Figure 6**: The different granulation mechanisms. Liquid binder is added to the moving powder bed, the liquid is distributed over the bed and nucleation starts. Addition to the powder bed is similar for all situations. A difference in nucleation originates in differences in the contact angle of the vessel wall material and the liquid sorption rate of the powder.

MFC and lactose are slowly imbibing powders, which means that water is slowly transported through the powder bed. These powders nucleate and grow via mechanism C in Figure 6 when granulated in a vessel with a high contact angle, like PMMA. If granulated in glass or stainless steel, nucleation and growth takes place via mechanism D. Both powders show a broader granule size distribution than MCC. MCC is a fast imbibing powder, which nucleates via mechanism A (in a vessel with a high contact angle, like PMMA) or via mechanism B (in a vessel with a low contact angle, like glass and stainless steel). MCC needs a fast liquid distribution over the powder bed to obtain a narrow particle size distribution; this can be achieved in the PMMA vessel.

PTFE is a material which is used because of its low friction. When water is present, friction is decreased even more [11]. Granule size distributions of all three powders tested show irreproducible results. In high-shear granulation high shear forces are needed. Shear is caused by the rotation of the impeller, by granule-granule collisions, and by wall friction. In the small scale used, the wall friction is important. Clearly, friction of PTFE with the powder bed is too low to give a reproducible granulation process.
It can be concluded that the type of vessel wall material chosen significantly affects the granulation mechanism and the final product obtained in high shear granulation. The contact angle of the vessel material and the sorption rate of the powder used determine the nucleation process and the final granule size distribution. Glass and stainless steel vessels produce similar granules, whereas PMMA and PTFE vessels give different granule size distributions. In this study we have used small laboratory equipment which makes the effects of the wall of the vessel large. In large equipment the effects may be smaller. However, when scaling down it is important that the properties of the vessel wall of the small scale laboratory granulator match the properties of the wall of the large scale production granulator, especially with regard to contact angle and friction properties.

3.6 References


12. Radelczuk, H., L. Holysz, and E. Chibowski, *Comparison of the Lifschitz-van der Waals/acid-base and contact angle hysteresis approaches for*
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