3 PRODUCTION PROCESSES

3.1 Introduction

In chapter two the available delayed or controlled release formulations have been reviewed. From that literature study we concluded that the reservoir device would be most suitable for our needs. A reservoir device consists of two essential parts, a coating and a core. The production methods for these components are discussed in this chapter.

3.2 Core production

Spherical particles with a narrow particle size distribution are preferred as cores. The influence on the release characteristics is minimized when the variation in particle size and shape are small.

We define pelletization as a production technique to produce spherical particles with a narrow particle size distribution. Three types of pelletization are discussed here: wet high shear pelletization with microcrystalline cellulose, melt pelletization with polyethylene glycol and prilling. As will be shown in next paragraphs wet high shear pelletization is the most efficient pelletization technique in terms of time and material consumption while melt pelletization has the advantage of producing water-soluble particles. Prilling is used to produce mono-sized and perfectly spherical particles.

3.2.1 Wet high shear pelletization

Introduction

As discussed in paragraph 2.5.3 and 2.5.7 the particle size of the cores (also referred to as pellets) has to be between 300 and 1000 µm and the core should be mostly or for a large part water-soluble. Furthermore, the coating process requires the particles to be spherical, to have a narrow particle size distribution, to have a low friability and a high strength. One production process that can achieve these requirements is wet high-shear pelletization with microcrystalline cellulose as an excipient.
Wet high-shear pelletization is a size enlargement process agglomerating small particles into larger, permanent aggregates in which the original particles can still be identified [1]. This process is also referred to as granulation; the term pelletization usually refers to the manufacture of aggregates with a narrow size distribution. The term “wet” refers to the fact that water is used as the binder liquid, i.e. water initiates the growth from small initial particles to larger aggregates. The term high-shear refers to the fact that the shear forces exerted on the material during the process are high compared to other production processes such as fluid bed agglomeration or spray drying.

Wet high shear pelletization can be applied to agglomerate a wide range of materials. However the resulting particles will often be irregular of shape and have a wide particle size distribution. For coating purposes this is not desired and therefore the excipient microcrystalline cellulose (MCC) is needed to obtain spherical particles with a narrow size distribution. High-shear pelletization of mixtures containing MCC can result in very narrow particle size distributions (80% within a range of 0.1 mm relative to an average value of 0.95 mm [2]).

**Theory**

Although high-shear pelletization is a well-established process in the pharmaceutical industry the control of these processes is to a large extent based on trial and error. Only recently some attempts [3] [4] [5] [6] were made to achieve a more mechanistic approach to describe the high-shear pelletization process.

In general the size change in granulation is thought to be a process in which the growth mechanisms, nucleation, coalescence, crushing layering and abrasion transfer [7] compete with the destructive mechanisms shattering, breakage and attrition (see figure 3.1). Depending on the type of granulator, the shear forces exerted on the material, the amount and properties of the binder liquid and the properties of the materials used, these mechanisms result in increase or reduction of the particle size.

More specific for wet high-shear pelletization with MCC as an excipient the growth of pellets
can be divided into four stages (see figure 3.2): initial nucleation with minor growth, exponential growth by coalescence, linear growth and finally equilibrium with zero net growth [3]. During liquid addition, large primary nuclei are formed as soon as liquid drops reach the powder bed.

Due to the impact of the impeller, the weak primary nuclei are crushed into several stronger and denser secondary nuclei. More densification of the secondary nuclei results in exponential growth by coalescence [9]. During kneading, the mean pellet size increases until a dynamic equilibrium is reached in which zero net growth occurs. The rates of growth and break-up of pellets become equal. In other words, although the pellet size does not change anymore pellet break-up and growth still occur.

![Figure 3.2 Growth stages in wet high-shear pelletization process; I: initial nucleation with minor growth, II: exponential growth by coalescence, III: linear growth and finally IV: equilibrium with zero net growth [9].](image)

**Materials and methods**

In our experiments we used a Gral 10 high-shear mixer (Machines Collete, Belgium) for the preparation of pellets. A schematic representation is given in figure 3.3; some technical data is given in table 3.1. The impeller speed of the Gral is continuously adjustable within the range of 0-660 rpm. For the breakdown of lumps formed during the process a chopper is present, the chopper speed could be varied between 0, 1500 and 3000 rpm.
The temperature of the bowl was kept constant by flowing water of 25 °C through the double-sided wall. The binder liquid (demineralised water) was added to the powder mixture through a pneumatic nozzle (Two fluid nozzle 2304.22, Aeromatic, U.S.A).

As granulating materials were used microcrystalline cellulose (MCC) and sodium chloride. The MCC was used as received (Pharmacel 102, DMV, The Netherlands), the sodium chloride (sodium chloride USP 7540 powder, Mallinckrodt Baker, The Netherlands) was milled before use with a Pulverisette 14 mill (Fritsch GmbH, Germany). The total batch size was 800 grams, with 500 grams of sodium chloride and 300 grams of MCC.

<table>
<thead>
<tr>
<th>Volume bowl (l)</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter bowl (m)</td>
<td>0.245</td>
</tr>
<tr>
<td>Impeller radius (m)</td>
<td>0.115</td>
</tr>
<tr>
<td>Batch size (g)</td>
<td>800 (500 g NaCl, 300 g MCC)</td>
</tr>
<tr>
<td>Relative swept volume (s⁻¹)</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 3.1 Technical data Gral 10.

We used sodium chloride as the main ingredient in the core in the experiments for three reasons. Firstly the osmotic pressure of a sodium chloride solution is very high. This means that if water is transported through the coating the osmotic pressure on the coating resulting from the dissolved sodium chloride is very high. Thus sodium chloride can be seen as a “worst case scenario”, if the formulation has the desired release properties (the desired lag-time before release) with sodium chloride it will probably give better results with other core ingredients which do not cause such a high osmotic pressure when dissolved. The second reason is that water-soluble salts are commonly used in detergents as filler or as a stabilizer for enzymes. The last reason is that the release of sodium chloride from the formulations can be monitored with conductivity measurements, which are easy to perform and have a small experimental error.

The sieving analyses were carried out with a set of sieves with openings of 150, 300, 600, 710, 850, 1112 and 1400 µm.

The pelletization procedure was as follows: after 5 minutes of premixing a precisely determined amount of binder liquid was added during 30 seconds and
the mass was kneaded for 5 minutes. Subsequently, any material present on the wall of the mixer was removed and the mass was kneaded for another 15 minutes. During the whole experiment the impeller speed was set on 600 rpm. During the pre-mixing and water addition the chopper was set on 3000 rpm, the chopper was turned off during the last 15 minutes of the kneading stage. The pellets were dried for 12 hours at 60 °C in a circulating air oven.

**Results and discussion wet high-shear pelletization**

In figure 3.4 an indication of the reproducibility of the wet high-shear pelletization experiments is given. The reproducibility of the experiments is good and also a large amount of pellets (80-w/w%) can be produced in the desired size range.

![Average particle size distribution 4 wet high-shear pelletization experiments, error bars denote standard deviation between the experiments.](image)

In figure 3.5 the influence of the initial sodium chloride particle size is given. An increase in the sodium chloride particle size gives larger particles. Another effect is that the surface roughness of the pellets produced increases with the larger sodium chloride particles (see SEM photographs, figure 3.6). Since for coating purposes the surface roughness has to be as low as possible only pellets with sodium chloride particles smaller than 75 µm have been used in the coating experiments in chapters 4, 5 and 6.
Figure 3.5 Influence of the initial sodium chloride particle size on the particle size distribution obtained with wet high shear pelletization.

Figure 3.6 SEM photographs of pellets produced with NaCl particles < 75 µm (left) and pellets produced with NaCl particles < 212 µm (right).

In figure 3.7 the influence of the amount of and the droplet size of the binder liquid is given. The droplet size is varied by varying the atomizing pressure of the pneumatic nozzle.

A small increase in the amount of liquid will increase the average particle size. Also the droplet size influences the particle size distribution, larger droplets results in larger pellets.
In conclusion it can be stated that wet high shear pelletization with MCC is a suitable method to produce spherical particles with a narrow particle size distribution. A disadvantage of the method is that the resulting pellet size is very sensitive to the amount of water added. Another disadvantage is that MCC is water-insoluble.

3.2.2 Melt pelletization

Introduction

Melt agglomeration/pelletization is a process by which agglomeration is obtained through the addition of either a molten binder liquid or a solid binder that melts during the mixing process. The product temperature is raised by an external heating of the high-shear equipment and/or by a development of heat caused by friction [10]. Cooling the mixture below the melt-temperature of the binder forms the final pellets. Melt pelletization has the advantage over wet high-shear pelletization that the process is dry; water-sensitive products can be agglomerated and a drying step is not required.

The objective of the following experiments was to determine the suitability of high-shear melt pelletization for the production of spherical pellets with a narrow particle size distribution.
Theory

Schæfer et al wrote a number of articles [10-18] on melt pelletization. A short review of their findings and some other authors on the influence of some process and formulation variables on melt pelletization is presented below.

The temperature of the mixture in the high-shear mixer plays an important role. When the temperature increase of the powder mixture, as caused by the high shear forces exerted on the mixture, is low to moderate (10 to 20 °C) the bowl temperature should be well above the melting temperature of the binder. Otherwise lumps and large agglomerates will be formed due to solidification of the binder on the walls of the bowl. Schæfer et al found that a higher bowl temperature resulted in larger agglomerates. They claim the increase in particle size is caused by a combination of a lower viscosity and a higher liquid saturation of the formed pellets [10]. The lower viscosity increases the deformability of the pellets, thereby increasing the potential to agglomerate by coalescence. The higher deformability also decreases the porosity. This, in combination with the thermal expansion of the binder liquid, transports more binder liquid to the surface of the pellet and thus growth is promoted.

Another important process parameter is the massing time, the time during which the binder is present in a molten state. The agglomerate growth rate and the mean pellet size both increase with the massing time [10], this might give rise to uncontrolled agglomerate growth at a long massing time. However particle size distributions become narrower during massing as a result of break-up of lumps [10] and thus an optimum massing time has to be found.

According to Schæfer the effects of a higher impeller speed should be equal to that of the prolonged massing time since both are increasing the total energy input during the process. Thus increasing the impeller speed will result in larger pellets. The influence of the chopper speed is ambiguous; much depends on the design and the location of the chopper [12].

As with wet high-shear pelletization the binder concentration has a large influence on the mean particle size. Increasing the amount of binder liquid causes a higher liquid saturation, which will result in a higher agglomerate growth rate [19]. At higher binder concentrations the agglomerate growth becomes uncontrolled.

The effect of changing the viscosity of the binder, i.e. the molecular weight of the PEG used, is not quite clear. Schæfer et al. [16] found an increase in the average particle size when they decreased the viscosity of the binder. However some investigators [20] found a decrease in the particle size when using a lower viscosity binder and others [21] did not find any effect on the particle size. When investigating a whole range of binder viscosity’s Schaefer [16] found that a higher viscosity gives a lower initial growth rate and a higher subsequent growth rate and thus the process is difficult to control. With the lower viscosity binders they found a narrower particle size distribution.
(increased control over the pelletization process) but also an increase in the amount of lumps (particles larger than a few millimeters).

**Materials and methods**

The high shear equipment was equal to that of the wet high-shear pelletization. To heat the bowl above the melting temperature of the binder hot water was pumped through the double-sided wall (figure 3.3).

The materials used were lactose (450 mesh, DMV) and polyethylene glycol (PEG, molecular weights 1500, 2000 and 6000, Merck, Germany). Polyethylene glycol was used because it is the most water-soluble of the meltable binders.

The pelletization procedure was as follows: after premixing the lactose and PEG for 5 minutes in a bowl at room temperature hot water was pumped through the bowl to melt the PEG. When the bowl had reached the desired temperature the mixture was kneaded for a certain amount of time. The final pellets were obtained by cooling the mixture outside of the apparatus. During the whole experiment the impeller and chopper speed were set at 600 and 3000 rpm, respectively.

**Results and discussion melt pelletization**

In figure 3.8 the influence of the amount of binder liquid and binder viscosity (i.e. the molecular weight of the PEG) on the particle size distribution of a melt pelletization experiment are given. Increasing the amount of binder liquid increases the average particle size, which is consistent with the results found in the literature. We also found an increase in the average particle size at increased binder viscosities which is in agreement with the results of Schæfer [16].

The amount of binder liquid is very critical; a small increase in the amount of PEG has a profound effect on the particle size distribution. This is seen in figure 3.8 and is also illustrated in figure 3.9.
Figure 3.8 Melt pelletization experiments: influence amount of binder liquid and binder viscosity.

Figure 3.9 Melt pelletization experiments: influence amount of binder liquid.
In figure 3.11 (next page) the influence of the massing time on the particle size distribution is given. Again the results are consistent with the literature: an increase in the massing time gives an increase in the average particle size. It is also seen that above a certain massing time the growth of the pellets becomes uncontrolled and, as with the amount of binder liquid, this is a very critical parameter.

Figure 3.12 (next page) gives the influence of the bowl temperature on the particle size distribution. There is not a very clear effect of the temperature on the particle size distribution. This might be caused by the rather small change in the temperature; also Kinget and Kemel [19] also reported that a small change in the temperature (60 to 70 °C) showed no effect on the agglomerate properties.

Concluding: in comparison to wet high-shear granulation melt pelletization gives granules with a wider size distribution. Pellets produced by melt pelletization also have another unwanted property; they are less spherical than pellets produced by wet high-shear pelletization. Advantages of pellets produced by melt pelletization are the very smooth surface of the pellets (see SEM photos in figure 3.10) and the possibility of producing pellets which are totally water-soluble.
Figure 3.11  Melt pelletization: Influence massing time on particle size distribution.

Figure 3.12  Melt pelletization: Influence bowl temperature. Error bars denote deviation in three experiments.
3.2.3 Pelletization with molten droplets: prilling

Although it is possible to produce particles with a narrow particle size distribution with high-shear granulation we needed particles which were even more uniform in size and shape (see chapter 6). With these particles the influence of size and shape on the release properties were investigated. A technique for the production of almost perfectly spherical cores is atomizing a molten stream of polyethyleneglycol (PEG) into molten droplets and cool them in cold paraffin oil [22-24]. The droplets solidify and form spherical cores (figure 3.13). The droplets used in our experiments consist of 80-w/w% PEG 4000, 10-w/w % sodium chloride (all particles smaller than 45 micron) and 10-w/w% swelling agent (polyvinylpyrrolidone, PVPP, Fluka Chem- ika, Germany). The sodium chloride and PVPP particles were suspended in the molten PEG by stirring.

In figure 3.14 a photo taken with a light microscope is given to illustrate the particle size and shape obtained with this type of pelletization. Particle size data comparison for the different pelletization methods is given in chapter 6 (tables 6.4 and 6.5).

It is possible to produce perfectly spherical particles with a very narrow particle size distribution with this technique. However the time necessary to produce the necessary amount of particles is quite long. This is due to the limited liquid flow rate from the nozzle. At higher flow rates the molten polymer stream breaks up irregularly producing non-uniform particles.
Production processes

Figure 3.14  Pellets prepared by prilling (average size: 1.36 ± 0.07 mm)

3.2.4 Conclusions regarding core production

High shear pelletization is a suitable method to produce spherical pellets with a narrow particle size distribution. Wet high shear pelletization gives more spherical particles with a more narrow particle size distribution than melt pelletization. However with melt pelletization it is possible to produce particles which are totally water-soluble. Prilling is a time-consuming process but the produced pellets are perfectly spherical and mono-sized.

3.3  Fluid bed coating

3.3.1 Introduction

Fluid beds are used extensively in the pharmaceutical and powder processing industry for the agglomeration and drying of powders [25] [26] [27]. The utilization of a fluid bed as an apparatus to coat particulate matter was developed by Dale Wurster around 1953 [28]. The principle of the process is as follows; the substrate material is brought into a fluidized state while the coating is delivered in an appropriate solvent onto the substrate surface as small droplets. Many variations are possible for example in the way the substrate material is fluidized and in the way the coating solution is atomized [29]. Fluidization can be done in a normal fluid bed or to enforce a certain fluidization pattern a tube can be inserted in the fluid bed (Wurster insert) or the particles can be fluidized tangentially (Rotoprocessor [30]). The coating solution can be applied from above on the fluidized particles (top-spray), from below (bottom spray) [31] [32] and tangentially (see figure 3.15). The coating method used in this thesis is bottom spray.
No attempt was made to describe the complex fluid bed coating process in great detail in this thesis. There is one aspect of fluid bed coating that we do give a short description of below and that is the drying of atomized droplets in a fluid bed. We did this because the biggest problem with fluid bed coating that we encountered was the agglomeration of pellets during the coating process. This is mainly due to the droplet size of the atomized coating fluid, as we will show below.

The behaviour of coating solution droplets in the fluid bed coating process can be divided into three steps:

- droplet formation (atomization),
- droplet travel,
- droplet drying (during travel and on the pellet surface).

**Droplet formation**

The coating solution has to be applied on the substrate in the form of small droplets. This is done by atomization of the coating solution with the aid of a nozzle. Many types of nozzles exist (pressure or hydraulic nozzles, rotary devices or centrifugal nozzles, ultrasonic nozzles) but since in lab-scale coating processes the liquid rates are very low and the droplets need to have a small diameter the most suitable nozzle is a pneumatic or two fluid nozzle.

The most important parameter of a nozzle is the resulting droplet size distribution. Juslin et al. [33, 34] investigated the influence of a set of parameters on the droplet size from a pneumatic nozzle atomizing a polyvinylpyrrolidone solution with statistical methods (a normal $3^3$ factorial design). They found a
decrease in droplet size with increasing atomizing pressure and an increase in
droplet size with increasing liquid flow and viscosity of the liquid.

Nukiyama and Tanasawa [35] developed an empirical relationship for the
calculation of the average droplet size of small parallel flow atomizers (equation
3.1).

\[
d_{3,2} = \frac{0.585}{v} \sqrt{\frac{\sigma_l}{\rho_l} + 53.2 \left(\frac{Q_l}{Q_g}\right)^{1.5} \left(\frac{\eta_l}{\sqrt{\sigma_l \rho_l}}\right)^{0.45}}
\]  

(3.1)

The velocity \( v \) is the relative velocity between the gas and the liquid at the
discharge from the atomizer, \( \sigma_l, \rho_l \) and \( \eta_l \) are the surface tension, density and
viscosity of the liquid respectively, \( Q_l \) and \( Q_g \) are the volumetric flows of the
liquid and gas respectively. It is seen that \( d_{3,2} \) decreases as \( v \) increases and \( Q_l/Q_g \)
decreases which is in accordance with Juslin et al.

The gas velocity can be estimated by equation 3.2 from Bayvel [36].

\[
v_g = \sqrt{\frac{2}{\gamma - 1} \left(\frac{\rho_g}{\rho_g^f}\right)^{\frac{\gamma - 1}{\gamma}} - 1 - \left(\frac{p_g^H}{p_g^f}\right)^{\frac{\gamma}{\gamma - 1}}} \right)
\]  

(3.2)

In this equation \( \gamma \) is the polytropic coefficient of the gas, \( p_g^f \) and \( \rho_g^f \) are the
pressure and density of the gas before expansion respectively and \( p_g^H \) is the
pressure of the gas after expansion. When the physical parameters from our
experiments (\( \gamma = 1.4 \) [36], pressure before expansion 1.4 bar, pressure after
expansion 1.0 bar) are substituted in equation 3.2 the result is an air speed of 255
m/sec.

The droplet size was determined experimentally (figure 3.16) for two
atomizing pressures with a laser diffraction apparatus (Sympatec Helos). The
pneumatic nozzle used was a Schlick 970 (Schlick 970, Gustav Schlick GmbH &
Co., Germany), the solution atomized is a polymer solution (7-w/w%
polyvinylpyrrolidone) with a viscosity of 4 mPa-s. The spray rates of the
solutions were equal for the two experiments.
All the droplets atomized at 1.4 bar were smaller than 50 \(\mu\)m. Most of the droplets atomized at 0.9 bar are smaller than 50 \(\mu\)m but there is a second peak at approximately 100 \(\mu\)m. When we substitute the droplet size range of the atomized particles of the experiment with 1.4 bar in equation 3.1 we find a value of 250-300 m/sec for the gas velocity \(v\). This is consistent with the air speed calculated from equation 3.2.

The atomizing conditions depicted in figure 3.16 were also applied in fluid bed coating experiments with particles in the size range 0.6 to 0.71 mm (bottom spray). The experiment with 0.9 bar atomizing pressure gave severe agglomeration of the particles whereas the experiment with 1.4 bar atomization pressure gave no agglomeration. This is caused by the drying characteristics of the droplets and subsequent over-wetting of the particles, which is explained in the next two paragraphs.

**Droplet travel**

The air stream coming from the nozzle outlet will entrain the surrounding air and expand. Since the experimental setup used in the experiments is bottom spray the air jet in the vicinity of the nozzle will increase the speed of the droplets and pellets. To calculate the horizontal and vertical velocity distribution of a turbulent plane jet equations are used developed by Reichhardt.
The velocity components are consistent with the following equations of continuity (see for an extensive description of this subject [39] or [40]):

\[
\bar{v}_x / v = x^{-1/2} F'(\eta)
\]  (3.3)

\[
\bar{v}_y / v = \left[ -\frac{1}{2} x^{-1/2} F(\eta) + \eta x^{-1/2} F'(\eta) \right] \sigma^{-1}
\]  (3.4)

\[
\eta = \sigma (y / x)
\]  (3.5)

\[
F = \tanh \eta
\]  (3.6)

In these equations is \( x \) the horizontal distance from the nozzle, \( y \) the vertical distance from the nozzle, \( v \) a characteristic velocity, \( \bar{v}_y \) is the vertical velocity component, \( \bar{v}_x \) is the horizontal velocity component and \( \sigma \) an integration constant.

The droplet speed as function of the distance from the nozzle is given by equation 3.7.

\[
\frac{dv_{\text{drop}}}{dx} = \int_0^{x} \frac{1}{v_{\text{drop}}} \cdot \frac{F(v,x)}{m}
\]  (3.7)

In this equation is \( v_{\text{drop}} \) the speed of the droplet along the centerline, \( F \) the force acting on the droplet and \( m \) the mass of the droplet. The forces on the droplet \( F \) are the drag force and the gravity force and are calculated with equation 3.8; the value of the drag coefficient \( C_w \) is taken as a constant (0.43), which is a valid assumption at these high Reynolds numbers. Furthermore \( v \) denotes the relative speed between the droplet and the air, \( \rho_\text{air} \) the density of the air, \( d_{\text{drop}} \) the droplet diameter and \( g \) the gravitational constant. Other assumptions are; the drops are rigid and the air surrounding the air jet is stagnant. The initial speed of the liquid flow out of the nozzle is taken as 0.2 m/s.

\[
F(v,x) = C_w \cdot \frac{\pi}{4} \cdot d_{\text{drop}}^2(x) \cdot \left[ \frac{1}{2} \rho_{\text{air}} \cdot v(x)^2 \right] + mg
\]  (3.8)

**Droplet drying**

The influence on mass transfer coefficients of the motion of single spheres relative to a stationary continuous phase has been studied extensively. A generally accepted correlation for mass transfer from single spheres in a gas stream is given by equation 3.9 [41].
\[
Sh(v_{\text{drop}}, x, r_{\text{drop}}) = 2 + 0.6 \cdot Re(v_{\text{drop}}, x, r_{\text{drop}})^{\frac{1}{2}} \cdot Sc^{\frac{1}{3}} 
\]

(3.9)

In this equation is \( Sh \) the Sherwood number for mass transfer, \( Re \) the Reynolds number, \( Sc \) the Schmidt number and \( r_{\text{drop}} \) the radius of the droplet. A mass balance is derived for the decrease in radius as function of the distance from the nozzle, and as function of the speed and radius of the drop (equation 3.7).

\[
\frac{dr}{dt} = -2 \cdot D \cdot \frac{Sh(v_{\text{drop}}, x, r_{\text{drop}})}{r_{\text{drop}} \cdot \rho_{\text{drop}}} \cdot (C_{\text{sat}} - C) 
\]

(3.10)

In this equation is \( D \) the diffusion coefficient of water in air, \( \rho_{\text{drop}} \) the density of the atomized liquid, \( C_{\text{sat}} \) the saturation concentration of the liquid in air and \( C \) the bulk concentration of the liquid in the fluidization air. The equations 3.9 and 3.10 can be numerically integrated over time, in figure 3.17 the decrease of the relative radius of a pure water droplet with the air speed calculated with equations 3.3 through 3.6 is given as function of time.

Figure 3.17 Decrease in relative radius vs. time for four initial drop sizes, initial jet speed 250 m/sec, fluidizing air: inlet temperature 60 °C, relative humidity 60 %.

From figure 3.17 we see that the droplet size has a large influence on the drying time of the droplets. It must be noted that the influence of the film-
former dissolved or dispersed in the water droplet is not accounted for. The film-former will decrease the evaporation rate because of the decreasing diffusion coefficient with increasing film-former concentration. Another reason for overestimating the drying rate is the fact that the water concentration in the jet can be markedly higher than the water concentration in the drying air [42].

When the droplet has collided with the pellet further drying will take place on the pellet surface. When it is assumed that the base surface area of the droplet on the surface of the pellet does not change and that the droplet has the form of a cylinder the volume of the droplet is correlated with the height according to equation 3.11.

\[ V = \pi \cdot \frac{h}{6} \cdot (3r^2 + h^2) \] (3.11)

To calculate the drying time a mass balance is derived analogue to equation 3.10. The mass balance is then integrated from the initial height \( (h) \) to zero which gives the drying time. The results are analogue to the results found for drying droplets, smaller droplets have much shorter drying times than larger droplets.

**Conclusion droplet drying**

From fluid bed coating experiments we found that atomising at lower atomising pressures resulted in severe agglomeration of the particles. We have seen from the calculations that the drying time of a droplet with a radius of 50 µm is a magnitude 100 longer than the drying of a droplet with a radius of 5 µm. From laser diffraction data it was found that a relative small difference in atomising pressure (0.5 bar) can cause the formation of droplets with a radius of 50 µm. These larger droplets cause over-wetting of the particles and thus the possibility of creating liquid bridges between the particles to form agglomerates [43].

From equation 3.1 it is seen that the viscosity of the solution is important for the resulting droplet size of the nozzle. Increasing the viscosity can have the same effect as decreasing the atomising pressure: an increase in droplet size. As a consequence high viscosity polymer solutions are not suitable for fluid bed coating due to agglomeration problems. Considering the fact that the viscosity of polymer solutions increases fast with for example molecular weight of the polymer or polymer concentration the application of pneumatic nozzles in fluid bed coating is limited to polymer solutions with a low viscosity.
3.4 References

Production processes