5. INVESTIGATION OF POROSITY IN THE PASTILLES

5.1. Introduction

Many different types of controlled dosage forms have been developed to improve clinical efficiency of drug and patient compliance. In vivo performance of these dosage forms, however, depends greatly on their physical and structural properties, and consequently on their drug release mechanisms and its kinetics. A solid complex (matrix) mostly produced by tableting techniques are commonly used in pharmaceutical industries in order to retard the drug dissolution rate. The solid complex is, however, still not optimal since there are problems such as instability of tablet, selection of binder and excipient (additive). Under compressing pressure drug crystals agglomerate, thereby porosity is entrapped in the solid complex. Some researchers ([HOG02], [PAU03], [WES98]) already investigated the entrapment of porosity in the tablets, because it is an important parameters concerning bioavailability and quality of tablets.

Pharmaceutical materials require careful consideration of their porous structure and in fact their physical properties. Moreover, their application and performance are strongly influenced by their pore volume, size and shape. During the pastillation process, the pores and the cracks are formed in the bodies or on the surface of pastilles. Both pores and micro-cracks are critical surface features. Some researchers ([BUD69], [EME01]) investigated the kinetic equation of pore formation in granules of mineral materials with additives under firing. The obtained equations are recommended for mathematical modelling of the pore formation process. However, investigations of porosity (pores and cracks) in pastilles have not been studied until today. Therefore, the total porosity, the pore structure and the pore size distribution are investigated to determine the internal and external structure of the pastilles. These parameters are essentially influenced by manufacturing conditions of the pastille as the temperature gradient between surface of substrate and the melting point of the materials (degree of subcooling), the surface property of used substrate (surface roughness), the impacting velocity of droplet (Reynolds number) and the composition of the materials. The amount and the size
distribution of porosity should be estimated for the design of the drug delivery system and the selection of the solidification technology. The outlook of chapter 5 is therefore, as follows: introduction of mercury porosimetry technique is described in section 5.2. Pore structure and size distribution are determined in section 5.3. The phenomena of pores and cracks formation by experimental conditions is investigated in section 5.4. The relationship between the total porosity and the crystallization kinetic is numerically elucidated in section 5.5.

5. 2. Preparation of solid drugs and mercury incursion porosimeter

5.2.1. Preparation of pastille and tablet

In order to minimize the porosity of the pastilles, they are manufactured by a solidification technique [KIM03c] as described in chapter 4. The monosized hemispherical Bisacodyl pastilles are shown in Figure 5-1. A SEM (Scanning Electronic Microscope)\(^{1}\) technique is used to measure the surface morphology and the structure of the pastilles and the tablets. Manufacturing variables of the pastilles are: Reynolds number of impacting drops, degree of subcooling and characteristic of used substrate. To compare the pore structure, the total porosity and the pore size distribution, Bisacodyl tablets are manufactured by a tablet compression technology (HBM GmbH)\(^{2}\). It consists of a tablet compression machine and the molds, which hold a measured volume of material to be compressed, the upper punches, which exert pressure on the down stroke, and the lower punches, which control the volume of mold fill and thus the tablet weight. The lower punches moves upward after the compaction to eject the tablet from the molds. It is the most common tableting method. The operating conditions of the tablet manufacturing are summarized in Table 5-1.

\[\text{Figure 5-1: Monosized hemi-spherical Bisacodyl pastilles.}\]

\(^{1}\) The help of M.Sc. J. Choi, Max-Plank Institut in Halle is gratefully acknowledged.

\(^{2}\) The help of Prof. Dr. P. Kleinebudde and his team, faculty of pharmacy of the Martin-Luther-Univesity Halle-Wittenberg are gratefully acknowledged.
Table 5-1: Operating conditions of the tablet manufacturing.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (Max pressure: 20 MPa)</td>
<td>10, 13.5, 18 MPa</td>
</tr>
<tr>
<td>Type of mold</td>
<td>Flatted cylindrical form</td>
</tr>
<tr>
<td>Size of dies (Radius)</td>
<td>6, 9, 12 mm</td>
</tr>
<tr>
<td>Thickness of tablet</td>
<td>≈ 3.5 mm</td>
</tr>
</tbody>
</table>

5.2.2. Technique of mercury porosimetry

Physical and chemical gas adsorption (so called BET) as well as mercury intrusion porosimeter are the most widely used techniques to characterize powders and solid materials. These techniques can provide reliable information about the pore size/volume distribution, the particle size distribution, the bulk density and the specific surface area for porous solids regardless of their nature and shape. However, the applicable pore size ranges of each technique are different. Figure 5-2 shows a limit of application of both techniques and classifies three kinds of pores in the size.

![Figure 5-2: Limit of application of gas adsorption (BET) and mercury intrusion porosimetry.](image)

The mercury porosimetry technique (Instruments Pascal 140 and 440, *Thermo Finnigan*) used to measure the total porosity, the pore size distribution and the pore structure of the tablet and the pastille. The rate of the pressure change has been discussed to affect the result of the porosity measurement [MOS81]. The technique is based on the mercury property to behave as non-wetting liquid with a lot of solid materials. As results of this property mercury penetrates through the open pores of a solid sample under an increasing pressure. The pore radius is inversely proportional to
the applied pressure according to a relation proposed by the Washburn equation \( \Delta p = -2\gamma \cos \Theta \) \[KAM94\] in which some assumptions have to be taken into consideration: (1) The surface tension of mercury and contact angle of the solid material are constant during the analysis. (2) The intrusion pressure must be in equilibrium. (3) Solids are not deformed under the effect of pressure. By measuring the quantity of mercury penetration in the pores and the equilibrium pressure at which intrusion occurs, experimental data are obtained to calculate the pore volume distribution as a function of their radius. Here intrusion and extrusion pressure rates are approximately 0.098 and 0.186 MPa/s, respectively. The total pore volume, the total pore surface area, the mean pore diameters and the pore size distributions of tables and pastilles were determined by both a low- and a high-pressure mercury porosimeter. Determination range of pores can be measured starting from 4 nm (pressure = 400 MPa) up to 200 µm (pressure = 0.01 kPa). In addition, a microscopic image analyzing technique is employed to support the results of mercury porosimeter.

5.3. Structure and size distribution of pores in pastilles and tablets

5.3.1. Pores structure of pastilles and tablets

In this section, pore structures and pore size distributions are investigated by the mercury intrusion porosimeter and the scanning electron microscopy techniques. Mercury porosimeter data can enable the calculation of the specific surface area \( \text{m}^2/\text{g} \) of the samples. There are 4 models available for the surface area calculation. Here are the cylindrical, conical, plates and spherical models. It can be distinguished by intrusion or extrusion curves between the cumulative volume of mercury and the compression pressure.

Figure 5-3 shows the relationship between cumulative volume of mercury and the compressing pressure. According to the intrusion and the extrusion curve of the pastilles, a conical model can be applied to the pastille. Moreover, these types of pores are commonly found in natural materials, for instance in carbon coke, rocks and soils. The model represents that the pores are located on the surface and in internal of pastilles. The intrusion curve features a quite flat slope, indicating that mercury penetration
increases just according to the pressure. Pores of this type are progressively filled by mercury as the pressure rises. The extrusion curve is generally following the intrusion curve resulting in a very small hysteresis.

The cylindrical model can be applied to tablets. According to shape of Figure 5-2, pores are considered to be cylindrical. This type of model should be applied when the sample is a solid and the penetration curve shows a steep slope (sharp pore size distribution) and the extrusion curve follows the penetration with a hysteresis. In this case a small amount of mercury is retained by the sample in the interconnections between pores. According to the cylindrical model the surface area is calculated knowing the incremental specific pore volume and the relevant average pore radius.

![Volume vs Pressure Graph](image)

*Figure 5-3: Type of pore modes of tablets and pastilles.*

### 5.3.2. Pore size distribution of pastilles and tablets

Pore size distributions of pastilles and tablets are investigated by the mercury porosimeter and the scanning electron microscope images are used to support the result of pore size distribution. The pore size distribution can be displayed in a shape of histograms. The histograms numbers and dimension can be generated automatically by...
the software according to the radius limit selection given by operating conditions.

Figure 5-4: Pore size distribution of pastilles and tablets (radius range: 0.001 – 100; histograms number: 100).

Figure 5-4 shows the relationship between the relative pore volume and the pore radius of the pastilles and tablets, respectively. From the histogram the pore size distribution of pastilles and tablets are constituted as bimodal-model. In case of pastilles the first group of histogram (A) is occurrence of porosity due to rapid nucleation on the bottom side of the pastille. Nucleation usually takes place concentrically around the starting point of the cooled surface. However, the dominant pore in the pastilles is placed in a pore diameter range between 1 and 20 µm (B). In case of tablet the dominant pores are placed in a pore diameter range between 0.5 and 1 µm. From the results of analyses the dominant pore size distributions in tablets are smaller than those in pastilles. However, it is analytically found that the total porosity in pastilles is much smaller than the total porosity in tablets. Here the total porosity (%) is defined as the ratio of the sample void volumes (in- and external porosity) to its external volume (inverse of bulk density). It can be observed that cracks are the dominant “pores” that when present on the surface
of pastilles as the molten drop crystallizes. In case of the tablets, it can be seen that the main pore distribution is positioned in the body of tablets when the powder agglomerates.

Figure 5-5 shows SEM photos of the pastilles, surface morphology of the pastilles, grade cross-sections and cross-section of the pastilles. It can be visually confirmed by the SEM photos of Figures 5-5 (b) and (c) that the dominant pore distribution is ranging between 1 and 20 µm and the cracks are formed on the surface of the pastilles. Moreover, pores are constituted the conical form (see Figure 5-5 (d)). Unfortunately, it is impossible to investigate the length and width of porous depth.

Figure 5-5: SEM photos; (a) pastille, (b) surface morphology (magnification: 15000), (c) grade cross-section and (d) cross-section of pastille (magnification: 4000).

5.4. Total porosity

5.4.1. Total porosity in tablets

Figure 5-6 shows the relationship between the total porosity and the density of the tablet at various compressing pressures which are chosen to 10, 13.5 and 18 MPa. The SEM photos show cross-sections of the tablet. As mentioned before pores are entrapped in the inner body of the tablet. The total porosity is decreased with increasing the compressing pressure. Thereby the density is increased. The founding can be confirmed by SEM
photos, see Figure 5-6. At the low compressing pressure, 10 MPa, the structure of tablet was composed as a powder (agglomeration). The total porosity and the density are approximately 15 % and 1.29 g/ml, respectively. However, at the high compressing pressure, 18 MPa, the structure was more compact than the structure of other two compression pressures. The total porosity and the density are approximately 8.5 % and 1.35 g/ml, respectively.

![Figure 5-6: Amount of porosity at various compressing pressure (MPa).](image)

5.4.2. Total porosity in the pastille

While the molten drop impacts and crystallizes the cracks and the pores are generated on surface of the pastilles (e.g., Figure 5-7). Manufacturing parameters of pastilles should affect an occurrence of micro-pores and crack. The main factors are here: temperature gradient between the melting and the surface temperature of cooled substrate (degree of subcooling), Reynolds number of impacting drop and properties of the substrate. It will be discussed how manufacturing conditions of drops affect the
surface structure of pastilles and the total porosity in a pastille. However, the pore size distribution haven’t discussed due to the difficulty of distinguishing. These data will give a basis for a design of the drug delivery system and the improvement of the pastille quality.

Figure 5-7: Surface layer and growth direction of pastilles.

5.4.2.1. Effect of degree of subcooling

To investigate the total porosity, pastilles were produced at different temperatures of the cooled surface. Figure 5-8 shows SEM photos of surface morphology of the top part of a pastille and the total porosity at different degrees of subcooling. All other solidification parameters are kept constant such as final impacting velocity of 0.28 m/s, surface roughness of 0.23 µm and viscosity of 2.072 mPa·s.

In Figure 5-8 (a) are the top part of the pastilles at relatively lower degree of subcooling ($\Delta t = 113$ K) shown where no individual crystals and cracks can be identified. On the other hand in Figure 5-8 (c) and (d), the cracking phenomenon with increasing degree of subcooling ($\Delta t = 133$ and 143 K) is shown. This could be caused by relatively high nucleation and growth rates at the initial stage of solidification. According to the relationship between the total porosity and the degree of subcooling, it can be analytically confirmed that the total porosity is increased with increasing the degree of subcooling.
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Figure 5-8: Total porosity vs. degrees of the subcooling and surface morphology of the top part of the pastille at different degrees of subcooling ((a) $\Delta T = 113$ K, (b) $\Delta T = 123$ K, (c) $\Delta T = 133$ K, (d) $\Delta T = 143$ K (Magnification: 4000)).

5.4.2.2. Effect of surface properties

Figure 5-9 shows SEM photos of the surface morphology of the top and at the bottom of the pastilles resulting from different roughnesses of the surfaces of the cooling surface. The producing parameters of the pastilles are the final impacting velocity of 0.28 m/s, the viscosity of 2.072 mPa·s and the degree of subcooling of 133 K. The crystals at the bottom part of the pastille have been in contact with the cooled plate. After the impact the molten drops rapidly start to nucleate on the surface of cooled plate and then crystallize in vertical direction because of a high heat transfer. From the SEM photos of Figure 5-9 it is clearly visible that the size of crystal/pore at the bottom of the pastilles is smaller than these of the top part of the pastilles. Therefore, relatively high amounts of porosity are incorporated in the top part of pastille compare to the bottom part of the pastilles. Gum [GUM02] explained that the pores in the top part of surface of the pastille are approximately 10 times large than the pores at the bottom surface of the
pastille. The mentioned effect is, however, influenced by the manufacturing conditions and the physical properties of materials.

The size and the structure of pores on the top and bottom of the pastilles are investigated at different surface roughness, whose surface roughnesses are chosen ranging from 0.15 µm to 0.31 µm. According to Figures 5-9 (b-1), (c-1) and (d-1) the size of the pores at the top and bottom of pastilles with the surface roughness of 0.31 µm is larger than that on the surfaces with the two lower roughnesses.

Figure 5-9: Surface morphology of SEM photos of the top and the bottom of pastilles at different cooled plates. (a) side view of pastille, (b-1) and (b-2) surface morphologies of top and bottom of pastille at a smooth plate \((R_a = 0.15)\), (c-1) and (c-2) surface morphologies of top and bottom of pastille at a medium plate \((R_a = 0.23)\), (d-1) and (d-2) surface morphologies of top and bottom of pastille at a course plate \((R_a = 0.31)\).

Figure 5-10 illustrates a porosity measured by a porosimeter on three different surface roughnesses. Each sample of a pastille is analyzed 3 times under the same conditions. From the Figure 5-10 it can be seen that the total amount of pores is increased with increasing the surface roughness. All was confirmed by SEM photos, Figure 5-9.
5.4.2.3. Effect of Reynolds number

Figure 5-11 shows the correlation between the total porosity and the Reynolds number of two different masses of the drops. The Reynolds number is already defined in chapter 4. The surface roughness of 0.23 µm, the viscosity of 2.072 mPa·s and the degree of subcooling of 133 K are maintained constant. Figure 5-11 shows that the total porosity is logarithmically increasing with increasing Reynolds number. This is due to the effect of the degree of deformation and the effect of high growth rate of pastilles. Here the degree of deformation is defined as the ratio of the final diameter of a drop to initial diameter of a drop. As the impacting velocity is increased the degree of deformation is increased. Thereby, the nucleation and growth rates are increased since the contacted surface area between the drop and the surface of substrate is increased.
Figure 5-11: Porosity versus Re number at two-different masses of drops.

*Figure 5-12* illustrates the surface morphology of SEM photos on the top part of the pastilles at various final impacting velocities which are experimentally measured by the high-speed camera. The impacting velocity is corresponding to Reynolds numbers which are varied ranging from 200 to 3000. Increasing the impacting velocities leads to larger surface area of pastilles in contact with cooling plate. Therefore, at high velocities as 1.23 and 1.85 m/s relatively big amounts of porosity are entrapped, because of the high degree of deformation and the high growth rate of pastilles. However, at low velocities as 0.17 and 0.28 m/s relatively small amounts of porosity are entrapped in the pastille, because of the low degree of deformation and the low growth rate of pastilles. Therefore, it can be concluded that the formation of pores is related to the Reynolds number.
5.5. Correlation between total porosity and overall growth rate

During the solidification process the growth rate of liquidus drop is extremely fast due to a high temperature gradient. The high nucleation and growth rate evokes constitutional pores in the surface and the layer of the pastilles. In this section the relationship between the growth rate and total porosity will be investigated. The relationship will be given to determine the processing conditions that are required in order to minimize the porosity in pastilles.

The overall growth rate, \( G_f \) is already introduced in chapters 2 and 3. As mentioned previously in equations 2-5 and 4-10, the layer thickness of pastille, \( x_s \) is an input taken from the measured data while the crystallization time, \( t_c \) can be numerically found. The overall growth rate, \( G_f \) can be derived as:

\[
G_f = \frac{x_s}{t_c} = \frac{\Delta T k_s x_s}{0.36 \rho f L D_{o}^{2} Re^{0.4}} (5-1)
\]
Here surface roughness ($R_a = 0.23$ mm) is fixed. And assumed that the spreading and rebounding phenomena of drops don’t contribute the formation of porosity. Figure 5-13 shows the relationship between the overall crystal growth rate and the total porosity. It is found that the total porosity has a tendency to increase as the overall crystal growth rate is increasing. This means that the pores and cracks are influenced by the crystallization kinetics (nucleation, growth rate). Especially, pores and cracks are strongly depended the growth rate of the pastilles. The total porosity of the pastilles is increased with the increase of the overall crystallization rate. In case of the pure Bisacodyl the overall crystal growth rate can be explained as a function of total porosity, $\Phi$ by a regression method:

$$G_f = 0.00067 \times 10^{0.0768\Phi}$$

(5-2)

By combing equations 5-1 and 5-2 the total porosity, $\Phi$ can be described as a function of Reynolds number and degree of subcooling.

$$\Phi \approx 13.02 \log \left[ \frac{k_s x_s}{\rho_l D_o^2} \Delta T \frac{Re}{Re_0}^{0.4} \right] + 47.13$$

(5-3)

The entrapped total porosity can be minimized with decreasing the overall growth rate since the degree of subcooling and the Reynolds number is decreased. The relationship between the total porosity and the overall growth rate of pastilles will contribute to the design of the drug delivery system and the selection of manufacturing parameters of pastillation process.
Figure 5-13: Total porosity versus overall crystal growth rate.