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Investigation of entrapped pore in the pastilles by a mercury porosimetery technique

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Abstract

The pore in pastilles was investigated which are produced by a pastillation technology. Mercury intrusion porosimeter and scanning electron microscopy (SEM) techniques were used for the investigation. The formation of micro-pores and cracks were in dependence of the manufacturing conditions of the pastilles (final impacting velocity, degree of subcooling and surface roughness of cooled substrate). The total pore is decreased with decreasing degree of subcooling, final impacting velocity and surface roughness of the cooled substrate. In order to design a drug delivery system and to select an optimum manufacturing parameter the relationship between overall growth rate of the pastilles and total pore was experimentally investigated. The total pore increased with increasing the overall growth rate of pastilles.

Keywords: Pore; Pastille; Mercury intrusion porosimetry; Pastillation technology

1. Introduction

In previous works (Kim and Ulrich, 2003) it was investigated how the knowledge of the contact angle of drops being deposited on a surface can help to control the desired size and shape of pastilles. Furthermore, the contact angle can use to predict the crystallization time in the design of a solidification technology. In this follow up work, the entrapped pore in the Bisacodyl pastilles was investigated.

A certain pore is often desired and of importance in medicines, catalysts or adsorbents. Many researchers (Bronfenbrener and Korin, 1997; Donchev and Ulrich, 2002; Donchev et al., 2002; Fukusako and Yamada, 1999; Fukasawa et al., 2001a, 2001b) have already studied the entrapment of pore for example in the

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area of ceramics, foods and pharmaceuticals. An entrapment of pore in the body of tablets was studied by researchers (Hogekamp et al., 2002; Paul, 2003; Westermarck et al., 1998). The pore is an important parameter to improve the clinical efficiency of drugs or to control its bioavailability. Tableting techniques are commonly used in the production of a solid complex of pharmaceutical materials. Under compressing pressure drug crystals agglomerate, thereby a certain pore is entrapped in the solid complex. The solid complex is, however, still not always in an optimal condition for the medicine since there can be problems such as instability of tablets, selection of binders and excipients (additives) which can lead to, non-wanted side-effects. To help solving these problems here a solidification technology is introduced.

A solidification technology is an important step to control the transition from the liquid into the solid phase in such a way that the products are obtained in an appropriate form for their transport, storage and subsequent use. The solidification should be done by an economical process, employing the smallest and the simplest equipment possible. The transformation of a melt into a solid, which should have a certain form and specific physical properties is an important operation. In most cases the solidification is a crystallization process without the aim of separation (Delplanque and Rangel, 1997; Rangel and Bian, 1997; Prunet-Foch et al., 1998; Wang et al., 2002; Wintermantel and Wellinghoff, 2001). Hence just a solidification. An application of this technology in pharmaceutical industry is increasing, especially, in production of crystalline-formed medicines. A pastillation process (e.g., Rotoformer© system, Kaiser SBS System) is one of the solidification technologies to bring melts into dispersed solid form in high-speed almost monosized and dust free. In case of pastille production, many drops are positioned on a cooled surface. The pastillation of melts refers to the disintegration of the liquid directly into monosized individual volumes, which then solidify in most cases even. In dependence on the dispersed volume of the drops, the physical properties of the melt and the temperature differences the drops are flattened to a certain extent. The solidified drop therefore has a typical pastille-like flattened hemi-spherical shape (Buelau and Ulrich, 1998; Bülau, 1999). Crystalline-formed medicines should improve the stability and retard the drug dissolution rate.

In the pastillation process, micro-pores and cracks should be formed in the bodies or on the surface of pastilles since the liquid drop crystallizes what is going inline with a density change. The formation of pore is influenced essentially by the manufacturing conditions of pastilles such as the composition of the materials, the temperature difference between cooled substrate and the melting point of the materials (i.e., degree of subcooling), the surface property of used cooled substrate and the physical properties of the materials. The most important influencing factors are the composition of the materials and the degree of subcooling. Some researchers (Budnikov and Kharitonov, 1969; Emelyanov, 2001) investigated the kinetic equations of pore formation in granules of mineral materials with additives. The obtained equations are recommended for mathematical modelling of a pore formation process. Liu et al. (1994) have also reported results of a numerical simulation of a formation of micro-pore to be expected in the deformation and solidification behaviour of single drops taking place on a cooled substrate. However, they have only studied the entrapped pore in granules/pastilles by numerical modelling and simulation. In this work, therefore, the entrapped pore (micro-pores, cracks) in the pastilles will be experimentally investigated under consideration of the manufacturing conditions of the pastilles and physical properties of the materials. Furthermore, the pore structure and the pore size distribution of the pastilles will elucidate. Especially, in the focus are, however, the manufacturing conditions and how they affect the formation of micro-pores and cracks. Finally a relationship between total pore entrapped in the pastilles and growth rate of the pastilles is introduced.

2. Material and methods

Bisacodyl pastilles were manufactured by a pastillation process. Here investigated parameters are degree of subcooling, surface roughness of used substrate and impacting (final) velocity. The schematic diagram of the experimental apparatus of the pastillation process and the detailed technique are described by Kim and Ulrich (2003). The monosized hemi-spherical Bisacodyl pastilles are shown in Fig. 1. A scanning electronic microscope (SEM) technique was also used to mea-

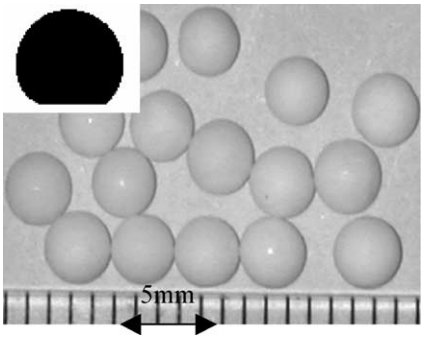

Fig. 1. Monosized hemi-spherical Bisacodyl pastilles.

sure the surface morphology and the structure of the pore.

A mercury porosimeter technique {Thermo Finnigan (Pascal 140 and 440) Italy} was used to measure the total pore, the pore size distribution and the pore structure of the Bisacodyl pastilles. The total pore volume, the total pore surface area, the mean pore diameters and the pore size distributions of pastilles are 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 SEM technique is employed to support the results of mercury porosimeter.

3. Results and discussion

3.1. Structure and pore size distribution

3.1.1. Pore structures of pastilles

Mercury porosimeter data can enable the calculation of the specific surface area (m^2/g) of the samples. There are four models available for the surface area calculation the cylindrical, conical, plates and spherical model, which can be distinguished by intrusion or extrusion curves between the cumulative volume of mercury and the compression pressure.

Fig. 2 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 (refer in Instruction manual porosimeter, (Thermo Finnigan, Italy, 2002)). Moreover, these types of pores are commonly found in natural materials, for instance in carbon coke, rocks and soils. The model shows that the pores are located on the surface and interior of the pastilles. The intrusion curve features a quite low 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.

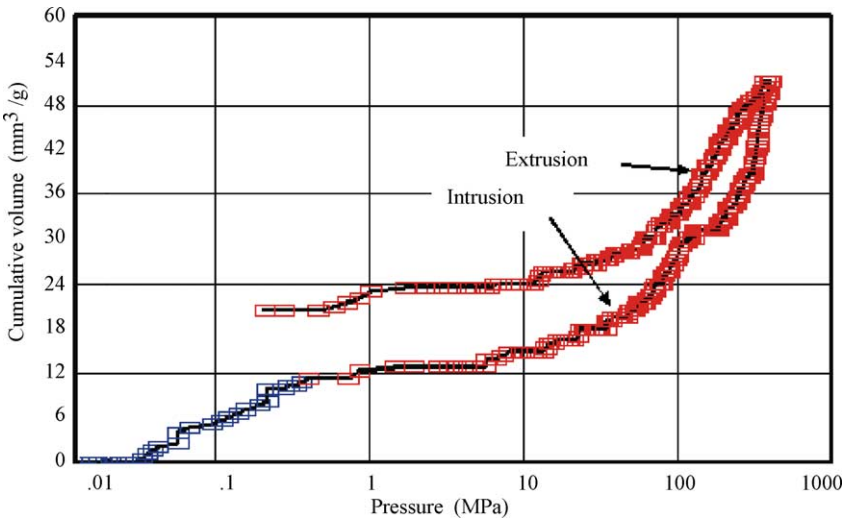

Fig. 2. Type of pore model of pastilles according to the cumulative volume and compressing pressure.

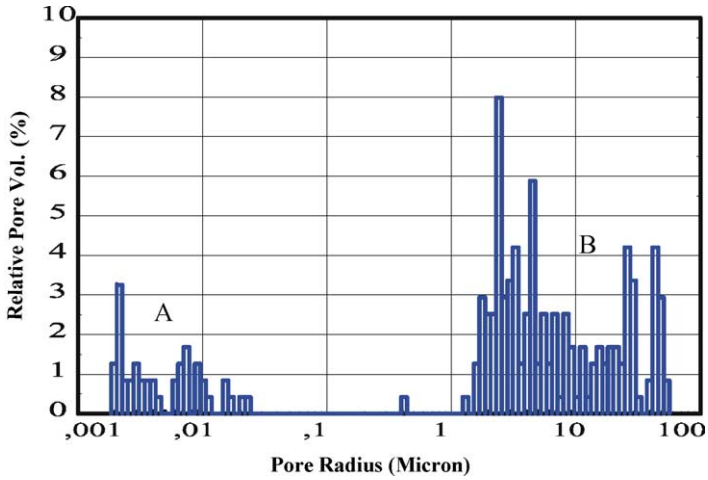

Fig. 3. Pore size distribution of pastilles and tablets (radius range: 0.001–100; total bars in the histograms: 100).

3.1.2. Pore size distribution

The bar of the histograms numbers and dimensions can be generated automatically by the software (Pascal 140 and 440) according to the radius limit selection given by operating conditions. Fig. 3 shows the relationship between relative pore volume and pore radius of the pastilles. From the histogram the pore size distribution of the pastilles was constituted as bimodal. It can be elucidated that the first group of bars (A) is the occurrence of pore due to rapid nucleation on the bottom side of the pastille. Nucleation usually takes place concentrically around the starting point of the cooled surface. As a consequence of high heat transfer, fast crystal growth takes place. However, the dominant pore in the pastilles is placed in a pore diameter range between 1 and 20 μm (B). The second group of bars are cracks and micro-pores. The growth rate during the crystallization process is extremely fast due to the high temperature gradient. A high growth rate evokes constructional micro-pores in the layer and cracks on the surface of the pastilles. It is, however, found that the total pore in the pastilles was less than 10%. Here the total pore (%) was defined as the ratio of the sample void volumes (internal and external pore) to its external volume (inverse of bulk density).

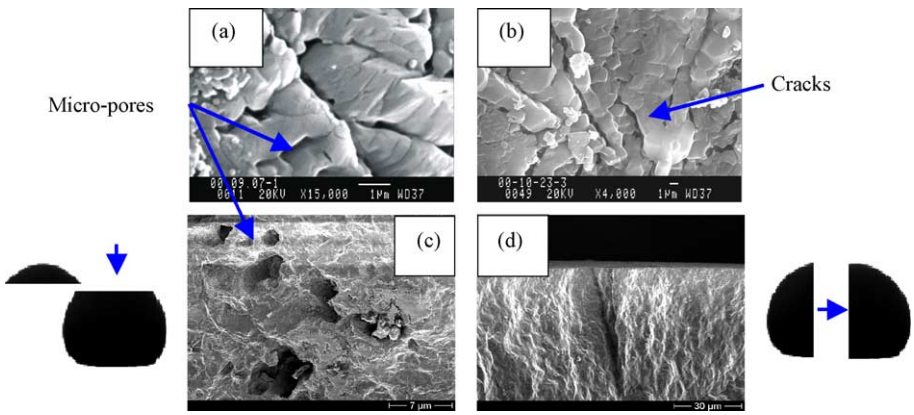

Fig. 4. SEM photos: (a) surface morphology (magnification ×15000), (b) surface morphology (magnification ×4000), (c) grade cross-section (magnification ×1000) and (d) cross-section of pastille (magnification ×500).

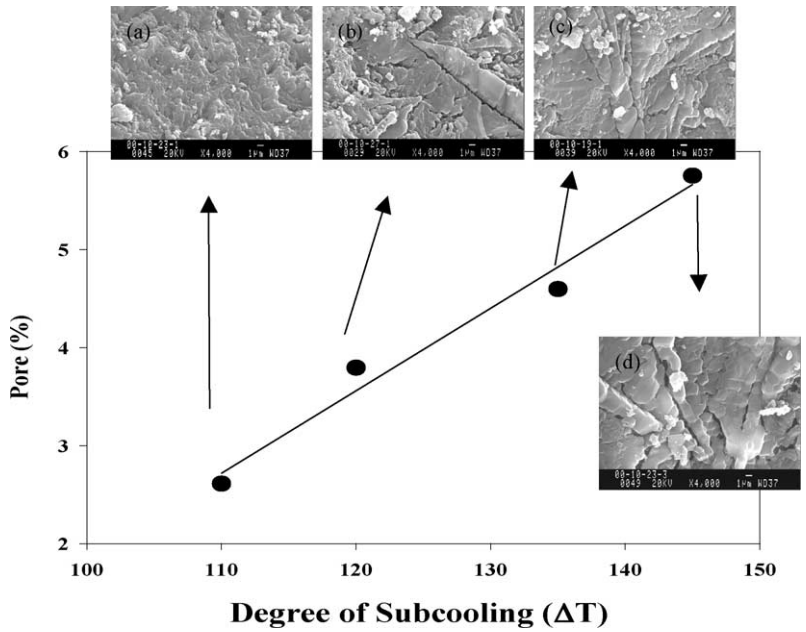

Fig. 5. Total pore vs. degrees of the subcooling and surface morphology of the top part of the pastille at different degrees of subcooling (ΔT): (a) 113 K, (b) 123 K, (c) 133 K and (d) 143 K (magnification ×4000).

Fig. 4 shows SEM photos of the surface morphology of the pastilles, grade cross-sections and cross-section of the pastilles. It can be visually confirmed by the SEM photos (Fig. 4(a–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, it can be observed that pores are formed in conical form (see Fig. 4(d)). Unfortunately, it is impossible to estimate the length and width of pore depth.

3.2. Total pore

While the molten drop impacts and crystallizes, the cracks and the micro-pores are generated on surface or body of the pastilles. Processing parameters of pastilles have an effect the occurrence of micro-pores and cracks. The main factors here are: temperature gradient between the molten and the surface temperature of cooled substrate (degree of subcooling), these impacting velocity (Reynolds number of impacting drop) and surface properties of the substrate. It will be discussed how conditions of pastilles affect the surface structure and the total pore. However, the pore size distribution is not discussed in this paper due to the difficulty of distinguishing.

3.2.1. Effect of degree of subcooling

To investigate the total pore, pastilles were produced at different temperatures of the cooled surface. All other crystallization parameters were 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. Fig. 5 shows SEM photos of the surface morphology of the top part of a pastille and the total pore at different degrees of subcooling. Fig. 5(a) are the top part of the pastilles at a relatively low degree of subcooling ($\Delta T = 113$ K) shown where no individual crystals and cracks can be identified. On the other hand is shown in Fig. 5(c and d), the cracking phenomenon with increasing degree of subcooling ($\Delta T = 133$ and 143 K). This is caused by relatively high nucleation and growth rates at the initial stage of crystallization. According to the relationship between the total pore and the degree of subcooling, it can be confirmed that the total pore increased with increasing degree of subcooling.

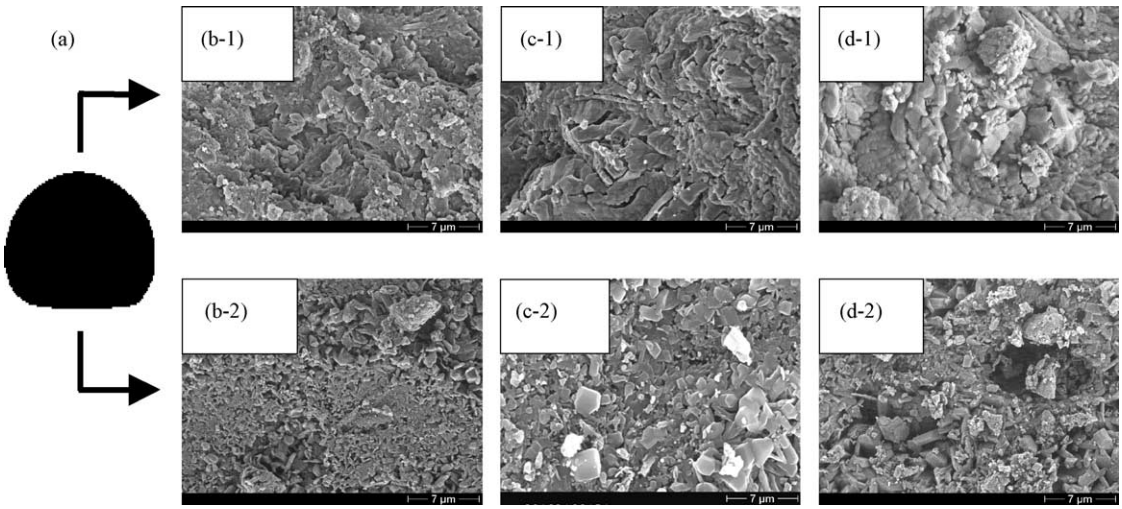

Fig. 6. SEM photos of the top and the bottom of pastilles (magnificaton ×4000) resulting from different cooled plates. (a): Side view of pastille, (b-1) and (b-2): surface morphologies of top and bottom of pastille at a smooth plate roughness (R_a = 0.15), (c-1) and (c-2): surface morphologies of top and bottom of pastille at a medium plate roughness (R_a = 0.23), (d-1) and (d-2): surface morphologies of top and bottom of pastille at a course plate roughness (R_a = 0.31).

3.2.2. Effect of surface properties

Fig. 6 shows SEM photos of the surface morphology of the top and at the bottom of the pastilles processed at 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. The SEM photos see Fig. 6 clearly show that the size of crystals/pores at the bottom of the pastilles are smaller than those of the top part of the pastilles. Therefore, a relatively high amount of the pore are incorporated at the top part of pastille compared to the bottom part. van der Gum (2002) numerically explained that the pores in the top part of surface are approximately 10 times larger than the pores at the bottom surface of the pastilles. The mentioned effect is, however, influenced by the processing conditions and the physical properties of materials.

The size and the structure of pores on top and bottom of the pastilles are investigated at different surface roughness. Surface roughnesses are chosen ranging from 0.15 to 0.31 μm. According to Fig. 6 (b-1)–(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.

Fig. 7 illustrates a pore resulting from experiments of three different surface roughnesses. Each sample was analysed 3 times under identical conditions. Fig. 7 shows that the total amount of pores increased with increasing the surface roughness. This was confirmed by SEM photos of Fig. 6.

3.2.3. Effect of final impacting velocity (Reynolds number)

Fig. 8 shows the correlation between the total pore and the Reynolds number of two-different masses of the drops. The impacting velocity is corresponding to Reynolds numbers, which are varied ranging from 200 to 3000 for the falling (impacting) drops. The Reynolds number used here is already defined in previous work (Kim and Ulrich, 2003). 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. Fig. 8 shows that the total pore is logarithmically increasing with the 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 de-

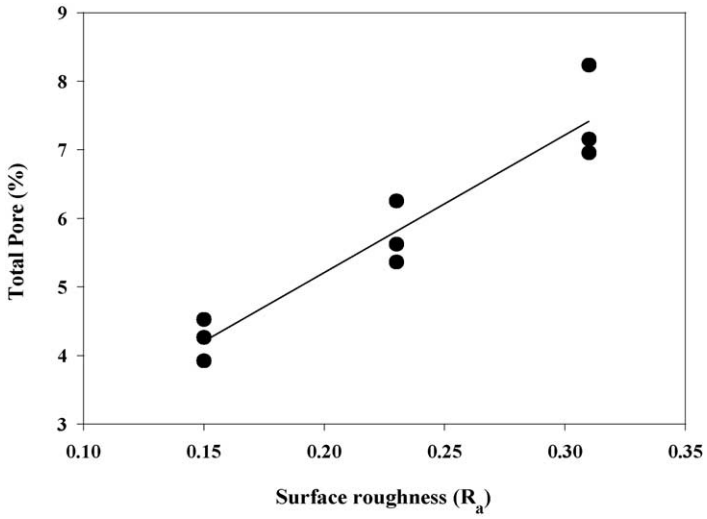

Fig. 7. Total pore of pastilles verses surface roughness of three different cooled plates.

formation 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.

Fig. 9 illustrates the surface morphology by SEM photos of the top part of the pastilles at various final impacting velocities, which are experimentally measured by a high-speed camera. The impacting velocity is corresponding to Reynolds numbers, which are varied ranging from 200 to 3000. In the case of low impacting velocities of 0.17 m/s only relatively small amount of pore are entrapped in the pastille, because of a decreasing surface area in contact with the cooling plate. However, at the low velocities (1.85 m/s) relatively big amounts of pore are entrapped due to the high degree of deformation Therefore, it can be con-

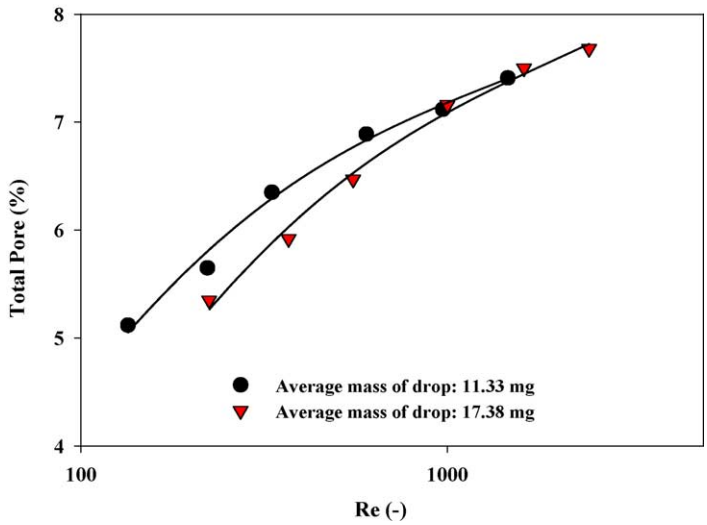

Fig. 8. Total pore vs. Re number at two-different masses of drops.

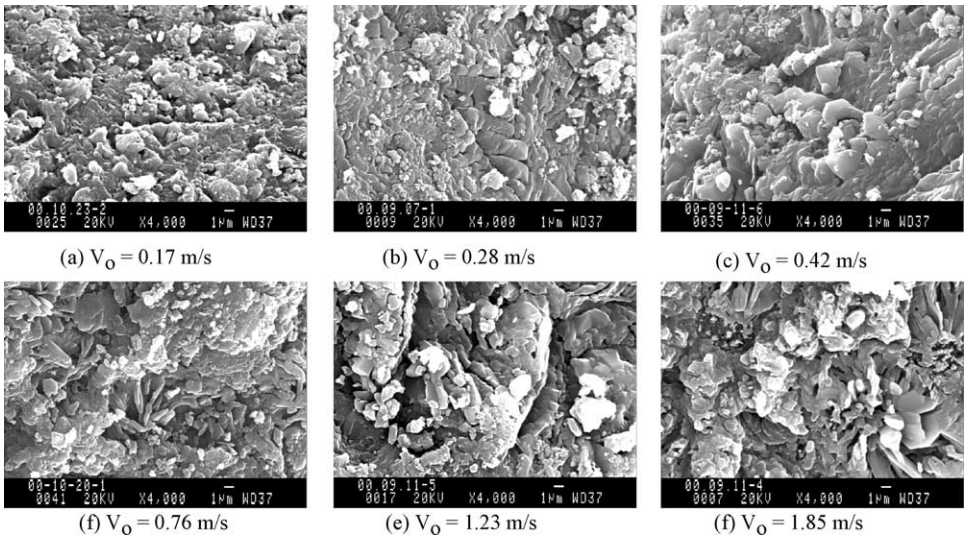

Fig. 9. Surface morphology shown by SEM photos at the top of pastilles at various impacting velocities (v_o): (a) 0.17 m/s, (b) 0.28 m/s, (c) 0.42 m/s, (d) 0.76 m/s, (e) 1.23 m/s and (f) 1.85 m/s (magnification ×4000).

cluded that the formation of pores can be desired by the Reynolds number of impacting drop.

3.3. Correlation between total pore and overall growth rate

During the crystallization process the crystal growth rate in liquid drop is extremely fast due to a very high temperature gradient. The high nucleation and growth rate evokes constitutional pores in the surface and the layer of the pastilles.

Prior study (Liu et al., 1994) has reported results of a performed numerical simulation on the formation of micro-pore. They investigate quantitatively the effect of processing parameters on the formation of micro-pores. The micro-pore are calculated using the data of the VOF (volume of fluid) function. The micro-pore was defined as the volume fraction of the micro-voids that were entrapped in the pastilles during deformation and rapid crystallization. The full Navier-Stokes equations coupled with VOF functions were solved to determine the exact movement of droplets. The two-phase flow continuum model and the two-domain method were used for the flow problem with a growing solid layer and for the thermal field and solidification problem. On the basis of the numerical results, the possible mechanisms governing the formation of micro-pores during the flattening and interaction in the drop were discussed. However, in the study of Liu et al. (1994) only a numerical simulation was undertaken. Therefore, the experimental investigation of the relationship between the pore and the crystallization kinetic (nucleation, growth rate) are still needed for a verification. The relationship between the growth rate and total pore is, therefore, investigated here. The relationship will be given to determine the processing conditions that are required in order to minimize the pore in the pastilles.

Here an overall growth rate, G_f is introduced. It is defined as the ratio of the vertical height of the pastille (crystalline layer thickness), x_s to the crystallization time (overall solidification time), t_c. It can be expressed as follows:

$$G_f = \frac{x_s}{t_c} \quad (1)$$

The crystalline layer thickness, x_s is an input of the measured experimental data and the crystallization time, t_c can be expressed numerically as a function of Reynolds number and degree of subcooling. Therefore, the pore, Φ can experimentally be obtained from the relationship and be expressed by a function of the crystal growth rate:

$$\Phi \approx F(G_f) \quad (2)$$

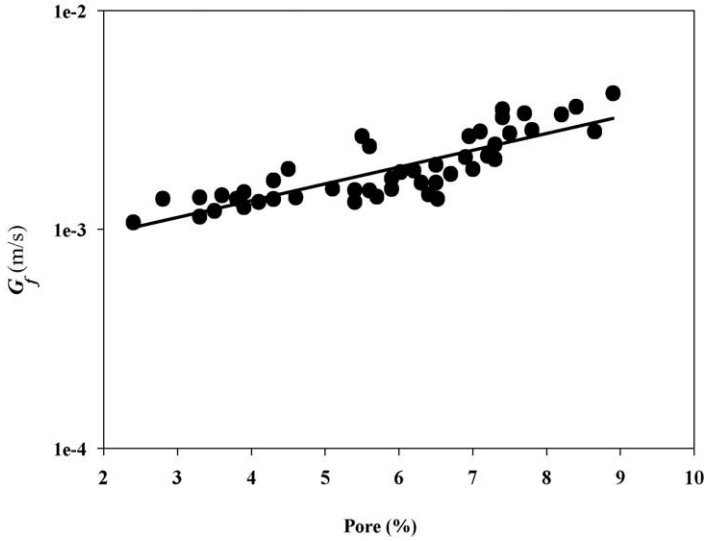

Fig. 10. Overall crystal growth rate vs. total pore.

As described in literature (Kim and Ulrich, 2003), in case of pure Bisacodyl the crystallization time, t_c can be numerically found as follows:

$$t_c = \frac{0.36\rho_l L Re^{-0.4} D_o^2}{k_s(T_{mp} - T_{sub})} \quad (3)$$

Here ρ, L, D_o and k_s are density, latent heat due to crystallization, initial drop diameter and thermal conductivity, respectively. Layer thickness of pastille, x_s is an input taken from the measured data. Therefore, the overall growth rate, G_f can be derived from equation (1):

$$G_f = \frac{x_s}{t_c} = \frac{\Delta T k_s x_s}{0.36\rho_l L D_o^2} Re^{0.4} \quad (4)$$

Fig. 10 shows the relationship between the overall crystal growth rate and the total pore. It is clearly to be seen that the total pore has a tendency to increase as the overall crystal growth rate is increasing. This means that the micro-pores and cracks are influenced by the crystallization kinetics (nucleation, growth rate). Especially, micro-pores and cracks strongly depended on the growth rate of the pastilles. The total pore of the pastilles increased with increasing the overall crystallization rate. In case of the pure Bisacodyl the overall crystal growth rate can be described as a function of total pore, Φ by a regression method:

$$G_f = 0.00067 \times 10^{0.0768\Phi} \quad (5)$$

By combning Eqs. (4) and (5) the total pore, Φ can be described as a function of Reynolds number and degree of subcooling.

$$\Phi \cong 13.02 \log\left[\frac{k_s x_s}{\rho_l L D_o^2} \Delta T Re^{0.4}\right] + 47.13 \quad (6)$$

The total pore can be minimized with decreasing the overall growth rate since the degree of subcooling and the Reynolds number is then decreased, too.

4. Conclusion

The entrapment of pore in pastilles was investigated in order to determine the total pore, the pore structure and the pore size distribution. A mercury intrusion porosimeter and a SEM technique are used. It is found that the pore size distribution of pastilles is bimodal and the pastilles modelled by a conical pore structure. The dominant pore in the pastilles is the cracks and micro-pores, which are placed in a pore diameter range between 1 and 20 μm. It is experimentally found that the processing parameters of the pastilles influence the occurrence of micro-pores and cracks while the molten drop impacts and crystallizes. The total pore

is increased with increasing the degree of subcooling, the Reynolds number and the surface roughness of the cooled substrate. The former is explained by the crystallization kinetic (growth rate). A relationship between overall crystal growth rate and total pore is experimentally proposed to minimize total entrapped pore of the pastilles. The total pore is increased with increasing overall growth rate of a pastille. The data of the calculated pore could be used the design of the drug delivery system and to select the optimum manufacturing parameters of pastillation process, which are determination of the speed and the operating temperature of cooling belt.

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