**This is a pre- or post-print of an article published in
Schrank, S., Kann, B., Windbergs, M., Glasser, B.J.,
Zimmer, A., Khinast, J., Roblegg, E.
Microstructure of calcium stearate matrix pellets: A
function of the drying process (2013) Journal of
Pharmaceutical Sciences, 102 (11), pp. 3987-3997.**

Microstructure of Calcium Stearate Matrix-Pellets: A Function of the Drying Process

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ABSTRACT

Drying is a common pharmaceutical process, whose potential to modify the final drug and/or dosage form properties is often underestimated. In the present study, pellets consisting of the matrix former calcium stearate incorporating the active pharmaceutical ingredient ibuprofen were prepared via wet extrusion and spheronization. Subsequent drying was performed by either desiccation, fluid-bed drying or lyophilization and the final pellets were compared with respect to their microstructure. To minimize the effect of solute ibuprofen molecules on the shrinking behavior of the calcium stearate, low ibuprofen loadings were used, as ibuprofen is soluble in the granulation liquid. Pellet porosity and specific surface area increased during desiccation, fluid-bed drying and lyophilization. The inlet-air temperature during fluid-bed drying affected the specific surface area, which increased at lower inlet-air temperatures rather than the pellet porosity. The in-vitro dissolution profiles were found to be a non-linear function of the specific surface area.

Overall, the microstructure, including porosity, pore size and specific surface area, of calcium stearate pellets was a strong function of the drying conditions.

1. INTRODUCTION

Drying is a standard unit operation in pharmaceutical processing with the goal to remove solvents (most often water) from wet materials providing sufficient product stability and enabling further processing. For example, pellets, manufactured by wet extrusion followed by spheronization still contain a certain amount of liquid after fabrication and thus, require a final drying step. Similarly, the product of high-shear granulation, i.e., pharmaceutical granules, is dried in a subsequent step. In literature it is described that drying of pellets can be performed in various types of equipment, including fluid-bed dryers,¹⁻²⁰ freeze dryers, ovens, microwave dryers, filter-bed dryers and other individually designed dryers.³⁴ In the pharmaceutical industry the fluid-bed drying process is of greatest relevance, as it provides high drying rates thereby, ensuring short drying times and reduced process costs. However, fluid-bed drying may not always yield in desired final dosage form properties. It is well-known to the pharmaceutical practitioner that the drying step may considerably alter the pellet's final properties, thus, affecting both, the excipient structure and the release-rate of the active pharmaceutical ingredient (API). As such, the bioavailability of the API in the human body is affected. Nevertheless, only few systematic studies of this unit operation have been published in literature, and a mechanistic understanding of the impact of drying on pellet properties is still a field of active research.

Excipients swelling in the granulation medium (and thereby, taking up liquid) are frequently used for wet extrusion/spheronization, as they ensure suitable rheological properties of the wet mass and the resulting extrudates. The opposite behavior (i.e., shrinkage) occurs upon solvent removal. For example, it was reported that several extrusion/spheronization excipients, including microcrystalline cellulose, cellulose,³⁸ pectinic acid,⁸ calcium stearate¹⁶ and κ-carrageenan,¹² can swell upon contact with liquid and tend to shrink (to a certain extent) during drying. Moreover, it was observed that the final porosity and the structure of the porous matrix strongly depend on the drying technique and/or drying conditions.

With regard to the drying rate, drying processes have two main periods: the constant rate period (CRP) and the falling rate period (FRP). The CRP is characterized by liquid

evaporation from the surface facilitated by sufficient liquid transport towards the surface, which in porous media occurs due to capillary pressure gradients with a flow rate following a modified Darcy's law. In this period, the surface is still wet, yet the moisture levels are decreasing. Once the liquid recedes into the pores, a drying front develops and liquid evaporation takes place mostly inside the pores. This condition is called the falling rate period (FRP). Subsequently, the vapor is transported through the pores towards the surface via diffusion and convection. In general, the FRP, where the outer shell of the particle is dry, is only observed under fast drying conditions. For mild drying conditions, liquid transport to the surface is usually sufficient to keep the surface wet. One further effect is the impact on the temperature: as long as the material is wet the temperature maintains the (low) "wet-bulb" temperature, due to endothermic evaporation. Once the material is dry, it approaches the (higher) temperature of the drying medium (and may soften if the temperature is sufficiently high).

Shrinkage occurs during reduction of the liquid content of a material, as mentioned above. Thus, shrinkage takes place in many materials upon solvent removal, i.e., during drying. During the CRP, this shrinkage occurs throughout the entire pellet as the whole pellet is wet, yet the moisture level is decreasing. Even though stress is involved in this process, this effect may be considered small as long as the whole pellet uniformly deforms (shrinks). Once the material is dry, it does not shrink anymore. Hence, as soon as the FRP starts, the outer (dry) region of the pellet resists deformation. If the internal stress overcomes the yield stress of the outer, dry shell, the particle still shrinks or deforms irregularly, as often observed in many materials (e.g., organic materials⁴¹). If the outer shell resists stress, the outer diameter of the pellet remains constant. Then, shrinkage occurs only inside the pellet, associated with an increase of internal porosity. Thus, it was conjectured that the main size reduction of pellets occurs during the constant rate period, and the internal porosity increases during the falling rate period. These effects are schematically illustrated in Figure 1. Clearly, the extent of shrinkage determines the pellet's microstructure and in turn the dissolution and compaction behavior.

In addition to impacting the microstructure, drying may cause a migration of API molecules that are dissolved in the granulation liquid, leading to non-uniform final API distribution profiles within the pellet.² In the literature, it was shown that the API distribution profile can significantly influence the in-vitro dissolution behavior. In non-spherical pharmaceutical granules, API migration was found to be induced by the drying technique.⁴⁴ However, different drying conditions (i.e., drying temperature) for the same drying technique do not necessarily affect API migration, most probably because the drying regime does not change.⁴⁵ It was even suggested that the burst effect, which is frequently observed during dissolution testing of some delivery forms, derives from API migration during drying and the resulting API accumulation close to the surface.⁴⁶ Physicochemical properties, including the API solubility, viscosity of the granulation liquid and the excipient's properties have an additional impact on the extent of API migration.

The present study addresses the effect of the drying process on the shrinking behavior (and consequently on the microstructure) of the pellet matrix (calcium stearate in the present case). Pellets were prepared via wet extrusion and spheronization with subsequent drying using three techniques: desiccation, fluid-bed drying (under different process conditions) and lyophilization. Since it was assumed that drug migration may influence the shrinking behavior due to osmotic pressure (generated by a concentration gradient after the API moved towards outer regions), a low ibuprofen loading (i.e., 3.5%) was used to prevent interactions. Consequently, the studied model formulation mimics the behavior of swellable extrusion/spheronization matrix excipients during drying; while any interactions between matrix shrinkage and API migration are not accounted for.

2. MATERIALS AND METHODS

2.1 Pellet Preparation

The formulation and process parameters were adapted from our previous studies. A two-component system based on vegetable calcium stearate (CaSt, by Werba-Chem GmbH, Vienna, Austria) and ibuprofen (GL Pharma, Lannach, Austria), was used. The drug loading was 3.5% (w/w). CaSt and ibuprofen were dry-blended in a TURBULA® T2F mixer (Willy A Bachofen AG Maschinenfabrik, Muttenz, Switzerland) at 50 rpm for 20 min. The blending parameters were optimized in pre-studies to ensure drug content deviation of below 5% from the theoretical ibuprofen loading (data not shown).

As it is described in literature that extrusion/spheronization parameters, including the spheronization time⁵² may impact the pellet microstructure, all process parameters throughout wetting, extrusion and spheronization were kept constant. Thereby, drying induced changes in the final pellet microstructure could be elucidated. 100 g of the powder mixture were manually wetted with 50 g of 50% (w/w) ethanol. 50% (w/w) ethanol was previously shown to result in favorable pellet properties. The extrusion/spheronization process was performed using the same equipment and parameters as previously described.¹⁶ The optimum spheronization time, which provides a narrow size distribution and appropriate sphericity (i.e., above 0.8), was six minutes.

2.1.1 Drying Procedures

After spheronization, three drying techniques were applied:

- desiccation (D) over silica gel at ambient temperature and pressure,
- fluid-bed drying (FB) at two different inlet-air temperatures (20 °C and 50 °C) and
- lyophilization (L) under vacuum (pressure below 6 mbar) and ambient temperature.

For each drying method, two batches were prepared and drying was continued until the final moisture content was below 1%. Additionally, the shrinking behavior, i.e., reduction in pellet outer volume (envelope volume), was determined by measuring the bulk (non-consolidated) volume of 50 g pellets before and after drying.

For desiccation, pellets were transferred into a flat-bottom bowl with a bed diameter of 17 cm and a height of 0.8 cm. The moisture content was determined as a function of time by measuring the pellets' weight after certain time intervals. The moisture content drop over time was calculated based on the dry pellets mass.

Fluid-bed drying was performed in a Mycrolab apparatus (Oystar Hüttlin, Schopfheim, Germany) equipped with a compressor to provide a constant inlet air flow of 40 m³/h. To evaluate the drying profile, samples of 1 g were manually taken every five minutes from the container opening, and the moisture content was determined offline with a moisture halogen analyzer. To exclude any possible physical and chemical interactions between CaSt and ibuprofen at the elevated inlet-air temperature of 50 °C, differential scanning calorimetry (DSC) measurements were performed with a DSC 204 F1 Phoenix (Netzsch, Selb, Germany) under nitrogen atmosphere. CaSt and ibuprofen were mixed at a ratio of 1 to 1 to increase the possibility of interactions. Samples were placed into aluminium pans closed with pierced lids.

Drying via lyophilization was performed in a LYOVAC GT 2 (Steris, Köln, Germany). The pellets were transferred into flat, kidney-shaped bowls, immersed into liquid nitrogen (-196 °C) for 15 min prior to drying and were then lyophilized for 24 hours.

2.2 Pellet Characterization

Pellet-size distributions were evaluated via sieve analyses according to Ph. Eur. 6.0 2.9.38. For further characterization studies, the yield fraction (defined between 1.4 and 1.8 mm) was divided into representative samples with a rotary cone divider. The shapes and sizes of at least 500 pellets were analyzed using the dynamic image processing system QicPic (Sympatec, GmbH, Clausthal-Zellerfeld, Germany) operated with the dry dispersing unit Rhodos/L. Size (Ferret's diameter) and shape (aspect ratio, AR) distributions (Q₃) were determined. Each batch was analyzed in triplicate.

The pellet microstructure was characterized in terms of pellet density, specific pellet inner-surface area and pellet porosity. Pellet density and porosity were determined via helium

pycnometry and mercury porosimetry, as described in our previous work.¹⁶ The specific surface area was evaluated via BET adsorption method using the ASAP 2000 (Micromeritics Norcross, USA) system and nitrogen as analytical gas. Prior to measurements, samples were degassed under vacuum. Nitrogen adsorption occurred at -196 °C (temperature of liquid nitrogen), and the volume of nitrogen adsorbed was recorded over a range of relative pressure between ≈ 0.05 and ≈ 0.2 .

A scanning electron microscope (Zeiss Ultra 55, Carl Zeiss NTS GmbH, Oberkochen, Germany) was used to evaluate the morphology of the pellet surface and the pellet cross-section. For that purpose, pellets were manually cut with a scalpel. Prior to scanning electron microscopy (SEM), all samples were sputter-coated with chromium.

The mechanical properties of the pellets were investigated with respect to the crushing strength. Here, a rheometer (MCR 301, Anton Paar, Graz, Austria) equipped with a parallel-plate measuring system was used in the non-rotational mode. The details of the method were previously published.⁵³ For each batch, 50 individual pellets were evaluated.

To determine the ibuprofen distribution throughout the pellets, Raman spectroscopy was performed with a confocal Raman microscope WITec alpha 300R+ (WITec GmbH, Ulm, Germany) using an implemented Zeiss objective with a 10-fold magnification (N.A. 0.25). Samples were manually cut in half with razor blades and fixed on glass slides. Raman spectra were acquired every 5 μm along the x- and y-axes at an excitation wavelength of 532 nm (Nd:YAG laser, operated at 10 mW) and an integration time of 0.3 sec. Subsequently, the spectral data sets were processed and converted into false-color images by cluster analysis using the software WITec Project Plus showing ibuprofen in red, whereas CaSt is represented in blue color.

In-vitro dissolution studies were carried out in a United States Pharmacopoeia (USP) apparatus I (Pharma Test Type PTWS III C, Pharma Test Apparatebau AG, Hainburg, Germany). According to the USP XXVIII monograph for ibuprofen tablets, 900 ml of pH 7.2 mono potassium phosphate buffer was used as dissolution medium. In order to ensure sink conditions throughout the experiment, a sample mass of 500 mg was selected. The

temperature was 37 ± 0.5 °C and the stirring speed was set to 100 rpm. Samples of 1 ml were withdrawn from the dissolution media at specific time intervals and analyzed via reversed-phase high-performance liquid chromatography (RP-HPLC). The HPLC method's details are described elsewhere [53](#). Each batch was analyzed at least three times.

3. RESULTS AND DISCUSSION

3.1 Pellet Preparation

Pellets were prepared via wet extrusion/spheronization. During the wetting step, two processes occur simultaneously: swelling of calcium stearate in the granulation liquid (i.e., 50% ethanolic solution) and/or ibuprofen dissolution in the granulation liquid. It was previously reported by our group that at ambient temperature and pressure calcium stearate swells in ethanol by a factor of 3.96 (volume-based) at equilibrium, i.e., the volume increases almost 4-fold.¹⁶ As in each experiment 100 g of the powder mixture (3.5% API) was used, CaSt weight was 96.5 g, which corresponds to 482.5 ml (poured bulk density of 200 g/l, data provided by the supplier). 50 g of 50% ethanol solution were used as granulation liquid, which approximately corresponds to 55 ml of 50% ethanol solution. Taking into account that CaSt powder can absorb a volumetric ethanol amount matching three times the powder volume, it can be assumed that in our experiments CaSt did not swell to a maximum.

From solubility experiments it was determined that the ibuprofen equilibrium solubility was 48 g/l.¹⁶ Each powder mixture contained 3.5 g ibuprofen. Thus, if the whole granulation liquid was available for dissolution, 75% of ibuprofen, corresponding to 2.64 g, could be dissolved in the 55 ml of the solvent. However, since a significant part of the solvent was absorbed by CaSt (i.e., inducing swelling) only a small fraction of ibuprofen was dissolved. It can be assumed that the major part of ibuprofen was present in the solid state. The moisture content, which was around 32% after wetting, dropped during the entire preparation process to 19% as a result of liquid evaporation (due to the open operating system). Consequently, after spheronization the amount of dissolved ibuprofen was likely to be even further decreased.

3.1.1 Drying Procedures

Drying curves (weight-based) and drying rates for desiccation and fluid-bed drying are shown in Figure 2. As expected, the graph indicates a much slower drying in the dessicator. During

desiccation, the rate of evaporation (i.e., dX_m/dt) was nearly constant for 8 hours (Figure 2a). After these 8 hours, drying was somewhat faster, yet decreased again to the initial level. Given the large standard deviation of the data at intermediate times, it can be concluded that the drying rate was rather constant over the whole process, indicating that internal transport was not rate-limiting. Thus, drying occurred in the CRP throughout the process⁵⁴ and the pellets fairly dried uniformly over the entire diameter.

During the fluid-bed drying processes, a CRP (Figure 2b) was not observed. This is typical for high drying rates, where the internal transport of liquid rather rapidly limits the transport of liquid to the surface.⁵⁵ The drying rate dropped promptly, indicating that the total drying process only took place in the FRP regime. (However, it is possible that a very short initial CRP occurred, shorter than the sampling time). The inlet-air temperatures (20 and 50 °C) had no significant influence on the drying rate (Figure 2b), as the mass transfer coefficients in the fluid-bed are very high, resulting in fast mass transfer and drying.

From the theoretical discussion above it can be concluded that the different drying conditions should have a different impact on the shrinkage behavior and thus, on the pellet volume. Material drying in the CRP should have a stronger reduction in pellet diameter and the corresponding volume. Indeed this was observed during our studies (Table 1): The pellet bulk volume was measured prior and after desiccation and it was found that pellets shrunk by $20.3 \pm 2.40\%$. In contrast, during fluid-bed drying the volume shrunk by 16.3 ± 1.91 and $15.7 \pm 0.743\%$ for an inlet-air temperature of 20 °C and 50 °C, respectively, which is significantly less than the shrinkage observed during desiccation. (Shrinking during fluid-bed drying is also in accordance with studies reporting that pellets do shrink during fluid-bed drying).

Lyophilization caused only little shrinkage; i.e., reduction in pellet volume by $3.77 \pm 0.693\%$ (Table 1). In general, lyophilization can be subdivided into three stages; i.e., freezing of the sample, primary drying and secondary drying.⁵⁶ During primary drying, which constitutes the largest part of the lyophilization process, the granulation liquid is removed via sublimation. During secondary drying solvent that did not freeze is removed by desorption from the solute phase.

As the pellets were frozen rapidly in liquid nitrogen (cooling rate of approximately 250 K/min),⁵⁷ pellet shrinkage was minor. This is supported by Balaxi et al.²² and Gomez-Carracedo et al.²⁶, who found that final pellet diameters increased with decreasing freezing temperature.

3.1.3 Differential Scanning Calorimetry

Figure 3a depicts DSC thermograms of the individual powders, as well as the physical powder mixture (ibuprofen and CaSt at a ratio of 1 to 1) in the dry state and wetted with ethanol (i.e., part of the granulation liquid). The DSC measurements were reproducible; for each sample one representative thermogram is shown. The characteristic peaks of ibuprofen and CaSt (Figure 3a curves 1 and 2) are in accordance with literature; for detailed description the reader is referred to elsewhere. The mixture of ibuprofen and CaSt (Figure 3a thermogram 3) showed a lowering of the melting temperature of ibuprofen (endothermic peak in Figure 3a thermogram 1) from 75.3 °C onset temperature to 55.5 °C onset temperature. This indicates the formation of an eutectic mixture between ibuprofen and CaSt and is in accordance with previous findings.⁶⁰ The addition of ethanol (Figure 2a 4) caused a broadening of the endothermic peak due to simultaneous evaporation of ethanol during the first heating cycle. As the evaporation of ethanol superimposed the endothermic melting peak, determination of the peak onset temperature was not possible. However, it seems that the endothermic peak was shifted towards the melting temperature of ibuprofen again. During the second heating cycle (Figure 3a thermogram 5), where ethanol had already been removed due to evaporation and subsequent vapor removal through the pierced lid, the endothermic peak was shifted towards lower values (i.e., below the melting temperature of pure ibuprofen).

Additionally, the dry and wet powder mixtures were kept constant at 50 °C and DSC thermograms were recorded (Figure 3b). Here, neither exothermic nor endothermic peaks were observed suggesting that no interactions occurred at 50 °C. The DSC signal of the

wetted powder mixture declined due to ethanol evaporation. Nevertheless, ethanol did not impact the physiochemical properties of ibuprofen and CaSt.

3.4 Pellet Characterization

The final pellet size distribution (PSDs) varied for the different drying techniques (data not shown). However, the amounts of pellets in the yield fraction (i.e., between 1.4 and 1.8 mm) were similar for all batches. The desiccated pellets showed higher amounts in the fractions below 1.4 mm in comparison to the other drying procedures, which correlates to the highest extent of shrinkage for desiccation (i.e., the pellet volume reduction by $20.3 \pm 2.4\%$). Lyophilization yielded a significant fraction of pellets above 1.8 mm due to low extent of shrinkage during lyophilization. Interestingly, the inlet-air temperature during the fluid-bed process had no impact on the pellet size distributions, which correlated to the equal extent of volume reduction in the fluid-bed apparatus (i.e., by 16.3 ± 1.9 and $15.7 \pm 0.7\%$ for FB 20 °C and FB 50 °C, respectively). Furthermore, the particle size distribution suggested that the fluid-bed process did not cause significant pellet abrasion. The amount of pellets with a diameter below 0.5 μm was not significantly increased compared to the pellets dried via lyophilization.

The median pellet diameter of the pellets produced via the three drying methods ranged between 1610 and 1656 μm (Table 2). Similar values were expected as only the yield fraction was subjected to image analysis. The aspect ratio was well above 0.8 (Table 2) and was identical for all batches. Evidently, the drying procedure influenced the pellet size distribution but not the pellet shape.

The parameters describing the pellet microstructure are listed in Table 2 as well. The apparent pellet density (obtained from helium pycnometry measurements) was similar for all batches (Table 2) and did not deviate from the apparent density of the powder mixture used for pellet preparation, i.e., $1.0571 \pm 0.0012 \text{ g/cm}^3$. This indicates the absence of closed pores independent upon the drying procedure. The presence of closed pores would have yielded a decreased density.

Due to shrinkage not only the pellet diameter and the corresponding size distributions, but also the porosities were affected. As shrinkage was minor during lyophilization, the initially present solvent-filled pore space was largely conserved. Thus, it is assumed that the final porosity was similar to the initial one (about 33%, see Table 2). Shrinkage during desiccation and fluid-bed drying, however, significantly reduced the internal porosity. As expected the largest shrinkage in case of desiccation led to the smallest final porosity at around 16.5%. Fluid-bed drying also led to a porosity reduction of about 28% (Table 2). Finally, the pellet crushing strength (Table 2) was inversely proportional to the porosity and decreased in the order $D > FB > L$.

The mercury intrusion/extursion curves showed the presence of ink-bottle-shaped pores (i.e., hysteresis; data not shown). Pore-size data obtained from mercury porosimetry are reported as well in Table 2 in terms of median and modal pore diameter. All pore diameters ranged between 0.02 and 1 μm . At higher pressures, corresponding to lower pore sizes, samples deformed and pores collapsed. Thus, data evaluation was performed between 0.02 and 1 μm . Median pore diameters were similar after desiccation, after fluid-bed drying at 50 °C and after lyophilization. Median pore diameters of fluid-bed dried pellets at 20 °C were slightly decreased compared to other batches. The modal pore diameters were similar after desiccation and fluid-bed drying at 20 °C, but slightly decreased after fluid-bed drying at 50 °C and significantly increased after lyophilization.

Although the porosity was not significantly affected by the inlet-air temperature during fluid-bed drying, the inlet-air temperature affected the pore size distributions. At 50 °C the median (0.23 μm for both) and modal pore diameters (0.23 and 0.24 μm) were equal, whereas for FB 20 °C modal diameters were increased (0.27 μm for both) and median diameters were decreased (0.19 and 0.18 μm) implying a broadened pore size distributions for FB 20 °C in comparison to FB 50 °C. Hence, drying conditions did not excessively impact the extent of shrinkage, but rather the mechanism of shrinkage: Obviously, fluid-bed drying at 50 °C favored the collapse of smaller pores (possibly due to softening of the material, leading to

pore collapse upon impact, see DSC section above), whereas at 20 °C smaller pores shrunk but still remained intact after drying.

Determination of the total pore surface area was not possible with mercury porosimetry, as the samples tended to deform at higher pressures. This yielded in excessively high surface areas. However, BET gas adsorption measurements were used to determine the specific surface area. The specific surface area was strongly influenced by the drying method and correlated with the porosity and the median pore diameter. In case of fluid-bed drying, the specific surface area was influenced by the inlet-air temperature (Table 2) and was significantly higher for 20 °C than for 50 °C. Since the values for the median pore diameter were obtained from the volume-based size distribution, it was assumed that for similar pore sizes the total number of pores increased for FB 20 °C, which is in accordance with the increased specific surface area for FB 20 °C (Table 2). The effects of inlet-air temperature on the pore size distributions may be attributed to temperature-dependent mechanical properties of the matrix,⁶¹ as described above. The DSC graphs (Figure 2) reveal that CaSt lowers the melting temperature onset from 75 to 55 °C. Although the higher fluid-bed drying temperature was “only” 50 °C, a certain local softening of the material may have occurred. Consequently, the mechanical properties and in turn the shrinkage behavior of the pellets were altered.

SEM images did not reveal particular differences in the pellet surface structure (Figures 4a) with respect to the different drying techniques. Magnifications (Figures 4b) showed a distinct porous system for all drying methods, which is supported by the porosity determinations. When the pellets were manually cut with a scalpel to investigate the pellet cross-section, the center broke off, i.e., fragmented as can be seen in Figures 4c. Although Figure 4 only shows a single pellet per batch, more than one pellet was investigated and fragmentation was generally observed during cutting, most notably for the pellets dried via lyophilization and desiccation. This characteristic was not that pronounced for FB dried pellets as during FB drying the pellets experienced mechanical loading due to collisions. According to the true densities (Table 2), no air pockets (i.e., closed pores) were formed due to collisions. Instead,

collisions caused densification. Magnification of the pellet cross-sections (Figures 4d) illustrates qualitative variations in the pellet structure. After desiccation comparatively few pores were detected, which corresponds to the low porosity (i.e., 16.0 and 16.7% for D1 and D2). Lyophilization seemed to create numerous small pores throughout the pellet cross-section. This was attributed to the fast freezing of pellets upon immersion into liquid nitrogen. Due to the high freezing rate a high number of ice/solid ethanol nuclei,⁶² which condition the final pore size, were formed. Consequently, for fast freezing more but smaller pores are formed than for slow freezing. The microstructure of the lyophilized pellet surface differed from that of the cross-section. In contrast, after fluid-bed drying, the surface and cross-section microstructures appeared similar regardless of the drying temperature.

Raman images in Figure 5 display the spatial ibuprofen distribution throughout the pellet cross-sections. As images were reproducible, one representative image of one batch for each drying method is shown. No preferred position of randomly distributed API within the pellet was found for any of the drying procedures. This may be related to the drying procedure: During fluid-bed drying, ibuprofen was not transported towards the external surface as no CRP was present (Figure 3b). Moreover, at 50 °C inlet-air temperature ibuprofen was likely to cause phase separation of 50% ethanol solution.⁶³ Hence, ibuprofen spontaneously re-crystallized in the aqueous phase⁶⁴ and was no longer available for re-distribution. Since during desiccation a long CRP occurred (Figure 3a), ibuprofen migration towards the outer surface could have occurred. However, the conditions during desiccation prevented ibuprofen from accumulating in specific regions of the final pellets due to the strength of back-diffusion relative to convection towards the pellet surface for these mild drying conditions.

Therefore, as expected, the impact of the drying procedure on the ibuprofen profile was minor: Although ibuprofen is highly soluble in the granulation liquid and has a high dissolution rate, the granulation liquid did not dissolve much of the ibuprofen but was rather absorbed by CaSt. Thus, only low fractions of ibuprofen might have been dissolved, being subject to migration. This is supported by the fact that the ibuprofen clusters observed in the Raman

images were in the size range of the primary ibuprofen particles (i.e., median Feret's diameter 104.67 μm , Figure 5).

The in-vitro dissolution profiles are depicted in Figure 6. As expected, ibuprofen release was found to be incomplete for all batches after six hours. This was caused by the low ibuprofen loading (3.5%), which was below the percolation threshold. Below the percolation threshold it can be assumed that accessibility of many ibuprofen particles to the dissolution medium is limited due to complete "encapsulation" of ibuprofen particles in the insoluble CaSt matrix (the so-called finite clusters). Hence, all dissolution data did not fit the Higuchi model,⁶⁵ although it is known from previous studies that the CaSt matrix remains intact during dissolution testing, providing controlled ibuprofen release.

The in-vitro dissolution profiles over six hours varied significantly ($p < 0.05$) as a function of the drying conditions (Figure 6). The rate of ibuprofen release decreased in the order L, FB 20 °C, FB 50 °C and D. After six hours, around 45% of ibuprofen was released from the pellets dried via lyophilization, whereas only around 4% was released from those dried via desiccation. During fluid-bed drying at 20 and 50 °C, a decrease in the inlet-air temperature yielded in an increased dissolution rate.

Since the Raman images revealed random ibuprofen distribution regardless of the drying procedure (Figure 5), a biased ibuprofen distribution in the pellets clearly does not contribute to the overall dissolution behavior. However, the pellet microstructure (porosity, pore size and surface area, see Table 2) correlates with the drug release rate. The rate of ibuprofen release tends to increase with the increasing porosity and modal pore diameter. It was reported in the literature that drug release from pellets increased with increasing porosity.⁶⁶ Moreover, Costa et al.⁶⁷ previously reported that drug release from pellets increased with the increasing mean pore diameter. This was also the case in our study with respect to the different drying techniques. After fluid-bed drying, FB 20 °C and FB 50 °C showed different release behavior despite similar porosities and modal pore diameters. However, the pore size distribution was impacted by the drying temperature as pointed out above, which can clearly be seen in the different BET surface areas for FB 20 °C and FB 50 °C (Table 2),

respectively FB 20 °C has a significantly higher specific surface area and thus also showed higher release rates.

As already mentioned, during dissolution studies the pellets remained intact due to the poor water solubility of CaSt. Hence, ibuprofen release occurred by dissolution through capillaries composed of the pore network and interconnecting drug particle clusters.⁶⁸ ibuprofen release occurred when the drug came into contact with the dissolution medium, subsequently dissolved and diffused through the porous system. Higher specific surface areas thus, provide a higher chance for the drug to come into contact with the dissolution medium, resulting in higher dissolution rates.

The pore shape, represented by the tortuosity, is another microstructure-related parameter that was shown to account for drug release characteristics.⁶⁹ For the presented pellets it was not possible to generate reliable values of the tortuosity: The calculation of the tortuosity requires the surface area obtained from mercury porosimetry,⁷⁰ which was difficult to determine, since the CaSt matrix tends to deform upon higher pressures.

Nevertheless, the results of the dissolution tests clearly indicate that the microstructure (porosity, pore size and corresponding pore size distribution) of CaSt matrix pellets governs the dissolution profiles. The microstructure can systematically be tailored by the drying step, the drying technique and the applied drying process parameters. Since many pellet properties (including dissolution characteristics) are frequently related to the microstructure, the drying process plays a crucial role in achieving desired pellet properties. This is especially true for pellets containing a swellable matrix, which is most often the case for formulations processed via wet extrusion/spheronization.

4. CONCLUSIONS

Although the microstructure of low ibuprofen-loaded calcium stearate pellets changed depending on the drying procedure, the ibuprofen distribution throughout the pellets was not altered by the drying conditions, since apparently only a minor portion of ibuprofen was dissolved during wetting. During desiccation at ambient conditions, shrinkage (in terms of diameter and resulting volume reduction) of the calcium stearate matrix occurred. Since drying took mainly place in the constant rate period, pellet porosity and specific surface area were decreased, leading to very low drug release rates. Also during fluid-bed drying particle shrinkage occurred to a lesser extent, which was possibly due to the absence of an overall constant rate period. Although different inlet-air temperatures during fluid-bed drying did not alter the pellet microstructure with respect to porosity, the specific surface area decreased at higher temperatures. Thus, drug release was accelerated for pellets dried at lower temperatures. The least shrinkage and consequently, the highest specific surface area were observed for lyophilization, leading to the highest drug release rates.

Summarizing the impact of the drying procedure on the CaSt matrix pellets, it was found that

- porosity decreased in the order lyophilization, fluid-bed drying (independent upon the drying temperature) and desiccation. This is due to the different shrinking mechanisms discussed above for the different drying modes.
- For fluid-bed drying the median pore diameter was a function of the drying temperature, where lower temperatures yielded in smaller diameters.
- The specific surface area was a function of porosity and pore size distribution and thus, decreased in the order lyophilization, fluid-bed drying at 20 °C, fluid-bed drying at 50 °C and desiccation.
- The in-vitro dissolution profiles were a function of the pellets' specific surface area.

These findings suggest that the pellet microstructure is a strong function of the drying process. Pellet properties related to their microstructure can selectively be modified by adjusting the drying procedure.

In summary, this study highlighted the impact of the drying process on the pellet matrix. Future work will cover the impact of the drying process on the API that is incorporated into matrix pellets. Thereby, the drying process can be applied for a rational design of pellet characteristics accounting for both, the impact of the drying process on the matrix and the API.

5. ACKNOWLEDGEMENTS

The authors thank GL Pharma (Lannach, Austria) for providing ibuprofen, Mario Hainschitz (RCPE GmbH, Graz, Austria) for his help with the BET measurements and Bettina Bauer (University of Graz, Austria) for her assistance with the HPLC measurements. Moreover, Julia Paller (University of Graz, Austria) is acknowledged for her assistance during pellet preparation.

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