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Characterization of the preferred orientation of δ-mannitol crystallites in tablets

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Abstract

The crystallographic texture, i.e. the preferred orientation of crystallites of δ-mannitol samples, has been experimentally determined by pole figure analysis. The pole figures were measured with an X-ray diffraction texture goniometer. It was found that already the uncompressed δ-mannitol powder sample was slightly texturized so that the (0 2 0) plane was parallel to the upper surface of the sample. The degree of preferred orientation was found to significantly increase when the powder was compressed to a tablet with the minimum (74 MPa) compression pressure. Nevertheless, the direction of the texture remained parallel to the tablet surface. Maximum compression (740 MPa) did not increase the degree of preferred orientation further. The compression time (0 or 60 s) was not found to noticeably affect the strength or direction of the texture. The extent of the texture inside the tablet was determined with a tablet surface grinding experiment. The degree of preferred orientation was found to decrease under the surface while the orientation remained the same. The results were confirmed with orientation distribution function (ODF) calculations.

Keywords: Preferred orientation; Texture; Pole figure; X-ray diffraction; δ-Mannitol; Tablet

1. Introduction

Many polycrystalline substances have macroscopic properties that are anisotropic, i.e. they depend on the orientation of the crystallites [1]. Sample is described as to having preferred orientation when certain crystallographic planes (h k l) are orientated to the same direction. In the present study, this preferred orientation of crystallites is also referred to texture, as opposed to the commonly used meaning of texture, which is for example, the roughness or patterns of surfaces. In polycrystalline materials, the forming of preferred orientation is a common phenomenon [2]. Usually the only way to quantify the texture of a sample is to use crystallographic methods such as X-ray diffraction.

In the field of pharmaceutical substances, the appearance of texture may affect for example the dissolution properties, breaking strengths and hardness of tablets. Also, the lamination and cap forming of tablets can be affected [3]. In consequence, studying the crystallographic texture of tablets may provide valuable non-destructive information of their integrities. Still, the effects of texture on pharmaceuticals are not widely discovered. For example, it is still uncertain whether the texturization of pharmaceuticals is problem in practice or not. However, there are some studies where the formation of texture has been investigated for tablets produced using different preparation methods. Kourula et al. [3] found that β-lactose and acetylsalicylic acid texturized in a certain way already at a minor compression pressure (75.3 MPa) while three other substances did not show texture at all. Nakagawa [4] studied the formation of texture to aspirin and phenacetin as a function of granulation process, punch-shape and amount of magnesium stearate. According to his

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observations, the granulation of the substance reduced the degree of preferred orientation while increasing the amount of magnesium stearate strengthened it. Nakagawa also observed that punches having different shapes caused different kinds of texture and that the degree of preferred orientation decreased rapidly below the tablet surface. Riippi et al. [5] have studied the effect of compression force on the properties of erythromycin acistrate tablets. They observed that the crystallite size of the tablets was not strongly dependent on the compression force used. However, they also noticed that intensities of certain peaks decreased as the compression force increased. They concluded that this phenomenon is due to the texture formed at the compression process.

Fukuoka et al. [6] have introduced a pattern-fitting procedure for the determination of texture of pharmaceutical samples using X-ray powder diffraction data. For the aspirin powder and tablet they obtained preferred orientation parameters of -0.007 Rad^{-2} and 0.134 Rad^{-2}, respectively. The procedure is based on the Rietveld method and it can also be used for the characterization of the lattice parameters [7]. Yamamura and Momose [8] used the same method for quantitative phase analysis of binary powders and tablets. Using this pattern-fitting procedure also the preferred orientation of crystallites in solid dosage forms can be determined in the course of the quantitative analysis. Other studies concerning the evaluation of the degree of preferred orientation using the Rietveld method have been performed by von Dreele [9] and Leventouri [10], for example.

In the present study, changes in the texture of δ-mannitol was characterized under compression to a tablet and compared to the texture of an uncompressed powder sample. Also, the extent of texture from the δ-mannitol tablet surface was examined. Mannitol was chosen as the model pharmaceutical substance because its polymorphs have been reported to have needle-shape morphology, which may produce preferred orientation effects when analyzed by X-ray powder diffractometry. For example, Campbell Roberts et al. [11] have studied the binary mixtures of β- and δ-mannitol and reported that with a rotating sampling accessory, the limits of detection and quantification were halved demonstrating the significant texturization of mannitol. The results of the present study are presented in the form of pole figures, which are used to illustrate a texture in the specific direction of a measured reflection. To our knowledge, the modern X-ray texture goniometry has not been used in the studies of pharmaceutical powders and tablets before. Therefore, we wanted to clarify and demonstrate the possibilities of the texture analysis in the field of pharmaceutical sciences.

2. Materials and methods

2.1. Sample preparation

Four distinct sets of tablets were compressed from δ-mannitol powder (supplied by Merck) using a hydraulic compression apparatus with a single 13 mm diameter flat-faced punch. The tablets were compressed at the minimum and maximum compression pressures of 74 and 740 MPa with compression times of zero (compression, instant release) and 60 s. Weight and thickness of the compressed tablets were 1.00 g and 5.3–6.9 mm, respectively.

In order to obtain a reference for the compressed tablets an uncompressed δ-mannitol powder sample was prepared for measurement. For this purpose, the δ-mannitol powder was poured to a plastic cylinder sample holder with the dimensions similar (diameter and height) to the compressed tablets. The excess powder was then carefully leveled out using a spatula with minimal compression.

To determine to what extent the entire tablet has been textured, a surface grinding experiment was carried out. For this purpose the tablet compressed with 740 MPa/60 s was carefully ground from the surface using sandpaper until 1.2 mm of the tablet upper surface was taken off. It was assumed that the grinding process did not affect the texture of the tightly compressed tablet.

2.2. Classification of the particle size and shape

The size and shape of the δ-mannitol particles were determined with Olympus BH-2 optical polarization microscope. The micrographs were transferred to a computer and analyzed using Image-Pro® Plus image-analysis software (Media Cybernetics). Approximately 750 particles were analyzed. The calculated parameters in addition to average particle size were elongation and roundness, as determined by Hellén and Yliruusi [12]. According to their study, roundness and elongation were the most efficient parameters for describing the pellet shape.

2.3. Pole figures and the orientation distribution function (ODF)

Pole figures and θ–2θ scans were obtained using a Philips X'Pert Pro MPD equipped with an automated texture cradle (ATC-3). At first, the X-ray diffraction patterns were measured from all of the δ-mannitol samples using the normal Bragg–Brentano θ–2θ reflection geometry with 0.04 Rad Soller and 1° divergence slits at both the incident and diffracted beam path. The height of the (programmable) receiving slit used was 0.4 mm. The normal θ–2θ scans were measured in order to observe the accurate 2θ positions for the diffraction peaks (crystallographic planes) to be investigated. The diffractographs were measured from a 2θ range of 8–42° with 0.02° steps and 1 s measuring time per step. Based on these measurements, crystallographic planes associated to the Miller (h k l) indices of (0 2 0), (1 2 0), ($\bar{1}$ 6 1) and (0 7 1) were selected as the planes for investigation because the reflections related to these planes were sufficiently intensive and represent the major different crystallographic directions. The plane indices for δ-mannitol having monoclinic unit cell were obtained from the PDF-2 database [13]. Diffractographs

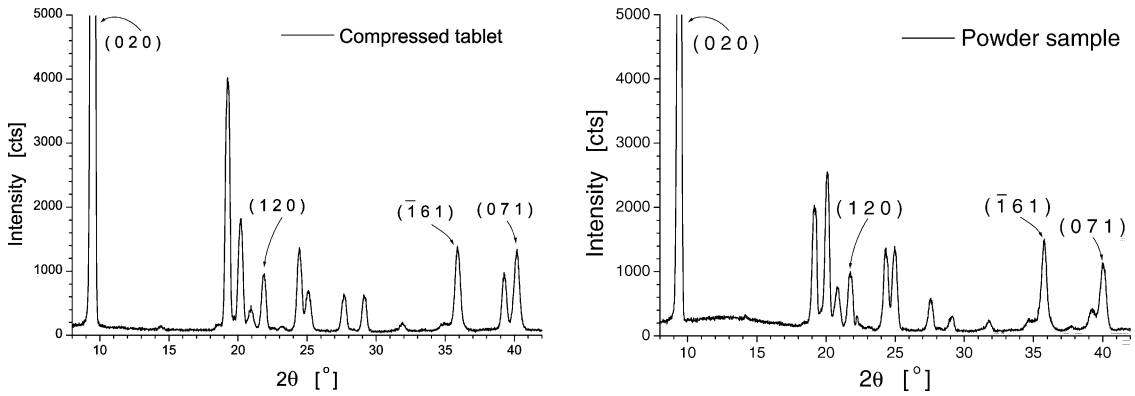

Fig. 1. X-ray diffraction patterns from the tablet sample (left) and the uncompressed δ-mannitol powder (right). The investigated planes are marked with their respective (h k l) indexes. The height of the (0 2 0) reflection is approximately 24,000 counts for the tablet and 10,000 counts for the powder, which might indicate the texturization of the (0 2 0) plane. However, the difference of the intensities could also be partly caused by the different sample preparation of the powder and tablet sample.

for the most tightly compressed tablet (740 MPa/60 s) and powder sample are shown in Fig. 1 with the investigated planes indicated. As well as the θ–2θ scans, the texture measurements were done using monochromated Cu Kα radiation (40 kV/50 mA) and a 0.6 mm receiving slit at the diffracted beam path. The axial and equatorial divergence slits at the incident beam path were 2 and 1 mm, respectively.

The texture data was measured using the Schultz reflection method [14]. The angles used were θ (normal Bragg angle), ψ (tilt angle) and φ (rotation angle). A single pole figure measurement was performed as follows: First, the 2θ angle was set to match with the value of the plane to be investigated. Then the sample was rotated continuously around φ-axis and the intensity value was recorded after 1 s of rotation. The

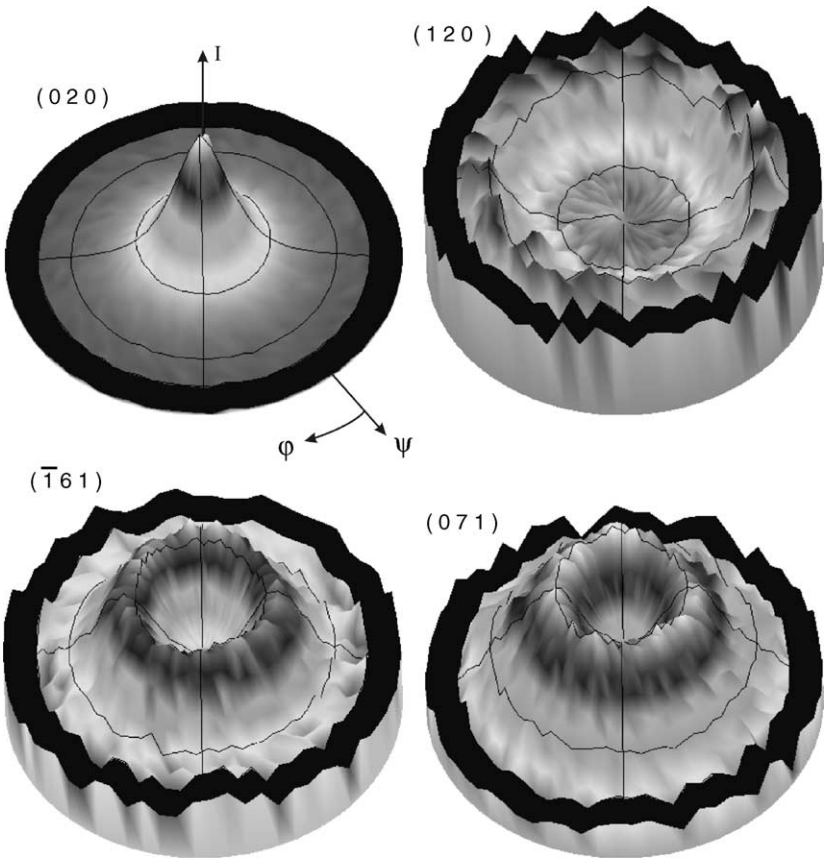

Fig. 2. Intensity corrected pole figures from 740 MPa/60 s compressed δ-mannitol tablet. From the different pole figures it is evident that the (0 2 0) plane is parallel to the tablet surface. The axes are described as follows: I = intensity, ψ = tilt angle and φ = rotation angle.

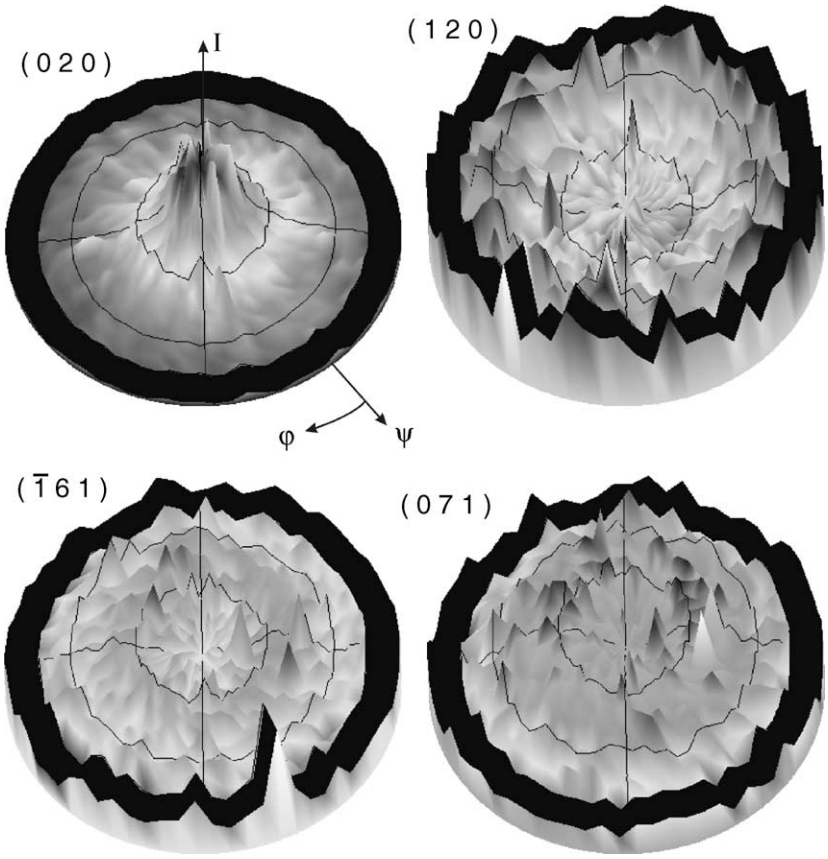

Fig. 3. Intensity corrected pole figures from uncompressed δ-mannitol powder sample. The pole figures indicate that the (0 2 0) plane is slightly orientated parallel to the tablet surface. The axes are described as follows: I = intensity, ψ = tilt angle and φ = rotation angle.

rotation speed was 5° per second. After one revolution the sample was tilted 5° and a similar rotation around φ-axis was performed as described above. This action was carried out until the value of ψ angle was 75°. In practice, all this was done automatically by the computer controlled texture cradle. The pole figures of all the selected peaks (planes) were recorded for every sample.

The data was processed using Philips X'Pert Texture software (version 1.0a, 1999) in order to obtain pole figures for the investigated crystallographic planes. The pole figures were corrected for contributions from background and defocusing. The defocusing correction was done mathematically using the method by Gale & Griffits [15] with the texture software. The background correction was done with measured data, which was obtained from the vicinity of the diffraction peak in question using ψ angle steps of 5° and a revolution time of 20 s for the φ angle.

The obtained pole figures are presented as 3-D polar plots. The radial axis of the plots corresponds to the ψ angle and the rotation axis to the φ angle. The height of the plot describes the intensity of the investigated crystallographic direction at certain values of ψ and φ. For example, if the pole figure consists of only one sharp peak the crystallographic planes of the investigated crystallites in question are orientated mostly to that direction (ψ and φ). If the intensity maxima is in the center of the pole figure, then the specific crystallographic plane (h k l) is orientated parallel to the surface of the sample. On the other hand, if no distinct intensity maxima are observed then the crystallites of the sample can be considered as randomly orientated.

The intensity corrected pole figure data was used to form an orientation distribution function (ODF) of the crystallites. The ODF describes the volume fraction of the crystallites that have a certain orientation with respect to the sample reference frame. The iterative WIMV algorithm [16] was used to create the ODF. Using the ODF formed, it is possible to (re)calculate pole figures and inverse pole figures of any Miller integer set of (h k l) and ψ angle up to 90°. By recalculating low indexed pole figures, for example (0 0 1), (0 1 0) or (1 0 0) it is easier to obtain crystallite orientation information for the sample in question. All of the calculations described above were performed with the texture software.

3. Results

3.1. Particle size and shape analysis

The average particle size of the studied δ-mannitol powder was 19 μm. The roundness and elongation were 0.84 and

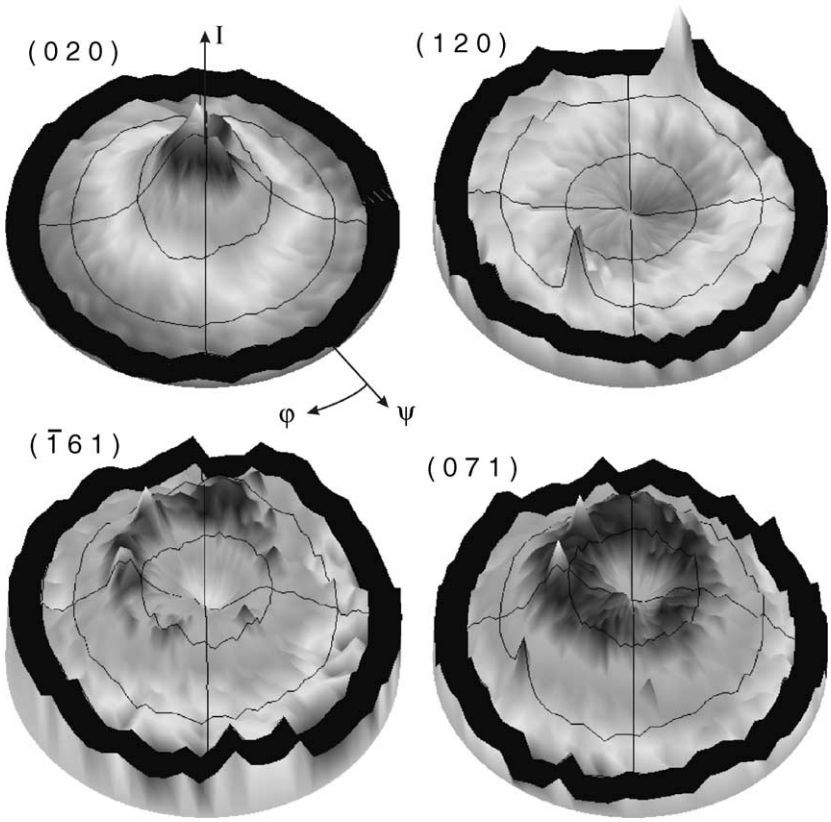

Fig. 4. Intensity corrected pole figures from 740 MPa/60 s compressed and surface ground δ-mannitol tablet. The pole figures show that the (0 2 0) plane is still noticeably parallel to the tablet surface. The axes are described as follows: I = intensity, ψ = tilt angle and φ = rotation angle.

2.2, respectively. The standard deviations of all of the measured parameters were quite significant meaning that the morphology of the mannitol particles was non-uniform. In other words, the size, roundness and elongation distributions were wide. Nevertheless, this result indicates that the general shape of the δ-mannitol particles used in this study, is oblong and thus, preferred orientation of crystallites due to the shape of the particles is expected for the samples.

3.2. Pole figures

It can be seen, that the (0 7 1) reflection overlaps slightly with another reflection on the left side (Fig. 1). However, this overlapping hardly affects on the shape of the obtained pole figures because the Bragg angle is constant during the pole figure measurement. Generally, overlapping might cause problems to the texture analysis if the overlapping peak is more intense and the crystallographic plane of the overlapping reflection has a strong preferred orientation compared with the studied reflection.

The intensity corrected pole figures of the tablet compressed with 740 MPa/60 s show that the (0 2 0) plane is parallel to the tablet upper surface (Fig. 2). The direction and degree of the preferred orientation of δ-mannitol crystallites were similar for all tablets compressed with different parameters. Also, the δ-mannitol powder sample shows similar orientation, yet the degree of preferred orientation is clearly weaker than in the tablets (Fig. 3). The pole figure of the ground tablet also indicates similar preferred orientation of crystallites as the unground tablets (Fig. 4). The degree of preferred orientation of the ground tablet is roughly between the degree of the compressed tablets and the powder sample.

4. Discussion

Based on the texture measurement results all of the tablets compressed of δ-mannitol show strong preferred orientation of the crystallites. The magnitude of orientation is not dependent on the compression force and time used. This result is in agreement with the result by Fukuoka et al. [7].

The results indicate that when a δ-mannitol powder sample is compressed the crystallites will orientate preferentially and that the influence of the compression over the orientation of the crystallites not only affects the surface of the tablet but also extends deeper into the tablet. However, the compressions effects upon the texture clearly diminish, as the interior of the tablet is examined. This type of distribution of texture indicates that the force of compression does not penetrate evenly through the tablet. This behavior is observed despite the high compression pressure (740 MPa) used to produce the tablet. The most apparent explanation for this is that the

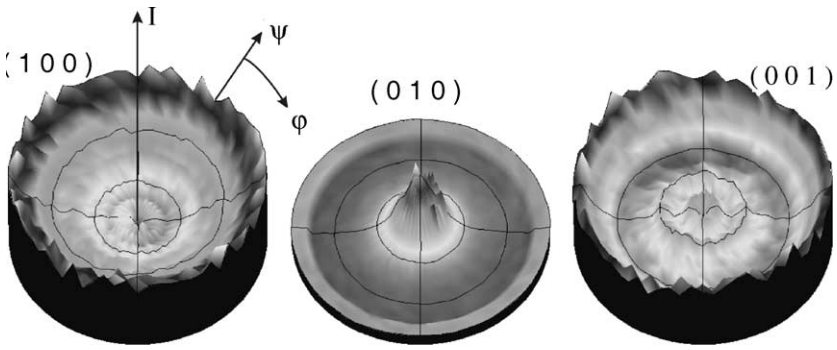

Fig. 5. Recalculated (from ODF) pole figures from 740 MPa/60 s compressed δ-mannitol tablet. The pole figures clearly show that the (0 1 0) plane and therefore, also the (0 2 0) plane is parallel to the tablet surface. The axes are described as follows: I = intensity, ψ = tilt angle and φ = rotation angle.

δ-mannitol particles, as most pharmaceutical substances, are quite soft and thus, the transmitted range of the force of compression is short [17].

According to the size and shape analysis, the studied δ-mannitol particles are oblong, which is in agreement with the properties of δ-mannitol. The unit cell of δ-mannitol is monoclinic and its lattice parameters are $a = 5.1$ Å, $b = 18.3$ Å, $c = 4.9$ Å and $\beta = 118^\circ$ [13], which means that also the unit cell of δ-mannitol is oblong. Thus, even if the particles of δ-mannitol observed with microscopy are not single crystals, there is still reason to believe that the distinct crystallites comprising a particle are parallel to each other.

The (0 2 0) plane is the top of the mannitol unit cell. The results of the texture measurements indicate that if the crystallites in the particles are parallel, then the δ-mannitol particles lay in an upright position at the surface of the tablet. However, this may not be the case because oblong particles will most likely lie edgewise in the tablet. Possible explanation could be that mannitol crystals tend to grow mainly along the *a* and/or *c* unit vectors.

The result that the (0 2 0) plane is oriented parallel to the tablet upper surface can be confirmed in two ways. Firstly, all of the four pole figures measured for a sample can be compared. Knowing the lattice parameters stated above, the angles between the examined crystallographic planes could be calculated. The angle between the (0 2 0) and $(\bar{1}\,6\,1)$ planes and the angle between the (0 2 0) and (0 7 1) planes are 35° and 31°, respectively. Then if the pole figures of $(\bar{1}\,6\,1)$ and (0 7 1) are carefully examined it can be seen that the intensity maxima stand almost exactly at the corresponding ψ angles, namely 35° and 31° (Fig. 2). Secondly, the inverse pole figures can be calculated using the determined ODF. As it can be seen the (1 0 0) and (0 0 1) planes are perpendicular and the (0 1 0) plane and therefore, also the (0 2 0) plane are parallel to the tablet surface (Fig. 5).

5. Conclusions

Based on this study the δ-mannitol crystallites were found to texturize under compression. It is evident that the crystallographic plane (0 2 0) of the δ-mannitol orientates parallel to the tablet surface and thus, perpendicular to the direction of the compression. The increase of compression pressure and time did not increase the degree of preferred orientation. Furthermore, there is already a weak but similar texture on the uncompressed powder sample confirming that the δ-mannitol crystallites are prone to preferred orientation. It is also obvious that the crystallites near or at the tablet surface are much more preferentially orientated than the crystallites deeper in the tablet. One reason for the preferred orientation of the δ-mannitol crystallites is the shape of the crystals and particles; the other possible explanation is the compression behavior of mannitol, which is a combination of brittle and plastic.

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