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Does the preferred orientation of crystallites in tablets affect the intrinsic dissolution?

Mikko Tenho [a,c,*], Paula Heinänen [b], Veli Pekka Tanninen [b], Vesa-Pekka Lehto [a]

[a] *Department of Physics, University of Turku, FI-20014 Turku, Finland*
[b] *Orion Corporation, Orion Pharma, P.O. Box 65, FI-02101 Espoo, Finland*
[c] *Graduate School of Materials Research, Turku, Finland*

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Abstract

The aim of this study was to examine the effect of preferred orientation of crystallites, i.e. texture, on the intrinsic dissolution rate of some active pharmaceutical ingredients. Although it has often been speculated that the intrinsic dissolution of pharmaceutical tablets is affected by texture, no experimental evidence of this effect has been reported. The texture of acetylsalicylic acid, tolbutamide, carbamazepine and entacapone tablets was measured using three different methods both before and after the dissolution measurements. To clarify the effect of texture, texturizing and less-texturizing batches of each material were used. The texturizing batches had big needle or plate-like particles and the less-texturizing batches were prepared by grinding the texturizing powders. The USP rotation disc method was used to measure the intrinsic dissolution rate of the samples. The results indicated that the acetylsalicylic acid, tolbutamide and entacapone tablets texturized strongly in compression and the grinding of the texturizing powders decreased the degree of texture. Also the carbamazepine tablets were slightly texturized. All of the texture measurement methods used were found to give acceptable and consistent results and therefore a special texture goniometer is not required to perform these measurements. The intrinsic dissolution rate of all the tablets compacted from the ground powder was slightly higher than the intrinsic dissolution rate of the more texturized samples. However, these differences were not significant on a large scale. After the dissolution tests the degree of texture of the samples was decreased. The intrinsic dissolution rates of the samples were presumably affected by several different parameters such as texture, solubility, pH, surface energetics and crystal strains. Although only small differences were found between the intrinsic dissolution rates of texturized and less texturized samples the effect of texture on the dissolution behavior of the pharmaceuticals should be considered when performing accurate intrinsic dissolution studies.

Keywords: Intrinsic dissolution; Preferred orientation of crystallites; Tablets; Texture

1. Introduction

Preferred orientation, also called texture, results when the crystallites comprising the polycrystalline samples are not truly randomly oriented [1]. This adverse effect is typical to the powders with anisotropic crystal habits, which tend to adopt a preferred alignment along the sample surface. The results of X-ray powder diffraction (XRPD) studies could be easily affected by the preferred orientation of the crystallites. Texture is especially likely to have an effect on the diffractograms of the sample when the crystallites are needle or plate-like. A short review of studies on texture and its effects in the field of pharmaceutical sciences has recently been reported [2]. The effects of preferred orientation in X-ray diffraction studies are described in a review by Stephenson et al. [3]. It has been previously reported that texturization often takes place when the powder sample is compacted to form a tablet [2,4,5]. Previous results have shown that the degree of texture in tablets is correlated with the compaction properties of the sample [4]. It is speculated that texture could affect other properties of the samples in addition to influencing the results of quantitative analysis of X-ray diffractograms.

During the preformulation stage, an understanding of the dissolution rate of the drug candidate is necessary since this property of the compound is recognized as a significant factor in the drug's bioavailability. Compressed discs of pure materi-

* Corresponding author at: Department of Physics, University of Turku, FI-20014 Turku, Finland. Tel.: +358 2 333 5672; fax: +358 2 333 5070.
E-mail address: mikko.tenho@utu.fi (M. Tenho).

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als were used in order to evaluate the intrinsic tendency of the test material to dissolve without formulation excipients. When applying the rotating disc method, the dissolution rate expression can be applied assuming laminar convective flow conditions and constant surface area [6]. It is important that when studying the effects of the form of the solid (e.g. polymorphism, pseudopolymorphism, amorphicity) on the drugs dissolution behavior, effects due to the particle size should be eliminated or minimized. It has been previously reported that when measuring the intrinsic dissolution rate (IDR) from compressed discs, effects due to particle size and habit can be neglected because the area of the discs is constant and cannot be influenced by particle size [7].

The motivation of this study was the speculation that the IDR of a highly texturized tablet could differ from the IDR of a non-texturized tablet of the same active pharmaceutical ingredient (API). The habit of the crystal arises from the different growth rates of the various crystal planes during crystallization. Since dissolution can be roughly considered as the inverse process of crystal growth, the dissolution rate can be assumed to be the sum of the dissolution rate of the individual crystal planes. In a highly texturized sample only certain crystal planes are represented on the tablet surface. If the energetic properties of these planes were exceptional, the properties of this kind of tablet could differ drastically from a tablet with a more isotropic nature. Danesh et al. [8] have studied the dissolution properties of single crystals of acetylsalicylic acid with atomic force microscopy and from their results calculated that the rate of flux of material from the crystal plane with Miller index (1 0 0) was six times greater than that from the crystal plane (0 0 1). Also Watanabe et al. [9] reported that in case of acetylsalicylic acid, the single crystal dissolution rate depends on the extent of exposure of different crystal planes. Prasad et al. [10] concluded that, according to their studies with paracetamol single crystals, the crystal face (1 1 0) showed a slightly faster dissolution rate than the face (0 0 1). A single crystal is effectively a totally texturized sample, therefore it is theoretically possible that the texturization could have an effect on the results of the intrinsic dissolution experiments. A slight difference in intrinsic dissolution rates due to texturization may complicate the analysis of the results and lead to misconclusions.

Burt and Mitchell [11] studied the effects of the different crystal habits on the dissolution rate of $NiSO_4{\cdot}6H_2O$ by comparing the USP I method and the rotating disc method. In the USP I dissolution method it was almost impossible to discern any differences between the crystal habits because the variations in the size and shape of the crystals and thus, a number of crystals, were taken to give approximately constant weights and surface areas. The dissolution rate of bipyramidal crystals was observed to be higher than that of platy crystals. However, the intrinsic dissolution rate obtained from rotating disc experiments showed no difference between habits.

This study had three main purposes: (1) to compare three different methods for determining texture, (2) to study the texturization of some unground and ground APIs, and (3) to examine the effect of preferred orientation on the IDR using compacted discs. To the best of our knowledge, there has to this date been no previous demonstration of any correlation between the sample texture and the intrinsic dissolution rate. Four APIs with different solubilities were chosen as model compounds. Two different batches of each material were used. The texturizing, batch had large, plate or needle-like particles and the other was ground from that powder. The texture of the tablet samples was evaluated using three different methods, both before and after the dissolution tests. The IDR of each sample was measured using USP rotation disc apparatus.

2. Materials and methods

2.1. Materials

The APIs used in this study were acetylsalicylic acid (Shandong Xinhua, China), tolbutamide (Dipharma Francis, France), carbamazepine (Fabrika Italiana Sintetici, Italy) and entacapone (Fermion, Orion Corporation, Finland). All the samples were of commercial grade. Different methods were used to obtain texturizing powders. Batches with less-texturizing behavior were produced by grinding the texturizing batch by hand in a mortar. The physical state and polymorphic purity of the samples were characterized with XRPD and differential scanning calorimetry (DSC). All samples were stored in closed containers at ambient conditions.

2.1.1. Acetylsalicylic acid

The texturizing batch was obtained by sieving the received acetylsalicylic acid sample to the particle size fraction from 500 to 800 μm.

2.1.2. Tolbutamide

The stable polymorphic form (I) was used in the present study. To obtain the texturizing batch tolbutamide was recrystallized from 10:1 EtOH:tolbutamide solution by drowning out with water. The dissolving and crystallization temperatures were 60 °C and the obtained crystals were dried in vacuum at 60 °C. As a result, sharp oblong tolbutamide particles were obtained.

2.1.3. Carbamazepine

To obtain the texturizing batch of carbamazepine the received carbamazepine powder was dissolved in EtOH (Primalco, Finland) and dried at 80 °C. The resulting acicular crystals were observed to be a mixture of the polymorphic forms I and III. In order to transform the carbamazepine sample to the pure polymorphic form I the sample was heated to 175 °C for a day.

2.1.4. Entacapone

The particles of the received entacapone sample were needle-like. Therefore the texturizing entacapone batch was the as received batch.

2.2. Methods

2.2.1. Tablet preparation

All tablets in this study were compressed with a mechanical compression tester (LLOYD LR 30K, Lloyd Instruments Ltd., NEXYGEN Software, 12 ton E-Z Press, ICL, USA) into the

Table 1
The thicknesses of the tablet samples

Sample	Before IDR test (mm)	After IDR test (mm)
Unground acetylsalicylic acid	1.5	1.2
Ground acetylsalicylic acid	1.3	1.0
Unground tolbutamide	1.5	1.4
Ground tolbutamide	1.5	1.3
Unground carbamazepine	1.6	1.5
Ground carbamazepine	1.6	1.5
Unground entacapone	1.4	1.4
Ground entacapone	1.3	1.3

mould cavity of the disc. The used compaction pressure was 100 MPa and the compaction time was 60 s. The weight of the tablets was 100 mg and diameter 8 mm. The thicknesses of the samples are given in Table 1. For the texture measurements, the compacted tablets were withdrawn from the intrinsic dissolution mould cavities before or after dissolution studies by pressing gently. The excess dissolution medium was immediately removed from the surface of the compact with a paper towel. All samples were stored in closed glass vials at ambient conditions. The compacted tablets were characterized right after compression with XRPD to check that the crystallinity or polymorphic form has not changed in compression.

2.2.2. Texture measurements

The texture of the samples was characterized with three different methods. These methods were pole figure analysis, calculated from the crystal structure and intensity comparison. All X-ray diffraction measurements were performed with a laboratory X-ray diffractometer, Philips (Panalytical) X'Pert Pro MPD (Almelo, The Netherlands). For the pole figure measurements, the diffractometer was equipped with ATC-3 texture goniometer. The pole figure measurements were taken using point-focused, Ni-filtered Cu Kα radiation, collimated using 1 mm axial and equatorial slits and received with a 0.18° parallel plate collimator. When measuring the ordinary X-ray diffractograms for the calculation from the crystal structure method and the intensity comparison method, line-focused, monochromated Cu Kα radiation was used. The primary beam was collimated using 0.25° fixed divergence slit and 10 mm equatorial mask. A 0.25° fixed anti-scatter slit and a 0.3 mm programmable receiving slit were used in the secondary beam line. The diffractograms were recorded at a scanning speed of 0.04° per 3 s. In all measurements the acceleration voltage and cathode current were 40 kV and 50 mA, respectively.

The Schultz reflection geometry [12] was used to measure the pole figures of the samples. In the Schultz method, the pole figures are measured as follows: first, the 2θ angle (normal Bragg angle) is set to match the value of the crystal plane to be investigated. Then the sample is rotated continuously around the φ-axis (rotation) and the intensity of the diffracted X-ray beam is measured. When one rotation has been performed, the sample is tilted around the ψ-axis (tilt), and similar rotation is performed again. This procedure is carried out until a certain ψ-value is reached. In this study the rotation speed was $5^\circ\ s^{-1}$ and the intensity value was measured in 1 s intervals. The tilt was increased in increments of 5° and the sample was tilted until 85°. The measured pole figures were corrected for background. No defocus correction was necessary since a parallel plate collimator was used to reduce the defocusing effect.

Since pole figures do not give an exact picture of the texture, the average intensity of each φ-circle was calculated and then plotted as a function of the corresponding ψ-value. This is valid where the pole figures are symmetrical with respect to rotation, as was the case in this study. Also, the intensity scale was normalized so that the intensity at $\psi = 0^\circ$ was equal to 1 (Fig. 1). From these graphs, it is possible to obtain a numerical value for texturization. The half width at the half maximum was used in the present study. A sharper intensity profile indicates that the sample has higher degree of preferred orientation.

Another method used to evaluate the texture of the sample is to calculate the ideal X-ray powder diffractogram from the known crystal structure of the sample and to compare it to the measured diffractogram. This method does not require

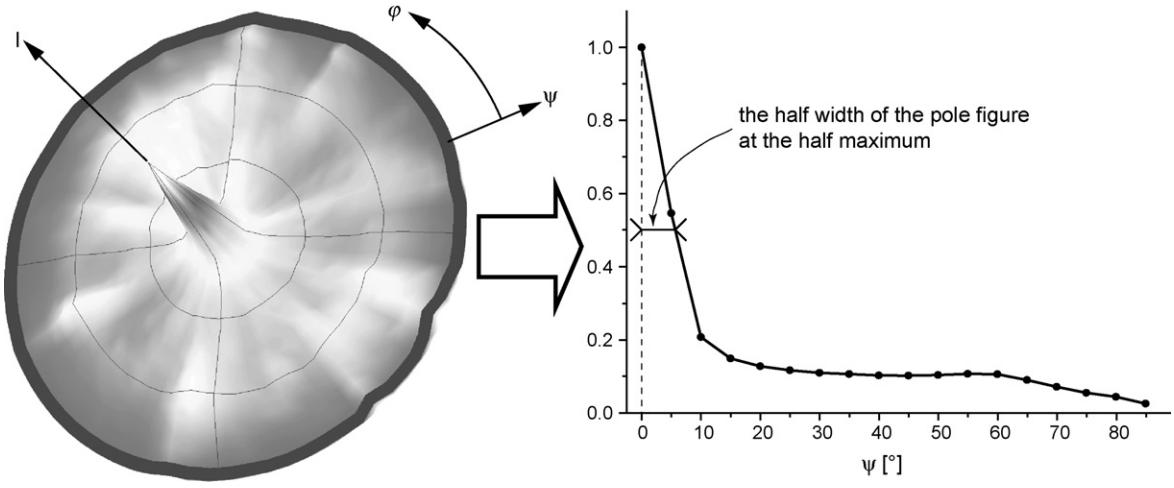

Fig. 1. Illustration of how a 3D pole figure (left) is transformed to the 2D graph (right). The half width of the pole figure at the half maximum represents the degree of texture in the sample. The pole figure axes are described as follows: I = intensity, ψ = tilt angle and φ = rotation angle.

any equipment additional to the ordinary laboratory diffractometer with Bragg–Brentano geometry. The other advantage of this method is the avoidance of the defocusing error, which is always present in the pole figure measurements to some extent. In the present study the crystal structures of the samples were retrieved from the Cambridge Structural Database (CSD) [13] and the data analysis was performed with winPLOTR [14] and FULLPROF [15] programs. The March–Dollase method [16] was used to obtain a preferred orientation parameter of the samples. In the March–Dollase method one crystal plane is taken to be the preferred orientation plane. This plane can be selected by comparing the measured and calculated diffractograms of the sample. The value of the preferred orientation parameter for a non-texturized sample is 1. If the value is less than 1 the sample texture is said to be plate-like and if the value is greater than 1 the texture is acicular. This method has previously been applied by Leventouri [17], amongst others.

If the crystal structure of the sample is unknown the texturization can be investigated by comparing the intensities of the diffraction maxima. This procedure only allows the texture of samples made from the same material to be compared. No knowledge of the degree or direction of the preferred orientation can be obtained. However, the diminution of the texture due to grinding could be seen quite well. In the present study, the comparison was done by comparing the intensity of the most intense peak to the average intensity of all the observed peaks in the diffractogram.

2.2.2.1. Acetylsalicylic acid. The CSD structure ACSALA01 was used to calculate the ideal X-ray powder diffractogram of the acetylsalicylic acid. The pole figures of the crystal planes (1 0 0), (0 0 2) and (3 1 2) were measured and the plane (1 0 0) was taken to be the primary preferred orientation plane. The ordinary X-ray powder diffractograms were measured from 7° to 42° of 2θ.

2.2.2.2. Tolbutamide. The crystal structure of the tolbutamide polymorph I in the CSD is ZZZPUS01. The diffractograms of the tolbutamide tablets were measured from 8° to 30° and the investigated pole figures were measured from the crystal planes (0 0 2), (1 0 1) and (1 1 1) of which the plane (2 0 0) was considered as the preferred orientation plane.

2.2.2.3. Carbamazepine. The carbamazepine polymorph I has a triclinic crystal structure, for which the CSD code is CBMZPN11. The pole figures were recorded from the crystal planes (0 3 2), (0 4 3) and (1 0 2). Since the carbamazepine tablets were not substantially texturized, selecting the preferred orientation plane was difficult. Moreover, due to the low crystal symmetry, strong peak overlapping occurs. However, by using the trial and error method, the best candidate for the texturization plane was deducted to be the plane (1 1 0).

2.2.2.4. Entacapone. For the reasons of confidentiality the crystal structure of entacapone was not available. Therefore, the calculations of the texture from the crystal structure are excluded. Since the indices of the diffraction peaks could not be used, the 2θ values of the peaks were used to identify them. The entacapone diffractograms were measured over the 2θ range of 8–30°. Since the peak at 9.1° was the most intense, it was taken to express the preferred orientation.

2.2.3. Intrinsic dissolution studies

2.2.3.1. Equipment. Dissolution tests were performed at 37 °C ($A = 0.5\ cm^2$). The equipment consisted of the dissolution bath (VanKel Vk 7000, VanKel Industries Inc., Edison, NJ, USA with intrinsic dissolution equipment), pump (Minipuls 3, Gilson Inc., USA) and UV–vis spectrophotometer (Unicam, Unicam Limited, United Kingdom) controlled by automated dissolution system (Dionysos IdisEE, Icalis Data Systems, United Kingdom).

2.2.3.2. Hydrodynamics. To obtain reliable dissolution data it is important to prevent turbulence and maintain reproducible laminar flow of the dissolution medium. Dissolution tests using a high speed of agitation lack discriminating value and can produce misleading results. It has been noted that *in vivo* and *in vitro* dissolution results correlate best when dissolution tests *in vitro* are carried out using very low agitation speeds [18]. It has also been concluded that the effects of pH changes on drug solubility and dissolution rate are less pronounced at higher agitation rates. To obtain reproducible results it is necessary to keep the agitation intensity constant in order to reduce variation in diffusion layer thickness, or to create a situation where the effect of a diffusional process can be neglected [19]. The rotation rate in this study was chosen to be 25 or 50 rpm. Those rates were sufficiently low to avoid turbulent flow while keeping within the optimal discriminating range.

2.2.3.3. Dissolution medium. Selection of a proper medium for dissolution depends mainly on the physicochemical properties of the drug. Many drugs show pH dependent solubility, so it is wise to apply defined pH conditions during the test. Buffers selected should be within the meaningful physiological range (pH 1–7). At pH values where the solubility of the drug compound is low, the rate of dissolution is low, but the discriminating power of the test is usually high [20].

Acetylsalicylic acid is a weak acid having pK_a of 3.5 [21]. Intrinsic dissolution studies were performed in a 20 mM HCl (pH 1.6) solution, which was prepared as follows: 1 l of 0.1N HCl solution (Ph. Eur., FF Chemicals Ab, Finland) and 10 g of NaCl (VWR international, Merck, Germany) was added to 5 l of water. The pH was adjusted to 1.6 using ortophosphoric acid (VWR international, Merck, Germany). Because acetylsalicylic acid has high solubility value (5.3–5.8 mg/ml (0.1N HCl, 37 °C)) [22] and rapidly dissolves, the selection of optimally discriminative conditions was quite problematic. A low rotation rate of 25 rpm and a low pH was used in order to lower the solubility and to decrease the dissolution rate and thus increase the discrimination power. Quantification was performed at a 265 nm wavelength.

Tolbutamide is a weak acid which a pK_a of 5.4 [21]. Intrinsic dissolution was tested in a phosphate buffer solution (pH 6.5) (USP grade, 50 mM, FF-Chemicals Ab, Finland). Since tolbutamide belongs to BCS class II its solubility value is low

(0.14 mg/ml (pH 1.5, 37 °C) and 0.82 mg/ml (pH 6.0, 37.5 °C)) [22–24]. For this reason, the rotation rate was set to 50 in order to achieve a sufficiently high level of absorbance. A dissolution medium with a high pH was chosen because in pH 6.5 most of the tolbutamide molecules are in the ionized form, where the solubility is much higher than in the molecular form. Dissolved tolbutamide was quantified using a wavelength of 226 nm.

Carbamazepine is in the unionized form throughout the whole physiological pH range (pH 1–7) [21], and thus the pH of the dissolution medium is unimportant. The intrinsic dissolution tests for carbamazepine were conducted in a phosphate buffer solution (pH 6.5) (USP grade, 50 mM, FF-Chemicals Ab, Finland). Carbamazepine has a very low solubility value (BCS class II substance) (0.10–0.95 mg/ml (approximately 20–25 °C)) [22–24]. To achieve sufficiently high absorbance level, the rpm was set at 50. Dissolved amounts were quantified using a wavelength of 285 nm.

The chemical properties of entacapone are not given here for the reasons of confidentiality. Intrinsic dissolution experiments on entacapone were conducted in a phosphate buffer solution (pH 5.5) (USP grade, 50 mM, FF-Chemicals Ab, Finland). A rotation rate of 50 rpm was used. Dissolved amounts were analyzed using 306 nm wavelength.

Six parallel intrinsic dissolution measurements were performed for the acetylsalicylic acid and tolbutamide samples. In the case of carbamazepine and entacapone triplicate measurements were conducted.

3. Results

3.1. Acetylsalicylic acid

The acetylsalicylic acid tablets compacted from the unground powder were strongly texturized and when the powder was ground the texture of the tablets was reduced (Fig. 2). As shown in Table 2 all the texture parameters are consistent with each other. Also the values obtained from the other measured pole figures are consistent with these findings.

After the intrinsic dissolution tests the texture as well as the difference between the different acetylsalicylic acid tablets was diminished. Since the dissolution rate of acetylsalicylic acid is quite high one possible explanation for this kind of behavior is the inhomogeneous texturization. It is evident that the surface region of the tablets was more texturized and when this region was dissolved the texture of the whole tablet was reduced. Based on the tablet thickness data (Table 1) approximately 0.3 mm of the acetylsalicylic tablets dissolved during the IDR test.

The other explanation for the decrease of the texture could be the faster dissolution of the particles with the crystal plane (1 0 0) towards the tablet surface. However, this might not be the case, because the IDR of the more texturized acetylsalicylic acid tablets was slightly smaller than the IDR measured from the tablets compacted from the ground powder. Moreover, the difference between the intrinsic dissolution rates of the ground and unground tablets was very small. As seen in Fig. 2 the dis-

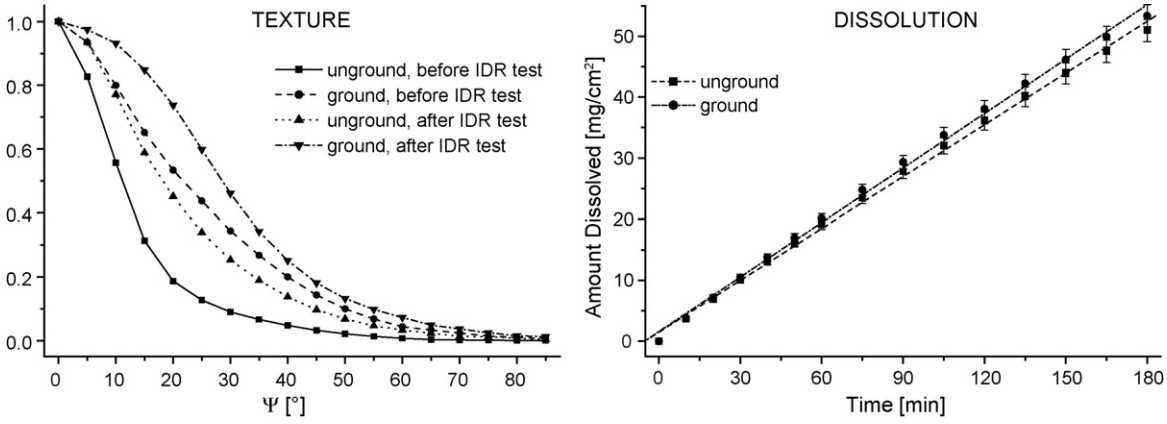

Fig. 2. The pole figure profiles of acetylsalicylic acid tablets measured from the crystal plane (1 0 0) (left) and the average intrinsic dissolution profiles of the acetylsalicylic acid samples (right). The standard deviation of the dissolution profiles is shown with error bars in the curves ($n = 6$).

Table 2
The preferred orientation and IDR values of acetylsalicylic acid

Sample	Half width of pole figure (1 0 0) (°)	Texture parameter		Intrinsic dissolution rate (mg/(cm² h))
		Structure refinement	Comparison method	
Unground, before IDR test	11.2	0.48	0.13	17 (2)[a]
Ground, before IDR test	27.8	0.65	0.24	18 (1)[a]
Unground, after IDR test	21.7	0.66	0.21	
Ground, after IDR test	28.6	0.69	0.25	

[a] Standard deviation in percents ($n = 6$).

Table 3
The preferred orientation and IDR values of tolbutamide

Sample	Half width of pole figure (2 0 0) (°)	Texture parameter		Intrinsic dissolution rate (mg/(cm^2 h))
		Structure refinement	Comparison method	
Unground, before IDR test	8.4	0.47	0.21	7.1 (0.4)[a]
Ground, before IDR test	20.6	0.66	0.62	7.7 (0.6)[b]
Unground, after IDR test	24.4	0.64	0.64	
Ground, after IDR test	30.9	0.74	0.97	

[a] Standard deviation in percents ($n = 3$).
[b] Standard deviation in percents ($n = 6$).

solution profiles almost overlap when the standard deviation of the measurements is considered.

3.2. Tolbutamide

The behavior of the tolbutamide tablets is similar to the behavior of the acetylsalicylic acid tablets (Table 3). The degree of texture of the tablets compacted from the unground tolbutamide particles is much higher than the texture of the tablets made from the ground powder. After the IDR experiment the texture of both of the tolbutamide tablets was diminished. However, unlike with the acetylsalicylic acid tablets, the intrinsic dissolution compacts are still clearly texturized. The pole figure profiles of the studied tolbutamide tablets are shown in Fig. 3.

The tolbutamide tablets compacted from the ground powder have slightly higher intrinsic dissolution rate than the more texturized tolbutamide tablets. The dissolution profiles are linear and the standard deviations of the different curves do not overlap. Moreover, according to the statistical analysis the difference between the intrinsic dissolution rates is significant (difference: 0.0111, $p = 0.0039$).

3.3. Carbamazepine

Based on the structure refinement of the texture parameters of the carbamazepine samples, the texture of the carbamazepine tablets is needle-like (Table 4). This can also be concluded from the measured pole figures. The angle between the planes (1 0 2) and (1 1 0) is approximately 30° and the intensity maxima of the pole figure of (1 0 2) is around $\psi = 60°$, therefore the intensity maximum of the pole figure of the (1 1 0) would be at approximately $\psi = 90°$. This would be the case if the particles are needle-like laying parallel to the surface and the needle ends form the crystal plane (1 1 0). However, this could not be measured using normal pole figure analysis based on the reflection of the X-rays.

When investigating the measured pole figures and diffractograms it could be seen that the carbamazepine tablets are not texturized to a large extent. According to the widths of the pole figures of (0 3 2) it could be seen that the differences between the carbamazepine samples are small (Fig. 4). However, the tablet compacted from the unground powder is most texturized. The lowest amount of texture is observed in the ground tablet after the dissolution test. The texture parameters obtained from the structure refinement and comparison methods are in agreement with these observations.

The intrinsic dissolution rates of the texturized and untexturized carbamazepine tablets are similar. However, the initial dissolution profile is not linear. This is due to the forming of carbamazepine dihydrate at the beginning of the dissolution test [25]. The dihydrate formation was confirmed by investigating the diffractograms measured form the tablets after the dissolution tests. Interestingly, although the preferred orientation does not seem to affect the dissolution rate, it affects rate of formation of the dihydrate. The rate of formation of the dihydrate is higher in the tablets compacted from the unground carbamazepine.

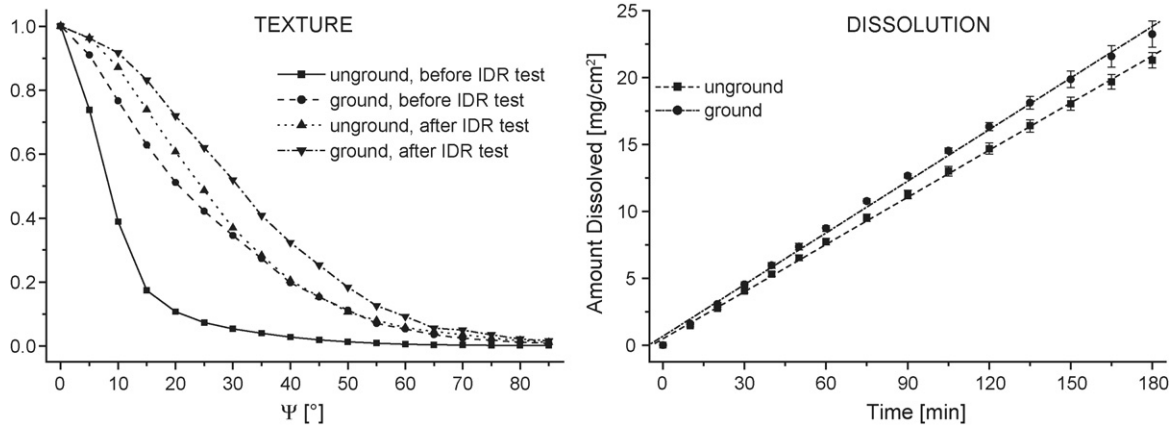

Fig. 3. The pole figure profiles of tolbutamide tablets measured from the crystal plane (2 0 0) (left) and the average intrinsic dissolution profiles of the tolbutamide samples (right). The standard deviation of the dissolution profiles is shown with error bars in the curves ($n = 6$).

Table 4
The preferred orientation and IDR values of carbamazepine

Sample	Half width of pole figure (0 3 2) (°)	Texture parameter		Intrinsic dissolution rate (mg/(cm^2 h))
		Structure refinement	Comparison method	
Unground, before IDR test	27.4	2.34	0.15	0.96 (0.1)[a]
Ground, before IDR test	39.8	1.54	0.18	0.96 (0.1)[a]
Unground, after IDR test	29.9	1.79	0.19	
Ground, after IDR test	46.8	1.07	0.40	

[a] Standard deviation in percents ($n = 3$).

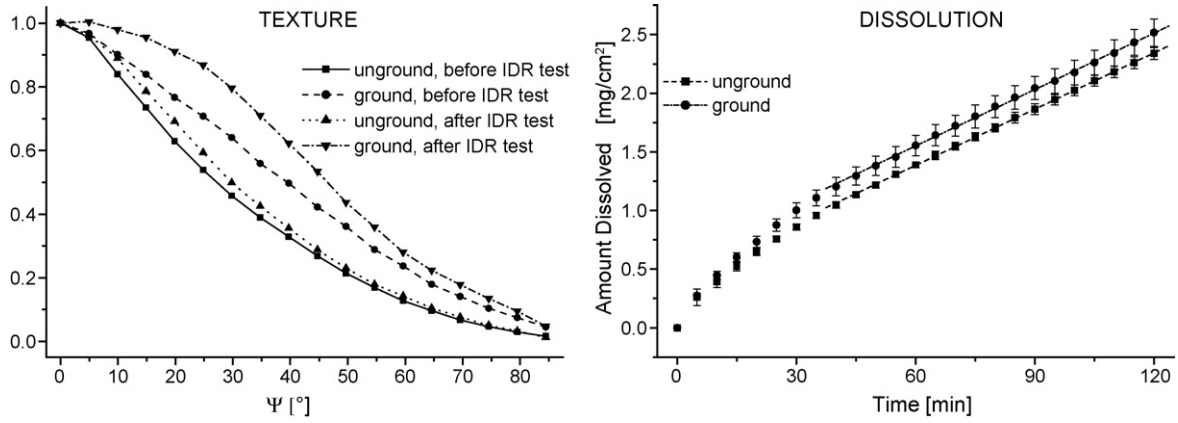

Fig. 4. The pole figure profiles of carbamazepine tablets measured from the crystal plane (0 3 2) (left) and the average intrinsic dissolution profiles of the carbamazepine samples (right). The standard deviation of the dissolution profiles is shown with error bars in the curves ($n = 3$).

After approximately 45 min of the dissolution experiment, the dissolution profiles represent the dissolution of a similar carbamazepine dihydrate layer on the top of the original tablet samples.

3.4. Entacapone

Since the crystal structure of entacapone was unknown, the structure refinement method to obtain texture parameters for the entacapone samples could not be performed. However, by investigating the diffractograms and using the pole figure and comparison methods, it could be concluded that the entacapone tablets compacted from unground powder were strongly texturized (Table 5). As seen in Fig. 5 there is less texture when the tablets were made from the ground entacapone particles.

The intrinsic dissolution rate of entacapone was low and no significant differences between samples could be found. However, once again the less texturized samples dissolved slightly faster. Moreover, in contrast with other samples, the degree of texture did not change noticeably after the dissolution experiment. This might be because only a small amount of entacapone dissolved during the measurement. In other words, not enough material dissolved from the surface of the samples to diminish the texture. The other possible explanation for this kind of behavior is the texture of the entacapone tablets is homogenous. Thus, it could be concluded that although entacapone will texturize in compression the texturization has no clear effect on the dissolution behavior. This might be due to the similar dissolution rates of different crystal planes.

4. Discussion

There are several studies which have suggested that the texture of the samples affects their dissolution properties, but no previous study has reported both texture and dissolution rate. To study the dissolution, the intrinsic dissolution test was chosen because the effect of the particle size and shape is minimized or even eliminated from the measurements [11]. It was rather

Table 5
The preferred orientation and IDR values of entacapone (the structure of entacapone was not available)

Sample	Half width of pole figure (9.1°) (°)	Texture parameter		Intrinsic dissolution rate (mg/(cm^2 h))
		Structure refinement	Comparison method	
Unground, before IDR test	13.7	–	0.12	1.1 (0.1)[a]
Ground, before IDR test	22.4	–	0.33	1.2 (0.1)[a]
Unground, after IDR test	14.4	–	0.11	
Ground, after IDR test	23.0	–	0.33	

[a] Standard deviation in percents ($n = 3$).

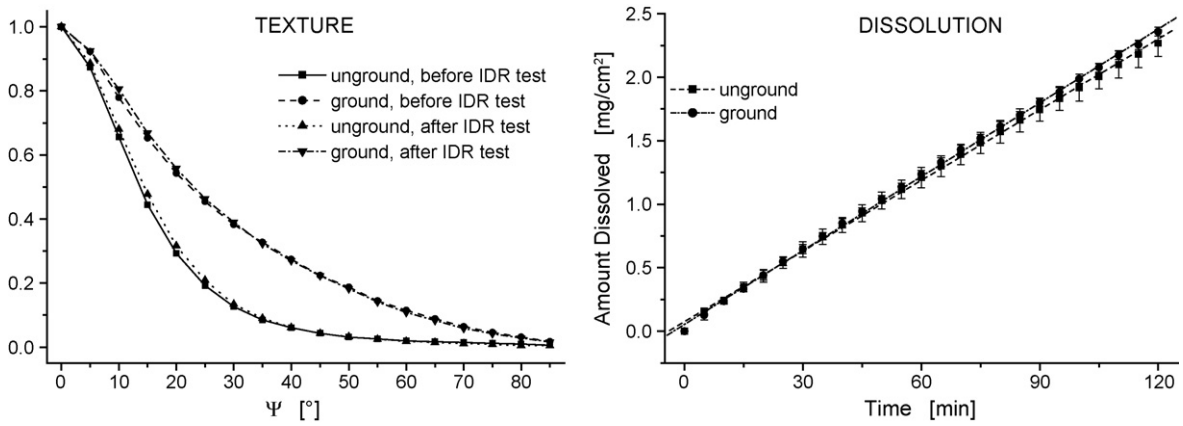

Fig. 5. The pole figure profiles of entacapone tablets measured from the crystal plane (9.1°) (left) and the average intrinsic dissolution profiles of the entacapone samples (right). The standard deviation of the dissolution profiles is shown with error bars in the curves ($n = 3$).

difficult to conclude whether the differences observed in the results are due to preferred orientation of the crystallites or to the grinding of the particles.

All of the studied APIs except carbamazepine were found to texturize strongly in compression. Moreover, the degree of texture decreased when the materials to be tabletted were ground. This was due to the decreasing particle size of the samples, which allowed a more random orientation of the particles in the tablet. The different texture measurement methods provided reasonable and comparable results. Although a perfect texture analysis would require a texture goniometer or an Eulerian cradle operated with synchrotron radiation, a very good indication of the texture can be obtained with normal laboratory Bragg–Brentano X-ray diffraction equipment.

The results of the intrinsic dissolution studies indicated that in all the samples, the tablets compacted from the ground powders dissolved slightly faster, however, the differences between the samples were small. The only appreciable difference in the intrinsic dissolution rates was obtained from the tolbutamide samples. The degree of texture was also highest in these samples. Although the dissolution rates of the carbamazepine samples were similar, the variations in the carbamazepine dihydrate formation rate were observed even if the degree of texture of carbamazepine samples was low.

The texture of the samples was also measured after the intrinsic dissolution tests. Generally, the IDR test decreased the degree of texture. The change was greatest in the tolbutamide samples but it was hardly observable in the entacapone samples. The magnitude of the change was also low in the carbamazepine samples. The primary explanation for this kind of behavior is the dissolution rate of the samples, which is lower for the entacapone and carbamazepine samples than for the acetylsalicylic acid and tolbutamide samples. The higher the rate of dissolution, the more material is dissolved during the dissolution measurement and if the texturization of the inner regions of the sample was lower than the texturization on the surface of the tablet then the degree of texture of the samples would decrease. However, this might not be the whole truth because the degree of change in the texture after the dissolution test was greatest in the tolbutamide samples although the IDR of acetylsalicylic acid was over two times higher than the IDR of the tolbutamide samples. Therefore, also the properties of the different crystal planes must also play a role in this case.

If dissolution is considered as the reverse process of crystal growth the effect of texture could be explained as follows. It is expected that the direction in which the crystals grow most intensively is also the direction in which the dissolution rate is greatest. For example, the edges of plate-like crystals dissolve most rapidly. Therefore, if the texture of the sample is plate-like, it would probably dissolve slower than a sample with a more random structure.

Theoretically, the effect of texture might be seen in the intrinsic dissolution measurements if the different crystal planes have different molecular properties. The different crystal planes might have different hydrophobicities, which may lead to easier wetting of more hydrophilic crystal planes, and therefore promote higher intrinsic solubility [8]. It is also possible that the tablet surfaces formed by texturized samples have different molecular groups in contact with the dissolution medium compared to the tablet surfaces formed by untexturized samples. Thus, the ionization degree of the molecules of weak acids and weak bases at the sample surface may vary depending on the pH of the boundary layer. The pH of the boundary layer can be quite different from the pH of the bulk solution and the magnitude of this difference depends on the buffer capacity of the bulk solution and the pK_a and solubility of the drug substance [26]. Thus, it is of importance to plan the dissolution conditions carefully. In the present study the drug substances that ionized in the physiological pH range (pH 1–7) were acetylsalicylic acid, tolbutamide and entacapone. Thus the pH may have played an important role in the intrinsic dissolution results. It would be very valuable if theoretical and/or empirical studies of the energetic properties of different crystal planes of the samples were performed in order to find out whether the crystal planes differ greatly.

The grinding process might also have an effect on the results by producing internal strains and defects in the crystals. According to most of the theories, the strain which develops around the dislocation core causes a higher free energy in that region of the surface. This would increase the solubility and dissolution rate

of the material. Theoretically, this could have increased the IDR of the ground samples in the present study.

It is expected that when the solubility is poor and dissolution rate is low, the discrimination between texturized and less texturized samples is best. However, although the unground entacapone samples texturized more and had lower intrinsic dissolution rate than the acetylsalicylic acid samples, there was no clear difference apparent between the entacapone dissolution samples. It is known that the aqueous solubility of the drug substance is one of the most important factors that determines the dissolution rate of the drug. However, there are many other physicochemical factors that may have role in controlling the dissolution rate. In most cases more than one factor has an influence on the results and therefore it is quite difficult to evaluate the effect of one particular factor to the overall dissolution process.

5. Conclusions

The differences in the intrinsic dissolution rates of the tablets compacted from the texturizing and less-texturizing powders were observed to be statistically insignificant, except in the case of tolbutamide. In all cases, however, the IDR of the tablets compacted from the ground material was slightly higher. Moreover, the degree of texture seemed to have some effect on the rate of hydration of carbamazepine at the beginning of the intrinsic dissolution test.

It is difficult to rationalize the results explicitly because there are several processes and sample properties, which control the dissolution process. Although the intrinsic dissolution method, which is believed to reduce the effect of particle size, was used, it is uncertain whether the differences between the intrinsic dissolution rates of the ground and unground samples resulted entirely from the different degree of texture of the samples. The grinding process, which was used to diminish the texturization tendency of the samples, could have altered the properties of the sample crystals. However, this effect might both increase (more crystal strains) and decrease (less effective surface) the dissolution rate of the samples.

The present study proved that the preferred orientation of the sample does not affect the intrinsic dissolution rates of the studied APIs to a great extent. The difference was statistically significant only with tolbutamide samples. However, if the sample tends to express polymorphism or pseudo-polymorphism, or if amorphicity is present in the samples, the effect of texture might be obscured by some of these phenomena. Still, although the preferred orientation effect is small, it must be considered as a possible source of error when performing accurate IDR studies.

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