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RESEARCH PAPER

Investigation of Solid Phase Composition on Tablet Surfaces by Grazing Incidence X-ray Diffraction

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ABSTRACT

Purpose To investigate solid state transformations of drug substances during compaction using grazing incidence X-ray diffraction (GIXD).

Methods The solid forms of three model drugs–theophylline (TP), nitrofurantoin (NF) and amlodipine besylate (AMB)–were compacted at different pressures (from 100 to 1000 MPa); prepared tablets were measured using GIXD. After the initial measurements of freshly compacted tablets, tablets were subjected to suitable recrystallization treatment, and analogous measurements were performed.

Results Solid forms of TP, NF and AMB showed partial amorphization as well as crystal disordering during compaction; the extent of these effects generally increased as a function of pressure. The changes were most pronounced at the outer surface region. The different solid forms showed difference in the formation of amorphicity/crystal disordering. Dehydration due to compaction was observed for the TP monohydrate, whereas hydrates of NF and AMB were stable towards dehydration.

Conclusions With GIXD measurements, it was possible to probe the solid form composition at the different depths of the tablet surfaces and to obtain depth-dependent information on the compaction-induced amorphization, crystal disordering and dehydration.

KEY WORDS amorphous · compaction · dehydration · grazing incidence diffraction · phase transformation

INTRODUCTION

Administration of drugs by the oral route is the most common method of drug delivery, and among the oral dosage forms, tablets are the preferred type of dosage form in use. The tablet manufacturing process involves an essential unit operation of compaction, in which powder material is converted to tablet by application of pressure (1). Pharmaceutical substances used in the tablet formulation can occur in various solid forms, such as polymorphs, hydrates and amorphous forms (2). These solid forms differ in their density, stability, solubility, dissolution rate, habit, and mechanical properties, for instance. The solid forms can influence the compaction behavior of a material, and on the other hand, compaction can induce solid-state phase transformations. Therefore, fundamental knowledge about

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the effect of solid forms on compaction, and vice versa, is required in order to ensure the adequate performance of tablets.

Various studies have shown the influence of the solid forms on the compaction behavior. For example, the orthorhombic form of paracetamol showed better tabletability than the monoclinic form, which was attributed to parallel sliding planes present in the crystal structure of the orthorhombic form (3). Sun and Grant have shown that the presence of slip planes in sulfamerazine form I crystals provides a better compressibility than form II (4). A similar phenomenon was observed for a homologous series of parabens (methyl, ethyl, propyl, butyl), in which lack of slip planes in methyl paraben led to poor tabletability compared to the other parabens studied (5). In the case of phenobarbital, tensile strength of the tablets was affected by the specific surface area of the different polymorphs (6). Jaffe and Foss observed that removal of water of crystallization from the hydrate structure dramatically reduces the tablet strength (7). The monohydrate form of p-hydroxybenzoic acid was found to make stronger tablets compared to the anhydrate form (8). These studies have revealed a relationship between the compaction behavior and the crystal structure of material, and this phenomenon has important ramifications for the pharmaceutical applications of different solid forms (9,10).

Application of high pressure during the compaction, on the other hand, can influence the solid form stability and can induce solid-state transformations, such as polymorphic transformations, desolvation and amorphization/crystal disordering (11). Polymorphic transformation during compaction has been observed for caffeine (12), sulfabenzamide (12), maprotiline hydrochloride (12), carbamazepine (13), sulfanilamide (14), phenylbutazone (15), piroxicam (16) and sulfathiazole (17). Pressure-induced polymorphic transformations have in fact been utilized to obtain the new polymorphic forms of material (18). For indomethacin and chlorpropamide, it has been observed that compaction leads to polymorphic transformation as well as amorphization (19–21). Compaction-induced amorphization was also observed for carbamazepine form III and tolbutamide form I (22). Two solvates of celecoxib, dimethyl acetamide and dimethyl formamide, have been shown to undergo desolvation during compaction (23). Considering that the different solid forms may behave differently in dissolution, the phase transformations due to compaction may also influence the tablet performance. In comparison to the number of studies reported on the phase transformations during other unit operations (e.g. milling (24), granulation (25) and drying (26)), reported work on the compaction-related phase transformations is limited so far. In particular, a systematic investigation of the effect of compaction on hydrate forms of pharmaceutical substances is lacking. To the best of our knowledge, dehydration of hydrates due to compaction has been previously reported for theophylline monohydrate (27,28), cyclophosphamide monohydrate (29) and carbamazepine dihydrate (24). Therefore, further work is needed to gain detailed understanding on the phase transformations during compaction and to elucidate the underlying mechanism.

The present study was undertaken to evaluate the compaction-induced solid-state changes in three model drug substances, viz. theophylline, nitrofurantoin and amlodipine besylate. The anhydrate and hydrate forms of these drugs were compacted, and the obtained tablets were analyzed using grazing incidence X-ray diffraction (GIXD). These three model drug substances were selected to study the compaction effect on 1) the different types of hydrates with theophylline monohydrate (channel) and nitrofurantoin monohydrate (isolated site), and 2) two hydrate forms of amlodipine besylate, namely monohydrate and dihydrate.

The GIXD technique is unique in the sense that it can provide detailed information on the phase composition at the different depths parallel to the tablet surface (22,30–32). As the surface is the first part of the tablet that comes into contact with dissolution medium, information on the surface layer is important with respect to the initial dissolution of the tablet. Moreover, pressure distribution during the compaction is not homogenous, specifically at the tablet surface, which may result in a different solid form composition on the surface as compared to the overall tablet. The bulk measurements of entire tablet mass usually do not provide detailed information about the surface. With GIXD technique, it is possible to carry out the depth-profiling of tablets in a non-invasive manner, and also to determine the phase composition on the surface.

MATERIALS AND METHODS

Materials

Theophylline (TP) anhydrate form II was purchased from Shandong Xinhua Pharmaceutical Co. Ltd (Shandong, China). Nitrofurantoin (NF) anhydrate β form was obtained from Unikem A/S (Copenhagen, Denmark). Amlodipine besylate (AMB) anhydrate was a gift from Matrix Laboratories Limited (Secunderabad, India). All materials conformed to European Pharmacopeial specifications. Milli-Q water and organic solvents (analytical or HPLC grade) were used for preparation of other solid forms of the drugs.

The theophylline anhydrate form II (TP-AH, CSD ref. code BAPLOT01) was recrystallized before use by dissolving 5 g of the received TP in 250 ml of ethanol at 70°C, followed by cooling to room temperature. The crystals were

separated by vacuum filtration and were dried at 50°C for 1 h in an oven. To prepare theophylline monohydrate (TP-MH, CSD ref. code THEOPH01), 50 g of TP was dissolved in 1000 ml of water at 85°C, and subsequently the solution was cooled to room temperature. Crystals were separated by vacuum filtration and were kept open in a fumehood for drying. The dehydrated form of theophylline (TP-DeH) was prepared by heating the TP-MH at 75°C in an oven for overnight.

The received nitrofurantoin anhydrate β form (NF-β, CSD ref. code: LABJON02) was dried at 120°C for 1 h in an oven prior to use. To prepare anhydrate α form of NF (NF-α, CSD ref. code LABJON01), the received NF (2.5 g) was dissolved in a mixture containing 160 ml of acetic acid and 40 ml of water at 80°C. The crystals obtained on cooling to room temperature were dissolved by re-heating to 80°C, and 200 ml of hot acetone was added. The flask was kept open at 40°C, and crystals were separated after 9 days by vacuum filtration and dried in a fumehood (33). Nitrofurantoin monohydrate Form II (NF-MH, CSD ref. code HAXBUD) was prepared by dissolving 15 g of received NF in a mixture containing 750 ml of acetone and 350 ml of water at 55°C. The solution was cooled to room temperature. After 24 h, the obtained crystals were separated by vacuum filtration and dried at 50°C for 1 h in an oven. The dehydrated form of nitrofurantoin (NF-DeH) was prepared by heating the NF-MH in an oven at 120°C for 2 h.

The anhydrate form of AMB (AMB-AH, CSD ref. code XOZRUZ) was used as received, and monohydrate (AMB-MH) and dihydrate (AMB-DH) forms were prepared by methods described elsewhere (34).

All materials were passed through a 300 μm sieve before the compaction. All batches were analyzed by X-ray powder diffraction (XRPD), and the measured patterns were compared with the diffractograms calculated from the crystal structures.

Methods

Compaction

The powder of each solid form was compacted using a hydraulic press (SPX Power Team, Rockford, IL, USA) with a flat-faced die (Ø 13 mm) providing a uni-axial compression. Two pressure cylinders, C53C (low-pressure range) and C254C (high-pressure range), were used. The compaction was carried out at pressures varying from 100 to 1000 MPa with a dwell time of 1 min. The tablets were prepared with an average weight of 200 mg, and thickness was between 1.5–2.0 mm. The compaction was done under controlled temperature and humidity conditions (21 ± 1°C, 35 ± 5% RH).

Grazing Incidence X-ray Diffraction (GIXD)

The GIXD measurements were performed using a PANalytical X'Pert Pro MPD diffractometer (PANalytical B.V., Almelo, Netherlands). The instrument was equipped with a $\theta/2\theta$ goniometer and a proportional counter detector. All measurements were carried out with nickel-filtered CuK_α radiation ($\lambda = 1.5418$ Å) generated at a tube voltage and current of 40 kV and 50 mA, respectively. The incident beam optics consisted of a 0.04- rad Soller slit, a 10 mm equatorial mask and a 0.25° axial divergence slit. The 0.04-rad Soller slit and a 0.18° parallel-plate collimator were placed in the diffracted beam prior to the proportional counter. The instrument alignment and calibration were performed according to the instructions given in the operation manual. A custom-built sample holder was used to carry out GIXD measurements of the tablets. Before each measurement, the height of the sample holder was carefully adjusted to achieve the desired alignment of compact.

By small variations in the incident angle during GIXD measurements, the penetration depth of the X-rays can be controlled, allowing depth profiling of the sample, and therefore, phase transformations on the surface can be effectively studied. For TP and NF tablets, measurements were performed with the incident angles of 0.25°, 0.5°, 1.0°, 2.0° and 5.0°, and the incident angles used for AMB tablets were 0.5°, 1.0°, 2.0°, 5.0° and 10.0°. At each incident angle, a corresponding penetration depth was calculated using the Parrat equation (31,35). The linear absorption coefficients were calculated from the molecular formula and the measured density (36). The density measurements were done using a helium pycnometer AccuPyc 1330 (Micromeritics, Norcross, GA, USA). The penetration depth was 3.3 to 94.5 μm for TP, 2.5 to 75.6 μm for NF and 3.6 to 76.4 μm for AMB tablets. Profile fitting of the diffractograms was performed with winPLOTR (37), and data were analyzed and plotted with Microsoft office Excel 2003 and Origin 8 (OriginLab Corporation, Northampton, MA, USA).

Measurement Procedure and Data Analysis

Two GIXD measurements were performed for each tablet. The first measurement was carried out immediately after the compaction. The tablet surface in contact with the upper punch was measured. Afterwards, the tablet was placed in a desiccator providing a suitable environment for recrystallization, and the second measurement was done on the next day (on the same tablet surface). The following environmental conditions were used for the recrystallization: 97% RH (from potassium nitrate solution) for TP-MH, NF-MH, AMB-MH and AMB-DH, ethanol atmo-

sphere for TP-AH and TP-DeH, acetone atmosphere for NF-α, NF-β and NF-DeH, and methanol atmosphere for AMB-AH. The specific recrystallization condition was chosen so that only original solid form used in tablet preparation would recrystallize, thus making comparison of the profile fitting results before and after the recrystallization treatment feasible.

From the conventional diffractograms of each material, a narrow range was selected for the GIXD measurements in order to reduce the experiment and data analysis time. The identification of the different solid forms of the same material was possible from the selected range. Data on measured density, critical angle, GIXD measurement range and peaks monitored are given in Table I. The critical angle (α_c) is the incidence angle (α) at which the decrease in the total external reflection is highest, and it was calculated from Eq. 1 (31):

$$\alpha_c = \cos^{-1}(1-\delta) = \cos^{-1}\left(1 - \frac{\mathcal{N}e^2\lambda^2}{4\pi\varepsilon_0(2\pi mc^2)}\right) \quad (1)$$

where δ is the real part of the complex refractive index, $\mathcal{N}$ is the number of electrons per irradiated unit volume, ε_0 is the permittivity of vacuum, e and m are the charge and mass of the electron, respectively, and c is the velocity of light.

The whole profile fit was performed on the diffractograms, and subsequently profile fitted data of the fresh tablet, were compared with the recrystallized sample. An example of such a comparison for AMB-AH is given in Fig. 1. It can be observed that the intensity of the peaks has increased and the width of the peaks based on FWHM has decreased due to the recrystallization treatment. After the recrystallization treatment, the relative increase in the cumulative peak height and the area, as well as the relative decrease in the full width at half maximum (FWHM), were calculated for each tablet. In this work, the extent of amorphization, i.e. reduction in three-dimensional molecular arrangement in the crystal lattice, was determined from peak area, whereas the manifestation of crystal disordering, i.e. the decrease in crystallite size and increase in crystal defects and lattice strain due to the compaction, was evaluated by the line-broadening analysis using full width at half maxima (FWHM).

RESULTS

The phase purity of all solid forms used in this work was verified using conventional XRPD measurements. The experimental powder pattern for each sample was in good agreement with the pattern calculated using the crystal structure, if available (data not shown). Additionally, all solid forms were analyzed using thermal methods (DSC, TGA) and Raman and NIR spectroscopy. The results from these techniques were in accordance with the data reported in literature (25,34,38–40). The phase identity of two forms, TP-DeH and NF-DeH, requires special mention here. The XRPD pattern of TP-DeH was identical to the TP-AH, and the NF-DeH was found as poorly crystalline NF-β.

Theophylline (TP)

Three solid forms of theophylline, TP-AH, TP-MH and TP-DeH, were compacted at three different pressures (100, 500 and 1000 MPa). After the recrystallization treatment, the peak area increased for all the TP tablets (Fig. 2a),

Table I Density, Critical Angle, GIXD Measurement Range and Peaks Monitored Along with the Corresponding Miller Indices for All Sample Materials

Material	Density[a] (g/cm^3)	Calculated critical angle (°)	GIXD measurement range (°2θ)	Peaks monitored[b] in GIXD measurement (°2θ)	Corresponding Miller indices[c]
TP-AH	1.48	0.181	6–14	7.3, 12.8	(200), (201)
TP-MH	1.45	0.170	6–14	9.0, 11.6, 13.4	(011), (020), (021)
TP-DeH	NM	0.180	6–14	7.3, 12.8	NA
NF-α	1.64	0.188	9–20	9.9, 14.5, 17.7, 18.8, 19.7	(001), (10$\bar{1}$), (011), (101), (002)
NF-β	1.59	0.185	9–20	14.5, 16.7, 18.7, 19.7	(011), (012), (004), (013)
NF-MH	1.55	0.176	9–20	10.3, 12.4, 14.1, 17.5, 19.6	(002), (102), (200), (211), (212)
NF-DeH	NM	0.190	9–20	14.5, 16.6, 19.0	NA
AMB-AH	1.33	0.172	4–16	5.9, 10.6, 11.7, 13.1, 14.4, 15.3	(002), (102), (004), (023), (122), (114)
AMB-MH	1.36	0.173	4–16	4.9, 9.8, 14.0	NA
AMB-DH	1.37	0.175	4–16	5.0, 10.5, 12.6, 13.5, 15.7	(100), (110), (201), (210), (30$\bar{2}$)

[a] From helium pycnometry

[b] Underlined peaks were monitored but not used in profile fitting

[c] From the crystal structure

NM not measured (the value for the anhydrate was used), *NA* crystal structure not available

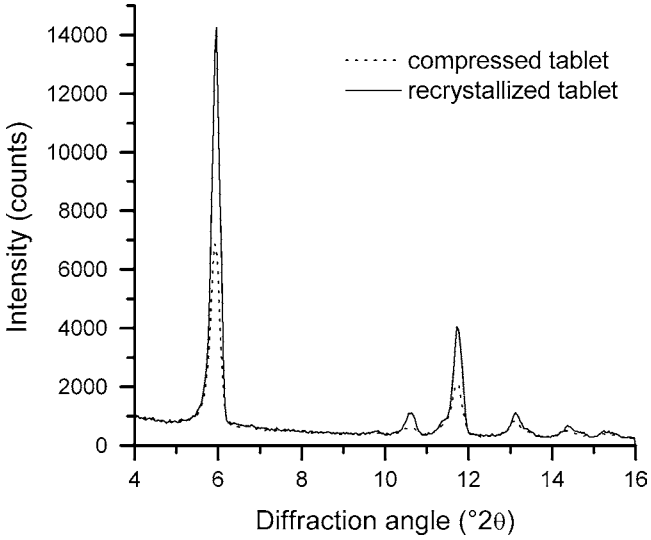

Fig. 1 Representative example of the effect of the recrystallization treatment. The tablet was prepared from amlodipine besylate anhydrate at 1000 MPa, and the penetration depth was 3.5 μm.

suggesting that the TP solid forms had undergone partial amorphization during the compaction. The extent of amorphization in the case of the TP-AH tablets increased as a function of the compaction pressure. This means that the higher energy input with increasing pressure had translated into the amorphous formation. In contrast, such a clear pressure dependency was not evident for the TP-DeH and TP-MH tablets. For TP-DeH, the increase in the peak area was higher for the tablets compacted at 100 MPa and 500 MPa, and it was lowest for the tablets compacted at 1000 MPa.

In Fig. 2a, the increase in peak area as a function of the penetration depth exemplifies the depth dependency of amorphization. For the TP-AH and TP-DeH tablets, the general trend was a decrease in amorphicity with increasing depth. The increase in the peak area at the top most surface layer (lowest depth) for some of the tablets (e.g. TP-AH at 1000 MPa) was lower than at the depth thereafter. This could be due to partial recrystallization of the generated amorphous form on the surface during the compaction. The depth-dependent amorphization in TP-AH was also related to the compaction pressure. The difference in extent of amorphization at the different depth levels was greatest in the tablets prepared at 1000 MPa and lowest in the tablets prepared at the 100 MPa.

As shown in Fig. 2b, the peak widths measured as FWHM decreased for all the TP tablets after the recrystallization treatment, indicating that crystal disordering had occurred in all three TP solid forms. The crystal disordering was found to be dependent on two factors: the solid form used and the pressure applied during the compaction. The relative decrease in FWHM was in the following order: TP-DeH tablets>TP-AH tablets>TP-MH tablets. The extent was lowest for the TP-MH, which indicates greater stability of this form towards crystal disordering. The decrease in peak widths after recrystallization was higher with increasing compaction pressure. The depth dependency of the decrease in FWHM was negligible, suggesting that for TP tablets magnitude of disordering was almost similar at the all depths.

The TP-MH tablets measured after the compaction showed characteristic peaks of anhydrate (Fig. 3a), implying a partial transformation of the TP-MH to the TP-AH during compression. The TP-AH peaks disappeared after the treatment of the tablet in 97% RH environment, which could be attributed to transformation of TP-AH to TP-

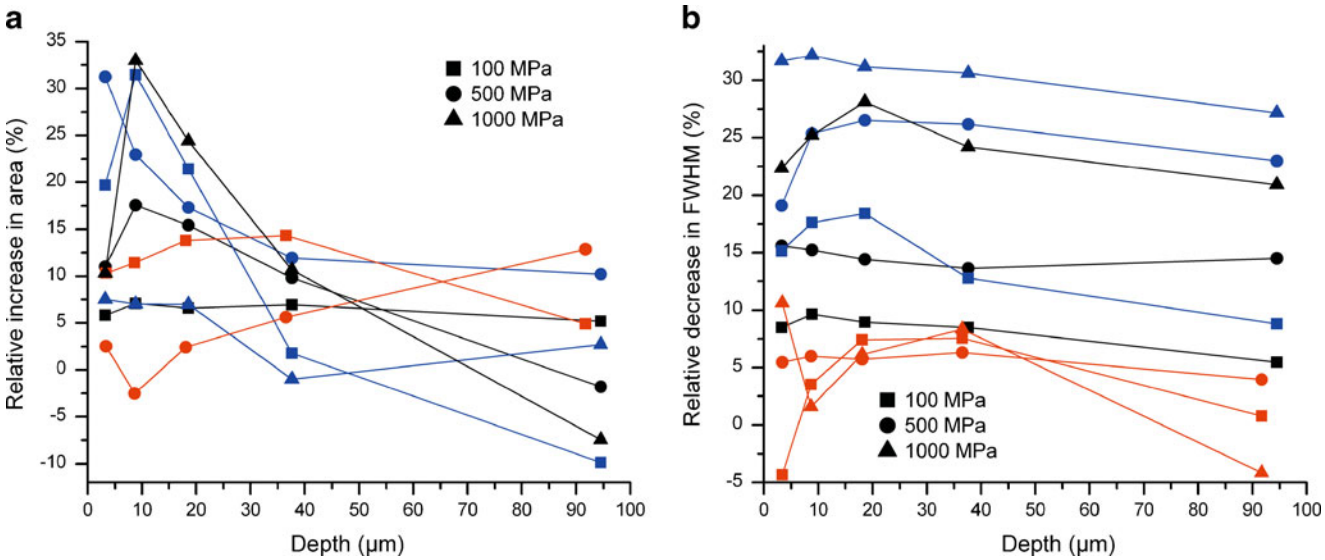

Fig. 2 The relative increase in peak area (**a**) and the relative decrease in peak FWHM (**b**) after the recrystallization treatment of the theophylline tablets as a function of the penetration depth and the compression pressure. ((—)) TP-AH, ((—)) TP-MH, ((—)) TP-DeH.

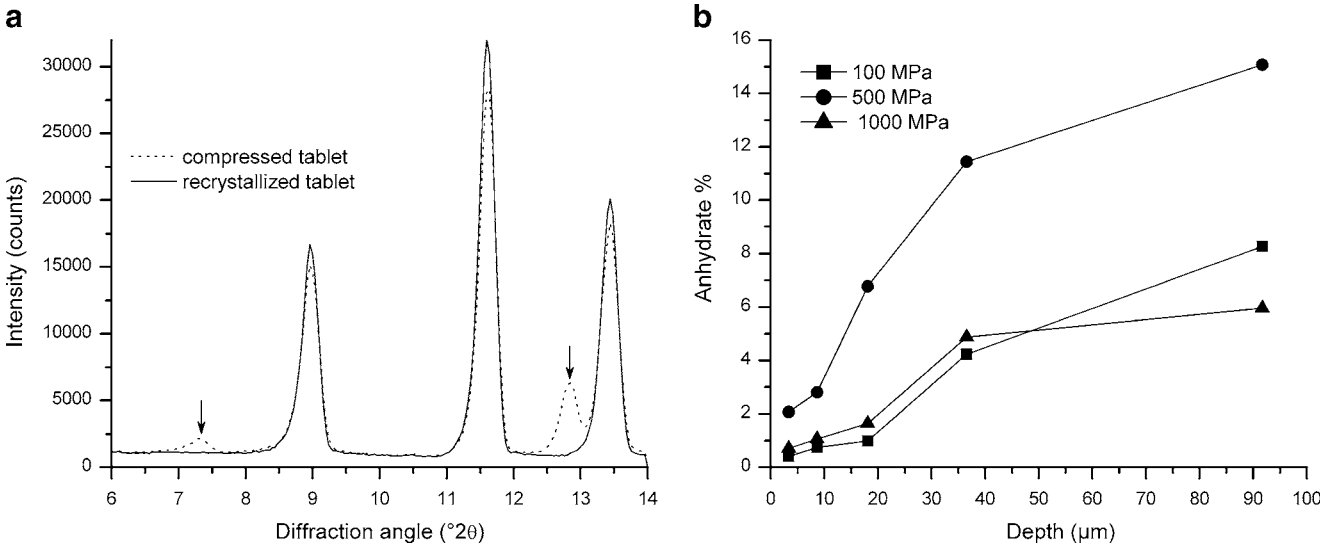

Fig. 3 (**a**) An example of dehydration of theophylline monohydrate observed immediately after the compaction. The tablet was prepared at 500 MPa, and the penetration depth was 36.6 μm. The arrows indicate characteristic diffractions of theophylline anhydrate in the compressed tablet that disappears after the treatment at 97% RH. (**b**) Amount of anhydrate formed as a function of the compression pressure and the penetration depth.

MH. This phenomenon of transformation of the TP-MH to TP-AH is interesting and also of significance to the dissolution of the tablets (41). The dehydration of TP-MH due to the compaction has been reported earlier by two research groups (27,28). They also observed transformation of TP-MH to TP-AH after compaction. However, our results are not in complete agreement with the previous work, and this is discussed later.

The amount of TP-AH in the tablets was calculated from the reference data obtained from TP-AH powder. At all three pressures, TP-AH fraction increased as a function of the depth (Fig. 3b), meaning that the surface had the lowest amount of TP-AH. Looking at the influence of pressure, the highest amount of TP-AH was found in the tablets prepared at 500 MPa, whereas the tablets compacted at 100 and 1000 MPa contained a lower amount. It was rather surprising that the extent of transformation was highest in the tablets compacted at the intermediate pressure of 500 MPa. Another intriguing aspect of this transformation was the increase in TP-AH amount with increasing depth, which could be due to one or more of the following explanations: 1) Several studies have shown that the regions of highest density are often located deeper in the tablets and that surface might have a lower density (42,43). This would mean that the particles would have experienced less friction on the surface and consequently less energy for transformation. 2) Water released due to the hydrate-to-anhydrate transformation from the inner layers will probably escape from the tablet surface. While escaping, the water molecules might actually cause TP-AH on the outer surface region to convert back to TP-MH. Thus, the amount of anhydrate will appear lower on the surface. 3) It could also be the case that the anhydrate conversion occurred after the compaction and during the GIXD measurements.

To evaluate the third hypothesis, we carried out continuous XRPD measurements of the TP-MH tablet compacted at 500 MPa. As can be seen in Fig. 4, the peak corresponding to TP-AH at 12.8°2θ evolved and increased in intensity with longer storage time, and simultaneously the intensity of the TP-MH peak at 13.5°2θ decreased. Thus, it can be concluded that TP-MH in tablets transforms to TP-AH with time. The complete transformation to

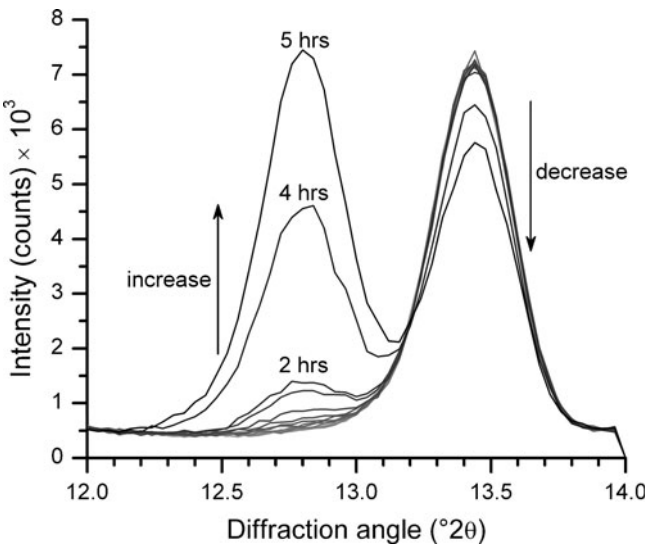

Fig. 4 The dehydration of theophylline monohydrate observed in the tablet (the measurement environmental conditions were 23 ± 2°C and 33 ± 5% RH).

the anhydrate was observed after 46 h. However, when measured in similar environmental conditions TP-MH powder did not show any transformation within 72 h, so it is logical to consider that the transformation of TP-MH to TP-AH is promoted by compaction.

This compaction-mediated phenomenon could be further explained by the concept of "mechanical activation" (10,44). Hüttenrauch *et al.* reported that the chemical decomposition of ergocalciferol was promoted after compaction, and this effect was also related to the applied compaction pressure during tablet preparation. They attributed this phenomenon to mechanical loading of the solid substance during compaction. This increases structural energy as well as spontaneity towards reaction, which in their case was chemical decomposition. In the current work, similar mechanical activation of TP-MH during compaction could increase the propensity for the physical reaction. Thus, the transformation of TP-MH to TP-AH occurs after compaction, but it does not take place for untreated powder material. Similarly, in the study concerning the compaction of carbamazepine polymorphs, it was observed that form II tablets showed conversion to the form III on storage (13). For cyclophosphamide monohydrate, also dehydration and transformation to the anhydrate form were found to be accelerated after milling or compression (29).

Overall, it can be concluded that the transformation of TP-MH to TP-AH, as observed here, occurs as a consequence of mechanical activation during the compaction. The obtained activated state has a higher susceptibility towards transformation to TP-AH in the environmental conditions employed. As observed in Fig. 4, the amount of transformation increased with time, which possibly explains the increase in the amount of TP-AH with increasing depth for the GIXD measurements (Fig. 3b). Furthermore, due to the influence of environment on the transformation, it is not found to be clearly pressure dependent (Fig. 3b). On the basis of available data, however, it is not possible completely to rule out the TP-MH to TP-AH transformation during the compaction, as well as the role of explanation no. 1 and 2 mentioned before. Nevertheless, the mechanical activation theory appears to be the best explanation for the observed transformation of TP-MH to TP-AH.

Nitrofurantoin (NF)

The four solid forms of NF were compacted at pressures of 250, 600 and 1000 MPa. The lowest pressure of 250 MPa was chosen so that it was possible to obtain intact tablets with flat surfaces within the 1 min dwell time. As seen in Fig. 5a, the increase in the peak area after the recrystallization treatment was highest in the NF-DeH tablets, indicating a substantial amount of amorphicity present in the compressed tablets. The increase in the peak area was higher in the upper surface region. In the case of the NF-DeH, a part of amorphization had occurred during the preparation itself. Though the conventional diffractogram of NF-DeH matched with the diffractogram of NF-β, peaks were broad and poorly resolved (data not shown). This indicates that the NF-DeH was a poorly crystalline material as reported earlier (39,45). Therefore, increase in the peak area due to the recrystallization of NF-DeH tablets should stem from the dehydration-induced as well as compaction-induced amorphization. It was not possible to resolve the individual contribution from these two effects. Nevertheless, the change in crystallinity after the compaction is still of relevance for pharmaceuticals, because the tablet properties could be altered by such a phase transformation. Moreover, the comparison of the NF-DeH and NF-β tablets after the recrystallization (both were exposed to the same environment) indicated that the crystallinity of the NF-DeH tablet was substantially higher than that of the NF-β tablets. The formation of poorly crystalline dehydrated material might take place during the post-crystallization drying step, and its crystallinity may increase during secondary manufacturing and/or storage. Moreover, the hydrate formation during granulation and dehydration during the drying of granules are often encountered, providing yet another situation for the formation of the dehydrated material. These scenarios could introduce dehydrated material in the tablets, which may then show different crystallinity as compared to the starting material.

The peak area also increased for the tablets prepared from two anhydrate forms, NF-α and NF-β. But in the case of the NF-MH tablets, the peak area was found to increase or decrease depending on the compaction pressure and depth (Fig. 5a). Overall, for the NF tablets' increase in peak area was not clearly dependent on the compaction pressure. Also, except for the NF-DeH tablets the increase in peak area remained almost constant at the all depths. The compaction-induced amorphization in the tablets prepared from the particular NF solid form was therefore comparable at all the depths.

The compaction-induced crystal disordering was clearly dependent on the solid form used in the preparation of the NF tablets (Fig. 5b). The relative decrease in the FWHM was in the order of NF-DeH>NF-β>NF-MH>NF-α, which indicated that the sensitivity of the solid forms towards the disordering differed. As was the case with peak area, the decrease in FWHM also remained almost constant, and it was dependent on neither the compaction pressure nor the depth.

Overall, the effect of compaction stress was evident in all the NF-tablets by means of the amorphization and crystal disordering. The extent of these mainly differed depending on the solid form used in the preparation of tablets. No

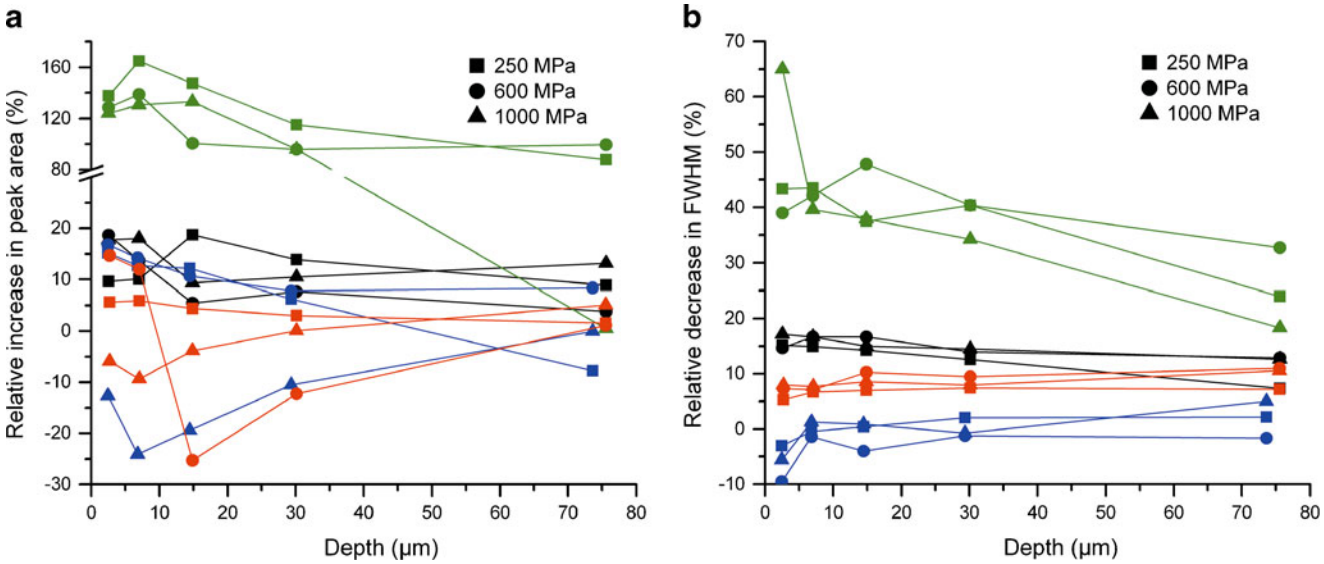

Fig. 5 The relative increase in peak area (**a**) and the relative decrease in peak FWHM (**b**) after the recrystallization treatment of the nitrofurantoin tablets as a function of the penetration depth and the compression pressure. ((——)) NF-β, ((——)) NF-α, ((——)) NF-MH, ((——)) NF-DeH.

polymorphic or hydrate-anhydrate transformation was observed in the NF tablets.

Amlodipine Besylate (AMB)

As can be seen in Fig. 6a, the tablets of AMB showed amorphization induced by the compaction done at 100, 500 and 1000 MPa. The magnitude of amorphization was higher in the upper region of the surface and decreased with the increase in depth. Moreover, in the AMB tablets, the amorphization was found to be dependent on the compaction pressure used, and the highest and lowest amorphicity levels were obtained with the pressure of 1000 and 100 MPa, respectively. At a closer look, Figure 6a indicated that the extent of amorphization at or above the depth of approximately 15 μm was also dependent on the solid form used, with AMB-MH, AMB-DH, and AMB-AH tablets showing the highest, intermediate and lowest amorphicity, respectively. Below a depth of 15 μm, the amorphization was comparable for all the tablets irrespective of the solid form, compaction pressure and depth of measurement.

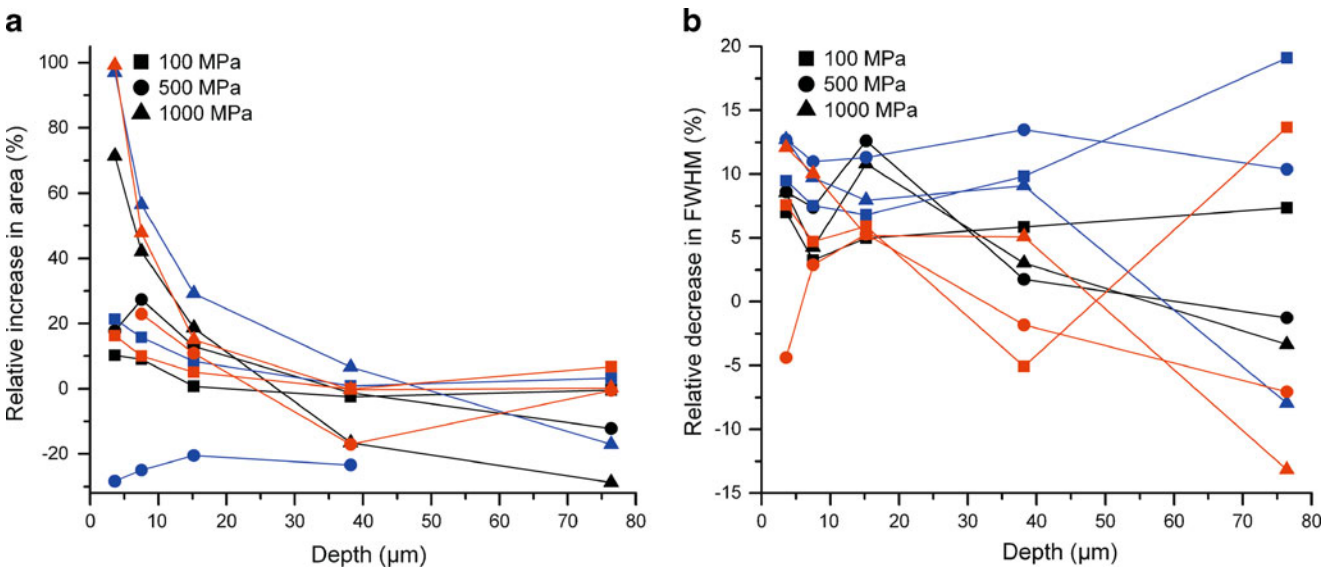

Fig. 6 The relative increase in peak area (**a**) and the relative decrease in peak FWHM (**b**) after the recrystallization treatment of the amlodipine besylate tablets as a function of the penetration depth and the compression pressure. ((——)) AMB-AH, ((——)) AMB-MH, ((——)) AMB-DH.

Based on the FWHM data, there are signs of disordering at the very surface regions of the tablets (Fig. 6b). At all the compaction pressures, the decrease in peak width was highest for the tablet prepared from AMB-MH. However, the pressure and the depth dependencies of the relative decrease in FWHM were not very clear. This is most probably due to data analysis errors. As evident in Fig. 1, several of the peaks in AMB-AH tablets were very weak and broad, and this was also the case for AMB-MH and AMB-DH tablets, giving rise to less accurate FWHM determinations. Nevertheless, based on the available data the compaction-induced disordering could still be verified for the AMB tablets.

DISCUSSION

The aim of this work was to understand the compaction-induced phase transformations by employing GIXD measurements of the tablets. To understand variation in the phase transformation at the different regions of the tablets, depth profiling was carried out. In pharmaceutical context, GIXD has been employed previously to study phase transformation during dissolution (31) and compaction (22) and to evaluate effective penetration depth of X-rays in the tablets (32). In the current work, the potential of GIXD was further extended to evaluate the difference in stability of the different solid forms of three model drug substances towards the compaction.

The solid forms of theophylline (TP), nitrofurantoin (NF) and amlodipine besylate (AMB) showed partial amorphization and crystal disordering due to the compaction. The crystal disordering here refers to decrease in crystallite size, increase in crystal defects and increase in lattice strain. The magnitude of these changes generally co-related with the applied compaction pressure, in such a way that the changes became more pronounced with higher compaction pressure. Also, the different solid forms of the same material showed difference in the extent of transformation. This is very important for the solid form selection in pharmaceutical development, where the stable form is usually preferred in order to avoid any transformation during processing and storage. This work has highlighted the difference in stability of the solid forms towards the compaction-induced stress.

The observed amorphization and crystal disordering could introduce high energy states of a substance in the obtained tablet. The stability and dissolution behavior of the high energy states differ from that of the crystalline substance. Generally, the amorphous form of a substance has the higher dissolution rate, and thus the tablet surface may show faster dissolution due to the compaction-induced amorphization. The practical dissolution rate, however, is also affected by the formulation and processing factors, and it is not possible to determine the exact effect of the compaction-induced changes based on the available results. Further work, including simultaneous dissolution and solid phase monitoring of the tablets with different amorphicity at the surface, is necessary to evaluate the effect on dissolution.

Moreover, the surface consisting of a disordered state may show higher propensity towards the chemical and physical reactions. This tendency was indeed observed for the TP-MH tablets, which showed conversion of TP-MH to TP-AH after compaction. On the contrary, TP-MH powder kept under similar conditions was stable. During compaction, primary friction and fracture of the particles can bring an increase of both entropy and enthalpy and can thus stimulate such a physical change (10,44). The role of shear stress has been described in detail for the polymorphic transformation of chlorpropamide (19). Hydrate-to-anhydrate transformation of theophylline due to compaction has been reported by Suihko *et al.* (28). They observed an increase in the extent of conversion with increasing pressure. In contrast, Otsuka *et al.* observed a decrease in conversion with increasing compaction pressure (27). Our results did not show a clear relation between conversion and compaction pressure. Due to the differences between the experimental procedures used in this work and the previous reports, direct comparison of results is not possible. Nevertheless, the hydrate-to-anhydrate transformation was observed in all. In this work, we were able to monitor the transformation at different depths in the tablets. Our results suggest that the transformation is likely to be a result of 'mechanical activation' induced by the compaction stress. It has been proposed that such a transformation proceeds by first loosening the bonding configuration in the initial phase, followed by the generation of a high-energy intermediate phase (11). If the energetics are favorable, nucleation of a new phase can take place in the intermediate phase, and the crystals of new phase can be generated from growth of the nuclei. The nucleation and growth steps are contingent upon the ability to cross the required energy barriers, and, thus, the final outcome of the mechanical activation will vary according to the conditions to which tablets are exposed. In the case of TP-MH, it can be suggested that the ambient environmental conditions are conducive for the nucleation and growth of the TP-AH from the intermediate phase.

The hydrate forms of the other two substances, NF and AMB, were stable towards transformation to the anhydrate form. The susceptibility of TP-MH towards the transformation to anhydrate could probably be associated with the structural factors. The water molecules in the crystal structure of TP-MH are located in channels, which might make it easier for the water molecules to exit the crystal

lattice and facilitate the transformation to the anhydrate. In NF-MH, on the other hand, water molecules which are isolated from each other by the host molecules need more energy to escape from the crystal structure. This inference is also supported on the basis of the dehydration temperature of hydrates. The dehydration onset temperatures of TP-MH and NF-MH measured using thermogravimetric analysis are about 60°C and 120°C, respectively. The lower dehydration temperature for TP-MH indicates that water molecules can be removed rather easily as compared to the NF-MH. However, this observation does not hold for AMB-DH, because with a lower dehydration temperature (45°C), compaction-induced dehydration was not observed in this case. Overall, in this work hydrate structures were found to be relatively stable towards conversion to the anhydrate form due to compaction. However, further work covering other pharmaceutical hydrates is necessary to obtain a complete picture of the effect of compaction on the hydrate stability. The current work has focused on the tablets prepared using pure drug substance, which is unlikely in the normal pharmaceutical operations. However, information on the compaction stability of the solid form can aid in solid form selection during early preformulation. Incorporation of the excipients in formulation can modify the observations made with the pure drug substance. One logical presumption would be that the cushioning effect of the excipients can minimize amorphization and crystal disordering of the drug substance. The studies involving excipient would be a logical extension of the current work and can enhance our understanding of the role of excipients during compaction-induced transformations.

CONCLUSIONS

Compaction-induced amorphization and crystal disordering were observed during the compaction of the solid forms of theophylline, nitrofurantoin and amlodipine besylate. For the individual drug substance, the changes were found to occur at different extents for the various solid forms. For nitrofurantoin and theophylline, the highest degree of amorphicity was observed in the tablets prepared from the dehydrated material. Generally, the changes due to compaction were more pronounced at the highest compaction pressure used. Moreover, for amlodipine and theophylline tablets, changes were highest at the outmost surface region, but the nitrofurantoin tablets did not show a clear depth dependency for the compaction-induced changes. In this work, hydrate-to-anhydrate transformation due to the compaction was only observed for the theophylline monohydrate, whereas hydrate forms of nitrofurantoin and amlodipine besylate did not show such a phenomenon. The structural aspects of the hydrate crystal were found to affect the solid-state stability of hydrates during compaction. However, to generalize the effects of the structural factors, more substances need to be studied. Overall, in this work, hydrate structures were found to be relatively stable towards compaction-induced transformation to the anhydrate form. The GIXD technique afforded a detailed understanding of the phase transformation occurring on the tablet surface. The unique ability of this technique to provide depth-dependent information makes it highly useful for obtaining relevant information from the surface regions of tablets.

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