Pharmaceutical Research, Vol. 23, No. 4, April 2006 (© 2006)
DOI: 10.1007/s11095-006-9785-8

Research Paper

Depth Profiling of Compression-Induced Disorders and Polymorphic Transition on Tablet Surfaces with Grazing Incidence X-ray Diffraction

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Received October 31, 2005; accepted December 16, 2005

Purpose. The importance of induced crystal disorders like crystallite size, crystal defects, and amorphicity with respect to the dissolution rate of the drug has been discussed in many cases. Thus, the characterization of these properties is of great importance in the pharmaceutical formulation development, although the exact correlation between disorders and dissolution rate is still unclear. The aim of this study was to analyze pharmaceutical tablets with grazing incidence X-ray diffraction, which enables the depth profiling of the crystallographic properties of the tablets. To study and clarify the potential of grazing incidence diffraction in the analysis of pharmaceutical materials, the effect of the compaction process on the surface of tablets was examined.

Methods. Carbamazepine, tolbutamide, and chlorpropamide tablets, compacted using different compression pressures, were studied using grazing incidence angle X-ray diffraction. The effects of compression on the crystallographic properties were investigated as a function of the distance from the tablet surface.

Results. The surfaces of the tolbutamide and chlorpropamide tablets were disordered due to the compression. The manifestation of the disorder was deduced to be due to amorphicity, small crystallite size, and amount of crystal defects. The changes were mainly on the surface and diminished strongly as a function of the distance from the surface of the tablet. Moreover, the changes were dependent on the compression pressure used. The changes on the surface of the carbamazepine tablets were also due to the compression but these changes were not clearly dependent on the depth nor the compression pressure. The partial phase transition took place in the chlorpropamide tablets due to the compression. The magnitude of the transition was not highest on the surface because amorphization and texturization also took place on the tablet surface during the compression.

Conclusions. The present study proved that grazing incidence X-ray diffraction is a potential novel research tool to reveal crystallographic transformations taking place on the surfaces of the tablets induced, for example, by compression pressure.

KEY WORDS: amorphicity; compression; disorder; grazing incidence diffraction; tablets.

INTRODUCTION

Of all pharmaceutical dosage forms, tablets are the most common way to deliver the medicament to the patient. As possible interactions with the environment (e.g., dissolution medium) preferably take place on the surface of the tablet, study of the tablet surface is crucial to obtain a more extensive conception of the tablet sample. There is a wide range of research techniques varying from spectroscopic methods to hardness measurements for studying the physicochemical properties of tablets. However, commonly used techniques, such as differential scanning calorimetry (DSC), conventional X-ray powder diffraction (XRPD), or infrared spectroscopy (IR), do not offer adequate information about the surface (1).

During the tablet compaction process, particles of the tablet formulation will fracture and/or deform to form the tablet. Because pressure distribution during the compression in the tablet die is not homogeneous, the compacted tablets could also be nonhomogeneous. The region in which the pressure is uneven is the surface of the tablet. This means that the physicochemical properties in the outer layers of the tablet surface could differ from the properties of the tablet interior. The surface could have lower crystallinity, for example, or some polymorphic transitions could have taken place on the surface of the tablet (2–4). Defects on the crystal surface or disorders in the lattice due to compaction are known to give rise to structure-sensitive diffusion of the solvent used (5). The nonuniform distribution of disorders in drug crystals or in different tablet batches of the same material can have a significant influence on drug dissolution from dosage forms.

The surface of pharmaceutical tablets can be studied with various methods. However, only a few techniques offer

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a possibility of depth profiling. With most of the applied methods, the information obtained comes either from a very thin surface layer or from the bulk of the sample. Grazing incidence X-ray diffraction (also called glancing angle X-ray diffraction) is an X-ray diffraction technique offering the possibility of depth profiling (1,6). With grazing incidence diffraction (GID) it is possible to record normal X-ray diffraction patterns as a function of X-ray penetration depth. Although GID is applicable with normal laboratory X-ray diffractometers, it has not yet been widely applied in the field of pharmaceutical materials research. However, GID is a standard method in other fields of materials research. It has been applied, for example, in the depth profiling of strain distribution and structure (7–10). With pharmaceuticals, Depnath *et al.* have used GID for the depth profiling of phase transformations during the dissolution of indomethacin and theophylline tablets (1).

The penetration depth of the X-rays is affected by the diffraction geometry, sample absorption, and reflectance of the X-rays. The penetration depth is normally calculated using the equation postulated by Parrat (11). The critical angle where the total reflection of the X-rays occurs is normally from 0.2° to 0.5°. The value of the critical angle depends on the wavelength of the X-ray radiation used, the sample density, and the electron density of the sample.

There are several reports of pharmaceuticals that undergo phase transition due to compression (4,12–15). The transition could be polymorphic (12,13), anhydration (14), or amorphization (15). Because the change in the crystal structure of the sample occurs in all these processes, they can be investigated with X-ray diffraction. Furthermore, the transformations could be depth profiled using GID.

In the present study, GID was applied to the depth profiling of the surface disorders after the compaction of some active pharmaceutical ingredients. The expression disorder here stands for small crystallite size and crystal defects (microstrains) as well as amorphicity. The materials studied were carbamazepine, tolbutamide, and chlorpropamide.

MATERIALS AND METHODS

Materials

All samples used were obtained from commercial sources. The samples were stored in closed containers in ambient conditions and were used as received. Chlorpropamide form C was prepared by heating the as-received chlorpropamide powder (form A) in the oven at 120°C for 12 h. The physical state of the samples was characterized with DSC and XRPD.

Carbamazepine is used as an anticonvulsant and has three anhydrous polymorphic forms. In compaction, the dihydrate form of carbamazepine has been reported to transform partly to the anhydrous β (III) form (14). The commercial polymorphic form (III or β) was used in this study.

Tolbutamide is an oral hypoglycemic agent that appears in four polymorphic forms (16). In this study, the most stable polymorphic form (I) was used. There are no reports of any transitions during compaction of tolbutamide.

Chlorpropamide is also an oral hypoglycemic agent existing in at least two polymorphic forms, of which the more stable form (A) was used in the present study. According to Matsumoto *et al.*, the stable form of chlorpropamide (A) transforms in compression partly to the metastable form C and a noncrystalline solid (15).

Methods

Tablet Preparation

The tablet samples investigated in this study were prepared using a hydraulic punch and a flat-faced tablet die with a diameter of 13 mm. The pressure cylinders used were C53C (low-pressure range) and C254C (high-pressure range), both made by SPX Power Team (Rockford, IL, USA). The compression pressures varied from 100 to 1000 MPa, and in all cases the compression was maintained for 1 min. The maximum relative error of the pressure measurement was estimated to be 5%. The average weight of the tablets was 252 mg with a standard deviation of 3%.

Grazing Incidence Diffraction

The GID measurements were performed with a laboratory X-ray diffractometer, Philips (Panalytical) X'Pert Pro MPD (Almelo, Netherlands). The radiation used was nickel-filtered CuKα, which was generated using an acceleration voltage of 40 kV and cathode current of 50 mA. The primary beam was collimated using a 0.25° axial divergence slit and a 10° equatorial mask. An 0.18° parallel-plate collimator was used prior to the proportional counter, and 0.04-rad Soller slits were placed in both the primary and secondary beam lines. Prior to the measurements, the instrument was aligned and calibrated carefully according to the instructions given in the operation manual. A special, height-adjustable, tablet-sample holder was made for the measurements.

GID is a technique in which the incident angle remains fixed as the detector turns normally around the axis of the goniometer. In this study the incident angles varied from 0.2° to 10°. Each incident angle corresponds to the penetration depth, which depends on the sample material. The penetration depth can be calculated using the Parrat equation (11). The absorption coefficients of the samples were calculated theoretically on the basis of the molecular formula of the samples. The densities of the samples were measured using a helium pycnometer AccuPyc 1330 from Micromeritics (Norcross, GA, USA).

To study the instrumental broadening, the reference sample was prepared by compressing silicon powder in the same tablet die that was used to prepare the tablet samples. The reference was measured with all the incident angles used with the pharmaceutical tablets. All obtained data were analyzed and plotted with winPLOTR (17), Excel (Microsoft), and Origin (OriginLab) programs.

Measurement Procedure

Each tablet was measured shortly after compaction. Then the sample was placed into a desiccator with H_2O–EtOH atmosphere to recrystallize it. The sample was measured again on the following day. The recrystallization efficiency of the H_2O–EtOH atmosphere was confirmed

(with conventional X-ray diffraction) by investigating the partly amorphous batches (prepared with milling) of each sample material. The adequacy of the duration of the treatment was also confirmed.

For the GID measurements, ten different incident angles were used and the measurements were performed in triplicate. The incident angles were selected so that the surface region from approximately 2 to 50 μm was measured. To reduce the measurement and the data analysis time, a small range was selected from the diffractograph of each material. The selected regions contained several characteristic reflections. To reduce the possible effect of preferred orientation, all the reflection peaks were used in the data analysis process. For the data analysis, the whole profile fit was performed to the measured diffractographs. When the proper fit was achieved, the fitted data were compared with the fitted data obtained from the same recrystallized sample. An example of the diffractographs of compressed and recrystallized tolbutamide tablets is given in Fig. 1. As can be seen, the intensity of the peaks has increased, and the width of the peaks has decreased, due to the recrystallization treatment. The relative increase in the cumulative peak height and the area was calculated, as well as the average relative decrease in the full width at half maximum (FWHM) and the integral breadth due to the recrystallization process. Both the Gaussian and the Lorentzian fractions of the integral breadth were determined. Moreover, by using the reference data obtained from the silicon tablet, the crystallite size and crystal defects of the tablets were calculated.

Carbamazepine. The carbamazepine samples were measured from 12° to 16.5° 2θ with incident angles varying from 0.2° to 2°. Thus, the depth of penetration varied from 2.6 to 50 μm. The diffraction peaks corresponded to the crystal planes (002), (100), $(10\bar{2})$, $(11\bar{1})$, (012), (110), and (020) (18). The calculated absorption coefficient of carbamazepine was 5.20 cm^2/g, and the measured density was 1.34 g/cm^3.

Tolbutamide. For the tolbutamide tablets, the diffractograph was measured from 8° to 14° 2θ. This region contains three peaks with Miller indices (200), (101), and (210) (18).

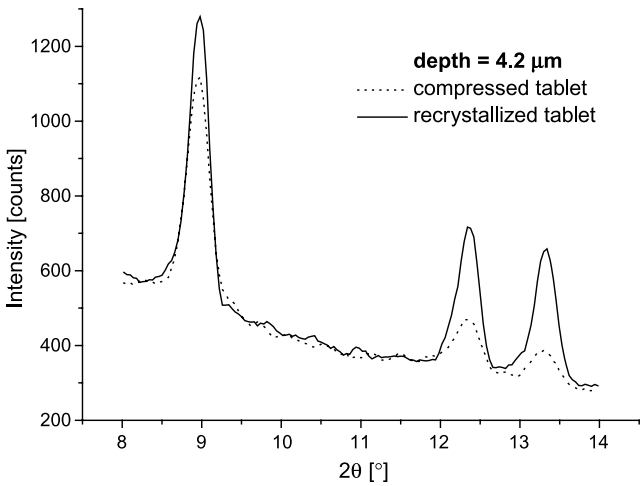

Fig. 1. An example of the effect of the recrystallization treatment on the tolbutamide tablet. The compression pressure was 700 MPa and the penetration depth was 4.2 μm.

The grazing angles used were from 0.25° to 5°, corresponding to the penetration depths 1.7 and 45 μm, respectively. The calculated absorption coefficient of tolbutamide was 15.9 cm^2/g, and the measured density was 1.25 g/cm^3.

Chlorpropamide. The calculated absorption coefficient of chlorpropamide was 28.7 cm^2/g, and the measured density was 1.45 g/cm^3. The diffraction peaks from the crystal planes (012), (200), (201), (112), (014), and (113) (18), with intensity maxima situated in the diffractograph of chlorpropamide between 17.5° and 23° 2θ, were measured. To study the pressure-induced transition from the polymorphic form A to the form C, a region between 11° and 16° 2θ was also measured. The penetration depths from 2.0 to 42 μm were obtained using grazing angles from 0.5° to 10°.

RESULTS

Carbamazepine

The compaction of carbamazepine tablets was difficult due to the obvious elasticity of the carbamazepine powder. As seen in Fig. 2A, the recrystallization treatment decreased the areas of the diffraction peaks in all the carbamazepine tablets except those compacted with 700 MPa. In this case, the trifling amorphization did not depend on the depth. The decrease in the peak widths was also small, and clear depth dependence was observed only in the tablets compacted with the smallest pressure (Fig. 2B).

The line broadening can be analyzed further using line profile analysis and the reference data obtained from the silicon reference sample measurements. When this was carried out, the crystallite size and the crystal defects could be clarified. The crystallite size of the carbamazepine tablets compacted at 100 MPa was smallest on the surface of the tablets, whereas the size of the crystallites was significantly greater in the inner regions of the tablets. On the contrary, the crystallite size of the other carbamazepine tablets decreased slightly as a function of depth.

The carbamazepine tablets contained many crystal defects with no dependence on the distance from the tablet surface. The relation between the tablet compression pressure and the amount of defects was logical but nevertheless significant. The tablets compacted at 100 MPa contained fewer defects.

In general, it was difficult to make any difference between the properties of the carbamazepine tablets compacted with various pressures. The most intact tablets were made with the smallest compression pressure (100 MPa). The tablets compacted at higher pressures often had cracks and/or cap formations. Sometimes carbamazepine tablets even broke immediately after they were removed from the tablet die. It can be said that the poor results obtained with GID measurements are related to the poor tabletting properties of carbamazepine.

Tolbutamide

According to Fig. 3, the surface regions of the tolbutamide tablets were disordered. The relative increase in the

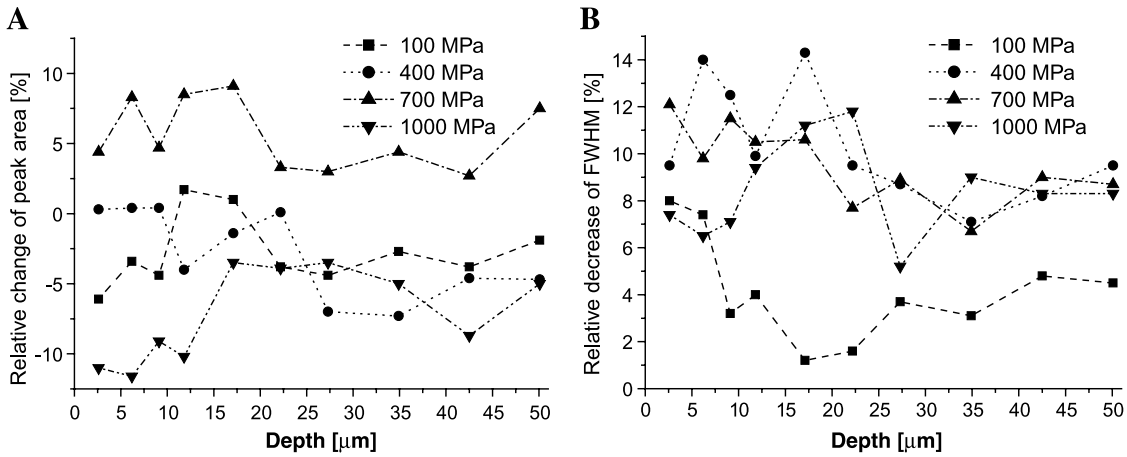

Fig. 2. The relative increase in peak area (A) and the relative decrease in peak FWHM (B) due to the recrystallization treatment of the carbamazepine tablets as a function of the penetration depth and the compression pressure.

peak area due to the recrystallization treatment was highest in the surface region (Fig. 3A), which meant that the surface of the tolbutamide tablets had undergone partial amorphization during the compaction process. The magnitude of this amorphization was highest in the tablets compacted at 400 MPa and lowest in the tablets that were made using the highest compression pressure (1000 MPa). The illogical order of the amount of amorphization of the tolbutamide tablets compacted with different pressures could be explained as follows: The lowest compression pressure (100 MPa) did not have enough energy to induce a significant amount of amorphicity on the tablet surface. The highest degree of amorphousness was generated using the compression pressures 400 and 700 MPa, which had a suitable amount of energy to induce amorphicity. However, the highest compression pressure (1000 MPa) had so much energy that the induced amorphicity already started to recrystallize during the time the compression was maintained (1 min).

In addition to the amorphization, the surface of the tolbutamide tablets contained more crystal defects and smaller crystallites than the interior of the tablets. This was manifested by wider peaks in the diffractographs measured using smaller incidence angles (Fig. 3B). The widest peaks were measured from the tablets compacted at 1000 MPa; however, the tablets compacted at the lowest pressure (100 MPa) had wider peaks closer to the tablet surface. In general, the higher the compression pressure used, the wider the peaks obtained. The inner regions of the tolbutamide tablets also had wider peaks before recrystallization treatment. This was probably partly because the received tolbutamide powder might, for example, have possessed crystals with incomplete crystallinity.

The crystallite size of the tolbutamide tablets was smallest on the surface of the tablets and increased as a function of depth (Fig. 4A). The tablet compacted with the lowest pressure (100 MPa) had a significantly larger crystal-

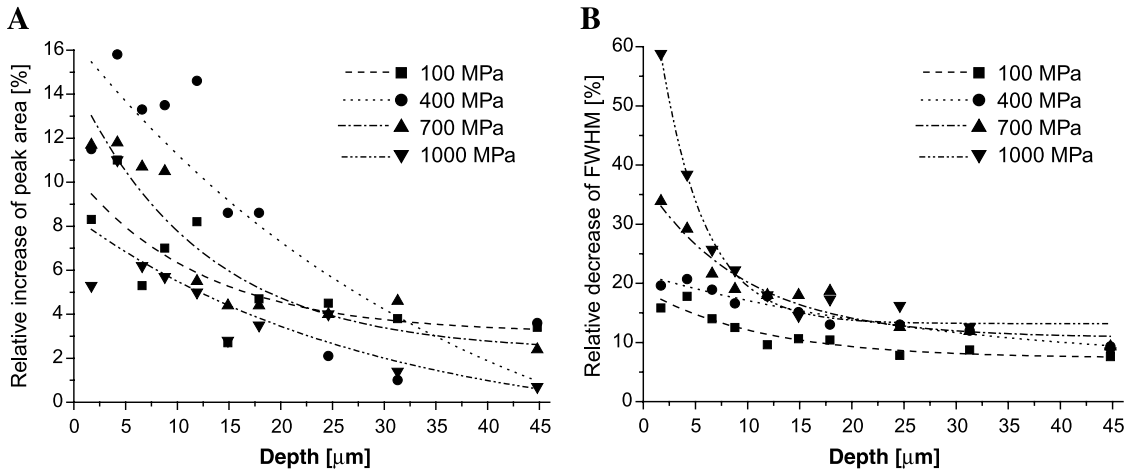

Fig. 3. The relative increase in peak area (A) and the relative decrease in peak FWHM (B) due to the recrystallization treatment of the tolbutamide tablets as a function of the penetration depth and the compression pressure used. The lines are exponential fits to the measurement points.

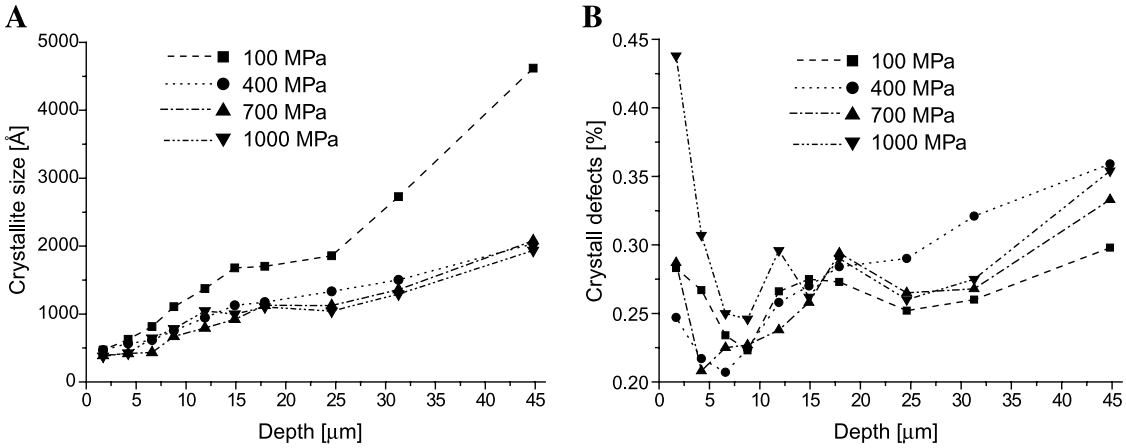

Fig. 4. The crystallite size (A) and crystal defects (B) of the tolbutamide tablets as a function of the penetration depth and the compression pressure used. The results were obtained from the compacted tablets using the silicon tablet as reference.

lite size than the other tablets. Although no reference data on the compaction properties of tolbutamide were available, based on Fig. 4A, the compaction behavior of tolbutamide is most probably brittle. Figure 4B shows that the compression-induced crystal defects on the thin surface layer of the tolbutamide tablets.

Chlorpropamide

The previously reported amorphization of chlorpropamide due to compression (15) was also confirmed in the present study, but the amorphization seemed to properly cover only the surface regions of the chlorpropamide tablets (Fig. 5A). The magnitude of the amorphization was highest in the tablets compacted at 700 MPa and lowest in the tablets compacted with the smallest pressure. As with the tolbutamide tablets, the highest pressure used was so high that presumably recrystallization took place in the tablet die during the compaction process.

The depth dependence of the relative decrease in peak width was not very clear. The peaks narrowed along the entire measuring range due to the recrystallization treatment. One possible explanation was imperfect crystals in the received chlorpropamide powder. However, as seen in Fig. 5B, the peak width of the tablets compacted at 700 and 1000 MPa had clearer depth dependence. Nevertheless, the variation in the results was high and the exponential fit drawn in Fig. 5B must be considered with caution. These exponential fits were calculated mainly only to guide the eye.

The chlorpropamide tablets compacted at 100 MPa had the largest crystallite size and fewer crystal defects than the tablet compacted at higher compression pressures. The crystallite size of the chlorpropamide tablets was higher in the inner regions of the tablets. However, the tablets compacted at 700 MPa had only a slight increase in crystallite size as a function of depth. This could be due to the some kind of measurement error but, more probably, was linked to the amorphicity of the tablets in question.

The amount of crystal defects in the chlorpropamide tablets increased as the more inner regions of the tablets were investigated. This might be due to the compression,

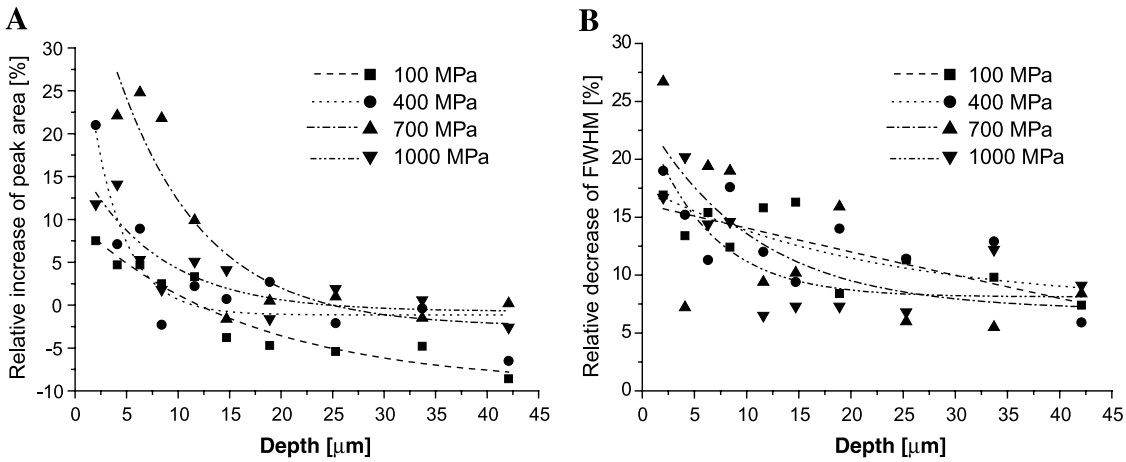

Fig. 5. The relative increase in peak area (A) and the relative decrease in peak FWHM (B) due to the recrystallization treatment of the chlorpropamide form A tablets as a function of the penetration depth and the compression pressure used. The lines are exponential fits to the measurement points.

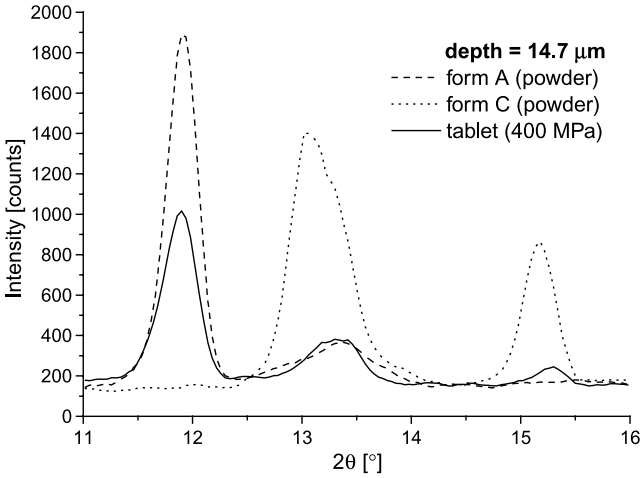

Fig. 6. The effect of compression on the chlorpropamide powder. The diffractographs of pure chlorpropamide A and C powder are drawn as reference.

which had broken up the crystallites on the tablet surface and thus had changed the crystal defects to the grain boundaries.

As previously reported (15) and as seen in Fig. 6, chlorpropamide undergoes a partial phase transition from form A to form C during the compaction process. According to the present results, the extent of change was proportional to the distance from the tablet surface. The reference data obtained from the form A and C powders were used to calculate the fraction of the different chlorpropamide forms in the compressed tablets.

As seen in Fig. 7A, the fraction of form A was smallest on the surface of the tablets. However, the fraction of form C was highest not on the surface but in the interiors of the tablets (Fig. 7B). The most obvious explanation for this is the other transformation taking place during the compression, namely, the amorphization of the surface. However, even this is not the whole truth because if the curves in Figs. 5A and 7A and B are summarized, the sum is not 100%. The missing part could be explained by probable measurement and data analysis errors and by the effect of preferred orientation because chlorpropamide crystals seemed to orient preferentially in compression. Moreover, the preferred orientation effect was probably dependent on the depth. However, the texture of the chlorpropamide tablets was not measured in the present study.

The pressure dependence of the phase transition of the chlorpropamide was quite poor. Nevertheless, the higher the pressure used, the less form A was observed in the compacted tablets. The lowest amount of form C was observed from tablets compacted using the lowest compression pressure (100 MPa).

DISCUSSION

The purpose of this study was to clarify the use of GID for analyzing pharmaceutical tablets. The characterization of phase transitions on the tablet surfaces using GID has previously been reported (1), but the present study is the first to demonstrate the use of GID for investigating the pressure-induced disorders on the tablet surfaces as a function of depth. The GID proved to be a useful addition to the wide range of research methods in pharmaceutical materials analysis. However, due to the specific nature of the GID, the measurements and the data analysis must be done with great care. Inaccurate instrument and/or sample alignment could affect the results dramatically. Moreover, as always, when studying polycrystalline samples with X-ray diffraction, the effect of the possible preferred orientation of the sample must be taken into account. To avoid the effect of texture, several diffraction peaks must be used for the data analysis, if possible. If a reference sample is needed, it is advisable to use the sample itself (after appropriate treatment, e.g., recrystallization) when possible.

To perform GID analysis, it is recommended to use flat-faced tablet samples with a rigid surface. If the surface of the sample is nonuniform, the sample could be misaligned in the goniometer, for example. The nonuniform surface could have an effect on the results. This might have been the case in this study with the carbamazepine tablets. Although no certain conclusions could be drawn on the basis of one specific case, the poorly tabletting compounds could be difficult to study using GID.

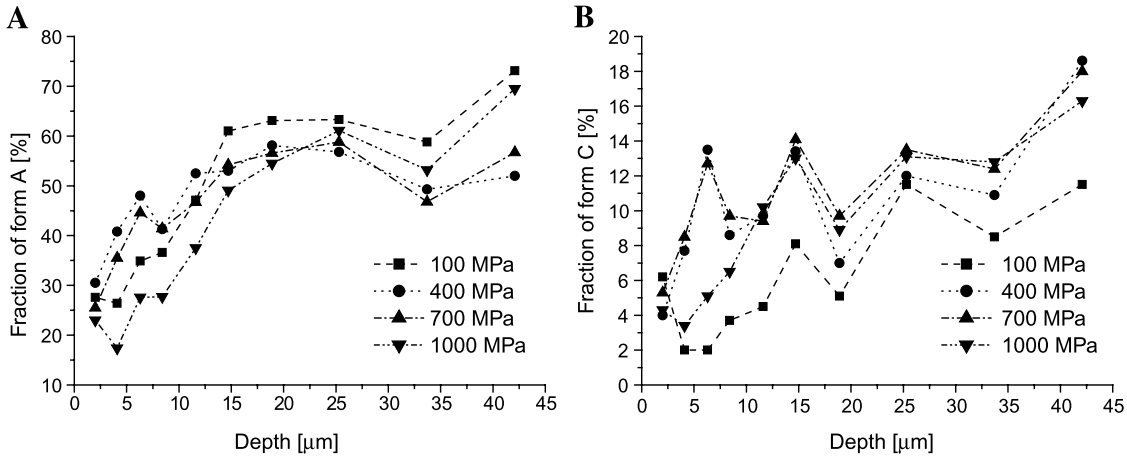

Fig. 7. The fraction of chlorpropamide form A (A) and form C (B) as a function of the penetration depth and the compression pressure used.

Another possible factor that could affect the results obtained with GID could be the physical dimensions of the tablet samples. In the present study, the used tablets weighed approximately 250 mg, and their diameter and thickness were 13 and approximately 1.5 mm, respectively. The bigger the tablet diameter, the more diffracting volume is present and good counting statistics could be obtained with shorter measurement times. The tablet dimensions also affect the pressure distribution in the compaction process. For example, if the studied tablets had been thicker and/or smaller (or thinner and/or bigger), the obtained results could have been different.

It is known that amorphous and crystalline materials have different dissolution properties. In general, the amorphous form of a drug substance will dissolve better because the transition of the molecule from the crystal lattice to the solution requires more energy than the transition from the amorphous phase (19,20). More extensively, if imperfections are present in the crystalline tablets, these imperfections might alter the properties of the crystals so that the energy needed to transit the drug molecule to the solution phase diminishes (21). In the light of these observations, it can be speculated that the tablets with more disordered surface could dissolve more rapidly, especially in the intrinsic dissolution experiments.

The tablets with more surface disorders were generally made with higher compression pressures. The increase of the compression force commonly increases the bonding and crushing of the particles. Usually, the dissolution rate decreases with increasing compression pressure but the effect of the compression force could also be opposite. Taking into account that high compression pressure may also inhibit the wettability of the tablet, the effect of compression pressure on the dissolution properties of the tablet is a complex matter. Thus, a correlation between the surface disorder and the dissolution properties of tablets will be searched in forthcoming studies.

It is important that when studying the effect of the polymorphism or the degree of crystallinity on the drug dissolution behavior, the effect of the particle size should be ruled out or minimized. Therefore, preformulation phase studies should preferably be conducted by nondisintegrating discs, i.e., by studying the intrinsic dissolution rate of the drug (22,23). For the estimation of the intrinsic dissolution rate of the drug, the characteristics of few molecular layers on the surface of the disc dominate. Therefore, the depth profiling of the crystal characteristics of the tablet surface is needed.

CONCLUSIONS

The surface regions of the tolbutamide and chlorpropamide tablets were found to be disordered due to compression in the present study. In the case of chlorpropamide, the disorder was mainly due to the decrease in crystallinity and, in the case of tolbutamide, mainly to the small crystallite size and the amount of crystal defects. Nevertheless, both effects were found in these two materials. The crystallite size and the amount of amorphicity and crystal defects were dependent on the distance from the tablet surface. The most amorphicity and the smallest crystallite size were found on the surface of the tablets. Moreover, the changes were also dependent on the compression pressure used. In general, fewer changes were observed in the tablets compacted with lower pressures. However, the correlation between the amount of changes and the compression pressure was not straightforward.

The surface of the carbamazepine tablets was also altered in the compression. However, the changes were not clearly dependent on the compression pressure or the depth. The carbamazepine tablets contained the most crystal defects. The compaction of the carbamazepine tablets was difficult due to the elastic nature of the substance. The tablets contained surface cracks, which could have affected the results. It is possible that tablets made from elastic materials cannot be studied efficiently with GID.

In the chlorpropamide tablets, a phase transition took place due to the compression. With GID, it was possible to show that the amount of transition of chlorpropamide form A to form C was dependent on the distance from the tablet surface. The compression pressure utilized in the present study had no significant effect on the magnitude of the change.

According to the present study, GID is a potential and useful research tool for studying tablet surfaces and the possible reactions on their surfaces. However, the GID measurements and data analysis must be done with great care.

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