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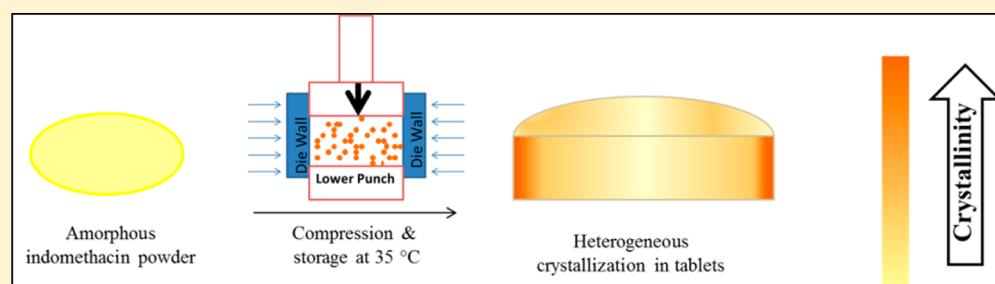
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# Compression-Induced Crystallization of Amorphous Indomethacin in Tablets: Characterization of Spatial Heterogeneity by Two-Dimensional X-ray Diffractometry

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**ABSTRACT:** Tablets of amorphous indomethacin were compressed at 10, 25, 50, or 100 MPa using either an unlubricated or a lubricated die and stored individually at 35 °C in sealed Mylar pouches. At selected time points, tablets were analyzed by two-dimensional X-ray diffractometry (2D-XRD), which enabled us to profile the extent of drug crystallization in tablets, in both the radial and axial directions. To evaluate the role of lubricant, magnesium stearate was used as “internal” and/or “external” lubricant. Indomethacin crystallization propensity increased as a function of compression pressure, with 100 MPa pressure causing crystallization immediately after compression (detected using synchrotron radiation). However, the drug crystallization was not uniform throughout the tablets. In unlubricated systems, pronounced crystallization at the radial surface could be attributed to die wall friction. The tablet core remained substantially amorphous, irrespective of the compression pressure. Lubrication of the die wall with magnesium stearate, as external lubricant, dramatically decreased drug crystallization at the radial surface. The spatial heterogeneity in drug crystallization, as a function of formulation composition and compression pressure, was systematically investigated. When formulating amorphous systems as tablets, the potential for compression induced crystallization warrants careful consideration. Very low levels of crystallization on the tablet surface, while profoundly affecting product performance (decrease in dissolution rate), may not be readily detected by conventional analytical techniques. Early detection of crystallization could be pivotal in the successful design of a dosage form where, in order to obtain the desired bioavailability, the drug may be in a high energy state. Specialized X-ray diffractometric techniques (2D; use of high intensity synchrotron radiation) enabled detection of very low levels of drug crystallization and revealed the heterogeneity in crystallization within the tablet.

**KEYWORDS:** compression, indomethacin, crystallization, amorphous, two-dimensional X-ray diffractometry, depth profiling, tablet, synchrotron

## INTRODUCTION

The identification of new chemical entities, often involving combinatorial chemistry and high throughput screening, is based on their binding affinity and specificity for biological targets. Though efficient, these methods often result in high molecular weight lipophilic drug candidates with poor aqueous solubility.<sup>1</sup> The seriousness of this problem is evident from the fact that 70–90% of the drug candidates in the pipeline are poorly water-soluble. The absorption of these compounds following oral administration is expected to be solubility or dissolution rate limited. From processing and stability considerations, the crystalline form would be desirable for use in solid oral dosage forms. However, the poor aqueous solubility of stable crystalline forms of these new compounds

often necessitates the use of amorphous forms. The enhanced solubility of the amorphous state makes it attractive for formulation development. However, the physical instability of amorphous drugs and their propensity to crystallize pose a major challenge. Crystallization risk is particularly acute during the processing of drugs into dosage forms. Since tablets are the most popular dosage forms, it is necessary to ensure that amorphous drugs can withstand the various processing stresses of tablet manufacturing.

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The broad goal of this work is to evaluate the effect of compression on the physical stability of amorphous drugs. This interest stems from the fact that compression is known to cause drug crystallization. For example, at compaction pressures ranging from 27.4 to 137.5 MPa, crystallization of celecoxib was observed. Compression induced crystallization was also evident in celecoxib solid dispersions.<sup>2</sup> The mechanism of compression induced crystallization has been elucidated in both the inorganic and organic literature. Amorphous compounds are known to have a lower density than their crystalline counterparts. Compression, by densifying amorphous materials, reduces the density difference between the amorphous and crystalline states. Densification may also promote intermolecular interactions and increase the probability of nucleation.<sup>3</sup> It has also been postulated that each amorphous material has an upper density limit, beyond which the external pressure induces strain and causes the materials to crystallize.<sup>4</sup> Other mechanisms have been proposed in the literature though they are not relevant to the current discussion.<sup>5</sup> The effect of compression on the crystallization behavior of supercooled indomethacin has been the subject of two publications, and these will be discussed in detail later.<sup>6,7</sup> If compression results in drug crystallization, the potential solubility advantage of the amorphous form will be lost. Therefore, whenever an amorphous drug is formulated as a tablet, the potential for drug crystallization is a concern. During tablet compaction, wherein a powder is confined in a die, the pressure is not transmitted uniformly throughout the powder bed. The restraint imposed by the die wall results in density gradients that affect the physical and mechanical properties.<sup>8</sup> Using X-ray computed tomography, large variations in bulk density within tablets were documented.<sup>9</sup> The density gradient is also expected to influence the nucleation and therefore the crystallization behavior. Thus, crystallization within a tablet may be highly nonuniform. Finally, if compression leads to nucleation, crystallization may occur during storage and may not be evident from the analyses of the tablets just after manufacture.

A major limitation of conventional X-ray powder diffractometry (XRD) is that it provides “average” information of the entire sample and does not reveal heterogeneity. Spectroscopic techniques (IR, Raman, solid-state NMR), widely used to detect crystallization, also provide “average” phase information in the sample. Depending on the depth of radiation penetration, the surface bias of each technique will be different. In order to obtain mechanistic insight into crystallization, an ideal technique should enable quantification of crystallization and provide this information with spatial resolution. Raman microscopic mapping has been used to detect polymorphic impurities in tablets containing low concentrations of API, but information is predominantly obtained from the tablet surface.<sup>10</sup> Likewise, grazing incidence X-ray diffractometry, when used to depth-profile phase transformation during tablet compaction, provided information predominantly from the surface regions of tablets.<sup>11</sup> In an effort to circumvent these problems, we used synchrotron X-ray diffractometry (SXRD) to detect crystallization and two-dimensional X-ray diffractometry (2D-XRD) to quantify crystallization in different tablet regions, for example progressively from the surface to the core.<sup>12</sup> In addition to providing a two-dimensional image, 2D-XRD enables rapid data collection, enhanced signal intensity, and potential reduction in errors due to preferred orientation since a substantial fraction of each diffraction ring is captured.<sup>13</sup>

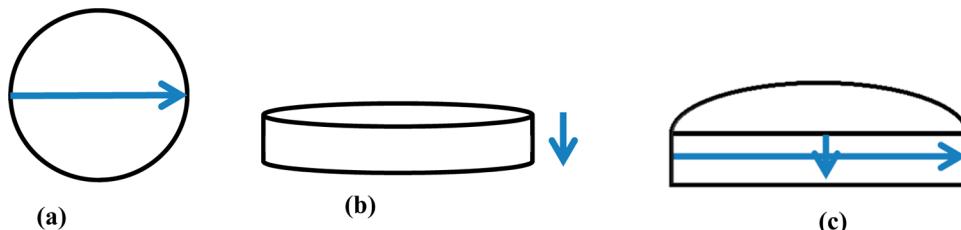
Indomethacin was selected as a model drug since it has been the subject of numerous investigations, and its crystallization behavior is well understood. Storage of amorphous indomethacin at low temperatures (<glass transition temperature,  $T_g$ ), yielded the thermodynamically stable (under ambient conditions)  $\gamma$ -form, while at temperatures above  $T_g$ , it crystallized as a mixture of the  $\alpha$ - and  $\gamma$ -forms.<sup>14</sup> Interestingly, even small variations in sample handling had a pronounced effect on its crystallization behavior.<sup>15</sup> Recently, amorphous indomethacin was prepared by either slow (0.2 °C/min) or rapid (25 °C/min) cooling of melt and then compressed (43.7 MPa). In both cases, there was no evidence of crystallization immediately after compression. However, on storage for 5 days at 25 °C (in a vacuum oven), the slowly cooled sample crystallized as a mixture of  $\alpha$ - and  $\gamma$ -polymorphs (the  $\gamma$ -form predominated). As the storage time was increased, crystallization continued, but the crystalline phase consisted only of the  $\alpha$ -form. On the other hand, in the rapidly cooled samples, after 5 days of storage, the  $\alpha$ -form predominated and this trend continued as the storage time was increased.<sup>16</sup> Our overall goal is to evaluate the potential for compression induced crystallization of amorphous drugs. As a first step, we evaluated the effect of compression on the physical stability of amorphous indomethacin in tablets. In an effort to simulate the processing conditions, the drug was milled, sieved, compressed at different pressures, and stored. Synchrotron radiation was used to detect onset of drug crystallization in intact tablets. More detailed information, specifically, the extent of crystallization as a function of depth (spatial information), was obtained using two-dimensional X-ray diffractometry. These studies were conducted in split tablets. Finally we evaluated the effect of magnesium stearate, a widely used lubricant, in modulating the compression-induced crystallization.

## EXPERIMENTAL SECTION

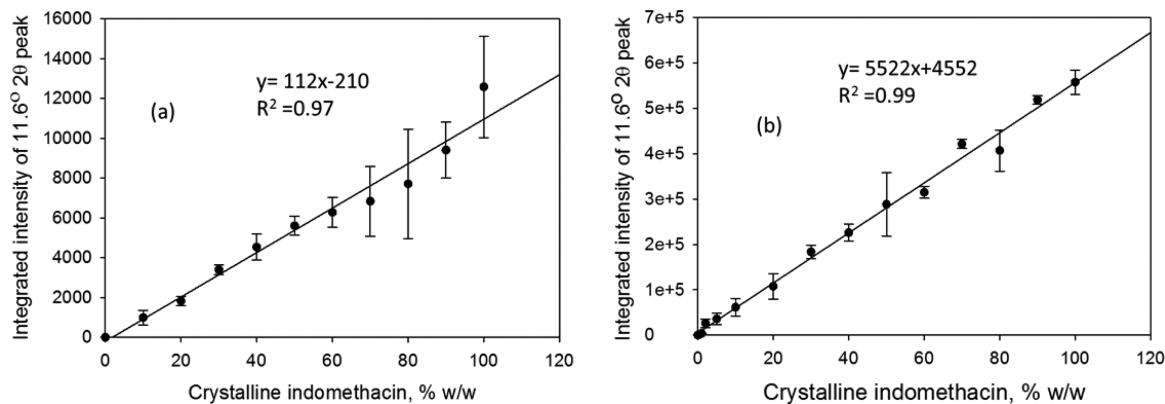
**Materials.** Indomethacin was a gift from Laborate Pharmaceuticals (India). Magnesium stearate (Fisher Scientific Company, NJ), ethyl alcohol (Decon Laboratories), and anhydrous calcium sulfate (Drierite; W. A. Hammond Drierite Co., Xenia, OH) were used as received.

**Preparation of Amorphous Indomethacin.** Amorphous indomethacin was prepared by melt-quenching.<sup>14</sup> The  $\gamma$ -polymorph was heated to 165 °C in an aluminum pan and held for 5 min, and the molten mass was quenched by dipping the pan in liquid nitrogen. It was transferred to a desiccator (containing anhydrous calcium sulfate) and stored under reduced pressure for 30 min (RT). The sample was powdered using an agate pestle and mortar in a glovebox (RH < 5%; RT), sieved (80 mesh), and stored at -20 °C until used. The water content was determined to be 0.1% w/w by Karl Fischer titrimetry.

**Preparation of Tablets.** Tablets of indomethacin (amorphous; 200 mg) were prepared using a universal material testing machine (Zwick/Roell, Zwick GmbH & Co., KG, Ulm, Germany), equipped with 8 mm diameter flat-faced punches. For site specific lubrication, before compressing each tablet, the die wall was lubricated with magnesium stearate slurry (1% w/v in ethanol). The suspension was applied with a fine brush and allowed to dry. This resulted in formation of a thin film of magnesium stearate in the die cavity. During compression, the lower punch was stationary while the upper punch moved at a constant speed of 1 mm/min. Tablets were compressed under ambient conditions (25 °C; 45% RH) at 10, 25, 50, or 100 MPa



**Figure 1.** Tablet mapping: (a) top (axial) tablet surface, (b) side (radial) tablet surface, and (c) split tablet showing the two directions of depth profiling. The arrows point in the scanning direction.



**Figure 2.** Plot of the intensity of  $11.6^\circ 2\theta$  peak of the  $\gamma$ -polymorph of indomethacin as a function of crystalline indomethacin in mixtures of amorphous and crystalline indomethacin ( $n = 3$ ). (a) In intact tablets determined by 2D-XRD. Each data point is the average of the intensity in 10 locations in each tablet, and three tablets were analyzed (overall  $n = 30$ ). (b) In powdered tablets determined using synchrotron XRD. Again, three tablets were analyzed.

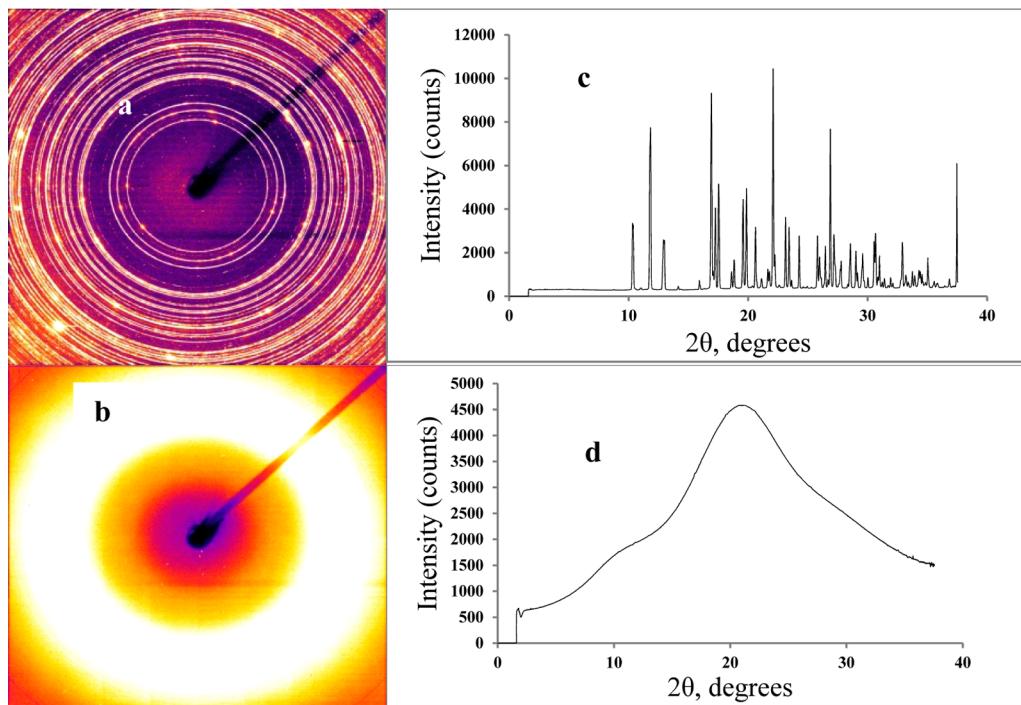
with a dwell time of 1 min. For ejection of the compressed tablets from the die, the lower punch was removed and a force was applied to the upper punch using a hydraulic press (Carver model C laboratory press, Menomonee Falls, WI, USA). Compressed tablets were individually sealed in Mylar pouches and stored at  $35^\circ\text{C}$  ( $\pm 1^\circ\text{C}$ ). The water content in the fresh tablets was  $\sim 0.3\%$  w/w. Storage did not cause any pronounced change in water content. “Seeded” tablets were prepared by mixing 5% w/w crystalline form ( $\gamma$ -polymorph) with amorphous indomethacin before compression.

**Two-Dimensional X-ray Diffractometry.** Intact or split tablets were exposed, at room temperature, to  $\text{Cu K}\alpha$  radiation ( $1.54 \text{ \AA}$ ;  $45 \text{ kV} \times 40 \text{ mA}$ ) in a two-dimensional X-ray diffractometer (D8 Discover 2D, Bruker with a 140 mm diameter window VÄNTAC-500 detector). XRD patterns were collected, using a 0.05 mm collimator set at a  $10^\circ$  angle of incidence and an area detector (angular range  $36^\circ$ ) set at an angle of diffraction of  $20^\circ 2\theta$ . The irradiated area can be described by an ellipse with a major axis of  $320 \mu\text{m}$  and minor axis of  $70 \mu\text{m}$ . To study the phase transformation on the tablet surfaces, the axial and radial surfaces were subjected to 2D-XRD, as shown in Figure 1a,b. For depth profiling, tablets were split into two halves and analyzed along the axial and radial directions as shown in Figure 1c. Data analyses were performed using commercially available software (JADE 2010).

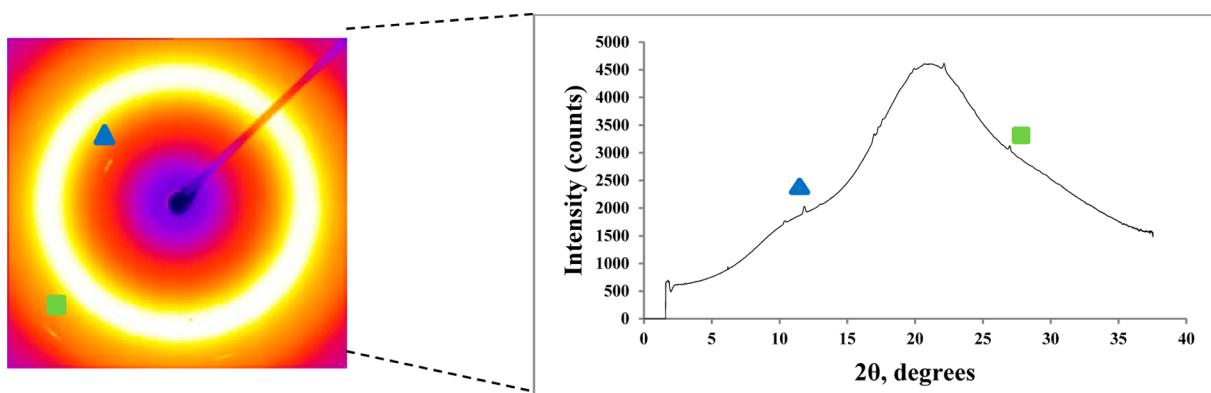
**Synchrotron X-ray Diffractometry (SXRD).** The intact tablet samples were mounted on the holder plate using double sided tape. In powder samples,  $\sim 20 \text{ mg}$  was filled in aluminum pans (used for differential scanning calorimetry, TA Instruments), crimped hermetically at room temperature and placed in a specially fabricated holder.

Experiments were performed in the transmission mode in the 17-BM-B beamline at Argonne National Laboratory (Argonne, IL, USA). A monochromatic X-ray beam [wavelength  $0.72808 \text{ \AA}$ ; beam size  $250 \mu\text{m}$  (horizontal)  $\times 160 \mu\text{m}$  (vertical)] and a two-dimensional area detector (XRD-1621, PerkinElmer) were used. A triple-bounce channel-cut Si single crystal monochromator with [111] faces polished was used which limited the line broadening to its theoretical low limit, i.e., the Darwin width. The flux of the incident X-ray was  $8 \times 10^{11}$  photons/s at 17 keV. Calibration was performed using an  $\text{Al}_2\text{O}_3$  standard (SRM 674a, NIST). Using a stepper motor, the sample was oscillated ( $\pm 1 \text{ mm}$  from the center along the horizontal axis) during data collection. Each sample was scanned 30 times, with an exposure time of 1 s for each scan, and the results were averaged. The raw images were integrated to yield one-dimensional  $d$ -spacing ( $\text{\AA}$ ) or  $2\theta$  (deg) scans using the FIT2D software developed by A. P. Hammersley of the European Synchrotron Radiation Facility.<sup>17,18</sup> Commercially available software (JADE 2010, Material Data, Inc.) was used for determining the integrated peak intensities.

**Quantification of Crystalline Indomethacin in Intact Tablets: Generation of Standard Curves.** Tablets containing amorphous and crystalline indomethacin were prepared, with the concentration of each ranging from 0 to 100% w/w (11 compositions; 3 tablets of each composition). Two-dimensional XRD was used to collect patterns from 10 locations (5 random locations on the radial surface and 5 locations in the “interior”, i.e. in split tablets) in each of the 3 tablets. The intensity (integrated) of the  $11.6^\circ 2\theta$  peak of the  $\gamma$ -polymorph was determined and then averaged for the 30 determinations and plotted as a function of crystalline indomethacin concentration. The relationship between inte-



**Figure 3.** Two-dimensional XRD patterns of (a) crystalline indomethacin ( $\gamma$ -polymorph) and (b) amorphous indomethacin obtained using synchrotron radiation. To facilitate visualization, the corresponding one-dimensional SXRD patterns of (c) crystalline and (d) amorphous indomethacin are also presented as intensity vs  $2\theta$  plots (calculated for Cu  $K\alpha$  radiation).



**Figure 4.** Two dimensional SXRD pattern of amorphous indomethacin tablet compressed at 100 MPa at time “0”, and corresponding one-dimensional pattern.

grated peak intensity ( $y$ ) and indomethacin crystalline fraction ( $x$ ; % w/w) was expressed as  $y = 112x - 210$  (Figure 2a). This standard curve was used to determine the recrystallized indomethacin concentration in the “unknown” systems.

For SXRD, the tablets of the same composition as described above were powdered, filled in DSC pans, and analyzed ( $n = 3$  tablets). The relationship between integrated peak intensity and indomethacin crystalline fraction was expressed as  $y = 5522x + 4552$  (Figure 2b). For calculating the recrystallized indomethacin content in stored tablets, appropriate data correction was made.

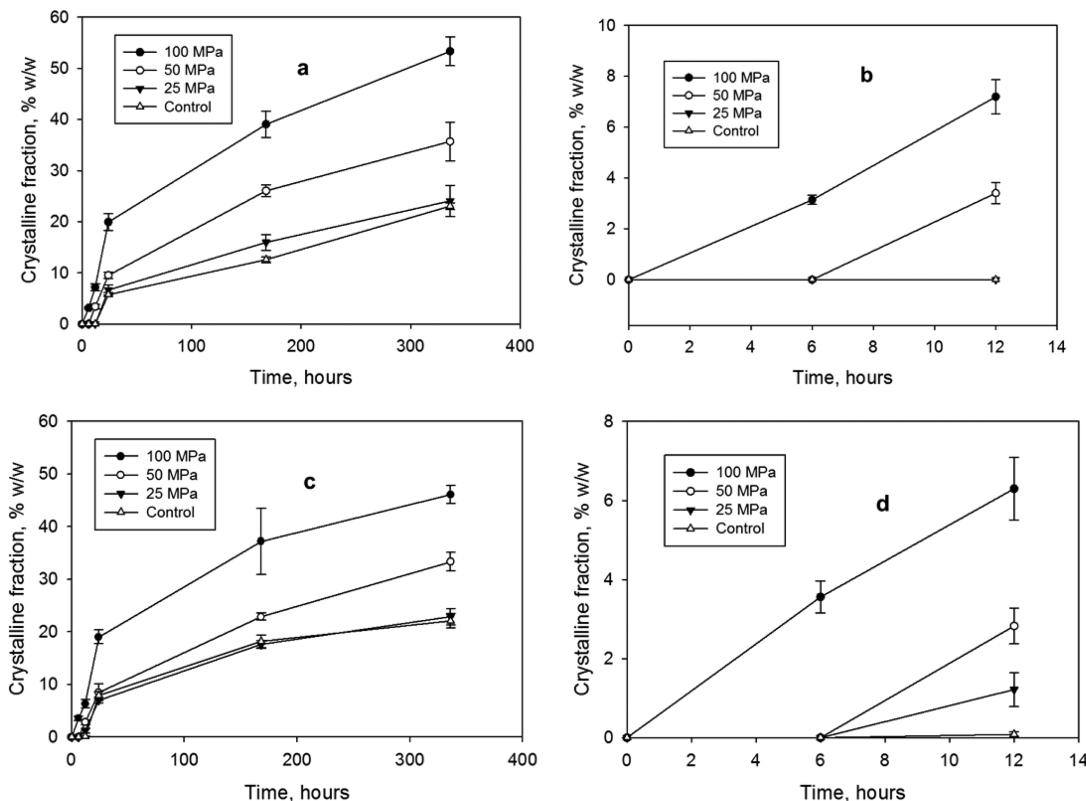
**Energy Dispersive Spectrometry (EDS).** Scanning electron microscopy in conjunction with energy dispersive spectroscopy (JEOL 6500F, Hitachi, Japan) was used for elemental mapping of the radial tablet surfaces. Both unlubricated tablets and externally lubricated tablets were analyzed. The tablet samples were carbon coated and fixed on a specimen holder using conductive double sided carbon

adhesive tape. The accelerating voltage was 15 kV, and the specimen to detector distance was 10 mm. Using the EDS software (Noran System Six), the live time was set at 60 s (with a dead time of ~25%) for signal acquisition.

## RESULTS AND DISCUSSION

XRD patterns of amorphous and crystalline ( $\gamma$ -polymorph) indomethacin are shown in Figure 3.

Indomethacin tablets were subjected to XRD, immediately after compression. Irrespective of the compression pressure, based on 2D-XRD, there was no sign of drug crystallization. However, with synchrotron XRD, a very weak reflection at 11.6 and 26.8°  $2\theta$  provided the first evidence of crystallization. This was observed only in the tablets compressed at the highest pressure (100 MPa). While Figure 4 is a representative example, crystallization was observed in all three tablets analyzed.



**Figure 5.** Effect of compression pressure on indomethacin crystallization in tablets. Amorphous indomethacin was compressed at different pressures, and the individual tablets were stored in sealed Mylar pouches at 35 °C. Amorphous indomethacin powder was used as control. The crystallization kinetics was monitored ( $n = 3$ ): (a) in powdered tablets using a two-dimensional X-ray diffractometer, (b) the results of the early time points from panel a ( $t \leq 12$  h of storage), (c) in intact tablets using SXRD, and (d) the results of the early time points from panel c. As pointed out earlier (Figure 4), while there was evidence of crystallization in tablets freshly compressed at 100 MPa, the crystalline fraction was assumed to be zero in light of its very low concentration.

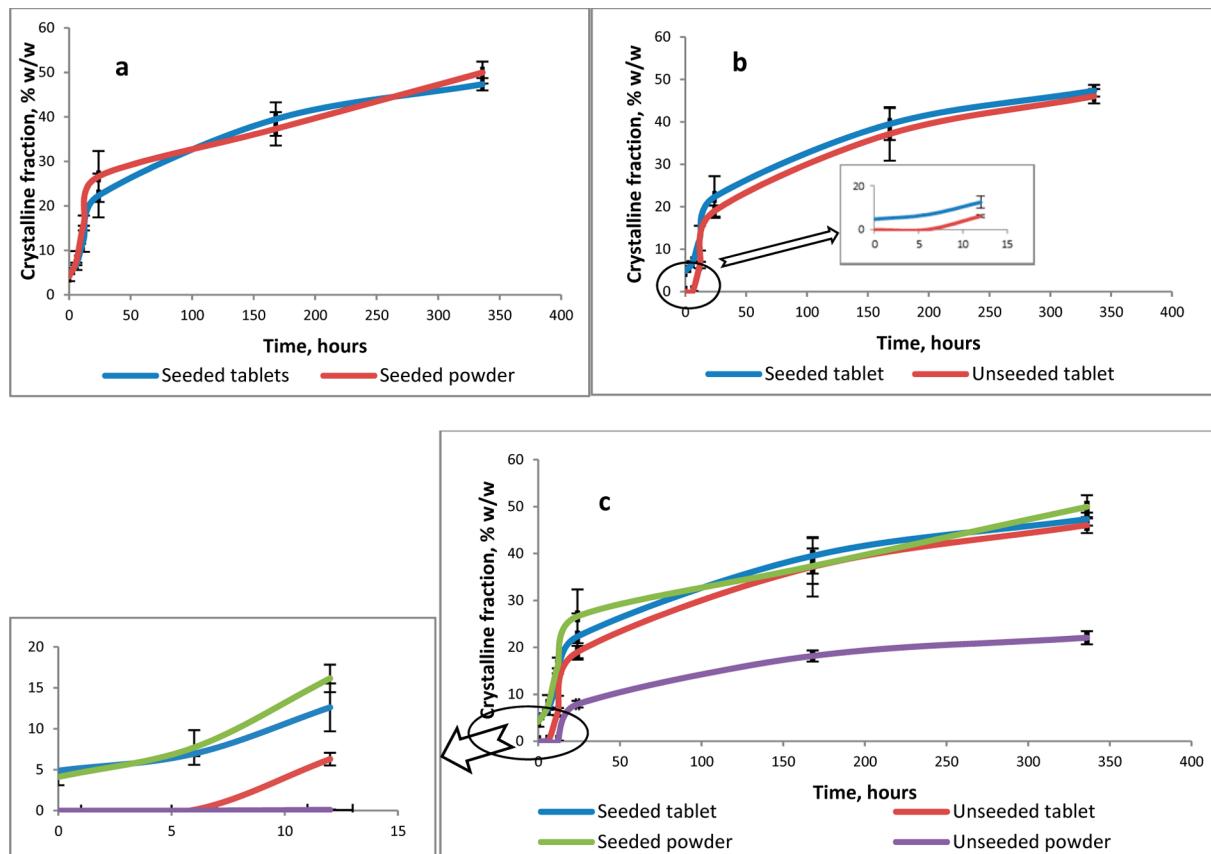
Figure 5 provides an estimate of the effect of compression pressure on crystallization kinetics of amorphous indomethacin, by both 2D-XRD (Figures 5a and 5b) and SXRD (Figures 5c and 5d). While the rate and extent of crystallization appeared to be approximately the same by these two approaches, an increase in compression pressure facilitated crystallization. The first evidence of crystallization was observed after 6 h of storage in tablets compressed at 25 and 50 MPa and immediately after compression (time “0”) in tablets compressed at 100 MPa. Thus, at lower compression pressures, crystallization appears to have been delayed. SXRD, as expected, was more sensitive than 2D-XRD. For example, the tablets compressed at 25 MPa exhibited ~1% crystallization after 12 h when analyzed by SXRD, but there was no evidence of crystallization by 2D-XRD (Figures 5b and 5d). Similarly in the control samples (uncompressed powder), after 12 h of storage, there was suggestion of crystallization only by SXRD. Thus, as the compression pressure is increased, crystallization is induced as well as accelerated. It has been reported that trituration, by reducing the thermodynamic barrier to nucleation on the particle surface, facilitated heterogeneous nucleation.<sup>14</sup> Compression may have a similar effect wherein densification is followed by the introduction of strain.

The effect of compression on the crystallization behavior of indomethacin in the supercooled state was the subject of two in-depth studies.<sup>6,7</sup> Under isothermal (372 or 386 K) and isobaric conditions (90, 135, or 226 MPa), there was no evidence of crystallization even after 2 weeks of storage. But

under so-called “isochronal” conditions, wherein the structural relaxation time was kept constant, compression facilitated crystallization of indomethacin in the examined pressure range of 0.1 to 220 MPa. Again, it is important to emphasize that we compressed indomethacin with a dwell time of 1 min and at room temperature wherein it exists in a glassy state.

Next, amorphous indomethacin was seeded with crystalline indomethacin ( $\gamma$ -polymorph; 5% w/w) and then compressed. This was done to confirm that seeding induced by compression affected the induction time and kinetics of indomethacin crystallization in tablets. Tablets were compressed at 100 MPa, and the individual tablets were stored in Mylar pouches at 35 °C. They were removed at desired time points and analyzed using SXRD. Amorphous indomethacin tablets or powder seeded with 5% w/w of crystalline indomethacin was used as control. Figure 6a compares the crystallization kinetics in these control systems. At each time point, the extent of crystallization was virtually identical. This is in contrast to the unseeded system, wherein, in 14 days, 20% crystallization was observed in the powder while the crystallization was 50% in the tablets (Figures 5a and 5c; 100 MPa compression pressure).

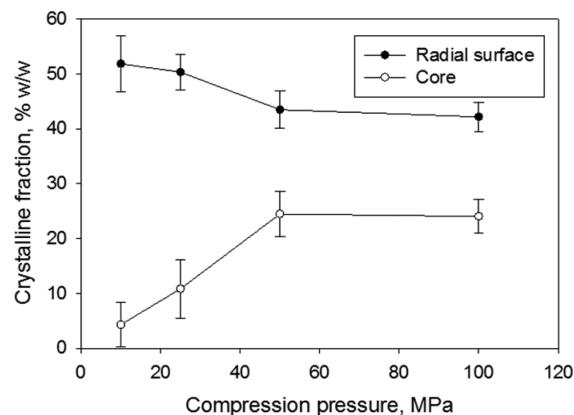
Figure 6b compares the kinetics of crystallization in seeded and unseeded tablets. Except for the induction time, there was no difference in crystallization kinetics (inset). From Figure 6c, a compilation of all the crystallization data, it is evident that only the unseeded powder (control) exhibits a pronounced difference in crystallization behavior. These results strongly indicate that compression induces crystallization.



**Figure 6.** Use of SXRD to determine the effect of seeding on crystallization of amorphous indomethacin in tablets. Amorphous indomethacin was seeded with the crystalline phase ( $\gamma$ -polymorph; 5% w/w), compressed at 100 MPa, and stored in sealed Mylar pouches at 35 °C. Amorphous indomethacin powder was used as control. (a) Seeded tablets (with seeded amorphous powder as control). (b) Seeded tablets (with unseeded tablet as control). (c) Compilation of the tablet and powder results.

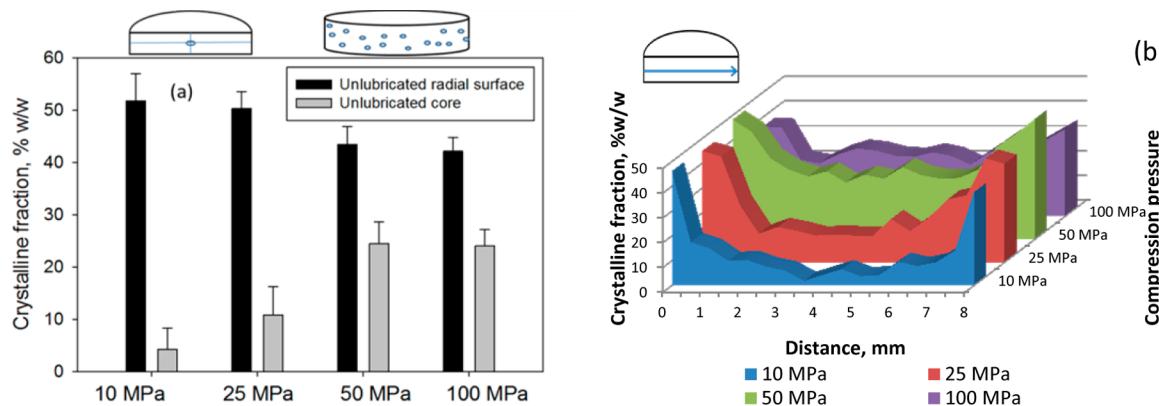
An added issue is that, during tablet compression, the pressure is not transmitted uniformly throughout the powder mass leading to heterogeneity in bulk density.<sup>8,19</sup> For example, in cylindrical compacts of uranium dioxide, three regions with distinctly different densities were identified. The inner axial and the outer peripheral region were of high density, while the annulus was of lower density.<sup>8</sup> Organic systems did not yield such nuanced information. Using X-ray computed tomography (CT), large variations in bulk density within tablets were documented.<sup>19</sup> Siiriä et al.<sup>20</sup> have developed a three-dimensional simulation of tablet strength distribution during compression. There was resemblance between their calculated bond strength distributions and the reported density distributions in various tablet regions.

If there is indeed inhomogeneity in bulk density, our next goal was to determine its effect on indomethacin crystallization. The tablets compressed at different pressures, in an unlubricated die, were analyzed (2D-XRD), immediately after compression and also after storage at 35 °C in sealed Mylar pouches for up to 2 weeks. We will restrict our initial discussion to the radial surface which comes in contact with the die wall. We could not detect drug crystallization immediately after compression. However, irrespective of the compression pressure, there was substantial indomethacin crystallization (~50%), 24 h after compression (Figures 7, 8a). On the radial surface, contrary to expectations, with a decrease in compression pressure there was an increase in the extent of crystallization (Figure 7).

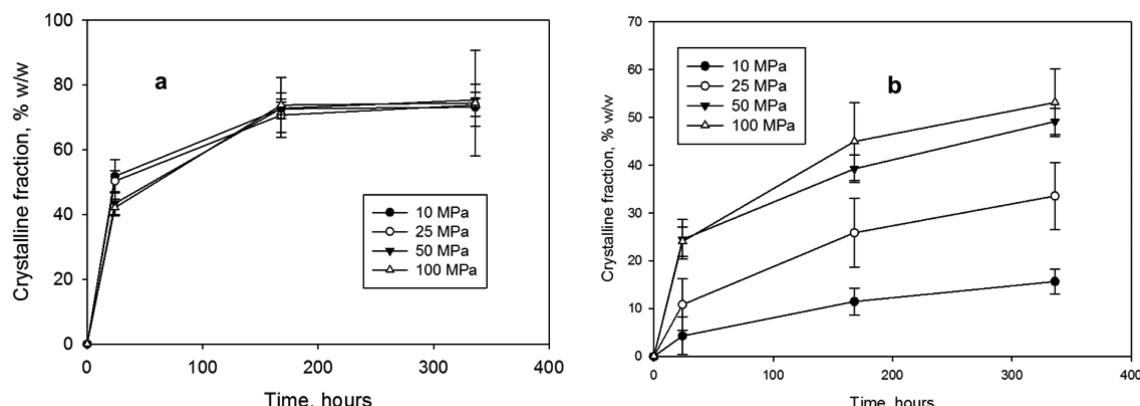


**Figure 7.** Extent of indomethacin crystallization (expressed as crystalline fraction) as a function of compression pressure. Amorphous indomethacin tablets were compressed in an unlubricated die and stored at 35 °C for 24 h.

As the powder is compressed, due to friction between powder and die wall, a fraction of the applied force is lost as radial stress.<sup>21</sup> This is manifested in the force required to eject the tablet after compression. The ejection force is proportional to the area of the tablet in contact with the die wall.<sup>22</sup> A decrease in die wall friction with increase in compression pressure has been reported.<sup>23,24</sup> This may be due to decrease in contact area of tablet and die wall, due to decrease in thickness at higher compression pressures. Compression at 10 MPa



**Figure 8.** Amorphous indomethacin tablets were compressed at different pressures (10 to 100 MPa) using an unlubricated die and stored at 35 °C for 24 h. (a) Crystalline fraction (% w/w) on radial surface and in the tablet core. On the radial surface, 19 regions in each tablet, and a total of 3 tablets, were analyzed (see schematic). Mean  $\pm$  SD;  $n = 3$  (core);  $n = 57$  (radial surface). (b) Spatial pattern of crystallization in split tablets.



**Figure 9.** Extent of indomethacin crystallization, as a function of time: (a) on the radial tablet surface and (b) in the tablet core. Mean  $\pm$  SD;  $n = 3$  (core);  $n = 57$  (radial surface). Amorphous indomethacin tablets were compressed at different pressures (10 to 100 MPa) in an unlubricated die and stored at 35 °C.

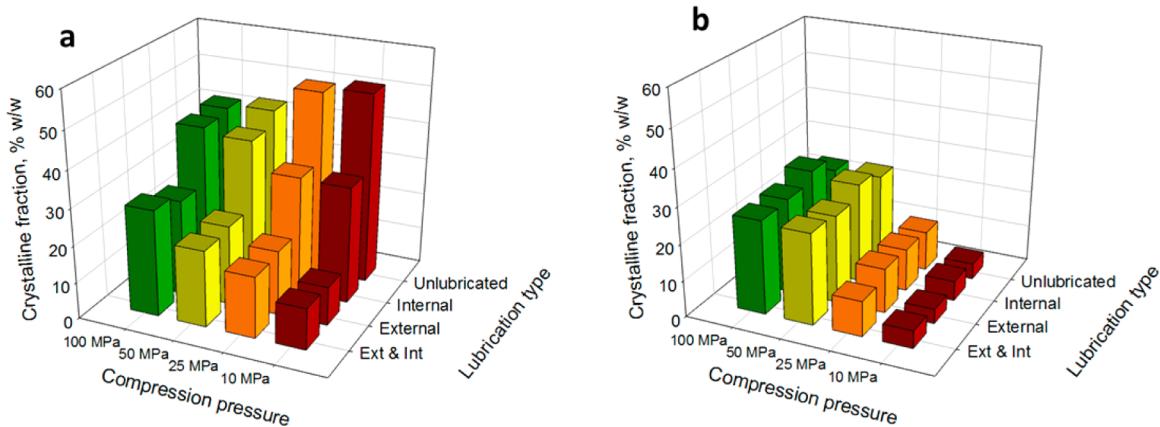
resulted in thicker tablets (3.5 mm) than at 100 MPa (3 mm). Thus, at lower compression pressures, the higher overall die wall friction may be responsible for the higher radial surface crystallization. Next, the tablet was split and the core was analyzed. Interestingly, in the tablet core, an increase in compression pressure resulted in increased crystallization (Figure 7, 8a). By monitoring the crystallization fraction as a function of distance (in the radial direction), we profiled the crystallization of amorphous indomethacin across the tablet (Figure 8b). In this figure, we have only shown results obtained in tablets stored for 24 h. Similar analyses were carried out in the fresh tablets and in tablets stored for 168 and 336 h. All of these results are summarized in Figures 9a and 9b.

A plot of the extent of crystallization at the radial surface as a function of storage time reveals that crystallization levels off very quickly (Figure 9a). The results appeared to be independent of the compression pressure. On the other hand, in the tablet core, the effect of compression pressure was retained even after 14 days (336 h) of storage (Figure 9b). The initial crystallization was very rapid, but after 7 days of storage, it leveled off. However, a substantial fraction of the core was still amorphous even after 14 days of storage. Thus, if a tablet is monitored from the radial surface toward the core, there will be a pronounced gradient in the degree of crystallinity even after 2 weeks of storage (Figures 9a and 9b). As the compression

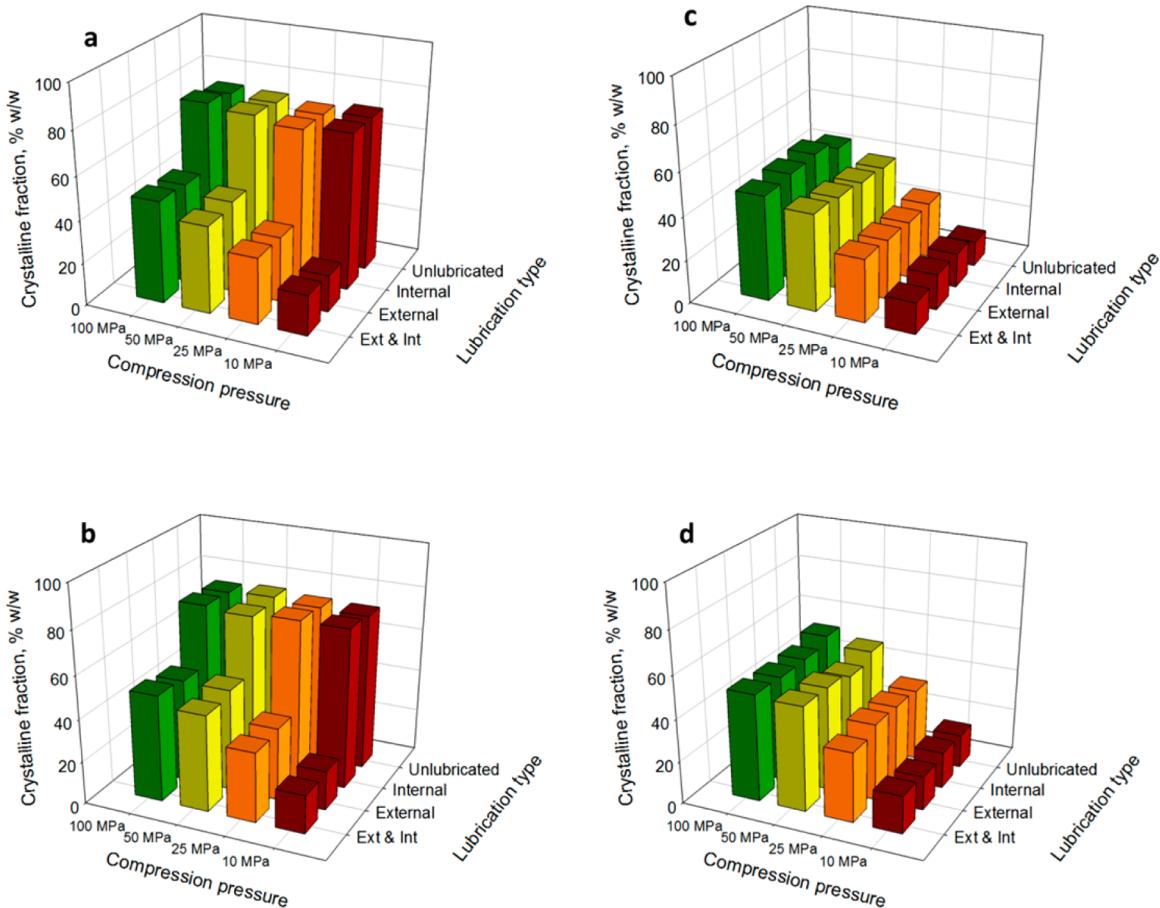
pressure is decreased, this gradient became more pronounced (Figures 8b and 9b).

To summarize, irrespective of compression pressure, crystallization was observed after 24 h of storage (Figures 8a, 8b, 9a, and 9b). Thus, the risk of crystallization cannot be mitigated by reducing the compression pressure. Second, a pronounced gradient in the degree of crystallinity was observed even after 2 weeks of storage (Figure 8). During the process of tablet compression, a large difference may exist between the maximum force exerted by the upper punch and the maximum force perceived by the lower punch.<sup>25</sup> As the powder is compressed, a fraction of the applied force is lost as radial stress normal to the die wall, due to friction between unlubricated powder and die wall.<sup>25</sup> This is manifested in the force required to eject the tablet after compression. The radial stress also causes deformation of powder asperities leading to increase in contact area and adhesive interaction between the tablet (radial surface) and metal die surfaces.<sup>26</sup> The pronounced friction between the tablet and die wall surfaces is the result of this radial stress which could be manifested in the crystallization observed in the tablet radial surface.<sup>26</sup>

Both the compression pressure and the die wall friction are expected to cause indomethacin crystallization. While the former would be responsible for crystallization throughout the tablet, the latter is expected to play a role only at the tablet surface (our discussion here is restricted to the radial surface).



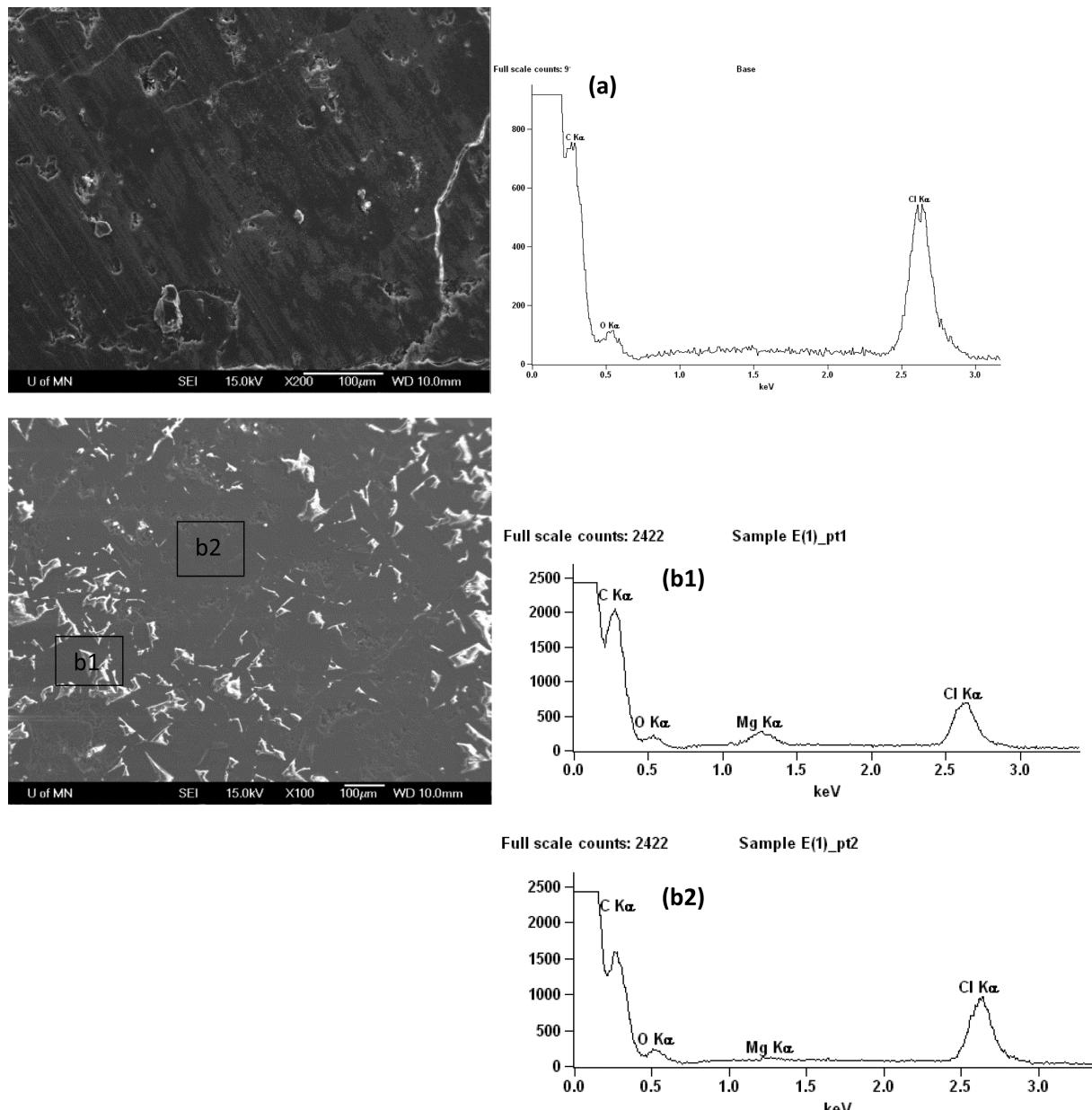
**Figure 10.** Effect of lubrication on the extent of indomethacin crystallization in tablets in the (a) radial surface and (b) tablet core. The tablets were compressed at 10, 25, 50, or 100 MPa and stored at 35 °C for 24 h.



**Figure 11.** Effect of lubrication on the extent of indomethacin crystallization in tablets compressed at 10, 25, 50, or 100 MPa and stored at 35 °C for 7 and 14 days: (a) radial surface, 7 days; (b) radial surface, 14 days; (c) tablet core, 7 days; and (d) tablet core, 14 days.

A lubricant such as magnesium stearate, used in the concentration range of 0.1–1% w/w, is known to reduce the friction during ejection.<sup>27</sup> By proper granule lubrication, the difference between the maximum force exerted by the upper punch and the maximum force perceived by the lower punch can be decreased.<sup>25</sup> During tablet manufacture, it is a common practice to blend the lubricant with the other formulation components, and this is referred to as “internal lubrication”. With the inclusion of magnesium stearate as internal lubricant (1% w/w), a decrease in indomethacin crystallization at the

radial surface was observed at low compression pressures ( $\leq 25$  MPa; Figure 10a). At higher compression pressures, internal lubrication did not influence the extent of crystallization at the radial surface, suggesting that the effect of die wall friction was not eliminated (Figure 10a). When the die cavity was directly lubricated with a magnesium stearate slurry (“external” or “site specific” lubrication), irrespective of the compression pressure, there was a marked decrease in indomethacin crystallization (Figure 10a). Thus, surface lubrication appeared to be effective in preventing “additional crystallization” on the radial surface



**Figure 12.** SEM image and corresponding EDS spectrum of radial surface of (a) unlubricated tablet and (b) tablet with external lubrication. In the lubricated tablets, EDS spectra were obtained of two different regions marked b1 and b2.

attributed to friction. The lubricant effectiveness was not increased when site specific lubrication was combined with internal lubrication (Figure 10a). Interestingly, in the tablet core, lubrication (internal, site specific, or a combination of the two) had no effect on the extent of crystallization (Figure 10b).

After 7 days of storage, irrespective of the compression pressure, the extent of crystallization on the radial surface was the same in the tablets with no lubricant or an internal lubricant (Figure 11a). Therefore, internal lubrication only had a short-term effect. On the other hand, the effectiveness of site specific lubrication persisted for 14 days (Figure 11b). Crystallization in the tablet core was unaffected by lubrication (Figures 11c and 11d).

In amorphous materials, due to enhanced mobility of surface molecules, surface crystallization is orders of magnitude faster than in the bulk.<sup>28,29</sup> Surface crystallization can be inhibited by coating.<sup>30</sup> Thus, the “extra” crystallization observed on the

radial tablet surface could be due to the mobility of the surface molecules. Magnesium stearate when used as a site specific lubricant, by coating the die surface, inhibited crystallization. However, this mechanism will only be effective if magnesium stearate completely coats the tablet surface. We have attributed the “extra” crystallization on the radial tablet surface to die wall friction. The radial surfaces of unlubricated and externally lubricated tablets were subjected to SEM and EDS. In the unlubricated tablets, the pronounced signal of chlorine was attributed to indomethacin (Figure 12a). When the tablets were externally lubricated, the presence of magnesium was also evident (Figure 12b). However, the signal of chlorine was still prominent on the tablet surface, indicating that a significant fraction of the surface was not coated with magnesium stearate. As expected, the surface coating with magnesium stearate was not uniform, based on analyses of two different regions in the same tablet. Interestingly, SEM did not reveal any pronounced

differences between the unlubricated and the lubricated tablets. Our results are in agreement with a recent report, wherein surface coating of amorphous indomethacin with various excipients including magnesium stearate did not affect the surface nucleation rate.<sup>31</sup>

**Significance.** If an amorphous API is prone to compression induced crystallization, formulating it into a tablet dosage form can be risky. In our model system, there was a strong suggestion that compression at low pressures induced nucleation with no evidence of immediate crystal growth. However, pronounced crystal growth was observed during storage. If the time scales of product shelf life and crystallization are comparable, there is risk of failure of the stored product. Identifying this problem can be analytically challenging since analysis of the dosage form immediately after preparation will not provide any clue of the physical instability of the API.

While conventional X-ray diffractometry provides “average” information, the use of 2D XRD enabled depth profiling of crystallization: from the tablet surface to the core. This nuanced information revealed that the extent of crystallization was much higher at the radial surface, an effect attributed to radial surface–die wall friction. “Site specific” lubrication of the die wall effectively eliminated this effect, by reducing the adhesive interaction between amorphous indomethacin and metal die surface. High speed rotary tablet machines with this capability have been reported in the literature.<sup>32</sup> It is interesting that internal lubrication with magnesium stearate appeared to be ineffective in minimizing the role of friction in crystallization.

These studies have been conducted on only one model compound, indomethacin, that is prone to crystallization. Detailed investigation of the effect of compression on numerous other APIs is warranted, before any generalizations can be made. Our work suggests that, during tabletting, crystallization can be brought about by compression as well as friction. The compression pressures used in our studies ( $\leq 100$  MPa) were substantially less than that used during commercial manufacture (typically 150 MPa), and our dwell time (1 min) was long. If an API is prone to compression induced crystallization, the role of radial surface–die wall friction warrants careful investigation.

**Conclusion.** The effect of compression on the physical stability of amorphous indomethacin has been comprehensively investigated.

- (i) At all compression pressures, there was evidence of crystallization. Even at a very low compression pressure of 25 MPa, crystallization was observed on product storage. Thus, the risk of crystallization cannot be mitigated by reducing the compression pressure.
- (ii) The crystallization propensity increased as a function of compression pressure. At 100 MPa, crystallization was observed immediately after compression. At lower compression pressures, crystallization was observed after several hours of storage. In these systems, compression induced nucleation.
- (iii) The extent of indomethacin crystallization was not uniform in all the regions of the tablets. Two-dimensional XRD enabled the study of spatial distribution of crystallization. The extent of crystallization was much higher at the radial surface, possibly due to radial surface–die wall friction.

- (iv) When the die wall was lubricated with magnesium stearate, there was a pronounced decrease in the extent of crystallization at the radial surface.

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### Notes

The authors declare no competing financial interest.

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