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Research paper

Effect of different preparation methods on the dissolution behaviour of amorphous indomethacin

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ABSTRACT

The aim of this study was to investigate whether amorphous indomethacin samples prepared using different preparative techniques and processing parameters exhibit different structural and thermodynamic characteristics and whether these differences can be correlated to their dissolution behaviour. Samples were prepared either by cooling the drug melt at different cooling rates or by cryo-milling the drug for different milling times. The resulting amorphous materials were characterised using X-ray diffraction, Raman spectroscopy and polarising light microscopy. All samples were entirely X-ray amorphous, except for the sample cryo-milled for 15 min, which exhibited residual crystallinity. The shape of the halos in the diffractograms, however, varied depending on the preparation method and processing parameters, suggesting structural variations in the near order of the molecules between the prepared amorphous forms. This finding was supported by principal component analysis of the Raman spectra, as the samples clustered in the scores plot according to processing parameters for both of the preparative methods used. When investigating the dissolution behaviour, the samples cooled at different cooling rates showed no significant differences in their dissolution profiles and dissolution rates (≈0.55 μg/ml/cm^2). In contrast, for cryo-milled samples, dissolution rate depended on the milling time, with samples milled for 120, 180 and 240 min, showing significantly increased dissolution rates of 0.28, 0.48 and 0.59 μg/ml/cm^2, respectively, when compared to crystalline indomethacin (≈0.06 and 0.05 μg/ml/cm^2 for α and γ-indomethacin, respectively). The milling processes appear to continue to affect the degree of disorder in the solid material, enhancing its dissolution rate, although all samples milled for >30 min were X-ray amorphous. Thus, choosing the right preparation technique and parameters for preparing amorphous solids is critical for producing materials with enhanced dissolution profiles.

1. Introduction

The dissolution behaviour of pharmaceutical drugs is a complex process depending *inter alia* on particle size and specific surface area of the drug [1,2], the polymorphic form present in the gastro-intestinal tract [3], the degree of crystallinity and the solvation state of the drug [4]. Many modern drugs are poorly soluble in aqueous media, limiting their peroral absorption and bioavailability due to their poor dissolution behaviour in gastrointestinal fluids [5]. Improving the oral bioavailability of compounds exhibiting poor aqueous solubility but high permeability (Biopharmaceutics Classification Systems (BCS) class II drugs) is thus one of the most challenging aspects of modern formulation development. Strategies to improve the solubility and dissolution rate of BCS class II drugs include the formation of salts [6], the selection of metastable polymorphic forms [3,7] or the formation of amorphous solids [4,8]. Salt formation is the most often used strategy to improve poor aqueous solubility and low dissolution rates. However, the applicability of this approach is limited. Under dissolution conditions in the gastro-intestinal tract, salts often convert into their free acid or base form, and the formation of salts cannot be achieved with neutral compounds [1]. When using a metastable polymorphic or the amorphous form of a bioactive, the activation energy required to bring the drug into solution is reduced as a solid state form with a higher free energy than the thermodynamically stable polymorphic form is used. This approach increases the dissolution rate as well as the solubility of the drug. The use of a metastable polymorphic form of a drug, however, may be limited, since metastable polymorphic forms tend to transform into thermodynamically more stable forms during processing, storage and dissolution [9–11], and often dissolution rate and solubility enhancement using this approach are only modest [12].

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The amorphous form is the highest energy form of a solid material with an inherently high level of molecular disorder. Thus, the activation energy needed to bring a drug into solution is least when compared to the more ordered metastable and stable crystalline forms of drugs, and consequently, high gains in dissolution rate and solubility, compared to crystalline forms of the drug, may be achieved using this approach [7,13–17]. Similar to metastable polymorphic forms, amorphous solids, however, also have a tendency to convert to less soluble crystalline forms, both during storage and during the dissolution of the drug [4,8,18,19]. The formulation of amorphous solids thus poses a major challenge to the formulator.

The most commonly used techniques to prepare amorphous forms are solution- or melt-mediated transformations of bulk material (*e.g.* quench cooling of a drug melt, melt extrusion, spray drying or freeze drying). Alternatively, amorphous forms of drugs may be obtained by mechanical activation (milling), involving the direct solid conversion from the crystalline to the amorphous form [20–22]. Generally, the physicochemical properties of amorphous drugs are characterised by the complete absence of long-range order [13]. The short-range order of amorphous solids, however, may substantially be influenced by the choice of the preparative technique [17] and processing parameters used [23]. Previously, we have found that using different preparation techniques to produce amorphous forms of the drug indomethacin affected the molecular structure of the solids [17]. These differences in the molecular structure were detectable using Raman spectroscopy and X-ray powder diffraction (XRPD) and may be responsible for differences observed in the physical stability of the amorphous drug during storage [17]. Whilst other studies have investigated the physical stability of amorphous solids during processing and under storage conditions [15–17], there is paucity in the literature about the influence of the preparative technique and processing parameters on the dissolution process of amorphous solids.

The aims of this study were to evaluate the effect of different preparative techniques (quench cooling of the melt and milling) and different processing parameters (cooling rate and milling time) on the dissolution rate of amorphous indomethacin. This model drug was used, since comprehensive information on the characterisation of amorphous indomethacin [24–26] and the dissolution behaviour of both crystalline and amorphous indomethacin was available [7].

2. Materials and methods

2.1. Materials

Indomethacin (>98% purity, γ-form) was purchased from Chemie Brunschwig AG (Basel, Switzerland). Ethanol (analytical grade) and phosphorus pentoxide were obtained from Merck (Darmstadt, Germany).

2.2. Methods

2.2.1. Preparation of amorphous samples

Amorphous indomethacin was prepared via two transformation routes: direct solid state transformation by milling and transformation by melting and quench cooling. The resulting amorphous solids were stored in a desiccator over phosphorus pentoxide at 22 ± 0.2 °C until characterisation (Section 2.2.2). All samples were prepared in triplicates.

2.2.1.1. Transformation by cryo-milling of the crystalline solid form. Amorphous indomethacin was prepared from the γ-form of the drug. The sample powder (1 g) was placed in a 25-ml stainless steel milling jar containing six stainless steel balls with a diameter of 9 mm. The jars were immersed in liquid nitrogen for 3 min after addition of the sample. Samples were then milled at a frequency of 30 Hz using an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Haan, Germany). Milling was performed for t = 15, 30, 60, 120, 180 and 240 min. The jars were re-cooled in liquid nitrogen for 3 min after every 15 min of milling.

2.2.1.2. Transformation by melting and quench-cooling. Indomethacin (γ-form) was heated in a stainless steel beaker to 165 °C and held at this temperature for 3 min. The resulting melt was then transferred into DSC pans (TA Instruments, New Castle, USA). The melt-containing pans were reheated to 165 °C and subsequently cooled at different cooling rates (1.2, 5, 10, 20 and 30 K min^{-1}) in a DSC instrument (DSC Q100, TA Instruments, New Castle, USA).

2.2.2. Characterisation of samples

All samples were analysed within 1 h after preparation and prior to dissolution testing using the following techniques.

2.2.2.1. X-ray powder diffraction (XRPD). Samples were analysed in a PANalytical X'Pert PROMPD system (PW3040/60, Philips, The Netherlands) using Cu Kα radiation with λ = 1.542 Å and a divergence slit of 1°. The samples were gently consolidated in flat aluminium sample holders and scanned at 40 kV and 30 mA from 5° to 35°2θ using a scanning speed of 0.1285° min^{-1} and a step size of 0.0084°2θ. The diffraction patterns were generated using X'Pert High Score software, version 2.2.0 (Philips, The Netherlands).

2.2.2.2. Raman spectroscopy. The same samples analysed as described in Section 2.2.2.1 were analysed using Raman spectroscopy prior to dissolution testing. Additionally, undissolved material following the dissolution study was also analysed. The FT-Raman instrument consisted of a Bruker FRA 106/S FT-Raman accessory (Bruker Optik, Ettlingen, Germany) with a Coherent Compass 1064–500 N laser (Coherent Inc., Santa Clara, USA) attached to a Bruker Equinox 55 FT interferometer, and a D 418T liquid nitrogen-cooled Ge diode detector. The analysis was carried out at room temperature utilising a laser wavelength of 1064 nm (Nd: YAG laser). Spectra were the average of 128 scans, taken at 4 cm^{-1} resolution with a laser power of 120 mW.

Principal components analysis (PCA) was used to visualise and interpret differences in the Raman spectra of the different samples. Prior to PCA, a standard normal variant (SNV) transformation was performed on the spectra in order to remove intensity differences unrelated to the sample composition. PCA was performed on the mean centred spectra in the ranges from 1000 cm^{-1} to 1720 cm^{-1} and 2800 cm^{-1} to 3100 cm^{-1}. PCA, spectral preprocessing and scaling were performed using The Unscrambler software, version 9.8 (CAMO Software AS, Oslo, Norway).

2.2.3. Intrinsic dissolution studies

Amorphous indomethacin samples were compressed into tablets, using a laboratory press (F. Carver Inc., Wisconsin, USA) equipped with a 13-mm flat faced punch and set at 250 MPa with a dwell time of 30 s. The tablets were placed into a PTFE sample holder with only one face of the tablet exposed to the dissolution medium, and the intrinsic dissolution rate was determined at 37 ± 0.5 °C in 900 ml of 0.2 M phosphate buffer pH 7.2 using the USP dissolution apparatus 1 (Erweka DT 600, Heusenstamm, Germany). Samples were rotated at 100 rpm, and 5 ml aliquots of test medium were withdrawn at predetermined time points. The withdrawn medium was replaced with fresh buffer. Samples were analysed for indomethacin concentration using a UV spectrophotometer (CARY Varian, Clayton South, Victoria, Australia) at a wavelength of 318 nm. All measurements were carried out in

triplicate. For quantification of indomethacin, a standard curve was prepared using six concentration levels of γ-indomethacin. Analysis of variance (ANOVA) was performed on the intrinsic dissolution rate values for all the differently quench-cooled and milled samples using Microsoft Excel (Microsoft Corporation, Washington, USA).

2.2.4. Polarising light microscopy (PLM)

PLM images of all undissolved solids were taken following the dissolution experiment (Section 2.2.3) using a polarising light microscope (Motic BA300pol, BA series, Motic incorporation Ltd., Hong Kong, China) equipped with cross polars, a 360° rotatable stage and a variable 30 W/6 V halogen light source. Images were taken using a Moticam 2300 digital camera (Motic incorporation Ltd., Hong Kong, China) with a resolution of 3 megapixels and minimum illumination of 3 lux.

3. Results and discussion

3.1. XRPD

3.1.1. Cryo-milling as preparative technique

Indomethacin samples milled for >30 min were entirely 'X-ray amorphous', regardless of the milling time, as indicated by the lack of diffraction peaks in the diffractograms (Fig. 1a). The characteristic peaks of the starting material (γ-form of indomethacin), however, were still observed in the samples cryo-milled for 15 min and are likely to stem from residual crystallinity present in the sample. The samples cryo-milled for 30 min only showed a halo with one broad maximum at ≈11°2θ, whilst samples cryo-milled for 60 or more minutes showed a halo with two broad maxima at ≈23°2θ and ≈11°2θ, respectively. No visible differences were observed between the diffractograms of samples milled for milling times >60 min.

3.1.2. Melting and quench-cooling as preparative technique

Indomethacin samples prepared by cooling the melt at different cooling rates were 'X-ray amorphous', regardless of the cooling rate, as indicated by the lack of diffraction peaks in the diffractograms (Fig. 1b). However, different shapes of the diffractograms of samples cooled at different cooling rates suggest structural variations between the different indomethacin samples. A halo with a broad maximum at ≈9°2θ for samples cooled at rates of 30 and 20 K min^{-1} and at ≈21°2θ for samples cooled at rates of 10, 5 and 1.2 K min^{-1} was obtained.

Overall, the differences in the halo shapes between differently prepared amorphous forms of indomethacin indicate structural differences (in the near order) of the amorphous samples.

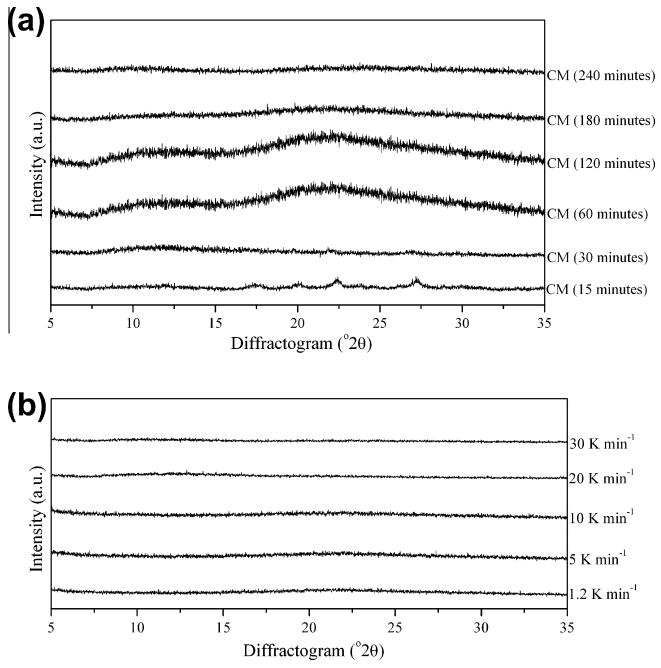

Fig. 1. Diffractograms of freshly prepared amorphous forms of indomethacin prepared (a) by cryo-milling for different milling times; and (b) by cooling of the indomethacin melt at different cooling rates.

3.2. Raman spectroscopy

Raman spectroscopy was performed on the same samples as in the XRPD study in order to visualise structural differences between the samples. The Raman spectra of all amorphous samples were characterised by peaks that were broader and more merged than those of the crystalline forms. Several peak position differences were found between the spectra of the amorphous and crystalline forms, in line with previous observations [27–29]. These differences can be explained by the inherently larger variations in molecular conformation and intermolecular interactions of the amorphous form, compared to their crystalline counterparts. PCA was performed on the Raman spectra of all samples prepared by the different preparative technique and processing parameter. The scores plot revealed that cryo-milled samples milled for ⩾180 min were similar to the samples prepared by cooling the melt (Fig. 2). Hence, it can be proposed that with an increase in milling time, the extent of disorder in the samples continues to increase and the material starts behaving like solids prepared by cooling the melt.

3.2.1. Cryo-milling as preparative technique

The Raman spectra of the amorphous forms of indomethacin milled for different times appeared visually similar, and thus PCA was used to investigate any spectral differences between them. Two principal components (PCs) explained 90% of the variation in the SNV-transformed and mean centred data. It can be seen in Fig. 3 that the samples were separated in the scores plot on the basis of milling times. The samples milled for 15 and 30 min formed separate clusters, whereas the samples milled for 60, 120, 180 and 240 min were positioned close to each other in the scores plot and formed one cluster. It can further be observed that the differences

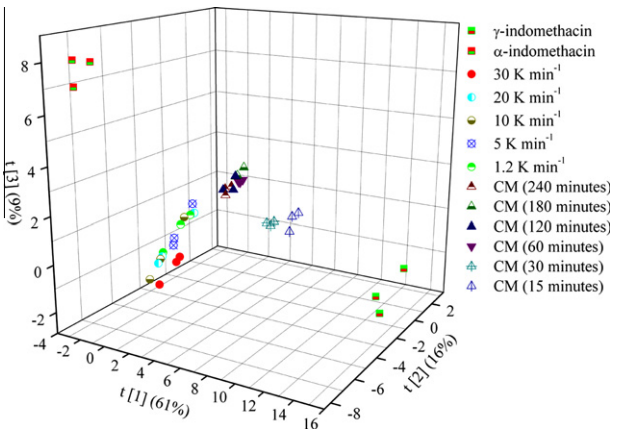

Fig. 2. PCA scores plot of the Raman spectra of samples prepared by milling at different milling times and cooling of the melt at different cooling rates. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

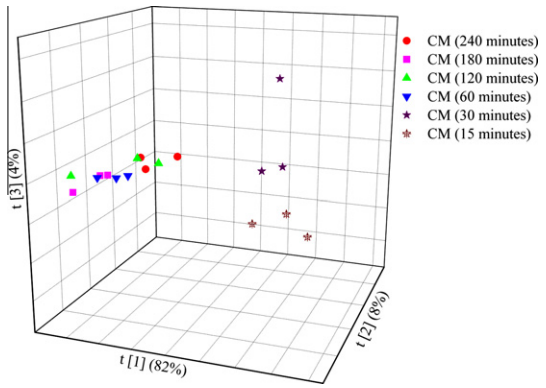

Fig. 3. PCA Scores plot of the Raman spectra of all freshly prepared cryo-milled samples prepared by different milling times. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

between the samples (milled for different times) get increasingly smaller as cryo-milling times were increased.

3.2.2. Melting and quench-cooling as preparative technique

The PCA plot utilised two principal components to explain 80% of the variation in the SNV-corrected and mean centred data. The scores plot (Fig. 4) was again used to investigate differences between the samples. The spectra of the differently cooled amorphous samples prepared in triplicate clustered separately in the scores plot for different cooling rates, suggesting that structural differences due to cooling rate are reproducible. In the scores plot, the samples prepared at cooling rates of 30, 20 and 10 K min^{-1} formed their own clusters, whilst the samples cooled at cooling rates of 5 and 1.2 K min^{-1} clustered separately.

3.3. Dissolution studies

The intrinsic dissolution experiments were performed under sink conditions to investigate the concentration–time profile of differently prepared amorphous indomethacin without reaching saturation in the medium (possible changes in the exposed surface area over time due to crystallisation of the samples were not taken into consideration since the focus was on detecting the effect of processing parameters on dissolution of the prepared amorphous forms, if these were treated under initially the same dissolution conditions). The phase transformation behaviour was evaluated by characterising the undissolved samples after 60 min of dissolution by Raman spectroscopy and PLM.

3.3.1. Cryo-milling as a preparative technique

Samples cryo-milled for 15 and 30 min appear to follow a dissolution rate similar to that of the α- and γ-crystalline form of indomethacin (Fig. 5), whilst on the contrary, the dissolution rates of these samples were statistically different to the crystalline indomethacin (p-value <0.01). The 15, 30 and 60 min milled samples showed dissolution rates of 0.08, 0.08 and 0.12 μg/ml/cm^2, respectively. The amount of drug dissolved appeared to increase when samples after 15, 30 and 60 min of milling time were compared to each other, but these differences did not reach statistical significance (p-value = 0.06) (Fig. 6). Samples cryo-milled for 120, 180 and 240 min, on the other hand, were characterised by significantly higher dissolution rates of 0.28, 0.48 and 0.59 μg/ml/cm^2, respectively, compared to samples milled for shorter times (p-value <0.01). The total amount of indomethacin in solution after 60 min was ≈5-fold and ≈8-fold higher for the sample milled for 120 and 180 min, respectively, as compared to the α- and γ-form, whilst the amount of indomethacin in solution after 60 min was ≈9-fold higher for the samples milled for 240 min compared to the α- and γ-form. The increase in dissolution rate for samples prepared at long milling times (120, 180 and 240 min) may be an indicator that besides the reduction in the number of nuclei, other processes occur upon milling, affecting the degree of disorder in the solid and enhancing the dissolution [23].

The increase in the amount of drug dissolved showed a correlation with the milling time. The longer the milling time, the higher dissolution rate was observed for indomethacin. A linear relation ($y = 0.0034x + 0.0272$; $r^2 = 0.99$) was obtained between dissolution rate of the cryo-milled indomethacin samples and the milling time (Fig. 6).

3.3.2. Melting and quench-cooling as preparative technique

In contrast to the samples prepared at different milling times, the amorphous indomethacin samples prepared at different cooling rates exhibited no significant differences in their concentration–time profiles (Fig. 7). Structural variations (confirmed by XRPD and Raman) in the differently cooled amorphous samples did not appear to have an impact on the dissolution rate. This can be further justified by the fact that the glass forming ability of indomethacin is very high when melt-quenching is employed as a preparative technique [30], suggesting that indomethacin is

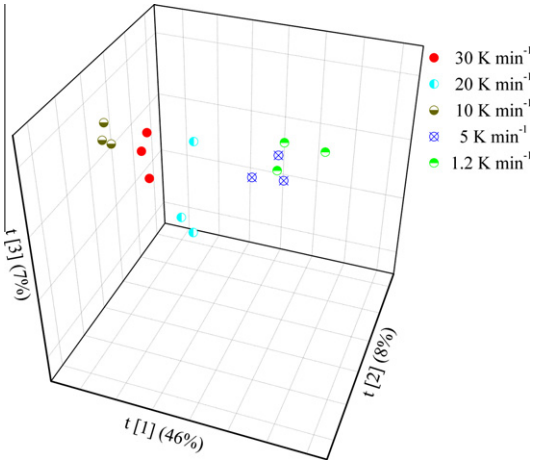

Fig. 4. PCA Scores plot of the Raman spectra of all freshly prepared amorphous samples prepared by different cooling rates. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

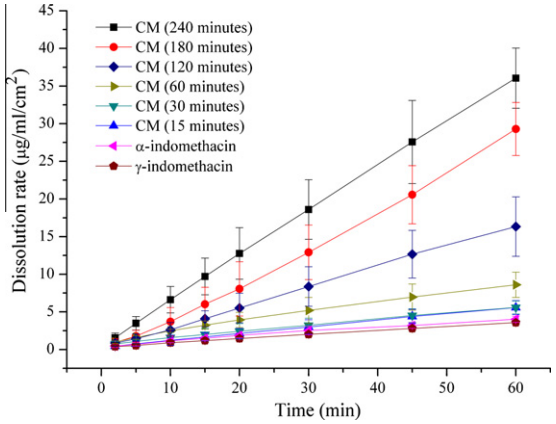

Fig. 5. Dissolution profiles of cryo-milled samples of indomethacin at 37 ± 0.5 °C for 60 min. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

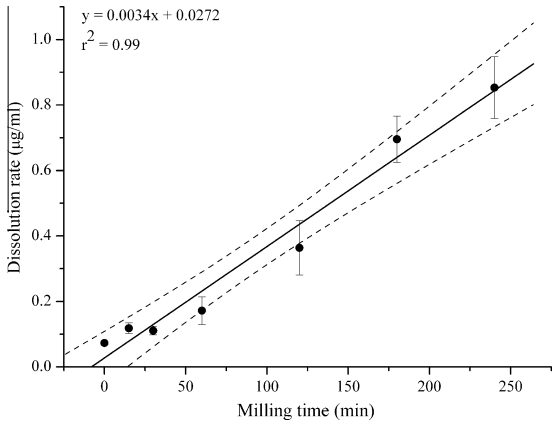

Fig. 6. Correlation between the milling time and the dissolution rate of all cryo-milled indomethacin samples (95% confidence interval is shown as dotted line and solid line is a linear regression fit).

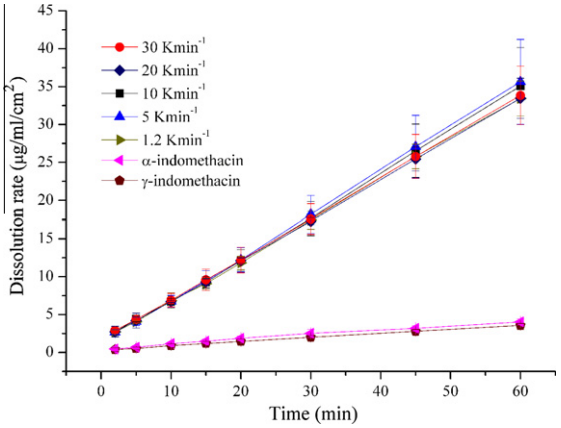

Fig. 7. Dissolution profiles of differently cooled samples of indomethacin at 37 ± 0.5 °C. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

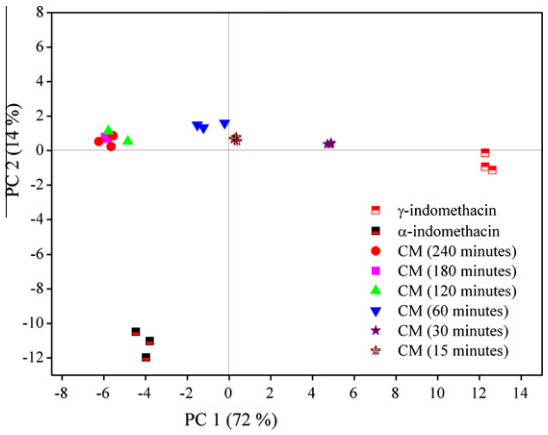

Fig. 8. PCA scores plot of the Raman spectra of undissolved solid material of all cryo-milled samples prepared by different milling times after termination of the intrinsic dissolution experiment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

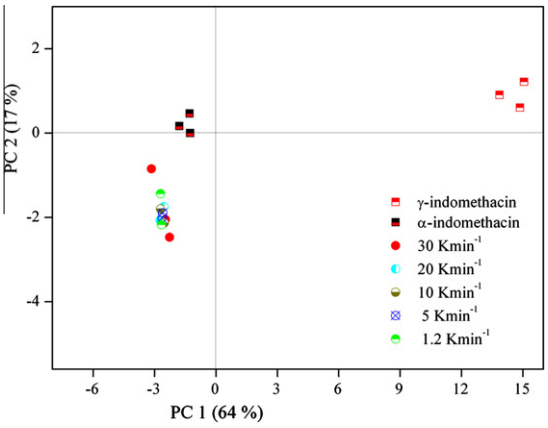

Fig. 9. PCA scores plot of the Raman spectra of undissolved solid material of all differently cooled samples prepared by different cooling rates after termination of the intrinsic dissolution experiment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

'completely amorphous' independent of the cooling rates used (no residual crystallinity and no significant differences in the thermal history), even though the prepared amorphous forms are structurally different at the molecular level.

The total amounts of indomethacin dissolved over time for all the samples prepared by different cooling rates were ≈42 mg after 60 min. In contrast, 15, 30 and 60 min cryo-milled samples of indomethacin showed dissolution of ≈6.6, 6.7 and 10.3 mg, respectively, after 60 min. This may be explained by the fact that the differently cooled samples are prepared from a melt, with no residual crystallinity or order remaining in the sample. The structural differences observed in the samples prepared by different cooling rates may be attributed to the time taken for the formation of the glass in the supercooled melt. Cryo-milled samples, on the other hand, may retain residual order from the starting material, even though there was a complete lack of peaks in the XRPD diffractograms.

3.4. Post-dissolution characterisation

3.4.1. Polarising light microscopy (PLM)

Using PLM, optically anisotropic samples may be identified (the orientation of incident light varies with the crystallographic axes of the sample). All prepared amorphous samples, with the exception of the sample cryo-milled for 15 min, showed no birefringence, suggesting complete amorphousness of the quench-cooled and cryo-milled materials. Following the dissolution study (Section 3.3), birefringence was observed in all the samples (images not shown), indicating the presence of crystalline material.

3.4.2. Raman spectroscopy

The Raman spectra of undissolved solid material, collected after dissolution of the 15, 30 and 60 min cryo-milled samples displayed remarkable differences in the phase transformation compared to the 120, 180 and 240 min cryo-milled samples. The Raman spectra of all undissolved cryo-milled samples after dissolution clustered differently in the scores plot, except for the samples cryo-milled for 120, 180 and 240 min (Fig. 8). It has been proposed that cryo-milling induces disorder in the samples as a function of cryo-milling time [23]. In this study, the increase in disorder as a function of cryo-milling time was small when cryo-milling was performed for ⩾120 min. This indicates that no or only little further disorder was introduced into the samples cryo-milled for milling times >60 min. The differences in the degree of disorder and the number of nuclei present in the 15, 30 and 60 min cryo-milled samples are mirrored in the scores plot of the undissolved materials of cryo-milled samples after dissolution. The samples cryo-milled for ⩽60 min showed

mainly the presence of γ-indomethacin, whilst samples cryo-milled for >60 min showed a mixture of α- and γ-indomethacin.

Phase transitions of undissolved solid material, collected after termination of the dissolution experiment of amorphous solids prepared by different cooling rates, were also monitored using Raman spectroscopy. The spectra of the undissolved solid materials clustered together in the scores plot and were resolved towards α-indomethacin, suggesting the presence of mostly α-indomethacin in the undissolved solid (Fig. 9). This suggests that all the differently cooled samples behave similarly in the dissolution medium, irrespective of their initial structural variations.

4. Conclusions

This study demonstrated that by using different processing parameters (of the same preparative techniques), different forms of amorphous indomethacin can be produced and the differences can be characterised using Raman spectroscopy and XRPD. The molecular variations within the different amorphous solids prepared by melting and quench-cooling (using different cooling rates) did not have an influence on the solubility and dissolution rate of the drug. However, the dissolution rate increases for samples prepared by cryo-milling of indomethacin after exceeding a critical minimal milling time ($\geqslant$120 min). This study has also shown that the degree of disorder in the solids may increase as a function of milling time and enhance the drug dissolution. This information may help the formulation scientist to select and optimise the preparation method and processing parameters for preparation of amorphous solids.

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