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Investigation of properties and recrystallisation behaviour of amorphous indomethacin samples prepared by different methods

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ABSTRACT

The aim of this study was to investigate if amorphous indomethacin samples, prepared using different preparation methods, exhibit different structural and kinetic characteristics and if these differences can be correlated to their physical stability (time to crystallisation). Samples were prepared by melt quenching, spray drying, ball milling, and cryo-milling. The resulting amorphous materials were characterised using X-ray diffraction, Raman spectroscopy and differential scanning calorimetry. All freshly prepared samples were completely X-ray amorphous (with a halo being the only feature in the diffractograms). The shape of the halos in the diffractograms, however, varied depending on the preparation method, suggesting structural variations in the near order of the molecules between the differently prepared amorphous forms. Principal component analysis of the Raman spectra of the various amorphous forms revealed that the samples clustered in the scores plot according to preparation method, again suggesting structural differences due to preparation method. The range of vibrations associated with the largest spectral differences in the loadings plot showed that these differences were due to a range of molecular conformations and intermolecular interactions. The ranking of the samples with respect to stability was: quench cooled amorphous samples > cryo-milled (α-form) > spray dried > ball milled (α-form) > ball milled (γ-form) = cryo-milled (γ-form). This ranking was not correlated with the diffractogram shapes or sample distribution in the scores plot of the Raman spectra, suggesting that physical stability was not directly affected by structural variation in the samples. However, ranking of stability of the differently prepared amorphous forms of the drug could be predicted by determining the relaxation time values, for all amorphous samples. The relaxation times, calculated by using the Adam Gibbs and Kohlrausch–Williams–Watts equations, were in accordance with the experimentally determined stability order.

This study showed that correlation of physical stability with calculated relaxation time is possible for the same amorphous systems prepared by different methods. This could aid in selecting the most appropriate preparation techniques in situations where there are a variety of suitable methods.

1. Introduction

Amorphous materials have a higher Gibb's free energy than their crystalline counterparts, and as a result have higher apparent solubilities and faster dissolution rates, which in turn can lead to higher bioavailability for drugs that exhibit dissolution-rate limited absorption (classified as Biopharmaceutical Classification System (BCS) class II drugs) (Amidon et al., 1995; Hancock and Zografi, 1996). However, the main problem in the development of amorphous drugs and dosage forms is the physical instability of the amorphous state.

The most common techniques to prepare amorphous forms in pharmaceutical systems (e.g. pure drugs or drug–polymer glass solutions) can be categorised according to two principal transformation mechanisms. In most cases the crystalline material is intermediately transformed into a thermodynamically stable non-crystalline form (either a melt or a solution) and the thermodynamically unstable amorphous solid material is then prepared by quench-cooling of the melt or rapid precipitation from solution e.g. during spray drying. A second transformation mechanism involves direct solid conversions from the crystalline to the amorphous forms, such as in mechanical activation (milling). Whilst in melt and solution mediated methods all crystallinity is lost in the intermediate phase (melt, solution) mechanical activation may not cause complete disruption of the molecular order (Craig et al., 1999; Hancock and Zograf, 1997; Hilden and Morris, 2004; Yu, 2001).

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There has been comparatively little research into understanding the effect of preparation methods on the physical stability of the resulting amorphous form. However, since the amorphous form of a material does not represent a minimum in the energy landscape (in contrast to crystalline polymorphs), and consequently no state equations exist to describe a resulting amorphous form, differences in the properties of an amorphous material as a function of the preparation method should be expected. In an analysis of amorphous simvastatin prepared by cryo-milling and melting and quench-cooling, it was found that the cryo-milled samples differed from the quench-cooled samples, with the cryo-milled samples having a lower physical stability (Graeser et al., 2008). It has also been reported that amorphous griseofulvin prepared by quench-cooling and by cryo-milling showed different thermal and structural properties (Feng et al., 2008). Similarly, differences in the thermal and structural properties of amorphous indomethacin prepared by different techniques have been observed (Savolainen et al., 2007b). Differences in the thermal, structural and physical properties of differently prepared amorphous forms also led to the suggestion that molecular mobility, which is considered to play a pivotal role in the recrystallisation process, may be different for the same drugs using different preparation techniques (Graeser et al., 2009).

The aim of this study was to investigate whether amorphous indomethacin samples prepared using different preparation methods (melt quenching, spray drying, ball milling, and cryo-milling) and different starting polymorphs of the drug (α- and γ-form, for the milled samples only), exhibit different structural characteristics (investigated by X-ray diffraction and Raman spectroscopy) and molecular mobility (calculated from differential scanning calorimetry measurements using the Adam Gibbs and Kohlrausch–Williams–Watts equations) and whether these can be correlated to their physical stability (time to crystallisation).

Indomethacin is an anti-pyretic and anti-inflammatory drug used in many pharmaceutical preparations (Shen et al., 1963; Winter et al., 1963). It has been proposed to have up to four polymorphic forms (Allen and Kwan, 1969; Yamamoto, 1968), though the α- and γ-forms are the most commonly studied (Borka, 1974) Amorphous indomethacin prepared using melt quenching has been found to recrystallise to γ-form when stored below its glass transition temperature (T_g) and to α-form when kept above its T_g (Savolainen et al., 2007b). It has been reported that the onset of crystallisation of amorphous indomethacin prepared by melting and quench-cooling was observed after approximately 25 days when stored at 25 °C (Bhugra et al., 2008). It has also been reported that 50% of the amorphous indomethacin transforms to its crystalline counterpart within eight days when stored at 20 °C under dry conditions (Imaizumi et al., 1980).

2. Materials and methods

2.1. Materials

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

2.2. Preparation of polymorphs

The γ-form of indomethacin was used as received. The α-form of indomethacin was obtained by dissolving the γ-form in ethanol at 80 °C and then adding distilled water (at room temperature) to initiate precipitation. The precipitated crystals were removed by filtration and then dried under vacuum at room temperature (Heinz et al., 2007; Kaneniwa et al., 1985).

2.3. Preparation of amorphous samples

Amorphous indomethacin was prepared via three transformation routes: melt quenching, spray drying and direct solid state transformation (milling).

2.3.1. Transformation via melt quenching

Indomethacin (γ-form) (1 g) was melted in a stainless steel beaker at 165 °C for 3 min and then cooled immediately by placing the beaker on ice. The resulting amorphous solid was then warmed to room temperature over silica gel and triturated lightly, before being stored in a desiccator over P_2O_5. Samples were prepared in triplicate and are referred to as QC (quench-cooled) samples.

2.3.2. Transformation via spray drying

Indomethacin (γ-form) (1 g) was dissolved in 100 ml methanol (99%) and the resulting 1% (m/v) indomethacin solution was spray dried under nitrogen atmosphere (800 kPa) using a Büchi Mini Spray Dryer B-290 (Büchi Labortechnik, AG, Switzerland). The inlet temperature was 38 °C; the aspirator was set to 100% and the pump to 10%. The outlet temperature varied between 25 and 30 °C. The resulting powder was stored in a desiccator over P_2O_5. Samples were prepared in triplicate and are referred to as SD (spray dried) samples.

2.3.3. Transformation by milling of the crystalline solid state

Amorphous indomethacin was prepared from both the α- and γ-forms of the drug. The material was milled using an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Haan, Germany). The sample powder (1 g) was placed in a 25 ml volume stainless steel milling jar containing six 9 mm diameter stainless steel balls. Two different milling methods were employed. In the first (referred to as ball milling, BM), the samples were milled at 4 ± 2 °C with a frequency of 30 Hz for up to 6 h. In the second (referred to as cryo-milling, CM), the jars were immersed in liquid nitrogen for 3 min after adding the sample, and then milled at 30 Hz for 60 min. The jars were recooled in liquid nitrogen every 15 min. Samples were prepared in triplicate for each polymorph and milling method and are referred to as BM and CM samples, respectively.

2.4. Storage

The freshly prepared amorphous samples were stored at 22 ± 0.2 °C (T_g – 20 °C) over P_2O_5 until crystallisation.

2.5. Characterisation

The freshly prepared and stored samples were characterised using the following techniques. The freshly prepared samples were analysed within 1 h of preparation.

2.5.1. X-ray powder diffraction (XRPD)

The samples were analysed using XRPD with 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°. The diffraction patterns were generated using X'Pert High Score version 2.2.0 (Philips, The Netherlands).

The experimental diffraction patterns were compared to the theoretical diffractograms, based on the crystal structures obtained from the Cambridge Crystallographic Data Centre (CCDC). The data from the ref. codes INDMET02 and INDMET were used to generate

the theoretical diffraction patterns of the α- and γ-forms, respectively (Cox and Manson, 2003).

2.5.2. Raman spectroscopy

The FT-Raman instrument consisted of a Bruker FRA 106/S FT-Raman accessory (Bruker Optik, Ettlingen, Germany) with a Coherent Compass 1064-500N 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 (approximately 4 min per spectrum), taken at 4 cm^{-1} resolution with a laser power of 120 mW.

Principal components analysis (PCA) was used to help interpret differences in the Raman spectra of the differently prepared amorphous forms. Before PCA, a standard normal variant (SNV) transformation was performed on the spectra to remove intensity differences unrelated to the sample composition and the spectra were then mean centred. PCA was performed on the spectral 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).

2.5.3. Differential scanning calorimetry (DSC)

DSC thermograms were recorded on a DSC Q100 calorimeter (V8.2 Build 268, TA Instruments, New Castle, USA) after temperature and enthalpy calibration using indium. Samples (2–5 mg) were crimped in an aluminium pan and heated at a rate of 10 K min^{-1} from 0 to 180 °C under a nitrogen gas flow of 50 ml min^{-1}. The glass transition temperature (T_g), crystallisation temperature (T_c) and melting temperature (T_m) were determined using TA Universal Analysis software (version 4.0C). The T_g was defined as the midpoint of the change in heat capacity of the sample, while both T_c and T_m were defined using the onset temperatures. Analysis of variance (ANOVA) was performed on the thermal events detected in the various samples using Microsoft Excel (Microsoft Corporation, Washington, USA).

2.6. Determination of molecular mobility

Molecular mobility is usually determined as the reciprocal of the relaxation time (τ). To date, no single equation exists to calculate the relaxation time as a variety of factors needs to be taken into account. However, the two most commonly used equations that give an indication on the mobility within an amorphous sample are the Kohlrausch–Williams–Watts equation (KWW) and the Adam Gibbs equation (AG). The underlying assumption for the empirical KWW equation is that the relaxation time of a sample can be determined by measuring the enthalpy lost during annealing (Graeser et al., 2009; Liu et al., 2002; Surana et al., 2005; Van den Mooter et al., 1999; Yoshioka et al., 2001). An amorphous compound will relax, thereby losing some of its excess thermodynamic properties, e.g. enthalpy. Upon reheating of the sample, the enthalpy is recovered and can be visualized in the DSC as an enthalpic overshoot at the T_g. In Eq. (1) the enthalpic relaxation, ΔH_{relax}, is related to the relaxation function φ and the maximal theoretical enthalpic relaxation.

Samples are aged for various lengths of time and φ is obtained for various time points.

$$\varphi = 1 - \frac{\Delta H_{relax}}{\Delta H_{\infty}} \quad (1)$$

where φ = relaxation function, ΔH_{relax} = enthalpic relaxation and ΔH_{∞} = maximal theoretical enthalpic relaxation.

The maximal theoretical enthalpic relaxation is obtained by Eq. (2)

$$\Delta H_{\infty} = \Delta C_p(T_g - T) \quad (2)$$

where ΔC_p = heat capacity change at T_g and T = ageing temperature.

The calculated relaxation functions are then fitted to Eq. (3), and the KWW parameters, relaxation time τ and the exponential parameter β are obtained.

$$\varphi = \exp\left[-\left(\frac{t}{\tau}\right)^{\beta}\right] \quad (3)$$

where t = time, τ = relaxation time and β = stretched exponential parameter ($0 < \beta < 1$).

In this study, amorphous samples were kept at approximately 20 °C below their respective T_g and held at that temperature for 0–4 and 8 h. The relaxation enthalpy was determined by re-heating the samples through their T_g and measuring the relaxation endotherm at T_g.

The AG equation takes the concept of configurational entropy into account when determining the relaxation time (Adam and Gibbs, 1965; Graeser et al., 2009; Olivares-Quiroz and Garcia-Colin, 2009). As a freshly prepared glass relaxes, it reduces its enthalpy and entropy, and this gives the configurational entropy not only a temperature dependent but also a time dependent component. Real glasses are not in equilibrium, however, thermodynamic principles have been applied in order to characterise real glasses by applying the fictive temperature, T_f. The fictive temperature is the temperature at which the equilibrium system has the same thermodynamic properties as the real system at temperature T and time t. In one of its forms, the AG equation can be written as Eq. (4):

$$\varphi = \tau_0 \exp\left(\frac{DT_0}{T(1 - T_0/T_f)}\right) \quad (4)$$

where τ = relaxation time, τ_0 = pre-exponential parameter; 10^{-14}, D = Angell's strength parameter, T_0 = temperature of zero configurational entropy and T_f = fictive temperature. The step-by-step procedure of obtaining the required values was carried out based on the published literature (Mao et al., 2006).

The heating rate dependence of the glass transition was measured at heating rates of 5, 10, 15 and 20 K min^{-1}. The glass transition temperature was taken as the inflection point of the step change. The amorphous samples were equilibrated at a starting temperature 50 °C below T_g. The drugs were then heated through the T_g at the given heating rates to 10 K above their T_g. All measurements were performed in triplicate.

3. Results and discussion

3.1. Freshly prepared samples

3.1.1. XRPD

Complete absence of diffraction peaks in the diffractograms of all freshly prepared samples revealed that indomethacin was completely "X-ray amorphous" regardless of preparation method (Fig. 1). However, the shape of these diffractograms varied, suggesting structural variations in the near order of the molecules between the differently prepared amorphous forms. All samples, except the SD sample, featured two relatively broad maxima in the halos. The diffractograms of the QC and CM γ-form, had relatively intense maxima at approximately 21° 2θ, and much a weaker feature centred below 15° 2θ. The two maxima in the diffractograms of the BM γ-form, BM α-form and CM α-form were of similar intensity and position, but slightly different shape. The single maximum in the halo of the SD sample was centred at approximately 11° 2θ. These data were reproducible for the three batches from each preparation

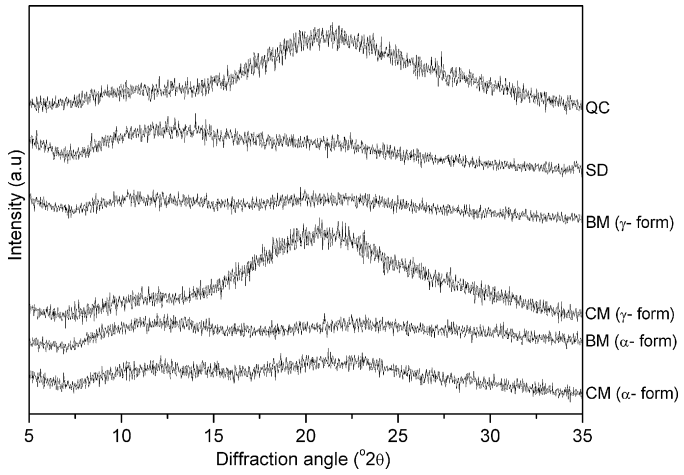

Fig. 1. Diffractograms of freshly prepared amorphous form of indomethacin prepared by different preparative techniques.

method (only one diffractogram is shown in Fig. 1 for each preparation method). Raman spectroscopy was performed on the same samples to help understand the nature of the structural differences between the samples.

3.1.2. Raman spectroscopy

The Raman spectra of all the freshly prepared amorphous samples contained peaks that were broader and more merged than those of the crystalline forms (Fig. 2(a)), which is due to the inherently larger variations in molecular conformation and intermolecular bonding of amorphous forms compared to their crystalline counterparts (Savolainen et al., 2007b; Strachan et al., 2007). There were several peak position differences between the amorphous and crystalline forms, confirming previous observations (Strachan et al., 2007). However, there were no spectral features specific to the α- or γ-forms for any of the amorphous samples.

PCA was used to investigate spectral variation between the different amorphous samples. Three principal components (PCs) explained 99% of the variation in the SNV transformed and centred data. The scores plot (Fig. 2(b)) was used to investigate the relationship between the different samples based on the PCA model. The spectra of the freshly prepared amorphous samples prepared in triplicate clustered in the scores plot according to preparation method, suggesting that structural differences due to preparation method are reproducible. In the scores plot, the QC and CM γ-form samples clustered beside one another and separate from the other samples. The SD sample also formed its own cluster. The BM γ-forms as well as the BM and CM α-forms were situated between these two clusters, with the BM γ-form slightly resolved from the other samples. These three clusters mirror the differences observed in the diffractograms of the differently prepared samples (Fig. 1).

The spectral loadings plots (Fig. 2(c)) were used in an attempt to interpret sample differences leading to the clustering observed in the scores plot. The loadings of the three PCs revealed that the largest spectral differences were observed in the regions from 1540 cm^{-1} to 1700 cm^{-1} (PC1 and PC3) and from 2930 cm^{-1} to 3100 cm^{-1} (PC1 and PC2) (Savolainen et al., 2007b; Strachan et al., 2007; Taylor and Zografi, 1997). The main vibrations associated with the bands in these regions have previously been assigned for QC indomethacin as follows: in-plane indole ring deformation (1580 cm^{-1}), chlorobenzoyl ring deformation (1591 cm^{-1}), C–O stretching associated with indole ring deformation (1613 cm^{-1}), benzoyl C=O stretching (1681 cm^{-1}), and aliphatic (2930 cm^{-1} and 2970 cm^{-1}) and aromatic C–H stretching (3000–3100 cm^{-1})

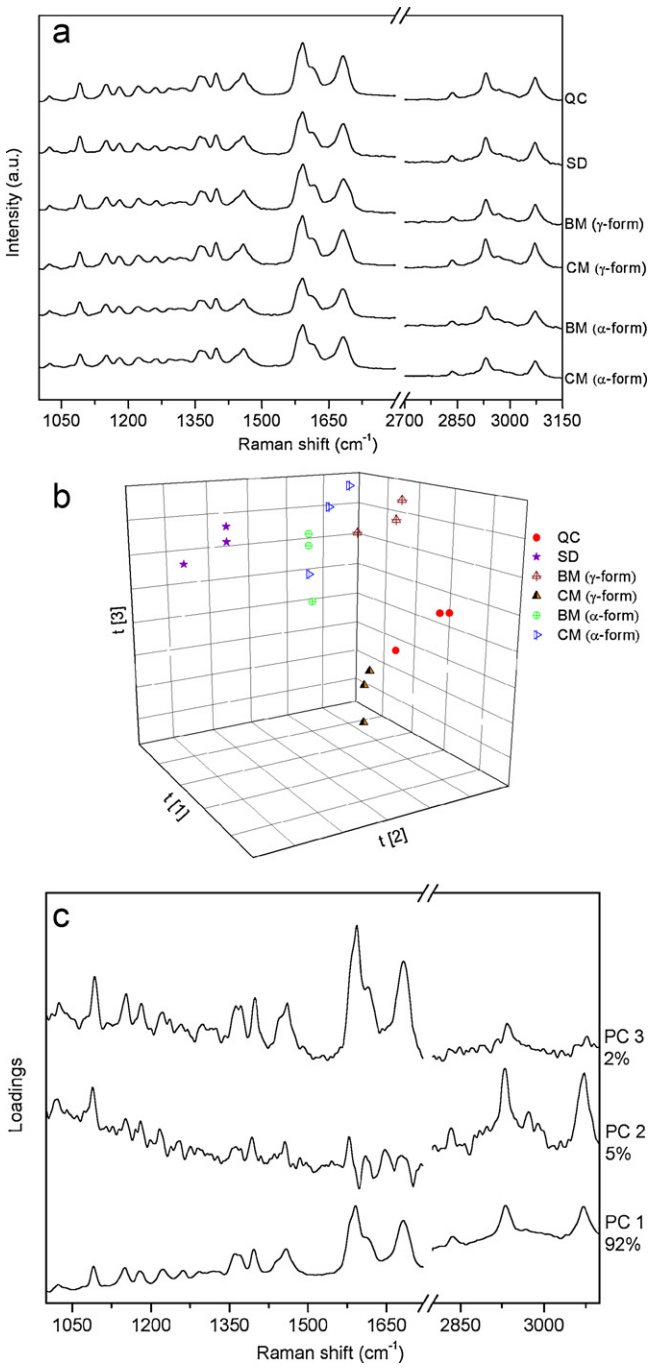

Fig. 2. Raman spectra (a); scores plot (b); and their corresponding loadings (c) of all freshly prepared amorphous samples.

(Savolainen et al., 2007b). The range of vibrations associated with the largest spectral differences suggests that the systematic differences associated with the differently prepared forms were due to a range of molecular conformations and intermolecular interactions, and cannot be attributed to one or a few vibrations only.

3.1.3. Thermal analysis

For all freshly prepared amorphous samples, the DSC thermograms exhibited a change in heat capacity (ΔC_p) at 40 ± 3 °C (Table 1), an exothermic event in the range of 60–100 °C depending on the preparative method (Table 1), and one or two endotherms at 155 ± 2 °C and 160 ± 2 °C. The change in heat capacity can be attributed to the glass transition (T_g) of the sample and the exother-

Table 1
Thermal properties of amorphous forms of indomethacin prepared by different preparative techniques (mean ± SD, $n = 3$).

Technique	T_g (°C)	C_p at T_g (J/g °C)	Onset of crystallisation (°C)	ΔH_{relax} (J/g)
QC	41.25 ± 1.16	0.50 ± 0.03	96.93 ± 1.02	1.03 ± 0.26
SD	41.25 ± 0.28	0.47 ± 0.28	73.59 ± 7.18	0.68 ± 0.31
BM (γ-form)	39.23 ± 2.19	0.57 ± 0.03	62.14 ± 4.16	0.28 ± 0.09
CM (γ-form)	40.27 ± 3.57	0.52 ± 0.16	60.84 ± 2.91	0.95 ± 0.84
BM (α-form)	37.92 ± 2.02	0.70 ± 0.09	70.16 ± 0.70	0.84 ± 0.43
CM (α-form)	43.19 ± 1.68	0.34 ± 0.11	62.88 ± 6.18	2.38 ± 0.47

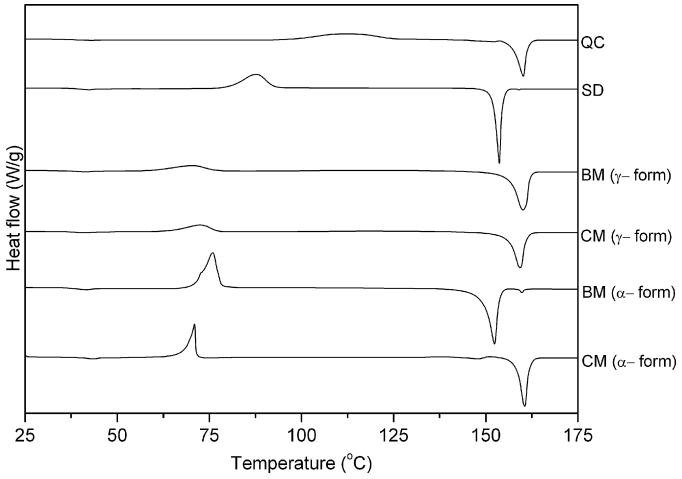

Fig. 3. Thermograms of freshly prepared amorphous form of indomethacin prepared by different preparative techniques.

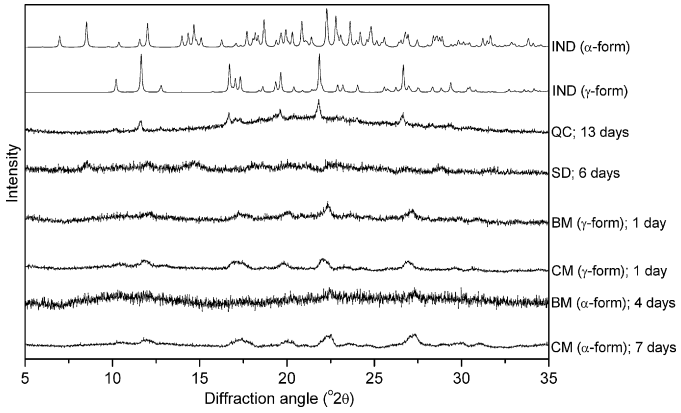

Fig. 4. Diffractograms showing the onset of crystallisation for differently prepared amorphous samples.

mic event (T_c) was associated with recrystallisation of amorphous indomethacin. The endotherms with onsets at 155 and 160 °C were due to melting of the α- and γ-forms of indomethacin, respectively (Fig. 3).

ANOVA analysis was performed on each thermal event and no significant difference was noted in the T_g and associated ΔC_p, but there were significant differences in the onset of crystallisation for the amorphous samples prepared by the different techniques. The difference in the recrystallisation temperature of the samples can be ascribed either to differences in the amorphous state or the presence of crystal seeds (Savolainen et al., 2007a). The milled samples recrystallised at the lowest temperatures, followed by the SD samples and the QC samples.

The freshly prepared amorphous QC samples showed a trace of the α-form on heating; however only α-form was observed for the freshly prepared spray dried samples (Fig. 3). The freshly prepared BM and CM samples prepared using γ-form transformed into the γ-form on heating, whereas the freshly prepared BM samples prepared from α-form exhibited an α-form melting endotherm. The freshly prepared CM α-form amorphous samples showed the presence of the γ-form, and a trace of α-form on heating (Fig. 3). The different thermal (recrystallisation temperature and enthalpy) and kinetic properties of the amorphous samples prepared by different methods and from different polymorphs were associated with different recrystallisation rates (Table 2) and resulting polymorphic forms.

Table 3
Onset of crystallisation for amorphous samples stored at T_g – 20 °C prepared by different preparative techniques (mean ± SD, $n = 3$).

Preparative techniques	Onset of crystallisation (days)
QC	13 ± 2
SD	6 ± 2
BM (γ-form)	≤1
CM (γ-form)	≤1
BM (α-form)	4 ± 1
CM (α-form)	7 ± 1

3.2. Recrystallisation

X-ray powder diffraction was used to determine the time to onset of crystallisation and the resulting polymorphic form of the drug (Fig. 4). The time to onset of crystallisation was defined as the time until diffraction peaks were visible in the diffractograms. The time to onset of crystallisation is shown for each preparation method in Table 3. The ranking of the samples with respect to stability was: QC > CM α-form > SD > BM α-form > BM γ-form = CM γ-form. This ranking could not be correlated with the diffractogram

Table 2
Kinetic parameters of amorphous samples prepared by different preparative techniques.

Preparative technique	QC	SD	BM (γ-form)	CM (γ-form)	BM (α-form)	CM (α-form)
ΔH^* (T_g) [kJ/mol]	569.43	179.53	234.13	189.55	424.83	356.77
D	7.37	42.62	25.20	37.8	10.65	13.50
m	95.93	29.82	39.38	31.59	71.34	59.66
β	0.29	0.41	0.48	0.65	0.75	0.33
τ (KWW) [s]	8.1×10^5	3.8×10^5	5.0×10^4	1.8×10^4	8.7×10^4	7.3×10^5
τ (AG) [s]	4.2×10^6	1.4×10^4	5.7×10^3	4.4×10^3	1.3×10^4	1.7×10^4

ΔH^* (T_g) = activation enthalpy at the T_g; D = measure of fragility of glass forming liquid (Angell's strength parameter); m = fragility index; β = stretched exponential parameter; τ = relaxation time.

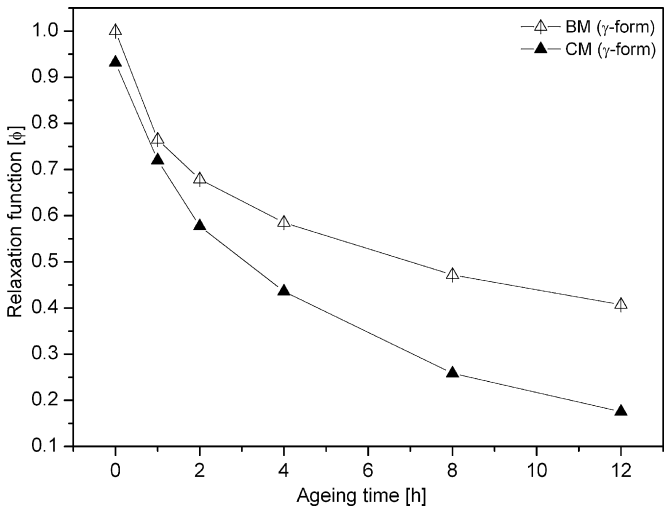

Fig. 5. Effect of annealing on the KWW relaxation function of BM γ-form and CM γ-form.

shapes or sample distribution in the scores plot of the Raman spectra, suggesting that the time until onset of crystallisation was not directly affected by structural variation in the samples.

The polymorphs formed during crystallisation depended on the preparation method and were consistent for each method. The QC and SD samples, in which the starting polymorph can be assumed to have no effect on the crystallisation behaviour (since the drug passes through a melt and solution state, respectively), crystallised to the γ- and α-forms, respectively. The milled samples, in which the starting polymorph was the γ-form, crystallised back to their original polymorph. However, the BM α-form crystallised directly to the γ-form and the CM α-form recrystallised to a mixture of the metastable α-form and the stable γ-form. This suggests that in the CM samples, the presence of nuclei was not the main factor influencing the resulting polymorph. Interestingly, the clustering of the spectra (freshly prepared samples) in the PCA scores plot largely correlated with the resulting polymorphs, with those samples crystallising to the γ-form generally to the right of those crystallising to the α-form in the scores plot (Fig. 2(b)). This suggests that structural differences in the differently prepared amorphous forms, independent of the presence of any nuclei, may influence the resulting polymorphic form.

3.3. Comparison of molecular relaxation processes and physical stability

The calculated values for the relaxation times were compared to the actual physical stability of the amorphous systems. It was noted that values calculated by the different equations gave different values for the relaxation time. This is, however, not unexpected as both equations rely on different underlying assumptions.

With these prerequisites it can be considered challenging to correlate the relaxation time with the physical stability using the absolute relaxation times. However, amorphous systems with the smallest relaxation time have the largest molecular mobility and should recrystallise the fastest. The effect of annealing on the relaxation function (φ) can be seen in Fig. 5, where Φ was fitted to the KWW equation for the BM γ-form and the CM γ-form. For the KWW and the AG approach, the order of predicted stability based on the relaxation times was the same: QC > CM α-form > SD > BM α-form > BM γ-form > CM γ-form.

The absolute values for the relaxation time did not agree with the observed stability, however, KWW approach gives a better fit in contrast to AG approach. Thus, QC indomethacin should be the most stable and CM γ-form should be the least stable amorphous system.

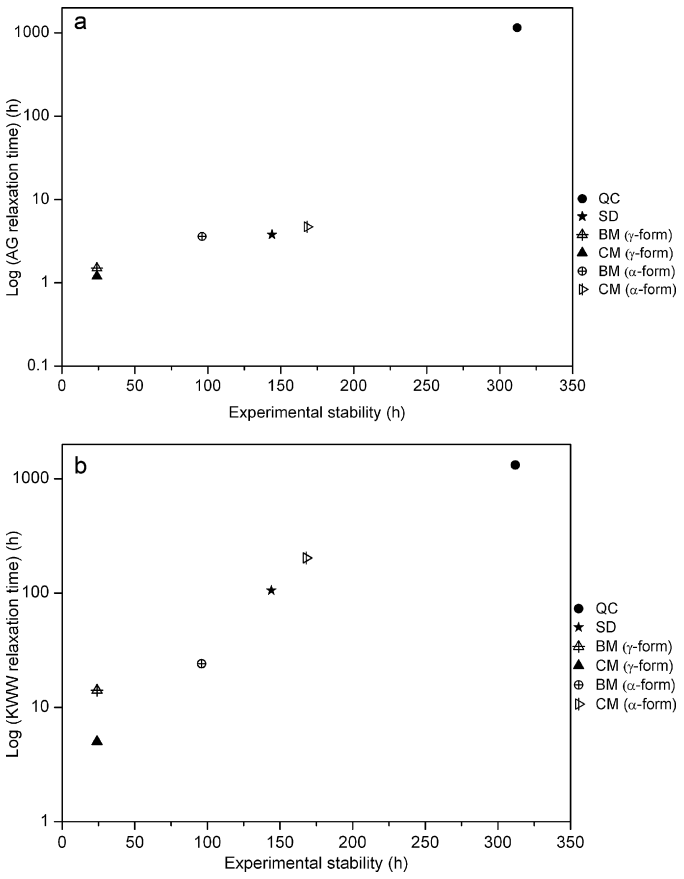

Fig. 6. Correlation of AG relaxation time (a) and KWW relaxation time (b) with the experimentally determined stability (onset of crystallisation) for differently prepared amorphous forms.

Indeed, the order of stability from relaxation time calculation was reflected in the observed physical stability of the stored samples (Fig. 6).

4. Conclusions

In this study it was demonstrated that differently prepared amorphous forms of the drug indomethacin showed differences on the molecular level (detected by Raman spectroscopy and XRPD). These differences however, could not be correlated directly to the physical stability of the samples. However, there was some evidence that the molecular level variation (and not the presence of crystal seeds) influenced the resulting polymorphic form during crystallisation.

This study has also shown that the relaxation time – determined either by the KWW or by the AG approach – could be used to rank the same amorphous systems prepared by different methods correctly according to their stability, using the relative relationships of the relaxation times. This information may help the formulation scientist to select (at an early stage in drug development) the preparation method that gives the most stable amorphous system.

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