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Research paper

Formation and physical stability of the amorphous phase of ranitidine hydrochloride polymorphs prepared by cryo-milling

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Abstract

The effect of cryo-milling on ranitidine hydrochloride polymorphs form 1 and 2 was investigated with particular interest in the formation and the stability of the amorphous phase. Cryo-milling was carried out using an oscillatory ball mill for periods up to 60 min, with re-cooling of the milling chamber with liquid nitrogen at 15 min intervals. Results showed that both ranitidine hydrochloride form 1 and form 2 could be fully converted to the amorphous form as determined by XRPD within 30 min. Upon 14 days storage, the amorphous samples crystallized back to their original forms. In the stability studies of amorphous drug with seeds, significant polymorphic transformation from form 1 to form 2 was not found when amorphous form prepared from form 1 was seeded with form 2 crystals by gentle physical mixing. In contrast, amorphous form prepared from form 1 seeded with form 2 crystals by ball milling for 1 min and simultaneous cryo-milling methods were found to transform amorphous form prepared from form 1 to crystalline form 2 under some storage conditions. The transformation was thought to be facilitated by interaction between seed crystals and amorphous drug and a storage temperature above the Tg. Amorphous form prepared from form 2 did not transform to crystalline form 1 under any conditions used in this study.

Keywords: Ranitidine hydrochloride; Cryo-milling; Amorphous; Stability; Polymorphic transformation; Seeding; Glass transition; Crystallization temperature

1. Introduction

Ranitidine hydrochloride is a drug widely used for the treatment of stomach ulcer. Two polymorphic forms are available in the market, form 1 and form 2. The physicochemical properties of the two forms are well characterized and can be found elsewhere [1–4], though the stability of the two polymorphic forms under different conditions remains unclear. Form 2 is thought to be more stable than form 1, partly because of a higher melting point of form 2 (140–144 °C) than form 1 (134–140 °C) [5]. In the clinical setting, the polymorphs were found to be bioequivalent. However due to patenting and commercial reasons, interest has been given to both forms [6]. Of particular interest is the potential for the polymorphs to interconvert. The ability of form 1 to convert to form 2 upon grinding was first reported by Forster et al. during sample preparation for FTIR studies [7]. Subsequently studies in our laboratory have confirmed that form 1 does convert to form 2 as a result of grinding or milling [8,9]. However other researchers have failed to show this conversion [10]. This could be due to limited grinding time and force they were exerting onto the powder.

Our earliest studies using a rolling porcelain mill showed that conversion occurred upon grinding after several days. Analysis showed that the conversion occurred via an amorphous phase, as shown by the appearance of a halo in the XRPD at intermediate milling times [8]. Further studies using an oscillatory ball mill containing two 9 mm diameter

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stainless steel balls also confirmed the conversion of form 1 to form 2 via the amorphous phase. In that study, up to 10 h was needed for the conversion to occur [9]. A similar experiment using two 12 mm diameter stainless steel balls again showed a conversion from form 1 to form 2, with the process occurring much faster (3 h), possibly due to larger energy impact on the powder [11]. The temperature of the powder (solid temperature) was 45 °C when milled at 12 °C ± 2 °C. DSC analysis of the same samples showed a glass transition temperature (Tg) in the range of 13–30 °C, and a crystallization temperature (Tc) in the range of 30–65 °C [11]. Subsequent studies at 4 °C ± 2 °C (solid temperature of 36 °C) showed only amorphous drug was produced since the milling temperature never exceeded the Tc during the milling process. Milling at 35 °C ± 2 °C led to a solid temperature of 65 °C, i.e. at the higher end of the Tc range. Following XRPD analysis, both form 1 and form 2 peaks, and a halo were observed on the powder diffraction patterns after a milling time of 120 min. At 240 min, only form 2 peaks were observed. It was concluded that the behaviour of the solid was influenced by the relationship between powder temperature and Tc. At a solid temperature below the Tc, only amorphous drug was formed; at a temperature close to Tc, amorphous drug content initially increased but later converted to form 2 provided the powder was continuously milled. At a solid temperature higher than Tc, form 1, form 2 and some amorphous drug were recovered at intermediate stages, but continued milling only gave form 2. Form 2 did not convert to form 1 under any of the conditions studied.

The objectives of the current study were: (i) to further investigate the conditions under which form 1 could be converted to form 2, (ii) to look at the effect of cryo-milling on both polymorphic forms and (iii) to evaluate the physical stability of the milled amorphous state under different storage conditions. A further aim of the study was to understand the effect of seeding on the solid-state stability of the amorphous drug. Cryo-milling was used in this study to avoid the solid temperature exceeding the Tg during the milling process. XRPD and DSC were used to characterize the samples.

2. Materials and method

2.1. Materials

Ranitidine hydrochloride form 1 (Salutas Pharma, batch number 10108336/540097/RHII 1099056) and ranitidine hydrochloride form 2 (Salutas Pharma, batch number 10201844/1180625) were used as received.

2.2. Methods

2.2.1. Cryo-milling (CM) procedure

Both ranitidine hydrochloride form 1 and form 2 were milled separately in an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany). A fresh 1 g batch of powder was used for each milling. The powder sample was placed in a 25 mL volume stainless steel milling jar containing two 12 mm diameter stainless steel balls. Milling jars were then sealed and immersed in liquid nitrogen for three min before milling at 30 Hz for up to 60 min. Re-cooling of the milling chambers with liquid nitrogen was performed every 15 min. The solid temperatures were monitored using an infrared thermometer (Model 42510, Extech Instrument, USA). Samples milled for 2, 4, 6, 8, 10, 12, 15, 18, 21, 30, 45 and 60 min were used to evaluate the effect of CM on the crystallinity of the drug. The 15, 30, 45 and 60 min milled samples were selected for investigation of the stability of the amorphous form. For the stability study using seeds, the 45 and 60 min milled samples were chosen. The methods of seeding are outlined in Section 2.2.2. The storage conditions (stability of amorphous drug and amorphous drug with seeds) are outlined in Section 2.3. Up to four sample points were taken for analysis over the storage period. In each sampling, a small amount of powder was withdrawn and immediately stored in an airtight container with silica gel at 4 °C until further analysis.

2.2.2. Methods of seeding of milled amorphous material

2.2.2.1. Gentle physical mixing. Using a flat-ended spatula, 50 mg of the opposite polymorph (seed) was gently triturated in a Petri dish with the amorphous samples (i.e. form 2 seeds were added to amorphous powder made from form 1 and vice versa). Samples were stored as outlined in Section 2.3.

2.2.2.2. Ball milling for 1 min. The seed powder was incorporated into the amorphous powder by ball milling (non-cryogenic) for 1 min. The powders were then spread evenly in a Petri dish and stored as outlined in Section 2.3.

2.2.2.3. Simultaneous cryo-milling. The two crystalline forms at a ratio of 1 g: 50 mg were cryo-milled (CM method as described in Section 2.2.1) concurrently to an amorphous form. The powders were then spread evenly in a Petri dish and stored as outlined in Section 2.3.

2.3. Storage conditions

In the stability study of the amorphous phase, samples (milled for 15, 30, 45 and 60 min) were stored for 14 days under dry conditions (silica gel) at 4, 20, 30 and 70 °C. In the stability studies using seeds, samples milled for 45 and 60 min and seeded with the opposite polymorphic crystals were stored for 14 and 28 days, respectively, under dry conditions (silica gel) at 20, 30 and 70 °C.

2.4. Characterization

2.4.1. X-Ray powder diffraction (XRPD)

XRPD analysis was performed using an X'Pert PRO X-ray diffractometer, PANalytical (MPD PW3040/60

XRD; CuKα anode; $\lambda = 1.541$ Å). The samples were gently consolidated in an aluminum holder and scanned at 40 kV and 30 mA from 5° to 35° 2θ using a scanning speed of 0.1285°/min and a step size of 0.0084°. The powder diffraction patterns were analyzed using X'Pert High Score software (version 2.2.0) and plotted using OriginPro 7.5.

2.4.2. Differential scanning calorimetry (DSC)

DSC curves (DSC Q100 V8.2 Build 268, TA Instruments) were obtained under a nitrogen gas flow of 50 mL/min. Calibration of the DSC was carried out using indium as a metal standard. Sample powders (3 to 5 mg) were crimped in an aluminum pan and heated at a rate of 10 K per min from 0 to 160 °C. The glass transition temperature (Tg), crystallization temperature (Tc), melting temperature (Tm), change in heat capacity at the glass transition (ΔC_p) and the enthalpy of crystallization (ΔH_c) and melting (ΔH_f) were determined using TA Universal Analysis software, version 4.0 C. The Tg was determined as the midpoint while both Tc and Tm were determined as the onset temperatures. ΔC_p was calculated from the height difference due to the baseline discontinuity, whereas enthalpies were estimated from the area under the curve. ΔC_p and ΔH_c were used to estimate the degree of amorphousness.

2.5. Limit of detection for XRPD and DSC

Form 1 (as received) was used as the crystalline material while 60 min cryo-milled form 1 sample was used as the 100% amorphous material. Known ratios (0–100%) of amorphous and crystalline material were physically mixed (using the ball mill method) for 1 min to ensure sample homogeneity. All samples were analyzed immediately by XRPD and DSC under the measuring conditions used in this study. The limit of detection (LOD) was performed using the Quant2 package that accompanies OPUS™ software (version 5.0). Both the powder diffraction patterns and DSC curves were mean centred. The powder diffraction patterns were pre-processed using *straight line subtraction* while the DSC curves were converted to their second derivative. The models were calculated using the PLS algorithm with the concept of cross-validation (one sample removed per cycle). The root-mean-squared errors were determined for two factors. Any outliers (95% prediction interval based on the validation curve) present were removed and the model was recalculated. The LOD was calculated based on the equation $\mathrm{LOD} = \frac{3.3\sigma}{S}$, where σ is the standard deviation of the regression fit and S is the slope of the curve [12]. In this study the LODs were calculated to be 3.6% for both XRPD ($R^2 = 0.9966$) and DSC ($R^2 = 0.9958$).

2.6. Calibration of IR thermometer

The IR thermometer was calibrated against Hart Model 9132 IR Calibrator based on the calibration procedure by Extech Instrument Corporation, MA, USA. The temperature calibration was confirmed by taking an average of ten measurements of absolute methanol, ethanol and HPLC water at their respective boiling points. ($R^2 = 0.9989$) The accuracy and precision were calculated as 1.2% and 1.19%, respectively.

3. Results

3.1. Effect of CM on ranitidine hydrochloride polymorphs

Figs. 1 and 2 show the XRPD and DSC results for the cryo-milled ranitidine hydrochloride polymorphs following different milling times. The XRPD powder diffraction patterns (Fig. 1) for form 1 and form 2 showed a rapid decrease in peak intensity within the first 15 min of milling. Milling beyond 30 min showed no detectable crystal phase in either form. The DSC findings were in agreement with XRPD, where a decrease in peak intensity (or an increase in halo) is paralleled by an increase in the change in heat capacity at the Tg (ΔC_p) and the crystallization enthalpy (ΔH_c) (Fig. 3). The observed Tg and Tc were in the range of 16–28 °C and 34–56 °C, respectively (Fig. 2 – subgraphs). Interestingly, the DSC and XRPD findings for the 60 min sample were not consistent. Whilst XRPD is a very valuable technique in detecting crystallinity, it may be insensitive to small amounts of amorphous material. DSC on the other hand directly probes presence of the amorphous phase (through detection of the glass transition). While XRPD showed no differences between 45 and 60 min cryo-milled samples (i.e. both samples appeared fully amorphous as determined by XRPD), the DSC showed a distinct increase in the ΔC_p and ΔH_c from 45 to 60 min milling times, peaking at 0.73 J/g °C and 80 J/g, respectively.

The average solid temperature recorded at 15 min intervals was 6.4 ± 2.1 °C. No polymorphic conversion was observed in all the samples cryo-milled for up to 60 min.

3.2. Stability study of amorphous samples

3.2.1. Stability at 4 °C (below Tg), 20 °C (at Tg) and 30 °C (above Tg)

Fig. 4 summarizes the XRPD findings of amorphous material prepared from form 1 and 2 samples before (Fig. 4a) and after 14 days storage at 4, 20 and 30 °C (Fig. 4b–d). At 4 °C, the 15 min milled samples showed a small increase in peak intensity after 14 days storage, indicating some crystallization had occurred. Crystallization was also observed in the 30 min form 2 sample, where two peaks (20.2 and 23.5°2θ) were found to emerge from the amorphous halo (Fig. 4b; arrows). Nonetheless, most samples remained unchanged (i.e. amorphous as determined by XRPD) at 4 °C. The DSC curves also showed a Tg and a Tc confirming the presence of amorphous drug (DSC results not shown). At 20 and 30 °C (Fig. 4c and d), the samples were found to have partially crystallized back to the starting material, but full crystallization was not observed. It was observed that an increase in CM time

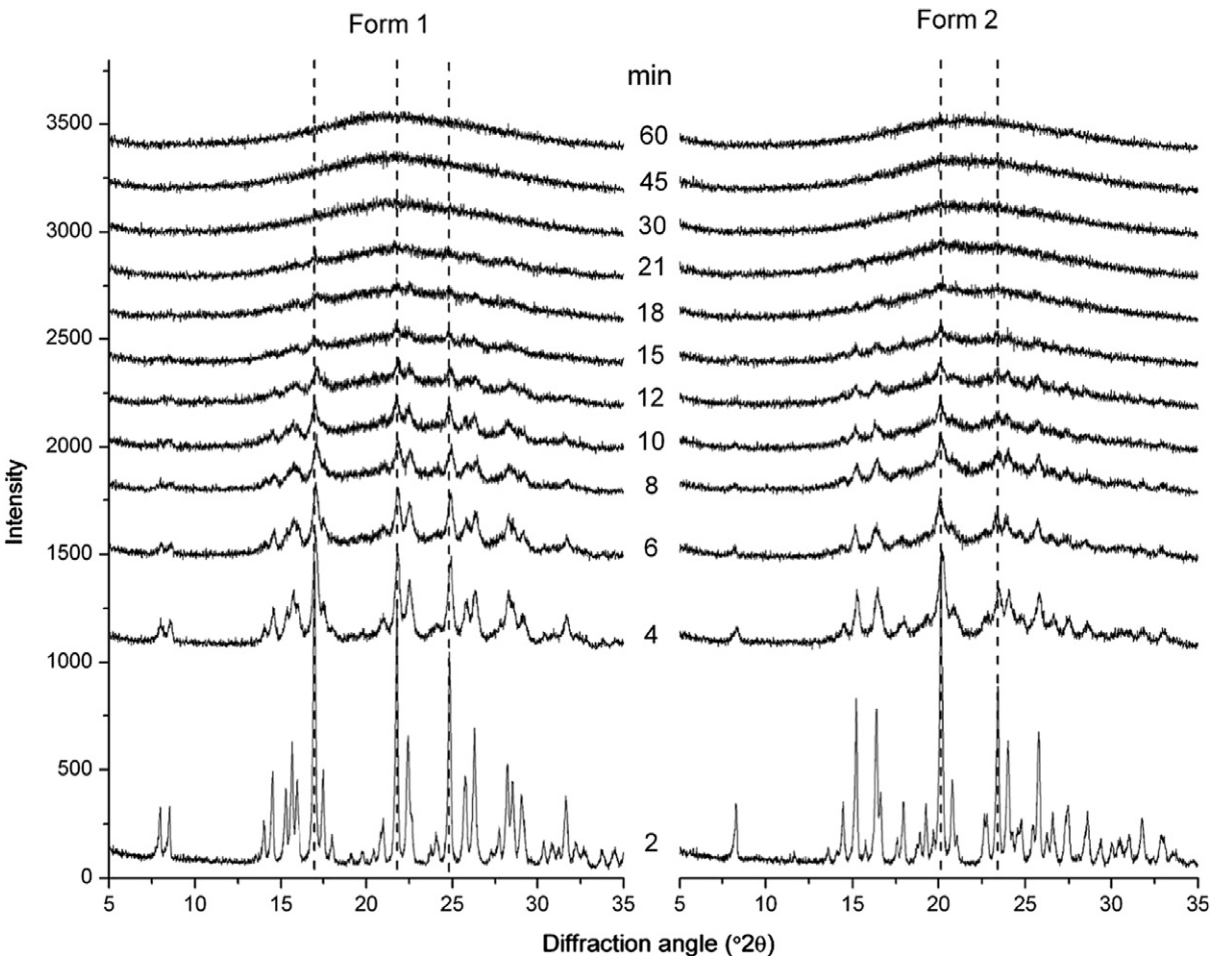

Fig. 1. Diffractograms of cryo-milled ranitidine hydrochloride polymorphs at various milling times. Characteristic peaks for form 1 and 2 are indicated by the dotted lines.

resulted in a longer time for recrystallization at any given storage temperature, possibly due to a higher crystal lattice disruption and a lower concentration of nucleation sites. On the other hand, storage at higher temperature resulted in a faster recrystallization. Amorphous drug prepared by CM of form 2 appeared to recrystallize faster and more completely (higher XRPD peak intensity) than amorphous drug prepared by CM of form 1 (Fig. 4b–d). The ΔC_p and ΔH_c were found to decrease with increase in storage temperature and duration, confirming a reduction in amorphous content. Recrystallization was not complete in the 14 days of storage. No crystallization to the respective other polymorphic form from which the amorphous form was prepared was observed in any case.

3.2.2. Stability at 70 °C (above Tc)

Fig. 5 shows the powder diffraction pattern of 60 min cryo-milled form 1 and form 2 after 12 h storage at 70 °C. All samples were found to have fully crystallized back to the original crystal form, regardless of milling duration. No further change was observed with continued storage up to 14 days (confirmed by DSC). A melting endotherm followed by an exothermic degradation was observed at 130–138 °C. Interestingly, the melting onset from recrystallized sample appears to be lower and has a broader endothermic peak compared to the starting material. No polymorphic conversion was observed in samples stored at 70 °C.

3.3. Stability study of amorphous samples (45 and 60 min) using opposite crystal seeds

3.3.1. Gentle physical mixing

Fig. 6 shows the XRPD findings of form 1 cryo-milled for 45 and 60 min and seeded by gentle physical mixing with the respective opposite polymorphic form from the starting material after storage at various temperatures. After 14 days storage at 20 and 30 °C, the 45 min milled samples remained predominantly amorphous (Fig. 6a and b). The 60 min sample also remained amorphous after storage of 27 days at 20 °C (Fig. 6d). On the other hand, powder diffraction patterns of the 45 min sample stored at 70 °C (Fig. 6c), and the 60 min sample stored at 30 and 70 °C (Fig. 6e and f) were found to crystallize back to form 1 (dotted lines). Even though small peaks associated with form 2 (arrows) were observed in these powder diffraction

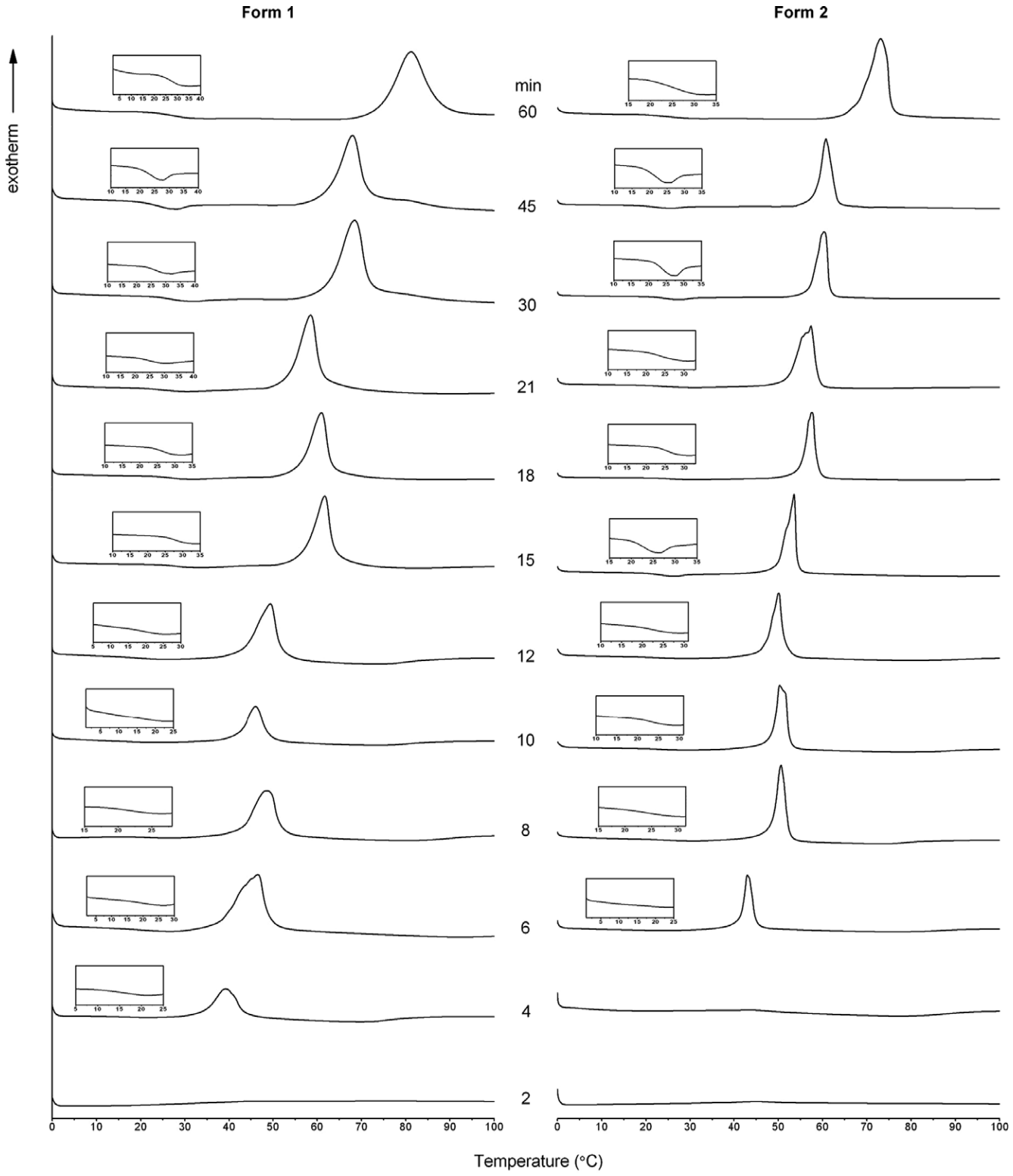

Fig. 2. Thermograms of cryo-milled ranitidine hydrochloride polymorphs at various milling times. The glass transition event is shown in the enlarged subgraphs.

patterns, polymorphic transformation was not found, as these peaks stem from the crystalline seed material. Likewise, amorphous material prepared by cryo-milling of form 2 and seeded with form 1 crystals was found to crystallize back to form 2 only (data not shown).

3.3.2. Ball milling for 1 min

Fig. 7 shows the XRPD findings of form 1 samples cryo-milled for 45 and 60 min seeded by ball milling for 1 min with the respective opposite polymorphic form from the starting material followed by storage at various

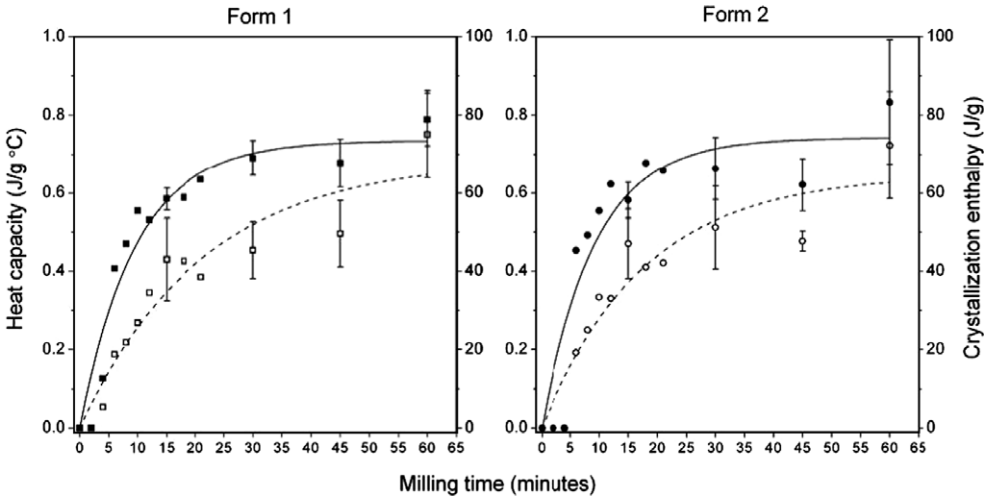

Fig. 3. Heat capacity (□ and ○; fitted with a dotted line) and crystallization enthalpy (■ and ●; fitted with a solid line) for cryo-milled ranitidine hydrochloride polymorphs ($n = 4$ for 15, 30, 45 and 60 min milling samples, $n = 2$ for all other samples). The vertical lines indicate the standard deviation of the change in heat capacity and the crystallization enthalpy for 15, 30, 45 and 60 min milling samples ($n = 4$). The lines were fitted using $y = a(1 - e^{-bx})$.

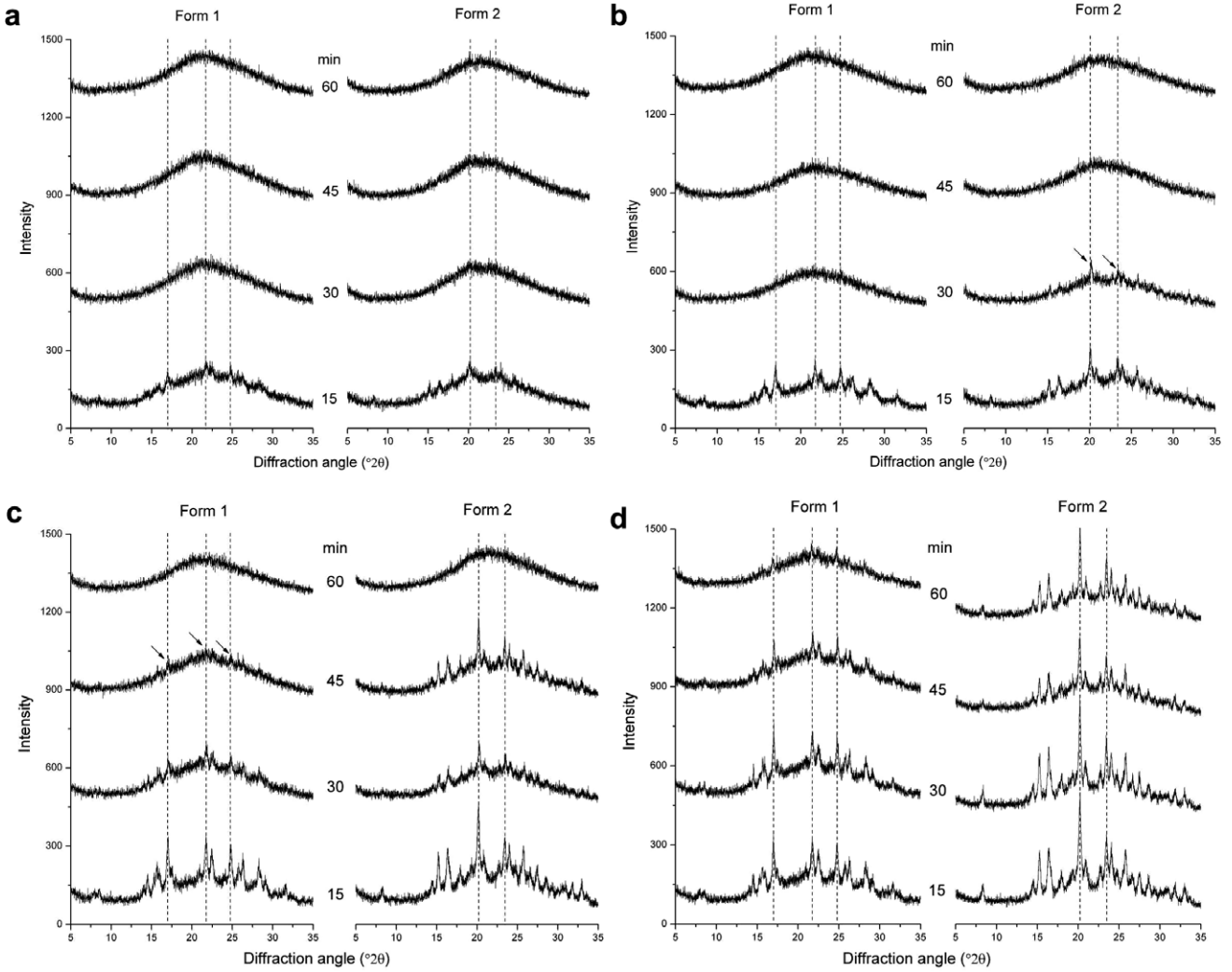

Fig. 4. Diffractograms of 15, 30, 45 and 60 min cryo-milled ranitidine hydrochloride polymorphs; (a) pre-storage, and after storage for 14 days at (b) 4 °C, (c) 20 °C and (d) 30 °C. Characteristic peaks of form 1 and 2 are indicated by the dotted lines. The arrows show the initial emergence of small crystalline peaks.

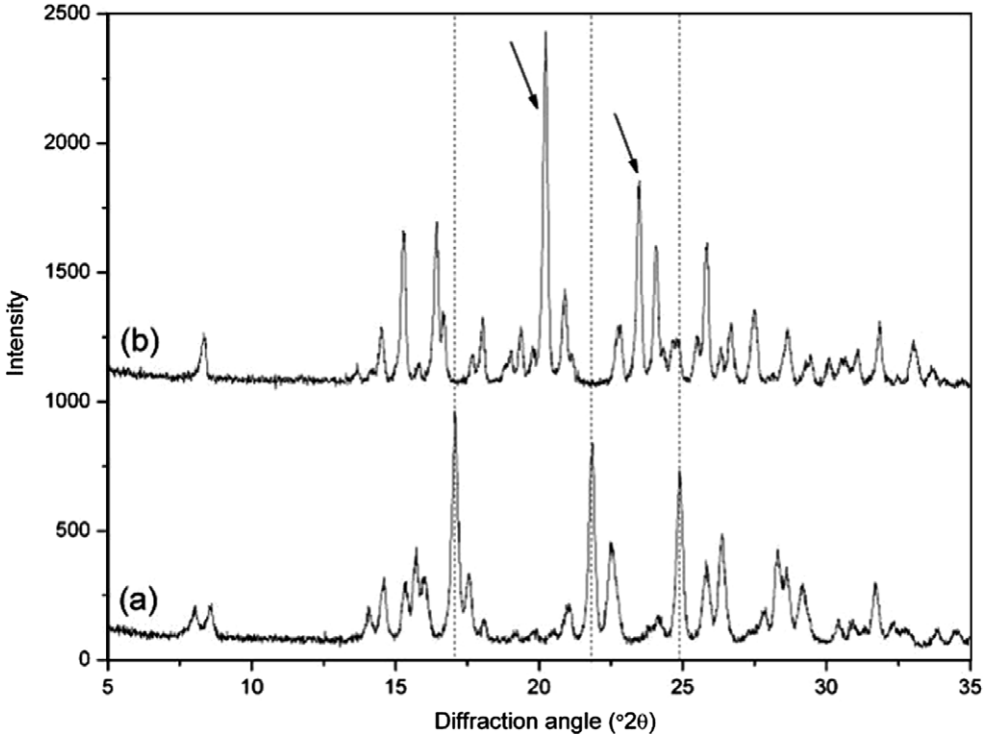

Fig. 5. Diffractograms of 60 min cryo-milled ranitidine hydrochloride (a) form 1 and (b) form 2, stored for 12 h at 70 °C. Dotted lines show characteristic peaks of form 1; arrows show characteristic peaks of form 2.

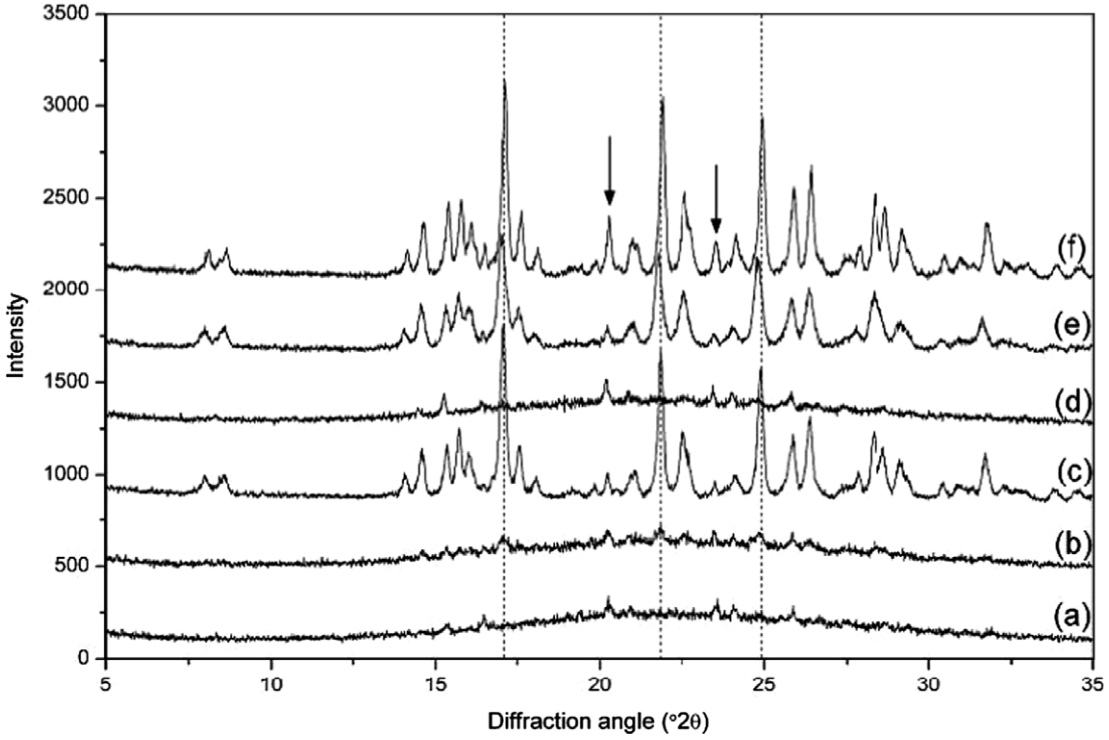

Fig. 6. Diffractograms of cryo-milled ranitidine hydrochloride form 1 seeded by gentle physical mixing: 45 min cryo-milled samples after storage for (a) 14 days at 20 °C, (b) 14 days at 30 °C and (c) 9 h at 70 °C; 60 min cryo-milled samples after storage for (d) 27 days at 20 °C, (e) 27 days at 30 °C and (f) 3 days at 70 °C. Dotted lines show characteristic peaks of form 1; arrows show characteristic peaks of form 2.

temperatures. When 50 mg 'seed' of form 2 was added to amorphous material (45 or 60 min) produced from form 1 by ball milling for 1 min, storage at 20 °C showed a powder diffraction pattern with a halo and peaks of the form 2 seeds (Fig. 7a and d). At 30 °C, the XRPD peak intensities of form 2 were higher compared to those found

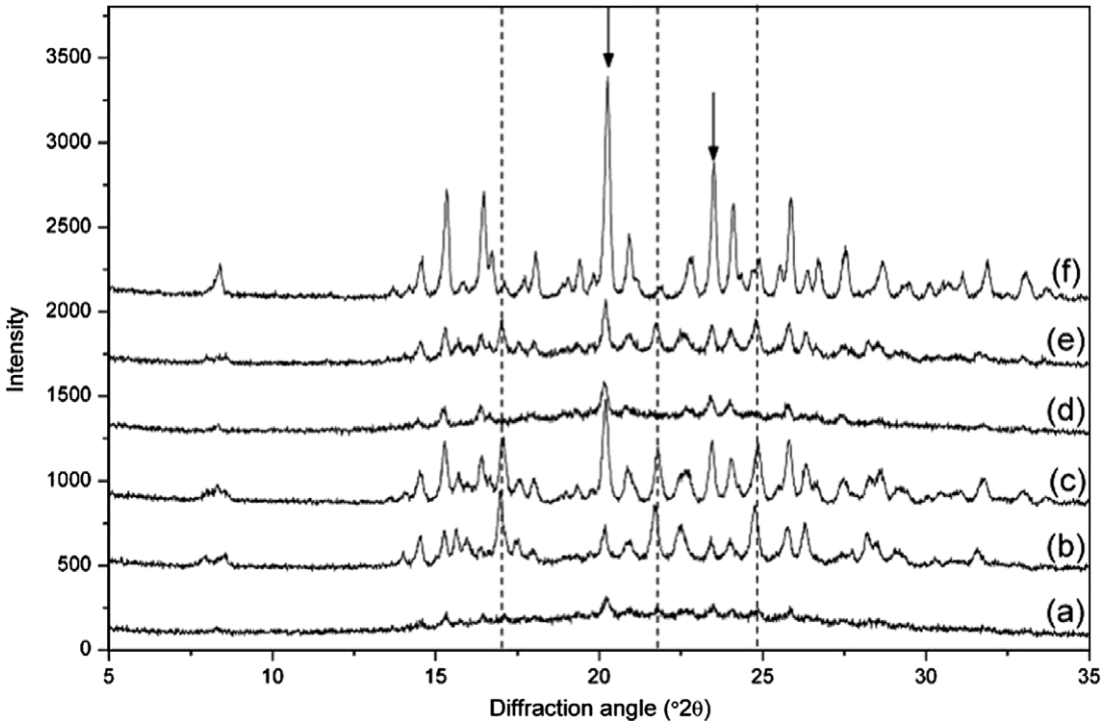

Fig. 7. Diffractograms of cryo-milled ranitidine hydrochloride form 1 seeded by 1 min brief ball milling with form 2: 45 min cryo-milled samples seeded with opposite polymorph and stored for (a) 14 days at 20 °C, (b) 14 days at 30 °C and (c) 15 h at 70 °C; 60 min cryo-milled samples after storage for (d) 26 days at 20 °C, (e) 26 days at 30 °C and (f) 2 days at 70 °C. Dotted lines show characteristic peaks of form 1; arrows show characteristic peaks of form 2.

at 20 °C. Some form 1 was also observed possibly due to the storage temperature being higher than the Tg, allowing some amorphous form prepared from form 1 to crystallize back. However, the crystallization process was again not complete (Fig. 7b and e). At 70 °C, full crystallization was observed from the amorphous powder (prepared from form 1). The 45 min sample stored at 70 °C (Fig. 7c) showed a mixture of both crystalline forms, while the 60 min milled samples stored at 70 °C showed complete crystallization to form 2 (Fig. 7f). The amorphous powders produced by milling form 2 and seeding with form 1 crystals still crystallized back to form 2. No transformation had occurred (data not shown).

3.3.3. Simultaneous CM

Fig. 8 shows the XRPD findings for amorphous drug prepared by simultaneous CM of form 1 (1 g) and form 2 (50 mg) stored at various temperatures. Compared to the samples seeded by ball milling for 1 min, the simultaneously milled (for 45 and 60 min, respectively) amorphous samples (form 1 with 50 mg of form 2) showed little crystallization at 20 or 30 °C in the time period studied. These small peaks could be traced back to the higher portion of form 1 crystalline solid (Fig. 8a, b, d, and e; dotted lines). However at 70 °C crystallization was complete. The 45 min milled samples showed almost complete transformation to form 2 (Fig. 8c), while in the 60 min milled samples showed a mix of form 1 and form 2 (Fig. 8f). No transformation was observed in all the amorphous material prepared from form 2 (with 50 mg of form 1) and stored at various temperatures.

4. Discussion

The current study demonstrates that cryo-milling was able to convert the crystalline drug to an amorphous form within 30 min compared to 60 min in our previous cold room (4 °C) milling study. At the low milling temperature, the material became rigid and brittle. Upon milling, the crystalline solids undergo a strong crystal lattice deformation, therefore leading to a faster physical change compared to the samples in cold room milling. As milling time increases, the DSC showed an increase in crystallization (exotherm) enthalpy. This event was comparable to the results of a cryogenic grinding study of indomethacin conducted by Crowley et al. [13]. The Tg and Tc of the amorphous ranitidine hydrochloride were at 16–28 °C and 34–56 °C respectively, which was similar to our previous findings (Tg: 13–30 °C and Tc: 30–65 °C) [11]. The narrower range of Tg and Tc observed in cryo-milled samples could be due to less water adsorbed as the samples were not scraped and remixed at regular intervals in contrast to our previous study where scraping and remixing was carried out every 30 min.

In the stability study, the cryo-milled samples (not seeded) were found to crystallize back to their original form upon storage. The crystallization process was found to be influenced by both storage temperature and CM duration.

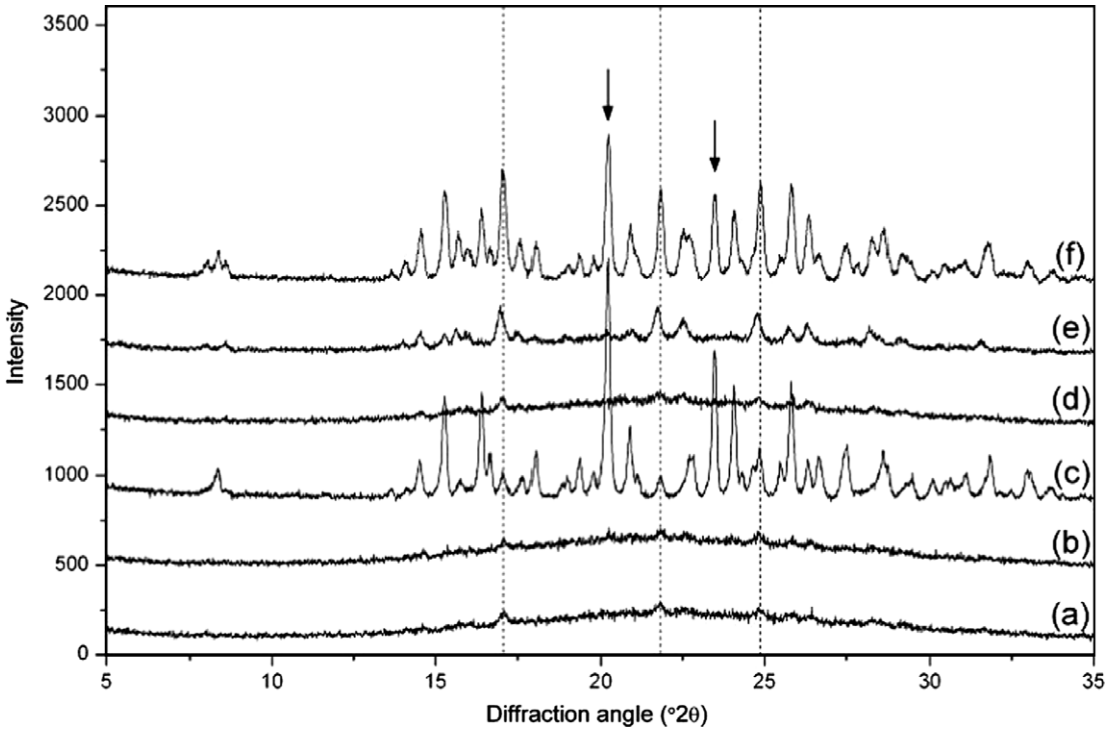

Fig. 8. Diffractograms of cryo-milled ranitidine hydrochloride form 1 (1 g) and form 2 seed (50 mg) prepared by simultaneous milling: 45 min simultaneously milled powder samples after storage for (a) 18 days at 20 °C, (b) 18 days at 30 °C and (c) 3.5 days at 70 °C; 60 min simultaneously milled powder samples after storage for (d) 27 days at 20 °C, (e) 27 days at 30 °C and (f) 3 days at 70 °C. Dotted lines show characteristic peaks of form 1; arrows show characteristic peaks of form 2.

At a temperature below the Tg, the amorphous solid is in the glassy state and crystallization is restricted. Above the Tg, amorphous solid is in the rubbery state thereby favouring recrystallization. Overall, crystallization rate was found to be fastest at 30 °C followed by storage at 20 °C and slowest at 4 °C. At 70 °C full crystallization was observed after 12 h of storage. It was noted that an increase in CM time resulted in a longer time for recrystallization at any given storage temperature, likely due to a higher crystal lattice disruption and a lower concentration of nucleation sites to act as growth centres. In a CM study of indomethacin by Crowley et al., a slower crystallization rate was observed in the 60 min cryo-milled samples compared to the 6 min sample when stored at the same temperature [13]. Interestingly amorphous form prepared from form 2 was found to crystallize faster than amorphous form prepared from form 1 throughout the study period, possibly due to the higher thermodynamic stability of form 2 [11]. In all cases, no transformation from form 1 to form 2 was found in cryo-milled samples up to 60 min possibly because of insufficient milling time to allow the formation of form 2 nuclei. In our previous milling study at room temperature and in a warm room, transformation of form 1 to form 2 was found to occur after 180 and 120 min of milling, respectively. This may suggest that using the current milling method (2×12 mm diameter balls and at 30 Hz), at least 120 min of milling time is required to generate form 2 nuclei before transformation to form 2 can occur.

In the stability studies using seeds, it became apparent that seeding by ball milling for 1 min and simultaneous CM were able to cause amorphous material made from form 1 to transform to form 2 at 70 °C. However the extent of form 2 crystallizing from amorphous form made from form 1 was quite different for the two seeding methods for 45 or 60 min CM. XRPD showed 45 min CM of samples seeded by ball milling for 1 min (Fig. 7c) and 60 min CM of simultaneously milled sample (Fig. 8f) led to an approximately equal ratio of crystalline form 1 and form 2, while 60 min CM samples seeded by ball milling (Fig. 7f) and 45 min CM of simultaneously milled samples (Fig. 8c) had a powder diffraction pattern showing mainly form 2 peaks. In the ball milling for 1 min method, it was hypothesized that at 45 min of CM, form 1 nuclei may not have been completely disrupted. Therefore upon storage at temperatures above the Tc, form 1 nuclei were able to recrystallize together with form 2 seeds (Fig. 7c), achieving an equal ratio of both polymorphs. At 60 min of CM, there were less form 1 but more form 2 nuclei within the sample, hence at 70 °C the amorphous drug crystallized mainly to form 2 (Fig. 7f). In the 45 min simultaneously milled sample where a majority of form 2 peaks was observed (Fig. 8c), it is possible that 45 min CM causes less crystal lattice disruption of form 2 in relation to form 1 within the mix. This leads to a higher concentration of nucleation sites of form 2 therefore favouring form 2 to crystallize. This supports the idea that form 2 is more stable than form

1 [5]. On the other hand CM for 60 min may have caused a similar degree of crystal lattice disruption to both polymorphs. Based on this assumption, crystallization of the 60 min simultaneously milled sample becomes an 'opportunistic' event at temperatures above Tc. However in seeding by simultaneous milling (45 and 60 min) and storage at 70 °C, XRPD showed a significant increase of form 2 crystals (higher peak intensity) even though only 50 mg (4.76%w/w) of form 2 seeds was added at the start.

Overall, the transformation was thought to occur because seeding by ball milling for 1 min and simultaneous milling were able to promote better interaction thus encouraging a good mix between the two solids. In addition, a temperature of greater than Tc appears to be crucial to promote 'conversion-crystallization'. Some evidence suggests that 'conversion-crystallization' can also occur to some extent when the storage temperature was above 30 °C, as seen using the ball milling for 1 min seeding technique. Crystallization above Tg is not unexpected because the rubbery amorphous state compared to the glassy amorphous state allows for an easier conversion to a thermodynamically stable crystal form due to the higher molecular mobility in the rubbery state [14]. However, the results were inconclusive whether the amorphous form prepared from form 1 would completely transform to form 2 under the conditions we studied at 20 and 30 °C (i.e. at and above Tg). Nevertheless it may be speculated that a temperature above Tg may be critical in the crystallization of amorphous drug, although the process was found to occur fastest when the storage temperature is above the Tc. In physical mix samples significant transformation was not observed. Whilst transformation was observed in most of the samples seeded with 50 mg of form 2 crystal at 70 °C, form 2 (1 g) seeded with form 1 (50 mg) samples did not undergo transformation.

5. Conclusion

Both form 1 and form 2 of ranitidine hydrochloride could be made fully amorphous as determined by XRPD within 30 min of CM. Upon storage without seeding, all amorphous samples were found to crystallize back to the original polymorphic form. No polymorphic transformation was observed. The recrystallization process was thought to occur when the storage temperature was above the Tg and was fastest when the storage temperature was above Tc. Form 2 was found to crystallize faster than form 1. In the stability study using seeds, some transformation of amorphous material made from form 1 to form 2 was found to occur at storage temperatures greater than the Tg, however transformation occurred fastest when the storage temperature was above the Tc. In all cases, only transformation from form 1 to 2 but not the other way around occurred, which suggests the two polymorph forms are a monotropic pair.

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