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Effect of milling conditions on the solid-state conversion of ranitidine hydrochloride form 1

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Abstract

Powder samples of ranitidine hydrochloride forms 1 and 2 were milled using a vibrational ball mill (Retsch MM301) for periods up to 240 min at 4, 12 and 35 °C. X-ray powder diffraction (XRPD), diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS), solid-state nuclear magnetic resonance (NMR) and differential scanning calorimetry (DSC) were used to monitor solid-state properties of the milled samples. Milling of form 1 at 4 °C led to a powder temperature of 36 °C in the milling chamber and produced only amorphous drug; at 12 °C (powder temperature 45 °C) and at 35 °C (powder temperature 62 °C) progressive transformation of form 1 via amorphous drug to form 2 occurred. DSC of the milled samples showed a glass transition at 13–30 °C and a crystallization exotherm (T_c) between 30 and 65 °C if the sample contained amorphous drug. The behaviour of the solid was speculated to be influenced by the relationship between powder temperature and T_c; at powder temperatures below T_c, amorphous drug is formed but no crystallization of form 2 occurs; at temperatures close to T_c, amorphous content initially increases with transformation to form 2 on continued milling. At temperatures much higher than T_c, at intermediate stages, less amorphous drug but both form 1 and form 2 are recovered, but continued milling gives only form 2. Form 2 did not transform to form 1 under any conditions used in this study.

Keywords: Ranitidine hydrochloride; Polymorphic transformation; Milling; Amorphous content; Glass transition; Crystallization

1. Introduction

Pharmaceutical solids often exhibit polymorphism, which may lead to differences in their physicochemical properties such as melting point, solubility, dissolution rate and stability (Vippagunta et al., 2001). As a result, bioavailability and effective dosage delivered to the patients may vary considerably. The understanding, manipulation and control of polymorphic forms are thus essential aspects for product development in the pharmaceutical industry (Knapman, 2000). The knowledge of how these solids behave is also important for the purpose of patenting and registration (Byrn et al., 1995).

Ranitidine hydrochloride, *N*-[2-[[[5[(dimethylamino) methyl]-2-furanyl] methyl] thio] ethyl]-*N*′-methyl-2-nitro-1,1-ethenediamine hydrochloride ($C_{13}H_{22}N_4O_3S{\cdot}HCl$), is a type 2 histamine antagonist, widely used for the treatment of stomach ulcer. The drug has been reported to exist in two crystalline states, termed form 1 and form 2, and several solvates (pseudopolymorphs) (Madan and Kakkar, 1994; Carstensen and Franchini, 1995; Hempel et al., 2000). The existence of polymorphism is suggested to be caused by tautomerism at the nitroethenediamine moiety, which can have three forms; enamine, nitronic acid and imine all of which can exist as E/Z isomers (Kojic-Prodic and Ruzic-Toros, 1982; Mirmehrabi et al., 2004a,b,c). Due to patenting issues and commercial value, attention has been given to both forms by manufacturers and researchers although bioavailability and therapeutic efficacy of both forms are equivalent (Shen et al., 1995; Bawazir et al., 1998).

The solid-state forms of ranitidine hydrochloride have been characterized by many techniques. Spectroscopic techniques (Fourier transform infrared spectroscopy (FTIR), diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS) and Raman spectroscopy) offer the advantage of detecting properties via both the lattice and molecular level (Agatonovic-Kustrin et al., 1999a,b; Sertsou et al., 1999; Agatonovic-Kustrin

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et al., 2001; Mirmehrabi et al., 2004a,b). Nevertheless, FTIR (using KBr pellets) has been reported to be an unsuitable technique to investigate ranitidine hydrochloride polymorphism because of the possibility of causing polymorphic conversion of ranitidine hydrochloride form 1 to form 2 during sample preparation (Forster et al., 1998). In DRIFTS, specific peaks at 1551 and 1046 cm^{-1} have been assigned to qualitatively differentiate form 1 from form 2. In Raman spectra, peaks at 1208 and 1185 cm^{-1} have been assigned for form 1 and form 2, respectively (Pratiwi et al., 2002). Using X-ray powder diffraction (XRPD) high intensity peaks at 17.0, 21.8 and 24.9° 2θ are specific to form 1. For form 2, strong peaks are observed at 20.2 and 23.5° 2θ (Madan and Kakkar, 1994; Agatonovic-Kustrin et al., 1999b; Wu et al., 2000). Whilst XRPD is comparatively straightforward in polymorph identification its use for quantification becomes limited if the sample exhibits preferred orientation during packing. For ranitidine hydrochloride this has been shown for different batches of form 1 by Forster et al. (1998). Differential scanning calorimetry (DSC) is another valuable technique to study thermal events such as glass transition, crystallization and melting. The onset of melting for form 1 and form 2 ranges between 134 and 140 °C and 140 and 144 °C, respectively (Fig. 1). The melting is accompanied by an exothermic degradation, which is related to the presence of the nitro moiety of ranitidine hydrochloride. Both melts are thus irreversible and produce a dark brown coloured degradation product.

More recently solid-state nuclear magnetic resonance (ss-NMR) has been introduced to identify crystallographic effects particularly polymorphism, intra-/inter-molecular hydrogen bonding and tautomerism (Mirmehrabi et al., 2004a) and is now widely used in conjunction with other analytical techniques. One of the advantages of ss-NMR is that it is very sensitive to minor conformational changes but is insensitive to particle size. In a ss-NMR study of ranitidine hydrochloride, the authors showed

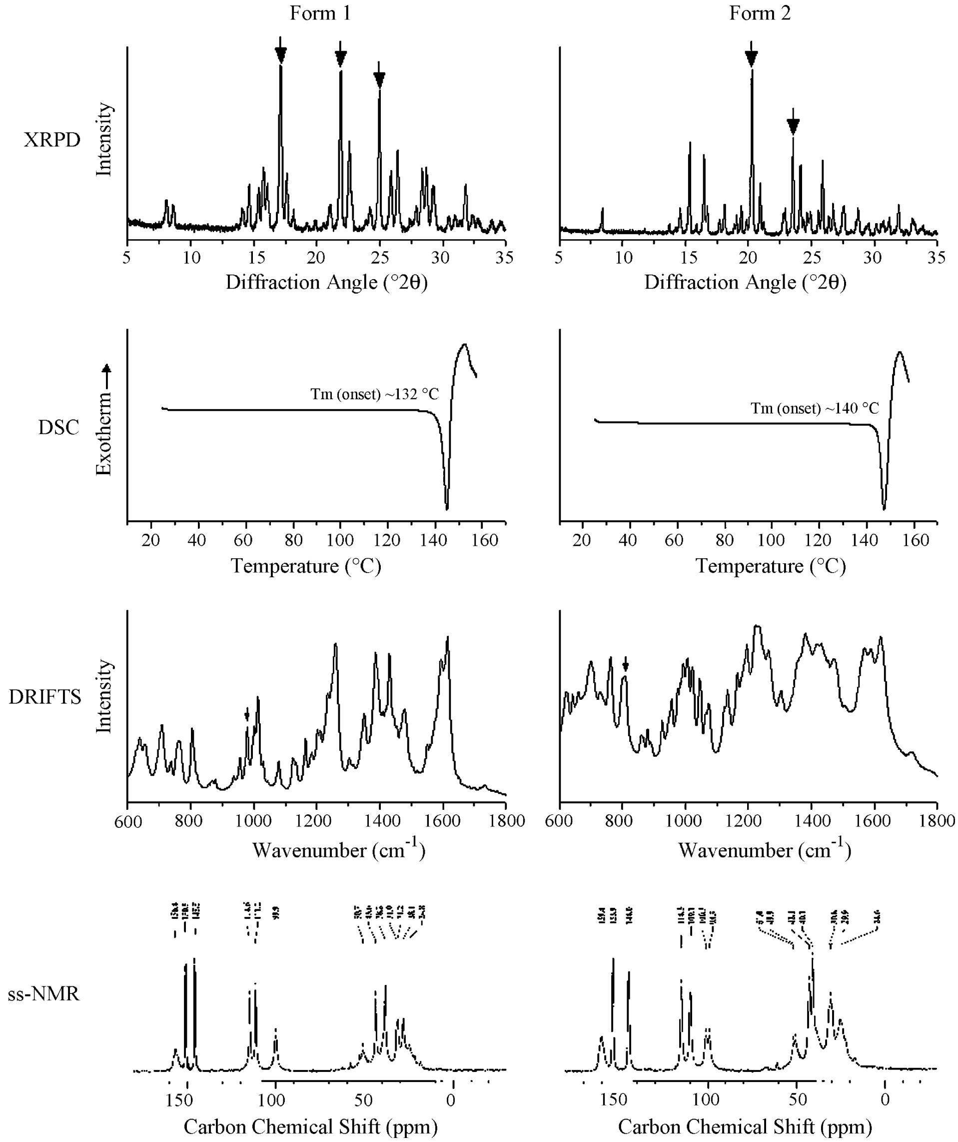

Fig. 1. Ranitidine hydrochloride form 1 and form 2 characterized by XRPD, DSC, DRIFTS and ss-NMR. Arrows indicate characteristic peaks of forms 1 and 2.

that form 2 exhibits molecular disorder crystals and contains two tautomers, nitronic acid and enamine. The molecular disorder was attributed to ranitidine hydrochloride–solvent intermolecular bonding (Mirmehrabi et al., 2004a). On the other hand Ishida et al. (1990) suggested the disordered structure of form 2 was due to hydrogen bonding of H^+ at the dimethylamino group to Cl^-. Nonetheless, the authors agreed that form 2 demonstrates disorder in its molecular packing while form 1 was found to be a more ordered crystal. Fig. 1 shows a comparison of form 1 and form 2 patterns characterized by XRPD, DSC, DRIFTS and ss-NMR.

The stability of the two polymorphic forms under different conditions is still not entirely clear but it has been suggested that form 2 is more stable than form 1 since it has the higher melting point (Madan and Kakkar, 1994). Mirmehrabi et al. (2004b) however found that form 2 was slightly more soluble than form 1 in isopropanol, *n*-propanol and methanol.

Studies have also been carried out to determine whether form 1 may be transformed to form 2 and vice versa (Mirmehrabi et al., 2004a,b). Studies in our laboratory (Wu et al., 2000) have shown the preferential disappearance of form 2, when a physical mix of the two polymorphs was exposed to moisture and a range of temperatures. This could simply indicate preferential dissolution of form 2, but could also indicate transformation of form 2 to form 1 via a solution-mediated process as later suggested by Mirmehrabi et al. (2004b).

Forster et al. reported in 1998 that form 1 transformed to form 2 during FTIR sample preparation. In the FTIR preparation, the sample was ground intimately with potassium bromide in a small agate mortar. Mirmehrabi et al. (2004b) were unable to show transformation of form 1 using pure form 1 in a mortar and pestle, arguing that the processes of grinding and compression would not have any risk of solid–solid transformation. Mirmehrabi et al. (2004b) also speculated that solution-mediated transformation was not possible from form 1 to form 2 but there was a possibility of transformation from form 2 to form 1 in the presence of moisture/solvent. Preliminary studies using a porcelain rolling mill have confirmed the transformation of form 1 to form 2 although several days of milling time was required (Dunkel et al., 2003). Dunkel et al. reported the transformation occurred via an amorphous form, shown by the appearance of an XRPD halo in the drug sample upon milling. Subsequently an oscillatory ball mill at ambient temperature has been used, again confirming transformation from form 1 to form 2, but achieving this transformation in hours rather than days (Talekar et al., 2005a,b). Again it was speculated that transformation occurred via amorphous drug. The transformation rate was influenced by ball size, with transformation being faster with larger balls. Additionally, heating of the powder was observed to occur during the milling process.

The aim of this paper was to study the effect of milling on the polymorphic stability of ranitidine hydrochloride form 1 using an oscillatory ball mill as a function of milling time and temperature. Form 2 was also milled for comparison. Milling was carried out using large (12 mm) balls under warm (35 °C) and cold (4 °C) conditions and compared with results obtained by milling under ambient (12 °C) conditions. XRPD, DRIFTS, DSC, ss-NMR and SEM were used to characterize the milled samples at milling times between 30 and 240 min.

2. Materials and methods

2.1. Materials

Ranitidine hydrochloride form 1 (Salutas Pharma, batch number 10195709/1170593) and ranitidine hydrochloride form 2 (Salutas Pharma, batch number 10201844/1180625) were used as received.

2.2. Milling procedure

Both ranitidine hydrochloride form 1 and form 2 were milled separately in an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany) at 30 Hz. A 1 g powder sample was placed in a 25 mL volume stainless steel milling jar containing two 12 mm diameter stainless steel balls. Milling was conducted at three temperatures: 12 ± 3 °C (“ambient” temperature), 35 ± 2 °C (warm room) and 4 ± 2 °C (cold room). Milling times were 30, 60, 90, 120, 150, 180, 210 and 240 min at ambient temperature and 30, 60, 120, 180, 240 min in both warm and cold room milling. A fresh 1 g batch of sample was used for each milling. The milling process was stopped every 30 min to scrape and remix powder cakes at the curvature end of the jars to ensure homogenous grinding. Temperatures of the samples were recorded using a non-contact infrared thermometer (Extech Instruments, USA). After opening each jar, the infrared thermometer was placed close to (but not touching) the powder. Milled samples were stored at 4 °C in an airtight container with silica gel until further analysis.

2.3. Characterization

2.3.1. X-ray powder diffraction

XRPD analysis was performed using a PANalytical X’Pert PRO X-ray diffractometer (MPD PW3040/60 XRD; Cu Kα anode). The samples were filled into an aluminum holder and gently consolidated. Measurements carried out from 5 to 35° 2θ, at a scanning speed of 0.1285°/min, step size of 0.0084°, voltage 40 kV and current 30 mA. The diffractograms were plotted using OriginPro 7.0. Percentage of halo area of the total diffractogram area was estimated using Macdiff 7.0.5.

2.3.2. Differential scanning calorimetry

Thermograms were obtained using a TA Instrument DSC Q100 (V8.2 Build 268) under a nitrogen gas flow of 50 mL/min. Sample powders (1–3 mg) were crimped in an aluminum sample pan and heated at a rate of 10 K/min from 0 to 160 °C. The glass transition temperature (T_g), crystallization temperature (T_c), melting temperature (T_m) and crystallization enthalpies were determined using TA Universal Analysis software 4.0 C. The T_g was taken at the midpoint of the discontinuity of the heat capacity while T_c and T_m were taken as onset temperatures.

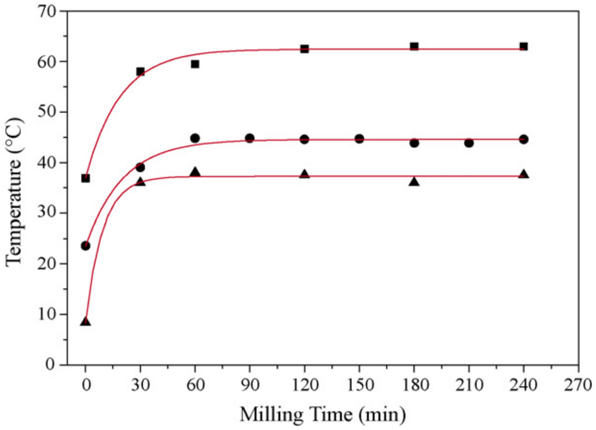

Fig. 2. Average temperature of ranitidine hydrochloride powder recorded during milling at three temperature conditions: (●) ambient (12 °C); (■) warm room (35 °C); and (▲) cold room (4 °C).

2.3.3. *Diffuse reflectance infrared Fourier transform spectroscopy*

DRIFTS spectra were obtained using a Bio-Rad FTS 175C spectrometer (Bio-Rad Laboratories, Cambridge, USA) equipped with Pike Technology Easidiff accessories. Data were captured using Digilab Resolution Pro software 4.0.0.030. The samples were dispersed (by gentle geometric mixing for 2 min using an agate mortar) as 5% (w/w) mix in KBr, and placed in a small cup sample holder. An average of 32 scans was performed for each sample at 4 cm^{-1} resolution. KBr background was recorded prior to the scanning of samples. Reflectance data was plotted as a function of Kubelka–Munk units versus wavenumber.

2.3.4. *Solid-state nuclear magnetic resonance*

Solid-state ^{13}C CPMAS spectra were recorded using a Bruker AVA 300 spectrometer operating at 300 MHz proton frequency. All experiments were carried out at 20 °C using a 7 mm Bruker spinning probe with zirconia rotors. The proton 90° pulse duration was 4.2 μs and the frequency of the decoupling field was 62.5 kHz. The contact time was 1.5 ms. Recycle delay was 5 s. The ^{13}C chemical shift scale is referenced to TMS. Samples were rotated at 7000 ± 1 Hz. The magic angle was adjusted by maximizing the sidebands of KBr.

3. Results

The average powder temperatures recorded for the three milling conditions are shown in Fig. 2. In all cases, the temperature of the powder was found to increase dramatically within the first 30 min, reaching a plateau within 30–60 min milling. Thereafter the temperature remained unchanged over the period up to 240 min. The maximum temperature recorded was approximately 45 °C in the ambient condition, 62 °C in the warm room and 36 °C in the cold room. The relationship of the powder temperature and milling time can be expressed as $Y = A + B(1 - e^{-kt})$, where the parameters A and B are constants, k a rate constant and t is the duration of milling (R^2 0.997 for ambient; 0.991 for both warm and cold rooms).

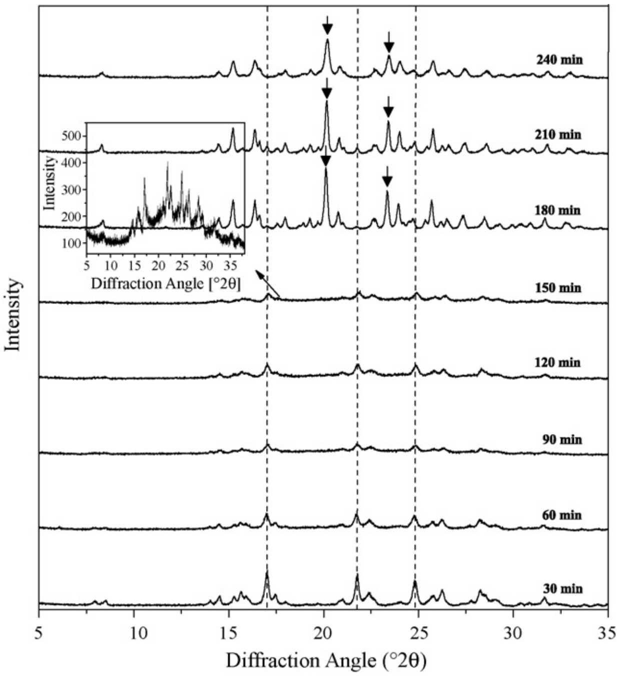

Fig. 3. Diffractograms of a form 1 batch milled for various times at ambient temperature. Dotted lines show the characteristic peaks of form 1; arrows show characteristic peaks of form 2; figure inset shows the XRPD halo of the 150 min milled sample.

3.1. *Milling at ambient temperature*

Fig. 3 shows the diffractograms of a form 1 batch milled for various times at ambient temperature (12 ± 3 °C). Overall, the XRPD responses showed a transformation from form 1 to form 2 via the formation of amorphous drug. This observation was consistent with the transformation found during earlier studies using a rolling ball mill (Dunkel et al., 2003) and studies with smaller balls in an oscillatory mill (Talekar et al., 2005a,b). Compared with the rolling ball mill studies where transformation required several days, oscillatory ball milling showed faster transformation, requiring a few hours only when using 12 mm balls. In this study (12 mm balls), after 30 min of milling, the form 1 peaks decreased and the baseline shifted up (“halo”) indicating the presence of amorphous drug. As the milling duration extended to 150 min, the diffractograms showed a system of ‘near-complete’ amorphousness of the form 1 sample, however no form 2 peaks were observed (Fig. 3, inset). When milling was carried out beyond 180 min, form 2 crystalline peaks were observed and at 240 min no form 1 peaks could be detected in the samples.

Repetition experiments showed similar form 1 to form 2 transformation but the powder temperature and rates of transformation were somewhat variable even though a halo (XRPD) was consistently observed. On the whole, if the maximum powder temperature was lower, transformation was slower (results not shown). This variability would suggest that transformation of ranitidine hydrochloride is influenced by the powder temperature which, in turn, is influenced by surrounding temperature and heat generated by the milling process.

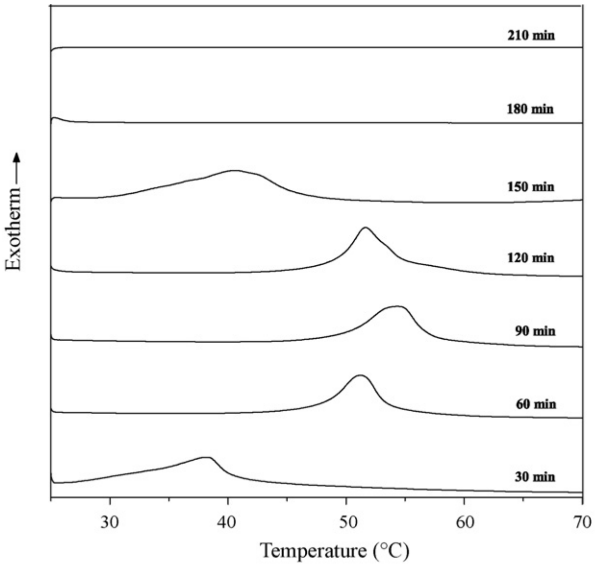

Fig. 4. Thermograms of a form 1 batch milled for various times at ambient temperature.

The observed transformation from form 1 to form 2 via an amorphous form was further supported by the DSC thermograms of a form 1 batch milled at ambient temperature (Fig. 4). Samples milled from 30 to 150 min all showed a crystallization peak. The peak maximum (T_c) was usually observed between 40 and 60 °C (60, 90 and 120 min) although some samples (e.g. 30 and 150 min in Fig. 4) had peaks at lower temperatures. These differences in thermal behaviour are thought to have been caused by different amounts of amorphous drug present. At a small amorphous content, crystallization began below 30 °C and peaked at approximately 40 °C. As the amorphous content increased (shown by a shift of the XRPD baseline), the crystallization exotherm set off at higher temperature. Water absorption may also have a role in the variation observed on the thermograms. Samples milled up to 180 and 210 min showed no crystallization peak, confirming the lack of a halo in XRPD (Fig. 3; 180 and 210 min). DSC thermograms of some samples showed a discontinuity of baseline below 25 °C and it is thought this corresponds to the glass transition (T_g) of ranitidine hydrochloride, where the amorphous glassy state changes to the rubbery state. The average recorded temperatures (T_g, T_c and T_m) and associated crystallization enthalpies at ambient milling conditions are given in Table 1. T_g was in the range of 14–25 °C and the crystallization temperature, T_c occurred between 38 and 55 °C. Crystallization enthalpies were in the range of 48–61 J/g although the 240 min milled powder had a T_c enthalpy of only 22.5 J/g (Table 1). The T_m was between 133 and 138 °C.

At the molecular level, both DRIFTS (not shown—spectra were identical to those of Forster et al., 1998) and ss-NMR confirmed the transformation of ranitidine hydrochloride from form 1 to form 2 upon milling at ambient temperature. Fig. 5 shows the spectra obtained by ss-NMR. The polymorphic transformation is a gradual process and the lowering and broadening of the peaks seen in 90, 120 and 150 min samples could indicate the formation of amorphous drug. Peaks in these samples showed the crystalline drug was mostly form 2, although some form 1 was still present. From 180 min onwards, only form 2 crystalline peaks were observed.

Milling of form 2 at ambient temperature over 240 min resulted in no polymorphic transformation, albeit amorphous drug was detected by XRPD and DSC.

Table 1
Glass transition temperatures (T_g), crystallization temperatures (T_c), melting temperatures (T_m) and crystallization enthalpies for milled form 1 samples

	Milling time (min)	Glass transition temperature, T_g (°C) (±S.D.)	Crystallization temperature, T_c (°C) (±S.D.)	Crystallization enthalpy (J/g) (±S.D.)	Melting temperature, T_m (°C) (±S.D.)
Form 1		–	–	–	142.73 (–)
Form 2		–	–	–	145.01 (–)
Ambient conditions (12 °C)	30	22.9 (–)	42.0 (10.7)	48.5 (20.4)	135.9 (2.0)
	60	14.4 (–)	41.7 (5.4)	48.7 (4.7)	138.1 (1.3)
	90	24.1 (–)	54.1 (5.4)	61.2 (8.3)	133.0 (1.8)
	120	24.0 (–)	55.7 (6.9)	68.0 (9.1)	136.1 (2.8)
	150	16.4 (–)	40.5 (7.2)	50.9 (9.1)	133.9 (4.7)
	180	–	–	–	136.1 (5.0)
	210	–	–	–	135.6 (4.3)
	240	–	38.87 (5.6)	22.5 (16.7)	135.3 (1.9)
Warm room (35 °C)	30	22.7 (–)	48.1 (–)	55.0 (–)	134.6 (–)
	60	21.6 (–)	43.0 (–)	34.9 (–)	132.6 (1.8)
	120	21.3 (3.4)	43.4 (7.4)	36.8 (3.5)	135.4 (1.3)
	180	15.5 (0.4)	36.8 (1.0)	30.5 (1.0)	134.4 (1.2)
	240	20.6 (1.0)	41.4 (3.0)	36.3 (3.0)	133.2 (1.6)
Cold room (4 °C)	30	30.3 (1.5)	59.9 (0.1)	77.5 (3.5)	*Not determined*
	60	23.7 (3.0)	57.0 (2.7)	70.1 (3.3)	*Not determined*
	120	21.4 (4.5)	65.0 (8.5)	71.5 (4.6)	*Not determined*
	180	14.5 (2.2)	52.4 (5.1)	69.5 (2.2)	*Not determined*
	240	13.7 (1.9)	49.4 (3.1)	59.5 (1.7)	*Not determined*

T_g was obtained from the midpoint, and T_c and T_m were taken from the extrapolated onset. (standard deviation is given in brackets).

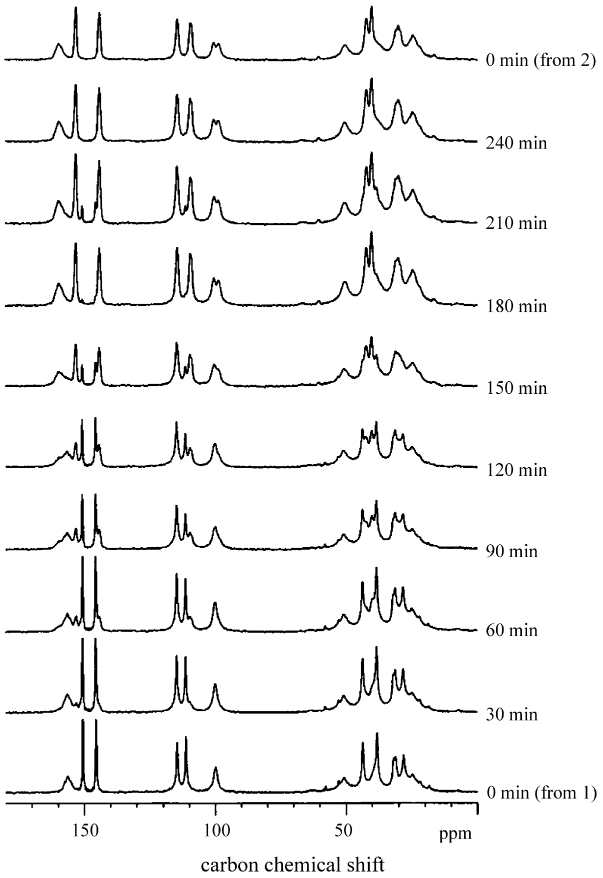

Fig. 5. Solid-state NMR spectra of a form 1 batch milled at various times at ambient temperature.

3.2. Milling at 35 °C (warm room)

Fig. 6 shows the diffractograms of a form 1 batch milled for various times in the warm room. The transformation of form 1 to form 2 was again observed but occurred faster than at ambient temperature. After 120 and 180 min milling, XRPD showed mostly crystalline form 2 but still a small proportion of form 1 (peaks at 17.0, 21.8 and 24.9° 2θ as shown by the dotted lines in Fig. 6) was found. At 240 min, only form 2 crystalline peaks (arrows) were observed. Halos (XRPD) were observed at intermediate stages but were smaller than for samples milled at ambient conditions. The concentration of amorphous drug (XRPD halo) reached a maximum of approximately 70% at 30 min and decreased to approximately 50% as milling time increased. At intermediate stages, the form 1/form 2 crystalline mix may result due to the continued presence of form 1 nuclei together with created form 2 nuclei. The higher powder temperature in warm room milling facilitates the crystallization process.

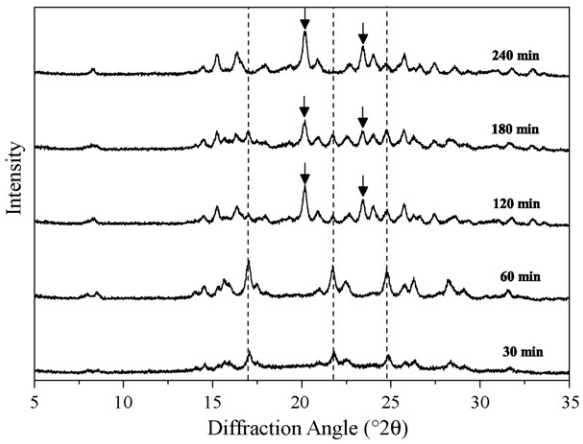

Fig. 6. Diffractograms of a form 1 batch milled for various times at 35 °C (warm room). Dotted lines show the characteristic peaks of form 1; arrows show characteristic peaks of form 2.

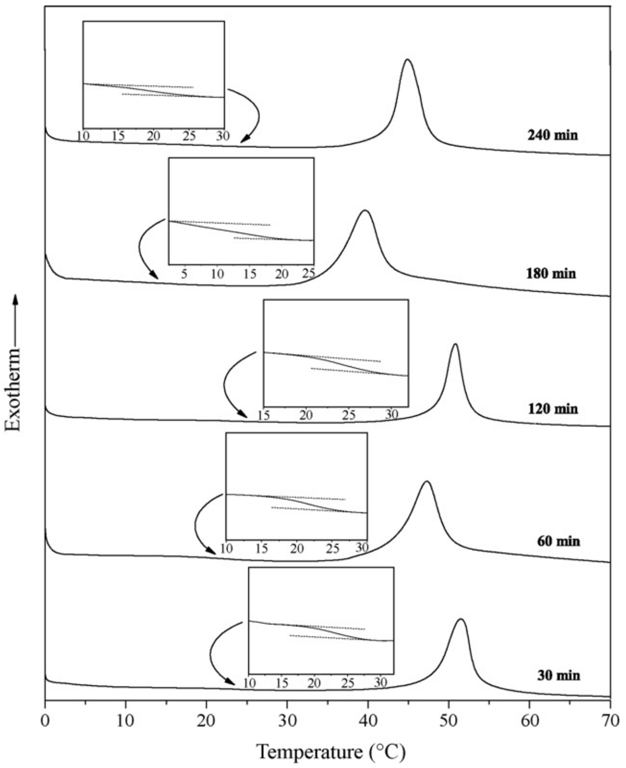

Fig. 7. Thermograms of a form 1 batch milled for various times at 35 °C (warm room). The glass transition event is shown in the enlarged sub-graphs.

The thermograms of a batch of form 1 samples milled in the warm room are shown in Fig. 7. The glass transition events are shown in the enlarged sub-graphs and were clearly visible in all thermograms with an average T_g of 15–23 °C (Table 1). The T_c was in the range 36–49 °C with the enthalpies between 30 and 51 J/g (Table 1). T_m (melting) occurred in the range 132–136 °C and was slightly below the usual melting points of both form 1 and form 2.

3.3. Milling at 4 °C (cold room)

When milling was carried out in the cold room, the powder temperature did not exceed 40 °C (Fig. 2). The diffractograms of samples milled at various time points are shown in Fig. 8. Only amorphous drug was found over the studied period, in contrast to the transformation of form 1 to form 2 observed in ambient and warm room milling. The 30 min sample still showed low intensity form 1 crystalline peaks (XRPD).

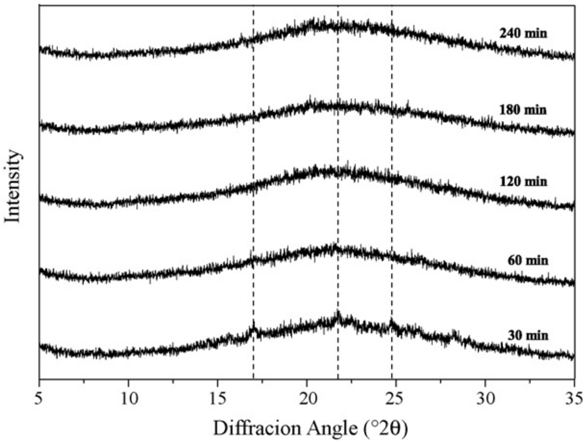

Fig. 8. Diffractograms of a form 1 batch milled for various times at 4 °C (cold room). Dotted lines show characteristic peaks of form 1.

In the thermograms of the cold room milled samples (Fig. 9), the crystallization peak maximum was in the range 40–65 °C, which was slightly wider than the range found for ambient temperature milling. Compared with other milling conditions, the crystallization events were much larger with average recorded crystallization enthalpies of 59–78 J/g (Fig. 10), confirming the presence of amorphous drug. The change in heat capacity at the T_g was also observed more clearly in the DSC analysis of cold room milled samples compared to ambient and warm room milled samples. The glass transition event is shown in the enlarged sub-graphs of Fig. 9. Interestingly, both T_g and T_c (Figs. 9 and 10) shifted to a lower temperature over the milling time. This was thought to be due to moisture uptake when samples were scraped and remixed at regular intervals. With an increase in specific surface area and more amorphous drug produced from extended milling, it is not surprising that these samples will be more susceptible to water absorption. As soon as water, a well known plasticizer, is absorbed by the amorphous drug, the free volume will increase causing a decrease in T_g, indirectly also reducing T_c (Ford and Timmins, 1989). Further studies monitoring moisture uptake and determining the relationship with T_g and T_c are needed.

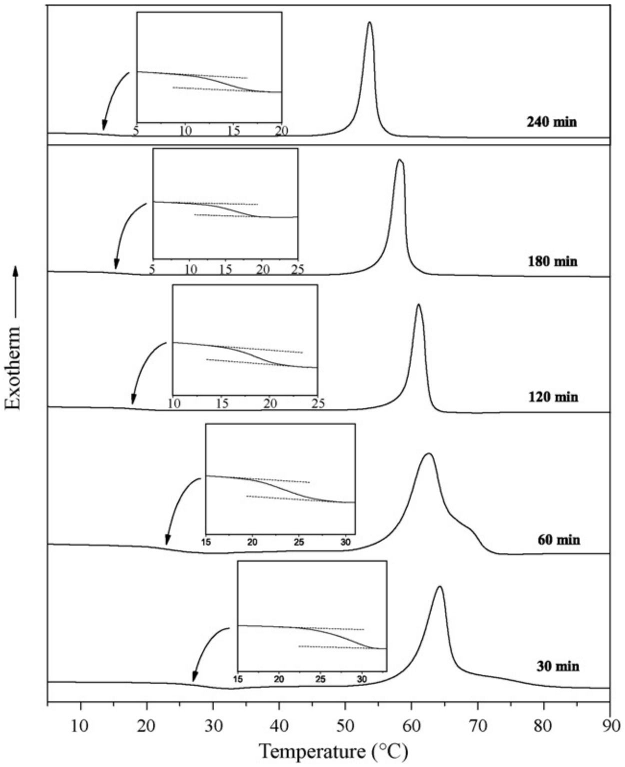

Fig. 9. Thermograms of a form 1 batch milled for various times at 4 °C (cold room). The glass transition event is shown in the enlarged sub-graphs.

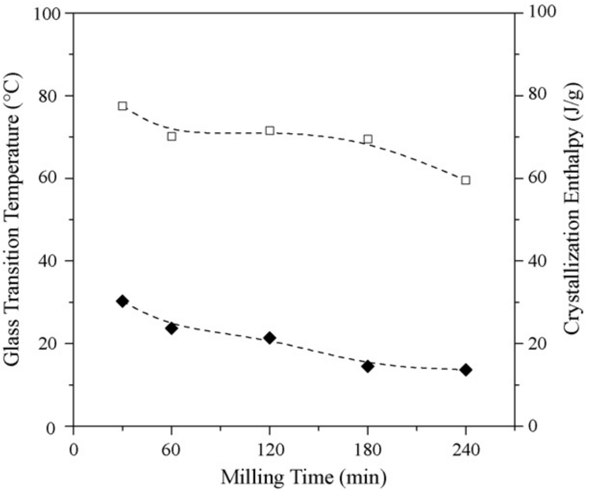

Fig. 10. Glass transition temperature (T_g) and crystallization enthalpy observed in the cold room milling. (♦) Shows the glass transition temperature and (☐) represents the crystallization enthalpy.

Form 2 samples also became amorphous when milled in the cold room. Neither form 1 nor form 2 crystalline peaks were observed on the diffractograms.

4. Discussion

Transformation of ranitidine hydrochloride form 1 to form 2 was observed in both ambient (12 °C) and warm room (35 °C) conditions after 180 and 120 min milling, respectively. In contrast, form 1 samples converted to the amorphous form in cold room milling. DSC showed a T_g (midpoint) range of 13–30 °C, T_c of 36–65 °C and a T_m of 132–138 °C.

The transformation of form 1 to form 2 could be attributed to the higher stability of the form 2 polymorph compared to form 1 polymorph, which is reflected in the higher melting point of form 2. On the other hand, another theory suggested that, at the molecular level, form 1 exists as an ordered crystal, whereas form 2 is arranged in a disordered crystal state (Ishida et al., 1990; Mirmehrabi et al., 2004a,c). Crowley and Zografi (2001) have commented that grinding is an energetically inefficient process that generates large amounts of heat and vibrational energy, giving rise to grinding-induced crystal lattice disruption or process-induced disorder. Thus, the transformation process was thought to be initiated when the order of form 1 crystals was disrupted by the energy impact from the milling balls. This simultaneously eliminates form 1 crystals from the mix and forms the amorphous intermediate. Eventually, through continuous milling, form 2 nuclei are produced. Even though form 2 nuclei are spread within the milling jar by the oscillating balls, it is clear from the cold room studies that the milling process itself does not spontaneously cause the growth of form 2 crystals. A second factor is involved, which is the powder temperature. From our observations, at temperatures close to T_c (i.e. ambient condition) some amorphous drug is found but all crystalline peaks are of form 2; at temperatures higher than T_c transformation to form 2 was faster, but at intermediate stages while form 1 nuclei remained, it is postulated some recrystallization of form 1 occurred (since the measured amorphous content was lower than at 12 and 4 °C milling); lastly, at powder temperatures below T_c the amorphous form is favored.

These different findings under different milling conditions may explain why milling of ranitidine hydrochloride form 1 does not always yield form 2 crystals (Mirmehrabi et al., 2004b). No transformation from form 2 to form 1 was observed in any of the conditions monitored. While a small amount of moisture may be involved, it is thought this merely results in a lowering of T_g with changes of amorphous drug to the rubbery state, thus facilitating crystallization if the temperature conditions are suitable. Our earlier milling studies in a rolling ball mill (Dunkel et al., 2003) showed consistent but very slow transformation with very little moisture uptake in spite of regular scrape down and remixing. Transformation was faster with larger balls, a finding which has also been shown by our studies with the oscillatory mill—the 12 mm balls showed faster transformation than 9 mm balls which in turn showed faster transformation than the larger number of small (5 mm) balls.

5. Conclusion

Milling is able to transform ranitidine hydrochloride form 1 to form 2 under a range of temperature conditions. The transformation was confirmed to occur via an amorphous form. The amorphous drug was characterized as having a T_g and T_c of 13–30 and 36–65 °C, respectively. The conversion process was thought to be initiated by the disruption of orderly form 1 crystal producing form 2 nuclei. With continued milling, heat generated (in combination with external temperature) provides the propagation factor for crystallization. It is believed that both the temperature of the solid and the impact energy (determined by ball size, quantity and oscillating speed) act collectively to influence the rate and outcome of milling.

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