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Research paper

Physical characterization and stability of amorphous indomethacin and ranitidine hydrochloride binary systems prepared by mechanical activation

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ABSTRACT

Co-milling of γ-indomethacin and ranitidine hydrochloride form 2 at various weight ratios (1:2, 1:1 and 2:1) was investigated with a particular interest in the physicochemical properties and the stability of the milled mixed amorphous form. Co-milling was carried out using an oscillatory ball mill for various periods of time up to 60 min in a cold room (4 °C). The maximum temperature of the solid material was 42 °C during co-milling in a cold room. Results showed that both indomethacin and ranitidine hydrochloride were fully converted into the amorphous state after 60 min of co-milling. In contrast individually milled drugs remained partially crystalline after co-milling under the same conditions. During co-milling, the XRPD characteristic peaks of indomethacin were found to decrease faster than those of ranitidine hydrochloride. DSC results were in agreement with XRPD, and T_gs of the fully converted amorphous mixtures of 29.3, 32.5 and 34.3 °C were measured for the 1:2, 1:1 and 2:1 mixtures, respectively. These T_g values were in good agreement with the predicted T_gs of the mixtures using the Gordon–Taylor equation. DRIFTS spectra of the co-milled amorphous samples showed peaks at 1610, 1679 and 1723 cm^{-1}, that were not present in the individually milled samples and that are indicative of an interaction at the carboxylic acid carbonyl (HO–C═O) and benzonyl amide (NC═O) of the indomethacin molecule with the aci-nitro (C═N) of ranitidine hydrochloride. Upon 30 days of storage, the 1:2 mixtures were found to crystallize; however, the amorphous 2:1 and 1:1 mixtures were stable when milled for 60 min and stored at 4 °C (for the 2:1 mixture) and at 4 and 25 °C (for the 1:1 mixture), respectively. Although XRPD, DSC and DRIFTS suggested an interaction between the two drugs, co-crystal formation was not observed between indomethacin and ranitidine hydrochloride.

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1. Introduction

Indomethacin (Fig. 1a) is a non-steroidal anti-inflammatory drug (NSAID) used in the symptomatic relief of musculoskeletal or joint pain. NSAIDs, however, are well known to cause side effects including gastrointestinal disturbances. Indomethacin exists in two polymorphic forms, termed γ-form and α-form, and an amorphous form [1–3]. The drug is poorly water soluble [4] and thus a good model drug to formulate in the amorphous state to enhance the dissolution of the drug. Ranitidine hydrochloride (Fig. 1b), a H_2-receptor antagonist, is commonly used in the treatment of stomach ulcer and to counteract gastric irritation resulting from NSAID treatment. It is therefore reasonable to co-administer these drugs [5]. Similar to indomethacin, ranitidine hydrochloride also has two known polymorphic forms, termed form 1 and form 2, and an amorphous form [6–10]. Numerous studies have been carried out to investigate the polymorphism of ranitidine hydrochloride. The pharmaceutical interest, however, is mainly based on patenting and commercial issues [11] since in the clinical setting, both polymorphic forms have been found to be bioequivalent [12,13].

It is well established that the solubility and the bioavailability of a poorly water soluble drug can be improved by converting it into the amorphous state. Several methods such as freeze-drying, spray-drying, melting and quench-cooling, melt extrusion and mechanical activation (milling) have been reported to successfully prepare amorphous forms of drugs [14]. An amorphous solid, unlike a crystalline solid, does not have a three-dimensional long range order of molecular packing. Amorphous solids have excess free energy compared to their crystalline counterparts, thus offering advantages in terms of solubility and dissolution rate [15]. Sometimes the compression characteristics of amorphous forms can also be better than those of the corresponding crystals [16]. However, being in a higher energy state the amorphous form is also physically unstable. Amorphous forms tend to release excess energy by structural relaxation and crystallization into lower energy forms during storage [16]. Stabilization of the amorphous state is thus necessary to exploit their advantages of higher solubility and bioavailability [17]. In most cases, the unstable amorphous solid (e.g., the drug) is combined with an inert carrier (most often a

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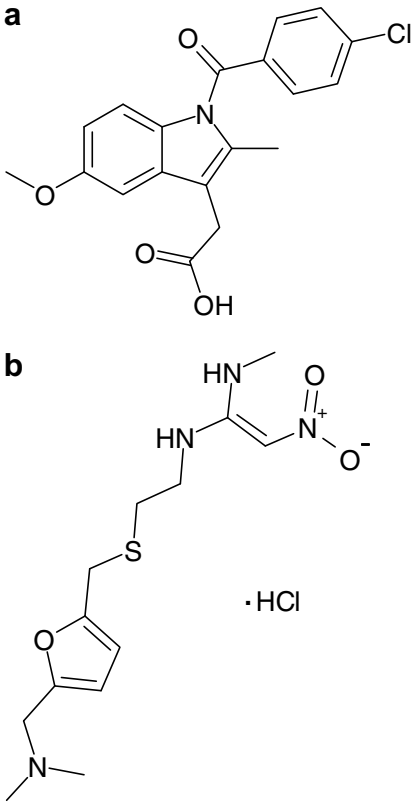

Fig. 1. Molecular structure of (a) indomethacin and (b) ranitidine hydrochloride.

polymer) to enhance the stability by decreasing the free volume, consequently increasing the glass transition temperature (T_g), and slowing down the crystallization process [17]. Drug–polymer combinations have been shown to offer a significant improvement in the physical stability of amorphous drugs [18–21].

In a binary mixture study by Yamamura et al., the authors showed that NSAID–H_2-receptor antagonist combinations, i.e. naproxen and cimetidine [22], indomethacin and cimetidine [23] and diflunisal and cimetidine [24] can all be made amorphous at a specific ratio by solvent evaporation or precipitation. The formation of the amorphous states was verified by XRPD analyses, in which the diffraction patterns only showed a halo with no crystalline peaks. Furthermore, no melting endotherms were observed in the DSC traces of these systems. Both ^{1}H and ^{13}C NMR showed a large chemical shift on the C–H proton bound to the imidazole ring of cimetidine and the carboxyl group of the NSAID, suggesting a non-bonding intermolecular interaction may have occurred between these groups [22–24]. As it was unusual for a molecular interaction to occur between a C–H moiety and a carboxyl group, the authors later claimed that the amorphous binary systems were formed as a result of salt formation at the N–H moiety of the imidazole ring and the carboxyl group, resulting in a change in the chemical shift observed at the adjacent C–H proton in the imidazole ring, although the ^{1}H NMR findings showed no detectable chemical shift on the N–H proton itself [24]. They also reasoned that the diflunisal–cimetidine combination had a greater pK_a difference compared to the naproxen–cimetidine and indomethacin–cimetidine combinations. Therefore, a larger change in the chemical shift of 1.39 ppm in diflunisal–cimetidine binary systems was not unexpected compared to naproxen–cimetidine and indomethacin–cimetidine systems, where a change of 0.05 and 0.06 ppm was observed at the C–H (imidazole) proton, respectively.

In this study, we investigated the physicochemical properties and the stability of indomethacin and ranitidine hydrochloride binary systems at different ratios prepared by mechanical activation in an oscillatory ball mill. The two main possible advantages of such a combination are (i) an increased dissolution of the poorly water soluble NSAIDs and (ii) a reduction in the side effects of NSAIDs such as gastrointestinal disturbance [24]. NSAID–cimetidine combinations have been well studied; however, NSAID–ranitidine hydrochloride combinations have not been explored. With ranitidine hydrochloride being used more frequently than cimetidine, it was interesting to investigate whether the furan ring in ranitidine hydrochloride that replaces the imidazole ring in cimetidine would also result in a similar drug–drug interaction with NSAIDs. Ranitidine hydrochloride also differs from cimetidine in that it is a salt and contains a nitro moiety at one end of the molecule. The solid state characteristics of the milled binary systems were analyzed by XRPD and DSC. To investigate a possible interaction of the co-milled indomethacin and ranitidine hydrochloride mixtures DRIFTS was used.

2. Materials and methods

2.1. Materials

γ-Indomethacin (M = 357.5 g/mol) (Hawkins Inc. USA, Lot PH05113013) and ranitidine hydrochloride form 2 (M = 350.5 g/mol) (Salutas Pharma, Germany, Batch No. 10201844/1180625) were used as received.

2.2. Ball milling

The drugs were co-milled using an oscillatory ball mill (Mixer Mill MM301, Retsch GmbH & Co., Germany). A total of 1 g of powder at varying ratios (indomethacin to ranitidine hydrochloride ratio; 2:1, 1:1, 1:2 w/w) was used for each milling. The individual pure drugs were also milled for comparison. The focus was placed on the 1:1 ratio. The sample powder was placed in a 25 mL volume stainless steel milling jar containing two 12 mm diameter stainless steel balls and milled at a milling frequency of 30 Hz. Milling was conducted at 4 ± 2 °C up to 60 min. A fresh 1 g batch of sample was used for each milling. The powder temperatures were recorded using an infrared thermometer (Model 42510, Extech Instrument, USA). Co-milled samples were stored in an air tight container over silica gel at 4 °C until further analysis.

2.3. Preparation of amorphous indomethacin and ranitidine hydrochloride

Amorphous indomethacin was prepared by quench-cooling γ-indomethacin followed by cryo-milling for 60 min. Amorphous ranitidine hydrochloride was prepared by cryo-milling form 2 for 60 min. In both cryo-milling processes, 1 g of sample powder was placed in a 25 mL jar with 2 × 12 mm diameter stainless steel balls. The jars were immersed in liquid nitrogen for 3 min before milling at 30 Hz for 60 min. Re-cooling of the milling jars with liquid nitrogen was performed every 20 min. XRPD was used to confirm that the samples were fully amorphous after preparation.

2.4. Storage conditions

In the stability study, the co-milled binary systems (2:1, 1:1 and 1:2 mixtures) were stored at 4, 25 and 40 °C under dry conditions (silica gel) up to 30 days.

2.5. Characterization

2.5.1. X-ray powder diffraction (XRPD)

XRPD analysis was performed using an X'Pert PRO X-ray diffractometer, (PANalytical, The Netherlands; MPD PW3040/60 XRD; CuKα anode; λ = 1.541 Å). The samples were gently consolidated in an aluminium holder and scanned at 40 kV and 30 mA from 5–35° 2θ using a scanning speed of 0.1285°/min and a step size of 0.0084°. The diffraction patterns were analyzed using X'Pert High Score software (version 2.2.0) and plotted using OriginPro 7.0 (OriginLab Corporation, USA).

2.5.2. Differential scanning calorimetry (DSC)

DSC thermograms (DSC Q100 V8.2 Build 268, TA Instruments, USA) were obtained under a nitrogen gas flow of 50 mL/min. Calibration of the DSC instrument was carried out using indium as a standard. Sample powders (3–5 mg) were crimped in an aluminium pan and heated at a rate of 10 K per min from 0 to 160 °C. The glass transition temperature (T_g), crystallization temperature (T_c) and melting temperature (T_m) were determined using TA Universal Analysis software, version 4.0C. The T_g was determined as the midpoint of the change in heat capacity of the sample, while both T_c and T_m were determined as the onset temperatures.

2.5.3. Diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS)

DRIFTS spectra were obtained using a Varian Excalibur 3100 FT-IR spectrometer (Varian Inc., 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 mixtures in KBr, and placed in a small cup sample holder. All the measurements were carried out at room temperature. An average of 32 scans was used for each sample at 4 cm^{-1} resolution. The KBr background was recorded prior to the scanning of samples. Reflectance data were plotted as a function of wavenumber. OPUS™ 4.0 (Bruker Optik, Germany) was used for the spectral analysis.

2.5.4. Density measurements

The densities of the pure amorphous compounds were obtained with a helium pycnometer (AccuPyc 1330 Gas Pycnometer, Micromeritics Instruments Corporation, USA). The amorphous samples were stored for 24 h over silica gel at 4 °C prior to the measurements. Measurements were performed in triplicate.

3. Results

3.1. XRPD

Fig. 2a shows the X-ray diffraction patterns for the three binary mixtures (2:1, 1:1 and 1:2, respectively) after various milling times. Unmilled, physically mixed (PM) binary systems are also shown for comparison. The diffraction patterns showed a rapid decrease in the peak intensity for both γ-indomethacin (characteristic peaks; 11.6°, 21.9° and 26.7° 2θ) and ranitidine hydrochloride form 2 (characteristic peaks; 20.1° and 23.5° 2θ) within the first 15 min of co-milling (Fig. 2a). After 30 min of co-milling, the XRPD characteristic peaks of γ-indomethacin had completely disappeared and only XRPD peaks of ranitidine hydrochloride form 2 could be observed (Fig. 2b; 30 min, arrows). When the milling duration was extended to 60 min, no peaks but only a halo was observed in the diffractograms for all the drug ratios (Fig. 2b; 60 min), demonstrating the binary mixtures had become fully amorphous. In contrast, when the drugs were individually milled for 60 min under the same condition, full amorphous conversion was not achieved. Low intensity peaks could still be observed in the diffraction pattern (Fig. 3). Interestingly, the rate of amorphous conversion was found to be relatively similar between the three mixtures regardless of the drug ratios. Within a ratio, the peaks corresponding to γ-indomethacin were always found to decrease faster than the peaks of ranitidine hydrochloride.

3.2. DSC

Using DSC, a glass transition could be observed in the 2:1 and 1:1 mixtures after milling for 5 min and after 10 min for the 1:2 mixture. The findings were in agreement with the XRPD diffraction pattern, where an increase in the halo is paralleled by the observation of a T_g in the DSC experiments. Overall the glass transition temperatures were found in the range of 26–44 °C, depending on the ratio of the drugs in the mixtures and the milling time (Fig. 4). Fig. 4 shows that as a general trend the higher the concentration of indomethacin in the mixtures, the higher the T_g at any milling time.

XRPD indicated that indomethacin becomes amorphous faster than ranitidine hydrochloride. It was thus expected that the T_gs would be high initially and gradually decrease as a function of milling time, for all mixtures. After 5 min of milling, the T_g of the 2:1 and 1:1 mixtures was found to be very close to that of pure amorphous indomethacin (43.3 and 43.7 °C, respectively), and the T_gs indeed decreased with increasing milling time. However, the T_g of the 1:1 mixture decreased sharply after 10 min of milling and remained between 25 and 30 °C up to 30 min. Although a slight increase was later observed in the 60 min co-milled sample, ANOVA showed that there were no significant differences between the recorded T_gs (excluding the 5 min sample). On the other hand, the 1:2 mixtures co-milled at various times (10, 15, 30 and 60 min) had a median T_g of 27 °C, which is close to the previously reported (median) T_g of the pure amorphous ranitidine hydrochloride (26 °C [25]).

Calculations were carried out to compare the experimental T_g for the fully amorphous 60 min co-milled mixtures with the predicted T_g using the Gordon–Taylor (GT) equation

$$T_{g(mix)} = (w_1 \cdot T_{g1} + K \cdot w_2 \cdot T_{g2})/(w_1 + K \cdot w_2) \quad (1)$$

where $T_{g(mix)}$ is the glass transition temperature of the mixture, K is a constant and w_1, T_{g1} and w_2, T_{g2} are the weight fractions and glass transition temperatures of components 1 and 2, respectively. The constant K can be further expressed as

$$K = (\rho_1 \cdot T_{g1})/(\rho_2 \cdot T_{g2}) \quad (2)$$

where ρ_1 and ρ_2 are the respective densities of the pure amorphous compounds [26]. The true densities of 60 min individually milled indomethacin and ranitidine hydrochloride were determined using a gas pycnometer and were found to be 1.457 (±0.0031) and 1.312 (±0.0005) g/mL, respectively. Substituting the T_g (45 °C for indomethacin and 26 °C for ranitidine hydrochloride) and density of the 60 min individual samples into the GT equation, the predicted T_gs were found to be similar (Table 1) suggesting the binary mixtures, after 60 min of milling, formed a homogeneous phase.

3.3. DRIFTS

Fig. 5a shows the DRIFTS spectrum of the amorphous 1:1 binary mixture (co-milled 60 min). The spectra of crystalline and amorphous form of the two drugs are also shown for comparison. The γ-indomethacin is characterized by two distinct peaks occurring at 1717 and 1692 cm^{-1}. The former is attributed to the C=O vibration of the carboxylic acid cyclic dimer and the latter is the C=O vibration of the non-protonated (benzoyl) amide [27–29] (Fig. 5a). In the amorphous indomethacin, the peak corresponding

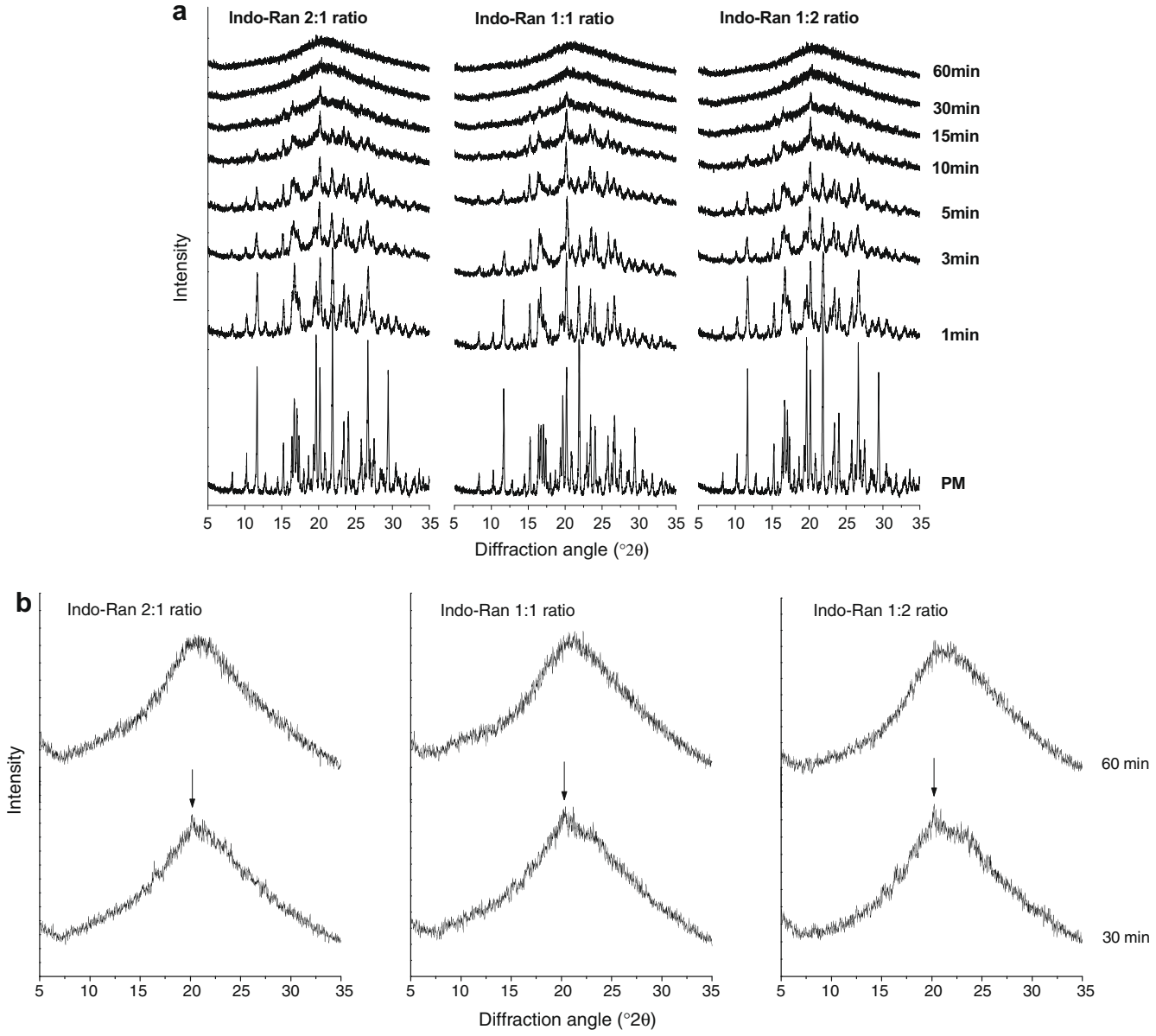

Fig. 2. (a) X-ray powder diffraction pattern of co-milled indomethacin–ranitidine hydrochloride binary mixtures at 2:1, 1:1 and 1:2 ratios and at various milling times. The physically mixed (PM) binary mixtures are also shown for comparison. (b) Enlarged diffraction patterns showing the 30 and 60 min co-milled indomethacin–ranitidine hydrochloride binary mixtures at 2:1, 1:1 and 1:2 ratios. The arrows indicate a characteristic peak (20.1° 2θ) of ranitidine hydrochloride form 2.

to the carboxylic acid cyclic dimer occurs at 1710 cm^{-1}, while the non-protonated amide peak is observed at 1684 cm^{-1}. In addition, amorphous indomethacin also has a shoulder peak at 1735 cm^{-1} (Fig. 5a) assigned to the non-hydrogen bonded acid C=O indicating the presence of free carboxylic acid monomer. The free carbonyl usually occurs at higher wavenumbers [29,30] compared to hydrogen bonded carbonyl groups.

In ranitidine hydrochloride, the form 2 polymorph is characterized by a peak at 1620 cm^{-1}, which is assigned to the C=N stretch (aci-nitro group) of the nitronic acid [31], while the two peaks at 1590 and 1570 cm^{-1} are thought to be due to the amidine moiety (N–C=N) [32]. The vibration occurs at a lower wavenumber for the amidine moiety (usually 1685–1580 cm^{-1}) in ranitidine hydrochloride form 2 [32] possibly because of the resonance and electron-withdrawing effect attributed to the nitro group located close by. The peaks associated with the dimethyl amino group have been reported to occur at 2640 and 2560 cm^{-1} (spectral region not shown) [31].

Comparing the spectra of the crystalline drugs and the co-milled sample, it was evident that the peaks of the sample became broader after 60 min of co-milling, demonstrating the initially crystalline binary mixture had been transformed into an amorphous state. This finding again supports the results obtained by XRPD and DSC. Furthermore, significant peak shifts could also be seen in the spectra of the 1:1 mixture (Fig. 5a), which was confirmed by the spectral subtraction as illustrated in Fig. 5b. In the 1650–1750 cm^{-1} region (related to indomethacin), the occurrence of a shoulder peak at 1735 cm^{-1} and the two peaks at 1713 and 1687 cm^{-1} indicate the presence of amorphous indomethacin, although the latter two peaks had a slightly higher wavenumber compared with the reported wavenumbers of pure amorphous indomethacin (1710 and 1684 cm^{-1} [29]).

In addition, two newly formed peaks, 1723 and 1679 cm^{-1}, were found in the spectra of the 1:1 mixtures (Fig. 5a). Fig. 5b also shows the presence of these two peaks confirming their significance. The former peak, 1723 cm^{-1}, is likely to be associated with

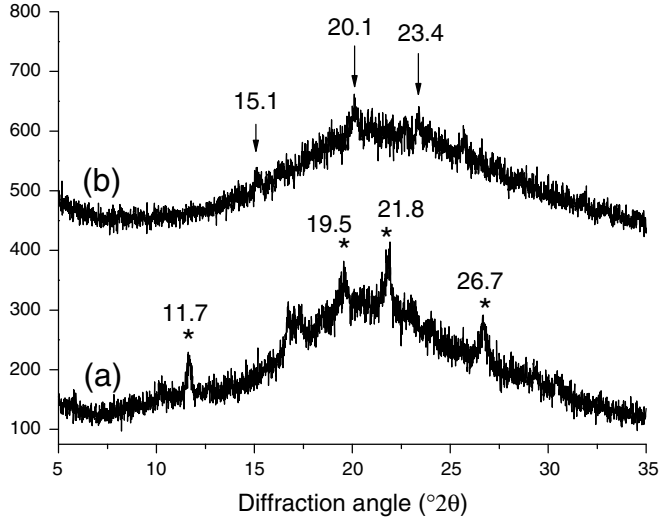

Fig. 3. X-ray powder diffraction pattern of (a) γ-indomethacin and (b) ranitidine hydrochloride form 2 after 60 min milling in a cold room. The asterisks and arrows indicate crystalline peaks of γ-indomethacin and ranitidine hydrochloride form 2, respectively.

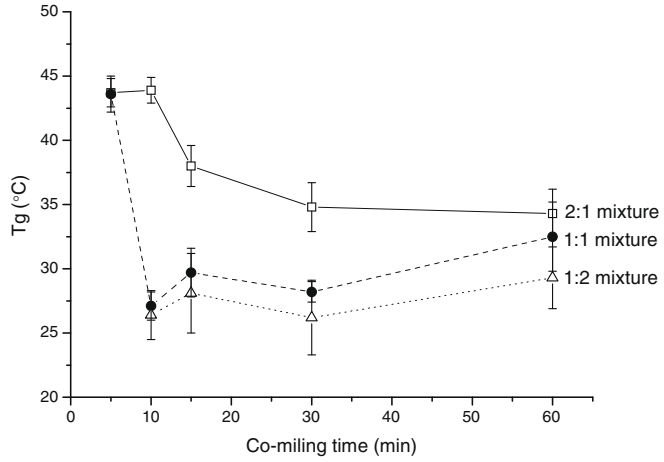

Fig. 4. Glass transition temperatures ($n = 3$) for the co-milled indomethacin–ranitidine hydrochloride binary mixtures at 2:1, 1:1 and 1:2 ratios milled for 5, 10, 15, 30 and 60 min. The lines indicate the general trends of the T_g (□/solid line, 2:1 mixture; ●/dashed line, 1:1 mixture and Δ/dotted line, 1:2 mixture).

Table 1
Average experimental ($n = 3$) and calculated T_g of the 60 min co-milled binary mixture at different ratios

Time (min)	Average experimental T_g ± std. dev. (°C) 60	Calculated T_g[a] (°C) 60
Ratio		
2:1	34.3 ± 1.9	35.7
1:1	32.5 ± 2.7	32.5
1:2	29.3 ± 2.4	29.9

[a] Calculated T_g is based on Gordon–Taylor equation.

the carbonyl acid group. A similar finding was also observed in a study of indomethacin and methylpyrrolidone mixture prepared by a solvent evaporation method [29]. The authors demonstrated that the amorphous indomethacin peak at 1710 cm^{-1} gradually disappeared, and the shoulder at 1735 cm^{-1} developed into a single peak at 1723 cm^{-1} as the concentration of methylpyrrolidone increased [29]. This peak, at 1723 cm^{-1}, could indicate the formation of conjugated carbonyl acid system.

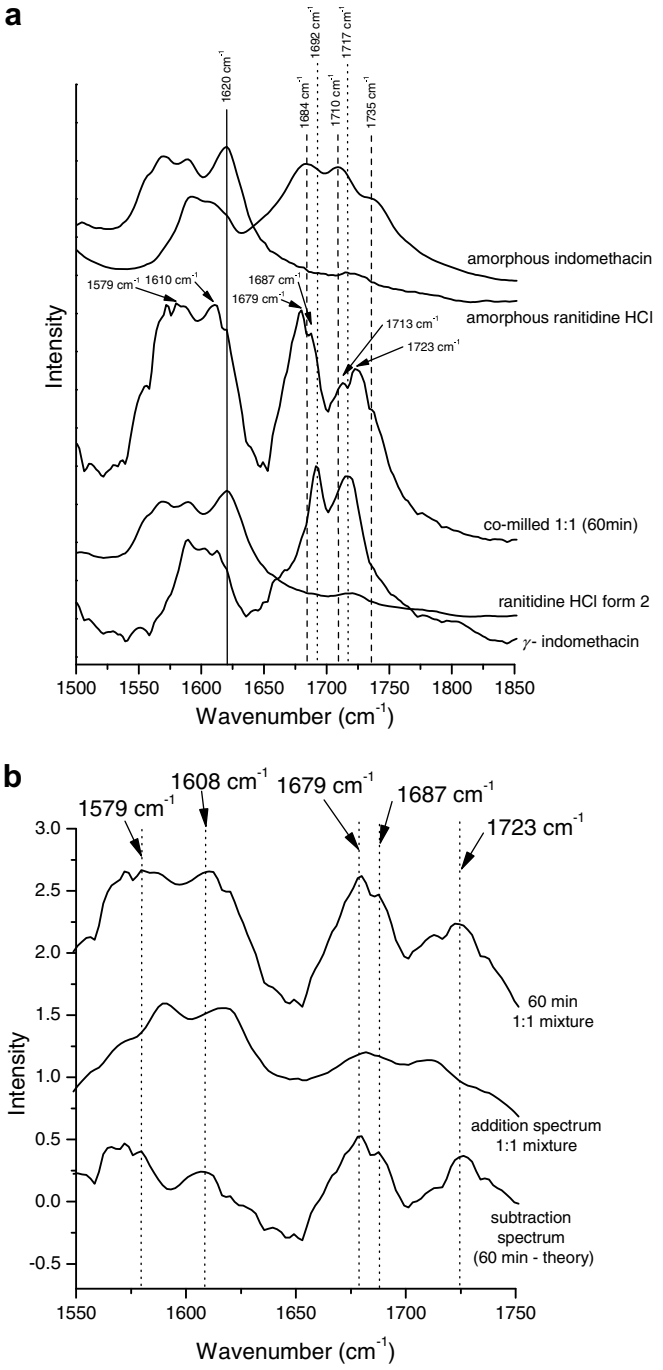

Fig. 5. (a) DRIFTS spectra of crystalline (γ-form) and amorphous indomethacin; crystalline (form 2) and amorphous ranitidine hydrochloride; and 60 min co-milled 1:1 mixture. The dotted lines (1717 and 1692 cm^{-1}) represent the characteristic peaks of the γ-indomethacin; dashed lines (1735, 1710 and 1684 cm^{-1}) represent the characteristic peaks of amorphous indomethacin and the solid line (1620 cm^{-1}) represent the characteristic peak of the aci-nitro group of ranitidine hydrochloride (form 2 and amorphous ranitidine hydrochloride). The main difference between form 2 and amorphous ranitidine hydrochloride is that the latter has broader peaks. The *y*-axis has been scaled and offset to improve the clarity of the spectra. (b) DRIFTS spectra of 60 min co-milled 1:1 mixture, addition spectrum of amorphous indomethacin and amorphous ranitidine hydrochloride, and resulting subtraction spectrum (addition spectrum subtracted from 60 min co-milled mixture spectrum), from top to bottom. Dotted lines indicate the remaining peaks observed after spectral subtraction. The spectra are offset for clarity.

The peak that occurs at 1679 cm^{-1} was thought to have originated from the 1692 cm^{-1} peak (benzoyl C=O vibration in γ-indomethacin). The observed shift (13 cm^{-1}) was slightly larger than

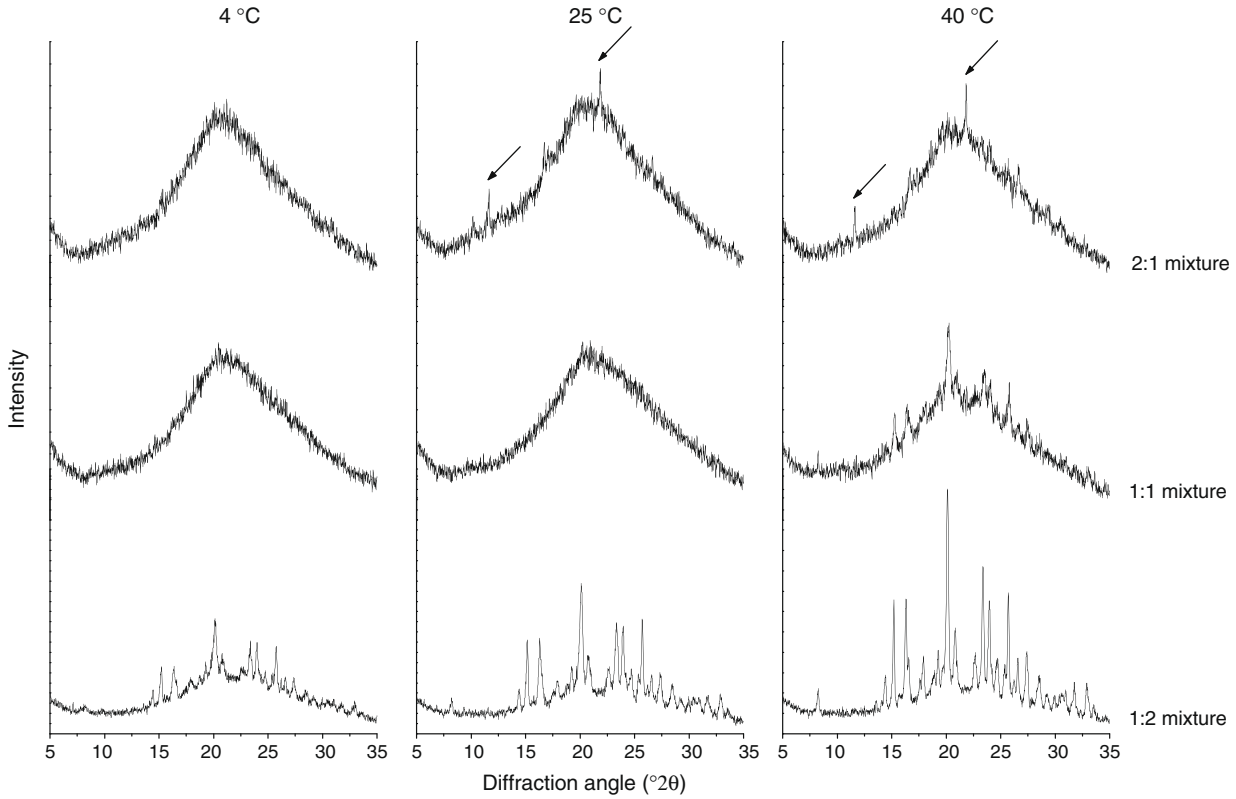

Fig. 6. X-ray diffraction patterns of 60 min co-milled indomethacin–ranitidine hydrochloride binary mixture at different ratios stored at 4, 25 and 40 °C for 30 days. The arrows show the initial emergence of γ-indomethacin peaks.

that usually observed in amorphous indomethacin (approx. 8 cm^{-1}). This peak shift has been linked to an increased movement at the amide bond, allowing a greater C=N double bond character and therefore resulting in a reduction in the adjacent C=O bond vibration [29]. In this situation, an additional shift of 5 cm^{-1} on top of the 8 cm^{-1} shift in the binary mixtures could mean that either a larger C=N double bond character is present (reduced force constant of the C=O bond, or alternatively a direct interaction at the benzoyl C=O may have occurred.

In the 1550–1650 cm^{-1} region (related to ranitidine hydrochloride) shown in Fig. 5a, the peak at 1620 cm^{-1} (aci-nitro C=N stretch) was found to have shifted by 10 cm^{-1}, to 1610 cm^{-1} (or 1608 cm^{-1} in subtraction spectrum, Fig. 5b) suggesting a change in the C=N double bond character at the aci-nitro group. This shift could be due to the nitro group forming a bond with indomethacin, thus indirectly reducing the C=N double bond character. While the peak shift of the C=N (aci-nitro) bond was seen clearly, it may be speculated that the small 'new' peak at 1579 cm^{-1} (Fig. 5b) is the result of an interaction at the amidine moiety. However, the finding remains inconclusive due to the complexity of the spectra and the presence of overlapping peaks in the 1570–1590 cm^{-1} region. On the other hand, the possibility of an interaction occurring at the dimethyl amino group was excluded because the spectra showed no peak shifts at 2640 and 2560 cm^{-1} (results not shown). The findings were not unexpected because this site is known to be protonated by HCl, and therefore less likely to be involved in an interaction [33].

3.4. Stability studies

The XRPD results of the stability study at various temperatures up to 30 days are shown in Fig. 6. Overall, the amorphous binary mixtures at 2:1 and 1:1 ratios were found to be more stable than the 1:2 mixtures after 30 days of storage. A halo could still be seen on the XRPD diffraction patterns of these samples. In the 2:1 mixture, XRPD diffraction patterns showed that the samples remained predominantly amorphous after 30 days of storage at all temperatures at 4 °C. However, at 25 and 40 °C, small crystalline peaks corresponding to the γ-indomethacin (11.6° and 21.9° 2θ) could be observed indicating a small portion of amorphous indomethacin had crystallized. This finding was not unexpected because indomethacin is the excess component in the 2:1 mixture.

At 1:1 ratio, the mixture was found to be stable up to 30 days under the storage temperature of 4 and 25 °C. However, when the sample was stored at 40 °C for 30 days, small crystalline peaks could be observed indicating partial crystallization. No characteristic peaks of crystalline indomethacin but only the peaks of ranitidine hydrochloride form 2 were observed. Interestingly, some features of α-indomethacin could, however, be seen in the DRIFTS spectrum (not shown).

In the 1:2 mixture stored at various temperatures up to 30 days, XRPD diffraction patterns showed a progressive increase in the peak intensity with an increase in storage temperature. The samples appeared to crystallize faster and more completely, with the diffraction patterns resembling mostly that of ranitidine hydrochloride form 2.

4. Discussion

Transformation of crystalline indomethacin to the amorphous form was observed when co-milled with ranitidine hydrochloride form 2 in a cold room. The crystalline to amorphous transformation was found to be faster compared to drugs that were individually milled. According to the co-milled XRPD diffraction patterns, it appears that the peaks of γ-indomethacin decrease faster than the

peaks of ranitidine hydrochloride form 2. There were no differences in the rate of amorphization when the samples were co-milled at either 2:1, 1:1 or 1:2 (indomethacin to ranitidine) ratio – all ratios achieved a fully amorphous state after 60 min of co-milling. In a separate study, we have found that milling of crystalline indomethacin alone can take up to several hours before amorphous indomethacin is obtained (unpublished work). For ranitidine hydrochloride form 2, a previous study showed that it takes at least 90 min for the crystalline drug to transform into a fully amorphous form when milled in a cold room [10].

The formation of an amorphous form observed with XRPD was also backed up with DSC. In general the higher the amount of indomethacin within the mix, the higher the observed T_g. This was not unexpected as the T_g of pure amorphous indomethacin (45 °C [34]) is higher than that of ranitidine hydrochloride (approx. 26 °C [25]). We previously reported variable T_g values for pure amorphous ranitidine hydrochloride when prepared by a milling technique [10]. Hence, the observed high T_g fluctuations in the 1:1 mixture are most likely caused by ranitidine hydrochloride. Moreover, XRPD showed that indomethacin converts faster to the amorphous state than ranitidine hydrochloride. Therefore, the fluctuations in the T_g could also be at least in part explained by the differences in the transformation kinetics of the two drugs. Interestingly, when ranitidine hydrochloride was the excess component (i.e. in the 1:2 mixture), the fluctuation of T_g was lower (25–30 °C) and closely resembled that of the pure amorphous ranitidine hydrochloride.

The T_g values predicted using the GT equation were similar to the experimental T_gs indicating the mixtures were homogeneous (i.e. no formation of two amorphous phases). The DRIFTS results clearly suggest that there is an interaction occurring between the two components. The newly observed peaks at 1610, 1679 and 1723 cm^{-1} in the DRIFTS spectra strongly suggest that an interaction had occurred between indomethacin and ranitidine hydrochloride but at the expense of indomethacin's dimer formation. While the peak at 1610 cm^{-1} shows that the aci-nitro group of the ranitidine hydrochloride is involved, the peaks at 1679 and 1723 cm^{-1} suggest that in indomethacin the two carbonyl groups (benzoyl and carboxylic acid) are involved in the interaction. Looking at the molecular structures (Fig. 1), it was not unexpected that an interaction would have occurred at these sites (benzoyl, carboxylic acid and nitronic acid) as they are able to complement each other in hydrogen bond formation. The amidine moiety was initially thought to be involved in the binary interaction as well; however, no strong data supporting this claim could be found because of overlapping of peaks. The most probable interaction is between the carboxylic acid groups and the nitronic acid group (i.e. O═C–OH···O═N^+–O). It remains unclear at this stage which moiety may have interacted with the benzoyl group of indomethacin causing the substantial reduction in the wavenumber observed at 1679 cm^{-1} even though the amidine group is a probable candidate for a benzoyl C═O–amidine interaction. The DRIFTS spectra can be analyzed in different ways: e.g., by a conventional search for shifts in the peak positions and/or by applying the spectral subtraction method to identify and analyze peak shifts. Here, the spectral subtraction method was found more convenient as small shifts can be more easily detected. Although DSC and DRIFTS suggest an interaction between the two drugs, there was no evidence of amorphous form-mediated co-crystal formation [35].

In the stability data of the 60 min co-milled sample, the overall observation was that the amorphous binary mixtures predominantly crystallized back to the excess component. Such findings were anticipated because the excess component would not be involved in the binary interaction and, thus, be able to crystallize more readily. However, when comparing the two mixtures with an excess component, the 1:2 mixture (excess ranitidine hydrochloride) was generally found to have a faster crystallization rate than the 2:1 mixture (excess indomethacin). At 40 °C, the 1:2 mixture showed almost complete crystallization of ranitidine hydrochloride form 2 after 3 days while the 2:1 mixture had barely crystallized. One possible explanation is the difference in the T_g values between the two mixtures. Although both samples were stored above the T_g, the difference between the storage temperature and T_g was higher for the 1:2 mixture (13 °C) compared to 2:1 mixture (5 °C). As the storage temperature increases, the molecular mobility also increases, allowing faster crystallization of the amorphous state. The faster crystallization rate of ranitidine hydrochloride can also be explained by the presence of residual ranitidine hydrochloride form 2 nuclei (XRPD in Fig. 2a and b showed that ranitidine hydrochloride peaks disappeared slower than those of indomethacin) which promotes the crystallization of amorphous ranitidine hydrochloride. The phenomenon can be seen clearly in the 1:1 mixture after 30 days of storage at 40 °C. In all storage conditions that we studied, full crystallization was not observed after 30 days of storage. It was interesting to note that the 1:1 mixture had the highest stability even though it did not have the highest T_g. This finding underlines that to fully understand the behaviour of amorphous systems, one needs to take into account the interactions at the bulk and molecular level.

5. Conclusions

This study has shown that crystalline indomethacin can be made amorphous and stabilized by co-milling with crystalline ranitidine hydrochloride. The indomethacin amorphization was also found to be faster when co-milled with ranitidine hydrochloride compared to the drug being milled alone. DRIFTS data suggested that an interaction may have occurred between the carbonyl acid and/or the benzoyl group of indomethacin and the aci-nitro group of ranitidine hydrochloride. In terms of the stability of the amorphous binary system, the 1:1 mixture was found to be stable after 30 days of storage at 4 and 25 °C. The amorphous binary system is a promising candidate to develop a dosage form of indomethacin with a higher solubility/dissolution rate. The inclusion of ranitidine hydrochloride in the system has two advantages. It not only improves the physical stability of the amorphous state but also reduces the gastrointestinal side effects of indomethacin.

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