Paracetamol–Propyphenazone Interaction and Formulation Difficulties Associated with Eutectic Formation in Combination Solid Dosage Forms

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Received August 28, 1998; accepted November 20, 1998

Polymorphic behaviours of paracetamol and propyphenazone and interaction between these two compounds were investigated using differential scanning calorimetry (DSC), X-ray powder diffraction and Fourier transform-infrared (FT-IR)-spectroscopy. Binary mixtures containing various ratios of the compounds were prepared as physical and fused mixtures and analysed by DSC to study their thermal behaviours. Phase diagrams obtained from the melting endotherms of the binary mixtures demonstrated formation of an eutectic mixture at a paracetamol–propyphenazone combination of about 35 : 65 (w/w) with an eutectic temperature of 56 °C. The FT-IR spectroscopy revealed no chemical interaction due to eutectic formation, and a lower degree of crystallinity of the eutectic mixture than individual substances was observed by X-ray powder diffraction analysis. The DSC and X-ray powder diffraction data demonstrated a polymorphic change in propyphenazone as a result of melting of the compound. Tablets, containing both paracetamol and propyphenazone in a combination formulation and prepared using standard wet granulation technology, were found to have physical instability when packed in either polyvinylchloride//aluminium or polyvinylchloride/polyvinyldienechloride//aluminium blisters and stored for one month at 40 °C with either 75% relative humidity or without any humidity control. The instability of the tablets was more apparent under the high humidity condition.

Key words paracetamol–propyphenazone interaction; phase diagram; eutectic mixture; polymorphism

Despite controversy about the rationale of using fixed combination preparations of antipyretics/analgesics due to concerns raised by pharmacologists/neurologists regarding possible increase in pharmacokinetic and neurological side effects in comparison to single preparations, their use among consumers as over-the-counter drugs still remains popular.[1] In fact, most cough/cold preparations currently available on the global market contain combinations of not only antipyretics/analgesics but, in addition, also therapeutic agent(s) of other pharmacological groups (*e.g.*, antihistamines, sympathomimetic agents).

Apart from pharmacological/neurological concerns, the commonly used antipyretics/analgesics combinations also cause formulation difficulties due to various physico-chemical interactions between the therapeutic agents. Formation of eutectic mixtures as a result of such interactions is a common phenomenon which is known to cause problems during manufacture of some combination formulations, particularly for solid dosage forms,[2] and their shelf-life.

Paracetamol is a well known analgesic/antipyretic used in both combination and single formulations. But due to the presence of -NH and -OH groups in its structure, paracetamol interacts with other compounds containing the same group(s) and/or the carbonyl group, such as phenazone[3,4] through dipolar- or hydrogen-bonding forming complexes. It has also been reported[5] that paracetamol forms eutectic mixtures with aspirin and propyphenazone, but the study lacks clarity since the conclusion drawn for the paracetamol–propyphenazone system contradicts the data presented by the authors in the phase diagram, and no other technique was used to support the phase diagram data obtained by differential scanning calorimetry (DSC).

During preformulation studies by DSC of a combination formulation containing paracetamol, propyphenazone, caffeine and codeine phosphate hemihydrate, we also observed an interaction between paracetamol and propyphenazone with formation of an eutectic mixture, but our results are in disagreement with the conclusion drawn in the previous report.[5] Accordingly, we report here the results of our DSC studies and phase diagrams obtained for samples of various paracetamol–propyphenazone combinations prepared as physical and fused mixtures. We also investigated the nature of the interaction between these two compounds by Fourier transform-infrared (FT-IR) spectroscopy and X-ray powder diffraction analysis and found that the data obtained are in agreement with the results of DSC studies. Furthermore, we prepared tablets containing about 450 mg paracetamol–propyphenazone combination (about 50 : 50, w/w) with caffeine (25 mg) and codeine phosphate hemihydrate (10 mg) using standard wet granulation technique and studied stability of the tablets under accelerated conditions (*i.e.*, at 40 °C without humidity control, and with 75% relative humidity). The stability data have been interpreted in terms of the results obtained from the DSC, FT- IR spectroscopy and X-ray powder diffraction analysis of paracetamol–propyphenazone mixtures.

Experimental

Materials For the interaction studies, paracetamol and propyphenazone were purchased from Cerapharm (Austria) and Höechst (Germany), respectively. Both compounds were of commercial grade and used as received. A special grade (granulated with polyvidone) of paracetamol was purchased from Rhône-Poulenc (France) to prepare the tablets.

Preparation of Samples Binary mixtures with paracetamol–propyphenazone ratios (w/w) of: 100 : 0, 90 : 10, 80 : 20, 70 : 30, 60 : 40, 50 : 50, 40 : 60, 35 : 65, 30 : 70, 20 : 80, 10 : 90 and 0 : 100 were used to study the interaction between paracetamol and propyphenazone using DSC. Samples were prepared as physical and fused mixtures of the compounds.

Physical mixtures were prepared by: (i) gentle mixing (without much pressure) and (ii) grinding the two compounds using a mortar and a pestle for few minutes. Fused mixtures were prepared by heating physical mixtures (gently prepared) of the two compounds in a glass tube in an oil bath to a temperature about 2 °C above that of complete fusion of both the com-

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pounds. The fused mixtures were stirred for a few seconds and then cooled to room temperature. The glassy masses obtained were stored at ambient temperature for at least 30 d for stabilization since preliminary experiments suggested the freshly prepared (or 5—10 d old) glassy mass to be metastable which did not produce reproducible thermograms.

DSC Analysis A Perkin-Elmer DSC 7 was used to analyse the samples. The instrument was calibrated with indium and zinc prior to analysing the samples under nitrogen. Samples (10—15 mg) were weighed in aluminium pans, closed and scanned at a heating rate of 10 °C/min over the temperature range of 20—200 °C. The heated samples were then cooled at the same scanning rate and reheated again under the same conditions. The onset temperatures of the exotherms/endotherms were considered as the temperatures of the peaks except for construction of the phase diagrams. Peak height temperature (T_m) was used for construction of phase diagrams because it was difficult to calculate onset temperatures for complex peaks representing multiple processes.

X-ray Powder Diffraction Analysis The X-ray diffraction patterns were recorded using a Philips 3710 automatic powder diffractometer (Philips PW 1877 APD, 3.6 g program) at 30 mA, 50 kV with monochromatised Cu$K\alpha$ radiation (λ=1.54056 Å). The samples were scanned at 20 °C temperature in the diffraction angle 2θ increasing at 0.02°/s over the range of 10—30°. Only samples of primary interest (*i.e.*, paracetamol–propyphenazone 35 : 65 mixtures) were analysed. A 65 : 35 paracetamol–propyphenazone physical mixture was analysed for comparison. Diffraction patterns of both the compounds in pure form (*i.e.*, 100 : 0 and 0 : 100) were also recorded to serve as controls. In case of the melted pure compounds, the samples were analysed in less than 24 h (after cooling to room temperature) as opposed to those analysed by DSC (stored for at least 30 d).

FT-IR Spectroscopy FT-IR spectra were obtained only for samples with paracetamol–propyphenazone ratios (w/w) of 30 : 70 and 35 : 65. A dispersion (about 1%) of the sample in potassium bromide (KBr) was prepared in two different ways: i) by grinding and mixing the mass with KBr and ii) by mixing nongrinded mass with grinded KBr and then compressed into discs using a 13 mm die at 10 tons pressure. FT-IR spectra of the prepared discs were obtained on a Nicolet Magna-IR 760 spectrometer over the 4000—400 cm^{-1} region. The number of scans were 16 and the resolution was 4 cm^{-1}.

Preparation of Tablets Propyphenazone, caffeine and codeine phosphate hemihydrate were blended with microcrystalline cellulose, corn starch and sodium starch glycollate, and granulated in a high shear mixer (P10, Diosna, Germany) using polyvidone aqueous solution as a binder. The granules, dried in a fluid bed drier (GPCG3, Glatt) and screened through a 14 mesh sieve, were mixed with granulated paracetamol (as purchased) and some tableting aid excipients and compressed into tablets using 13 mm (diameter) round and shallow concave punches on a rotary tablet press (Perfecta 21, Wilhelm Fette). The tablets were packed into two types of blisters: polyvinylchloride//aluminium and polyvinylchloride/polyvinyldienechloride//aluminium, and stored under two conditions at 40 °C, without humidity control and with 75% relative humidity, to test their stability and to compare the effect of moisture protection capacities of the contact packaging material on stability of the tablets since polyvinylchloride/polyvinyldienechloride// aluminium blister packaging is known to be more moisture protective than polyvinyl//aluminium type.

Results

DSC Analysis During the first heating, untreated paracetamol (100 : 0) gave only one sharp endothermic melting peak at 169 °C (T_m 174 °C) with an enthalpy of 180—185 J/g, but during the second heating (after cooling to room temperature) an exothermic peak appeared at about 76—77 °C followed by the melting peak at 168 °C (T_m 174 °C) (Fig. 1). Untreated propyphenazone (0 : 100) gave a broad melting peak at 100 °C with shouldering at the leading edge during the first run with an enthalpy of 104 J/g. The cooling curve produced an exothermic peak at 49 °C. During the second heating, a complex endothermic process was observed representing two peaks (T_ms) at 101 °C and 104 °C (Fig. 2). The thermograms obtained during first heating of physical (prepared by grinding) and fused mixtures of paracetamol and propyphenazone are presented in Fig. 3 and Fig. 4, respectively. Both the physical and fused mixtures produced al-

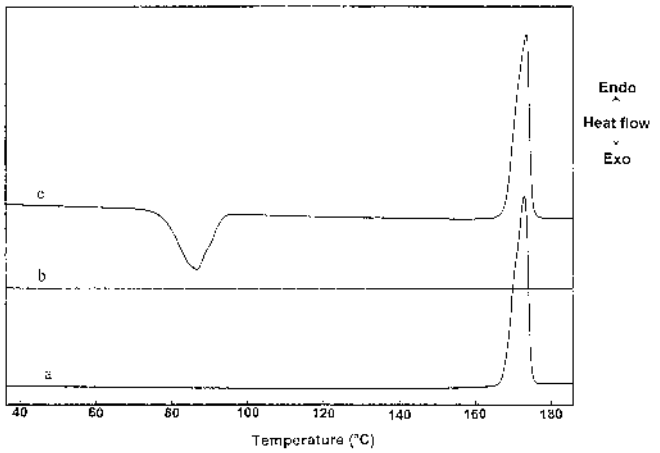

Fig. 1. DSC Thermograms of Paracetamol
(a) First heating, (b) cooling and (c) second heating.

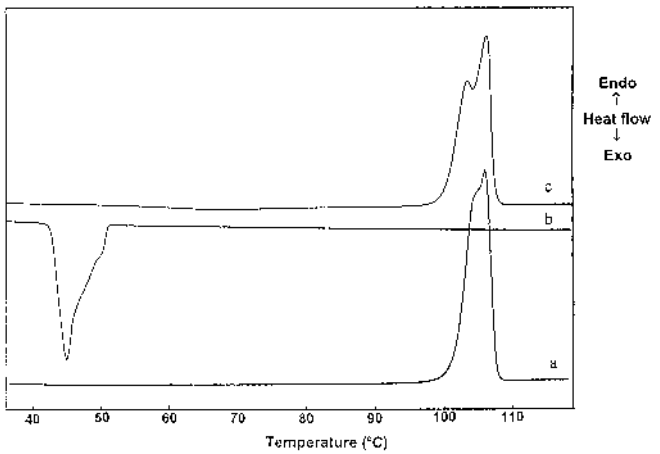

Fig. 2. DSC Thermograms of Propyphenazone
(a) First heating, (b) cooling and (c) second heating.

most identical thermograms at the same concentration of paracetamol–propyphenazone, but the peak temperatures were slightly different. All paracetamol–propyphenazone physical mixture samples prepared by grinding and containing 10—30% paracetamol showed two endothermic peaks: the first one at about a particular temperature (T_m 62—69 °C) and the second one at a higher temperature which varied according to the paracetamol–propyphenazone ratio (Fig. 3). The temperature of the second peak progressively decreased with the increase in concentration of paracetamol in the samples. This was also the case for samples prepared by gentle mixing of the two compounds, but the peaks (both first and second) appeared at slightly higher temperatures (data not shown). In the physical mixture samples, the second peak disappeared when the paracetamol concentration reached the 35% level. At this concentration only one endothermic peak appeared with T_m and onset values of 63 °C and 56 °C, respectively. Above the 35% paracetamol level, the combination samples also produced two peaks: the first one at about the same temperature as the samples containing 10—30% paracetamol with the second peak at a higher temperature which progressively increased with the increase in paracetamol concentration. In the fused mixtures, the T_m value of the first peak was within the range of 60—64 °C, and the disap-

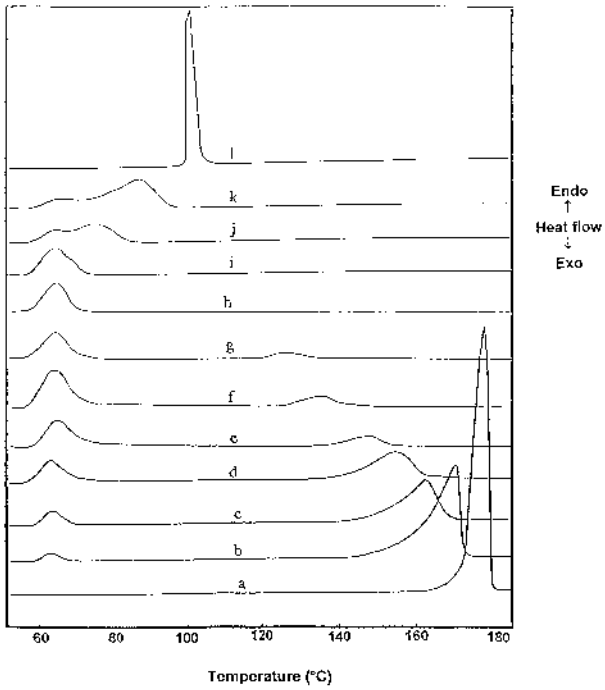

Fig. 3. DSC Thermograms Obtained during First Heating of Physical Mixtures of Paracetamol and Propyphenazone

Containing paracetamol : propyphenazone (w/w): (a) 100 : 0, (b) 90 : 10, (c) 80 : 20, (d) 70 : 30, (e) 60 : 40, (f) 50 : 50, (g) 40 : 60, (h) 35 : 65, (i) 30 : 70, (j) 20 : 80, (k) 10 : 90 and (l) 0 : 100.

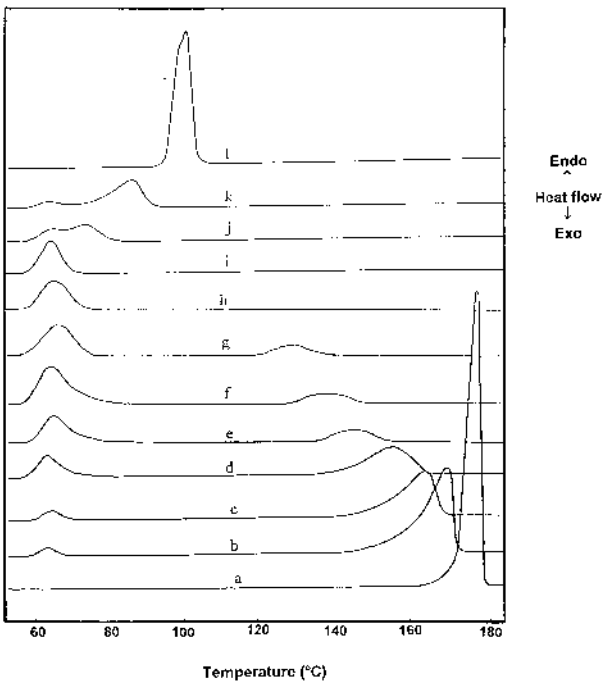

Fig. 4. DSC Thermograms Obtained during First Heating of Fused Mixtures of Paracetamol and Propyphenazone

Containing paracetamol : propyphenazone (w/w): (a) 100 : 0, (b) 90 : 10, (c) 80 : 20, (d) 70 : 30, (e) 60 : 40, (f) 50 : 50, (g) 40 : 60, (h) 35 : 65, (i) 30 : 70, (j) 20 : 80, (k) 10 : 90 and (l) 0 : 100.

pearance of the second peak was observed at 30% paracetamol level (Fig. 4). At this 30 : 70 paracetamol–propyphenazone concentration only one endothermic peak appeared with T_m and onset values of 65 °C and 56 °C, respectively. Samples containing ≥40% of paracetamol produced thermograms identical to the physical mixture samples. The melted (then cooled to room temperature and stored for at least 30 d) samples of both paracetamol (*i.e.*, 100 : 0) and propyphenazone (*i.e.*, 0 : 100) produced thermograms identical to those produced by untreated samples during first heatings (Fig. 4). Phase diagrams constructed from the T_m values obtained during first heatings of the physical and fused mixtures are presented in Fig. 5 and Fig. 6, respectively. These two diagrams are almost identical and of typical monotectic systems, and the data suggest formation of eutectic mixture at about 30—35 : 65—70 paracetamol–propyphenazone (w/w) ratio with an eutectic temperature of 56 °C (T_m 63—65 °C).

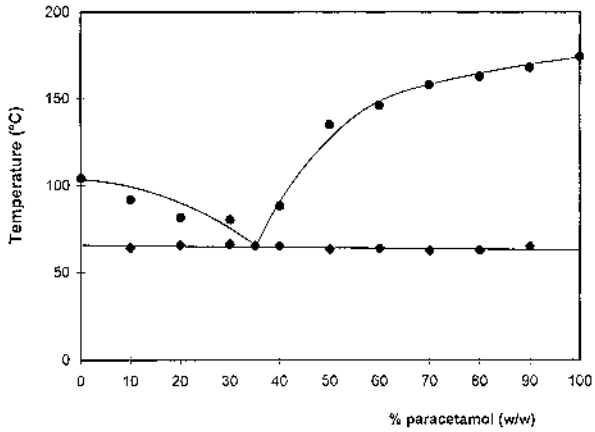

Fig. 5. Phase Diagrams Constructed from the Peak Height Temperatures (T_ms) Obtained during First Heating of Physical Mixtures of Paracetamol and Propyphenazone

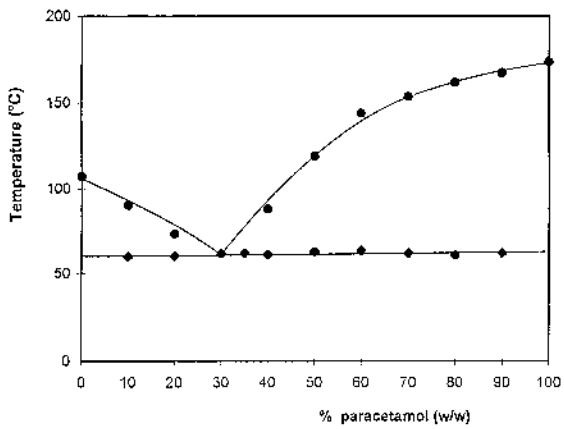

Fig. 6. Phase Diagrams Constructed from the Peak Height Temperatures (T_ms) Obtained during First Heating of Fused Mixtures of Paracetamol and Propyphenazone

Thermograms obtained during reheating of paracetamol–propyphenazone combination samples are not presented because they were not reproducible due to the kinetics of recrystallisation and have no relevance to the purpose of this study.

X-Ray Powder Diffraction Analysis The diffraction patterns of paracetamol (100 : 0) recorded for sample untreated (as purchased) and melted (then cooled to room temperature and analysed in less than 24 h) are identical but with

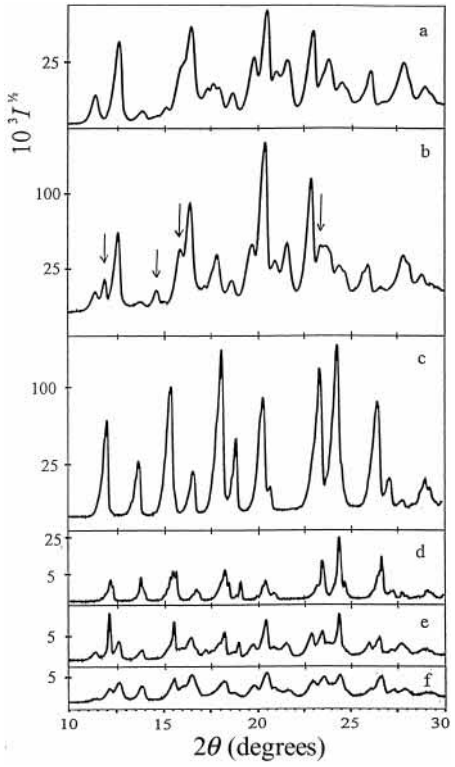

Fig. 7. X-Ray Powder Diffractograms

Obtained for: (a) propyphenazone before thermal treatment, (b) propyphenazone after melting and cooling, (c) paracetamol before thermal treatment, (d) paracetamol after melting and cooling, (e) paracetamol–propyphenazone physical mixture (35 : 65, w/w) and (f) paracetamol-propyphenazone fused mixture (35 : 65, w/w). The arrows indicate the main places of difference observed as a result of melting and cooling (analysed in less than 24 hours of preparation) of propyphenazone.

different intensities (Fig. 7). The peak intensities of the melted (and cooled) paracetamol were significantly weaker than those obtained for untreated paracetamol. For propyphenazone (0 : 100), different reflexes were observed in the diffractograms of samples prepared differently, *i.e.*, untreated (as received) and melted (then cooled to room temperature and analysed in less than 24 h) (Fig. 7). The resolidified sample had different patterns at 12, 14.8, 15.9 and 23.4° angles than the untreated sample.

The diffractograms obtained for the physical and fused mixtures (35 : 65) are almost identical. Both mixtures produced peaks characteristic of untreated samples of paracetamol and propyphenazone but with weak intensities, suggesting a lower degree of crystallinity of the eutectic mixtures than of the individual substances (Fig. 7). In addition, the 65 : 35 paracetamol–propyphenazone fused mixture produced distinctive peaks characteristic of paracetamol (Fig. 8).

FT-IR Spectroscopy The FT-IR spectra of pure paracetamol and propyphenazone were identical for samples prepared differently, *i.e.*, as received and melted (cooled to room temperature and stored for at least 30 d) (data not shown). The different ways of preparing the KBr discs, *i.e.*, sample mixed and ground with KBr or simply mixed with KBr, did not make significant differences in the spectra produced although slight differences were observed in peak intensities (data not shown). But there was no new peak or shifting of any peak.

Peaks corresponding to pure paracetamol and propyphenazone were present in the spectra of both the physical

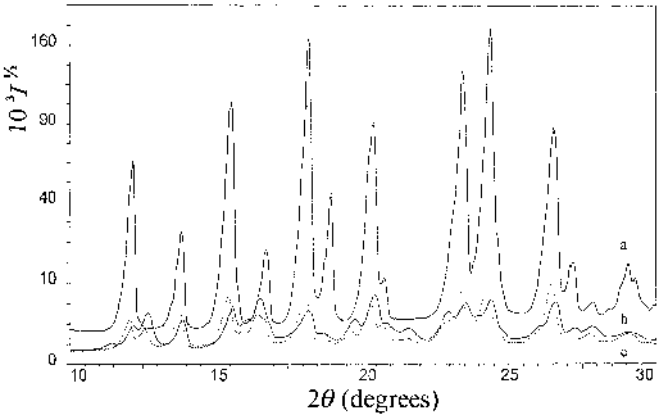

Fig. 8. X-Ray Powder Diffractograms

Obtained for: (a) paracetamol (before thermal treatment), (b) stabilized (at least for 30 d) paracetamol–propyphenazone 35 : 65 (w/w) fused mixture (eutectic), and (c) stabilized (at least for 30 d) paracetamol–propyphenazone 65 : 35 (w/w) fused mixture.

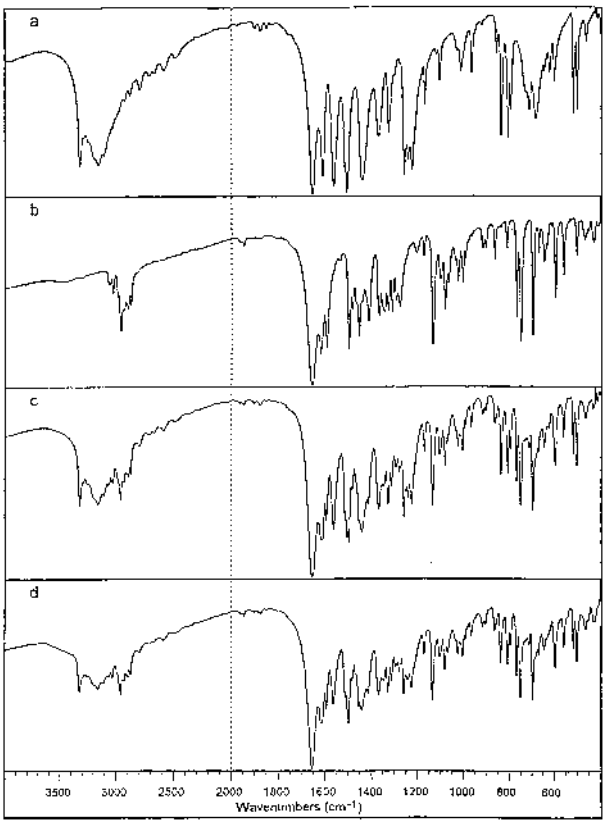

Fig. 9. FT-IR Spectra

Obtained for: (a) paracetamol, (b) propyphenazone, (c) paracetamol–propphenazone physical mixture (35 : 65, w/w) and (d) paracetamol–propyphenazone fused mixture (30 : 70, w/w).

and fused mixtures (Fig. 9), and the sample preparation technique did not make any difference. Neither any new peak nor shifting of any peak was observed in the combinations studied.

Stability of the Tablets The original white colour of the tablets packed in both types of blisters and stored for one month at 40 °C with 75% relative humidity was changed to off-white (brownish) and the tablets became unacceptably soft (hardness changed from 60—80 kp to about 30 kp, $n=10$), but the tablets stored at 40 °C without humidity control for the same period did not show significant change in

hardness, although the colour appeared less brownish than the tablets stored with 75% relative humidity. However, no significant change in the content of the active materials was observed in the tablets stored under either conditions.

Discussion

The sharp endothermic peak obtained for paracetamol at 168—169 °C is in line with other literature reports.[6—8] Although the commonly marketed form of paracetamol is known to have crystalline structure of monoclinic form (form I), the possibility of formation of other forms of crystalline structure has also been reported.[7—9] Haïsa *et al*.[9] obtained a form II polymorphic form of paracetamol by recrystallizing the form I type of paracetamol from ethanolic solution. More recently, Di Martino *et al*.[7,8] were able to obtain this form II of paracetamol by melting form I type under certain conditions and reported a melting temperature (T_m) of 157—158 °C for the form II polymorphic form.

The same melting temperature obtained during first and second heatings of our paracetamol sample suggests that the monoclinic form was not transformed into form II or another polymorphic form during the heating–cooling cycle. This is not surprising since the form I→II transition was reported to require a very slow cooling of the form I melt at room temperature.[8] But the same melting temperature obtained for the melted (then cooled to room temperature and stored for at least 30 d) and for the untreated sample suggests that either the form II polymorph did not form at all or a metastable form I→II transition occurred which converted to form I on storage. Formation of the metastable form can not be ruled out since DSC thermograms obtained during our preliminary studies from freshly prepared (or 5—10 d old) samples were not reproducible.

The exothermic peak observed at about 76—77 °C during the second heating suggests that during the cooling process in the DSC pan, the melted mass did not yet recrystallize into form I type due to kinetics of the recrystallization process but instead remained glassy which recrystallized at 76—77 °C into form I and then melted at 168 °C. A similar exothermic peak (at about the same temperature) was observed by Di Martino *et al*.[7,8] during second heating of a form I melt of paracetamol. The low intensity peaks observed in the X-ray diffraction pattern of the melted and cooled (tested in less than 24 h) paracetamol sample also support our speculation of formation of the glassy mass (see Fig. 7).

In contrast to paracetamol, the melting peak obtained for propyphenazone at 100 °C (T_m 104 °C) had slight shouldering at the leading edge. This may be attributable to the presence of impurities in the purchased propyphenazone which may be of any related substance or of a different polymorphic form of propyphenazone since existence of 2—3 different polymorphic forms of propyphenazone with melting points within the range of 101—104.3 °C (T_m) has been reported in the literature.[5,10] The observed melting point of 100 °C (T_m 104 °C) is in agreement with other literature reports.[5,10]

The exothermic peak obtained at 49 °C during cooling is probably due to recrystallization of the melted propyphenazone. Peaks with T_ms at 101 °C and 104 °C observed during the reheating process closely correspond to melting temperatures of two different polymorphic forms of propyphenazone, form III and form I, respectively, which were reported to form as a result of melting of a commercial grade (form II) of propyphenazone.[5] Similar complex endothermic behaviour was observed for mixtures of the polymorphic forms I and II of propyphenazone by Giron-Forest *et al*.[10] These results are supported by the data we obtained from X-ray powder diffraction analysis for propyphenazone before and after the melting process. But the identical DSC thermograms obtained during first heating of the melted (then cooled to room temperature and stored for at least 30 d) propyphenazone to the untreated sample suggest the polymorphs produced during the melting process were metastable and converted to form II during storage of the cooled sample. This is, probably, another reason why we were unable to have reproducible DSC thermograms from freshly prepared samples (melted and cooled to room temperature) during our preliminary experiments.

The phase diagrams obtained for both physical and fused binary mixtures suggest formation of a simple monotectic type of eutectic mixture at a composition between 30 : 70 and 35 : 65 paracetamol–propyphenazone ratios (w/w), and the eutectic temperature was the same, 56 °C (T_m 63—65 °C), for both types of mixtures. The FT-IR spectra and X-ray diffractograms also confirm the DSC data since there is no sign of any chemical interaction between the two compounds irrespective of the type of mixtures (physical or fused), although the fused mixture appears to have lower crystallinity than the physical mixture (see Fig. 7). Our results contradict a previous report[5] which suggested formation of an eutectic mixture at a 65 : 35 paracetamol–propyphenazone ratio (w/w). Distinctive paracetamol reflexes observed in the diffractograms of the studied paracetamol–propyphenazone fused mixture of 65 : 35 ratio suggest the presence of excessive paracetamol in this combination and support our viewpoint (see Fig. 8).

Apparently, the preparation technique (gentle mixing or grinding) made slight differences in the peak temperatures of the physical mixture samples. Application of pressure in preparing the samples seems to enhance the eutectic formation process because of better mixing of the compounds, and not surprisingly, the fused mixtures had the lowest sample to sample variation in the T_m values of the first (common) peak among all three types of samples. The sample to sample variation observed in detecting the first peak was anticipated due to the composition variations of the samples since the thermodynamic process is affected by the presence (and level) of other compound(s) and homogeneity of the analysed sample[11,12] which is supported by the fact that the eutectic composition had the same eutectic temperature (56 °C) irrespective of the sample type (either physical or fused mixture).

Apart from paracetamol and propyphenazone, the tablets under investigation contained codeine phosphate hemihydrate and caffeine (in relatively small quantities) as actives and also some auxiliary substances including microcrystalline cellulose (5%, w/w) and corn starch (2.4%, w/w) as main fillers/disintegrants and sodium starch glycollate (3%, w/w) as a super disintegrant. Although the two other actives and the auxiliary substances theoretically could have some influence on the stability of the tablets, in this case it is unlikely since we did not experience such physical instability

with tablets containing paracetamol (but no propyphenazone) with other similar actives (*e.g.*, codeine phosphate and pseudoephedrine hydrochloride) and prepared with similar auxiliary substances. The technology used to prepare the studied tablets did not exclude possibility of formation of the eutectic between paracetamol and propyphenazone in the tablets. Therefore, the observed physical instability of the studied tablets stored under accelerated conditions can be linked to the eutectic formation between these two compounds because the melting temperature of the eutectic mixture is significantly lower than the individual compounds. It is also well known that moisture can plasticise amorphous materials and influence their properties (*e.g.*, glass transition temperature, crystallisation temperature and molecular mobility).[13,14] Similar to temperature effect, small amounts of adsorbed moisture can affect the rate of deteriorative reactions in amorphous substances.[13] Therefore, the observed effect of high humidity on stability of the studied tablets is not surprising since the X-ray powder diffractograms demonstrated a low degree of crystallinity of the studied paracetamol–propyphenazone mixtures. The data also demonstrated that neither of the studied types of packaging material could improve the instability problem associated with the studied formulation although they are known to have different moisture barrier properties. Since the instability problem is of physical nature without loss of chemical potency or appearance of any degraded product, the FT-IR spectroscopy data are in agreement with the stability findings.

Conclusions

The data presented here clearly demonstrate that paracetamol and propyphenazone physically interact with each other forming a simple eutectic mixture at a paracetamol–propyphenazone ratio (w/w) of about 35 : 65 with an eutectic temperature of 56 °C, irrespective of whether the two compounds are mixed physically or as melted. This formation of eutectic mixture has significant impact in formulating combination dosage forms containing both the compounds and can cause instability during storage of the dosage form. Therefore, formulation of such dosage forms would require an advanced technological procedure in order to combat (or minimise) the interaction between these two compounds so as to obtain a stable product.

Acknowledgements We would like to thank Mr. Marijan Piščak and Mr. Josip Botički for their technical assistance in preparing the tablets and in performing DSC analysis, respectively.

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