Journal of Thermal Analysis and Calorimetry, Vol. 77 (2004) 445–457

THE THERMAL STABILITY OF TRIPROLIDINE HYDROCHLORIDE AND ITS MIXTURES WITH CYCLODEXTRIN AND GLUCOSE

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Abstract

Triprolidine hydrochloride ($C_{19}H_{22}N_2 \cdot HCl \cdot H_2O$) (TPH) is a well-known antihistamine drug which is reported as being photosensitive. The thermal stabilities of TPH and of 1:1 molar and 1:1 mass ratio physical mixtures of TPH with β-cyclodextrin (BCD) and with glucose have been examined using DSC, TG and TG-FTIR, complemented by X-ray powder diffraction (XRD) and infrared spectroscopic (IR) studies. Thermal studies of the solid TPH/BCD mixtures indicated that interaction between the components occurs and it is possible that the TPH molecule may be least partially accommodated in the cavity of the BCD host molecule. XRD results support this indication of inclusion. The results of molecular modelling suggest that TPH is most likely to be accommodated in the BCD cavity as a neutral triprolidine molecule with the toluene portion of the molecule preferentially included in the cavity.

The results obtained illustrate the general stability of TPH. The study has also shown TPH to be compatible with both glucose and BCD, which are potential excipients both in solid and liquid dosage forms. The presence of these excipients in dosage forms will thus not adversely affect the stability and the therapeutic efficacy of TPH.

Keywords: β-cyclodextrin, cyclodextrins, excipients, glucose, thermal stability, triprolidine, triprolidine hydrochloride

Introduction

Triprolidine hydrochloride, $C_{19}H_{22}N_2 \cdot HCl \cdot H_2O$, (TPH), a white, crystalline powder, melting between 118–122°C, is photosensitive [1–3]. Triprolidine can exist as both the *Z*- and *E*-isomers (Fig. 1), but only the *E*-isomer [4], (*E*)-2-[3-(pyrrolidinyl)-1-*p*-tolylpropenyl] pyridine mono-hydrochloride [5] is pharmaceutically active as an antihistamine, commonly used as an over the counter drug in both liquid and solid dosage forms.

In the propylamine derivatives, which are unsaturated compounds, the co-planar aromatic double bond system has been suggested to be an important factor for anti-

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1388–6150/2004/ $ 20.00

Akadémiai Kiadó, Budapest
Kluwer Academic Publishers, Dordrecht

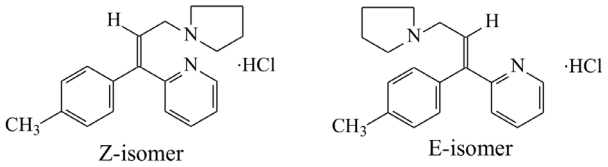

Fig. 1 Molecular structures of the *Z*- and *E*-isomers of triprolidine hydrochloride (TPH), $C_{19}H_{22}N_2 \cdot HCl$ [6]

histamine activity [7]. Isomers of triprolidine and pyrrobutamine have been prepared [8, 9] and their geometrical configurations established by proton NMR spectroscopy. The differences in the reactivity of the isomers have been ascribed to the interactions possible when the α-pyridyl and aminomethyl groups are *trans* to each other, or when the *p*-tolyl and amino methyl groups are *cis* to each other.

Many factors have been found to affect the stability of TPH in the liquid dosage form. These include pH, UV-light, water and some excipients [10, 11], with the light stability reported to be pH-dependent. At pH 2 the degradation rate was slower than at pH 8, and in pure water TPH was unstable [11]. Conversion of the active *E*-isomer to the inactive *Z*-isomer occurs under the influence of UV-light [10]. Some excipients, such as sorbitol, mannitol and glycerin, have been found to stabilise TPH, while others, such as propylene glycol and sodium saccharine, have no effect on its stability. Glucose as an excipient affects the stability of TPH [11]. However, after two years at 37°C, TPH in a syrup had not decomposed by more than 10%. BCD was found to have a small positive effect on the stability of aqueous solutions of TPH but had no effect in the presence of sucrose.

In general, very much less is known about the solid-state reactions of pharmaceuticals than is known about their reactions in aqueous solution. During formulation, the processing effects and/or interactions with excipients, can result in solid-state reactions (including dehydration, desolvation, cyclization, oxidation and hydrolysis) taking place in the drug substances, which may accelerate degradation. Excipients that are present in formulated products may not be directly involved in the degradation, but may add components, e.g. water, which may take part in solid-state reactions.

Experimental

Materials

Samples of triprolidine hydrochloride – *E*-isomer (TPH), glucose and β-cyclodextrin (BCD) were supplied by Aspen Pharmacare Laboratories in Port Elizabeth (South Africa) and their molecular masses and water contents are listed in Table 1.

Physical mixtures were prepared in the usual 1:1 mole ratios used for initial complexation studies, by weighing the appropriate amounts of TPH, BCD and glucose (which had been stored in desiccators over P_2O_5). The individual components were simply blended until thoroughly mixed and stored away from light in sealed

Table 1 Molecular masses and water content of materials

Compound	Molar mass/g mol^{-1}	Water content/% *w/w*
Triprolidine hydrochloride-*E*-isomer (TPH)	332.85	4.5
β-Cyclodextrin (BCD)	1135	14.9*
Glucose (anhydrous)	180.16	–

*The water content of BCD was determined by Karl Fischer titration (Mettler DL 18 Karl Fischer, Mettler-Toledo, Switzerland)

containers in a desiccator. In addition, to investigate the effects of having excess drug present, physical mixtures were also prepared in 1:1 mass ratios. {1:1 mass ratio TPH/β-cyclodextrin (equivalent to a 3.41:1.00 mole ratio); 1:1 mass ratio TPH/glucose (equivalent to a 0.54:1.00 mole ratio); 1:1 mass ratio glucose/β-cyclodextrin (equivalent to a 6.30:1.00 mole ratio)}

Thermal analysis equipment

A PerkinElmer Series 7 DSC and TG system was used. DSC sample pans were either (*i*) aluminium pans, or (*ii*) stainless-steel high pressure pans with gold gaskets. TG experiments were done in an open platinum pan. Unless otherwise stated, samples were heated at 10°C min^{-1} under a nitrogen purge. The thermobalance could be connected to a PerkinElmer Spectrum 2000 FTIR via a heated interface (PerkinElmer). The purge gas, containing the volatile decomposition products, was passed through a heated gas cell for analysis.

Other equipment

A PerkinElmer Spectrum 2000 FTIR spectrometer was used to record the infrared absorption spectrum of TPH (in KBr disk) over the range 4000 and 400 cm^{-1}. The absorption bands were consistent with literature values [2, 10].

X-ray powder diffraction patterns were measured using a Rigaku Denki Max III diffractometer fitted with a horizontal goniometer, graphite monochromator and scintillation detector. Na-filtered Cu-K_α radiation was generated at a voltage of 40 kV and a current of 20 mA. A fixed time-step scanning method was employed. Step-scans were recorded for all samples for 2θ from 5 to 60°. A powder pattern was simulated using data taken from the *Cambridge Structural Database* [12] and the results were compared with the experimental pattern.

The thermal behaviours of triprolidine hydrochloride, β-cyclodextrin and glucose

The DSC curves for TPH (Fig. 2) show a sharp melting endotherm at 122–123°C which corresponds to the literature value [2], and onset of a broad exotherm above

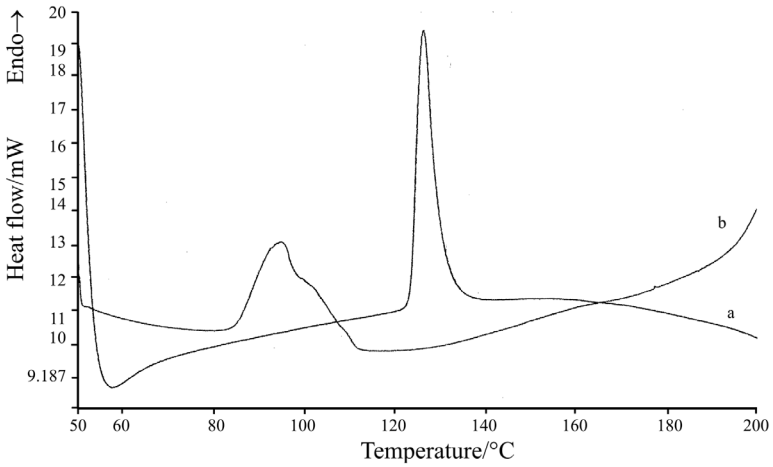

Fig. 2 DSC curves for TPH heated at 10°C min^{-1} in flowing nitrogen, using a – a sealed pressure pan and b – an uncrimped aluminium pan

190°C. The endotherm is broadened and more complex in the aluminium pan and a variety of processes may be taking place, e.g. sublimation, decomposition, melting.

The TG curve for TPH is shown in Fig. 3. The curve shows a multi-step loss of components. There is an initial mass-loss between 50 and 100°C of 4.9%. For the formula, $C_{19}H_{22}N_2 \cdot HCl \cdot H_2O$ (molar mass = 332.5 g mol^{-1}), loss of water corresponds to a 5.4% by mass, whereas loss of HCl corresponds to 11.0% by mass. The major mass-loss to a residue of about 20% of the original mass by 400°C occurs in two overlapping stages. The onset of the first stage of the major mass-loss occurs soon af-

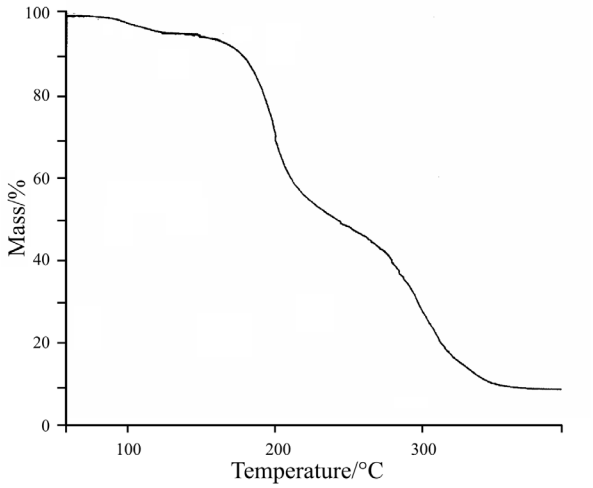

Fig. 3 TG curve for TPH heated at 10°C min^{-1} in flowing nitrogen in an open platinum pan

ter the melting endotherm on the corresponding DSC curve (Fig. 2). The mass loss may include contributions from evaporation and decomposition of the liquid.

TG–FTIR was used to detect gases evolved by TPH on heating in nitrogen. As expected, evolution of HCl resulted in strong absorbances at just above and just below 3000 cm^{-1}. This occurred between 10 and 30 min, which, at a heating rate of 10°C min^{-1} from a starting temperature of 50°C, corresponds to release between 150 and 350°C, which is the temperature range of the overall mass loss in the TG curve (Fig. 3).

The DSC curve for β-cyclodextrin (BCD) (Fig. 4, curve (b)) shows a broad dehydration endotherm between 65 and 110°C with ΔH = 279±10 J g^{-1}, and a small exotherm at 220°C with ΔH = 2.2±0.5 J g^{-1}. The TG curve (Fig. 5, curve (b)) shows that the BCD contains 12.5% by mass of water. This is lower than the 14.9% (Table 1) determined by Karl Fischer titration, thus indicating differences in stability of H_2O in its different environments in BCD.

Table 2 Summary of the thermal behaviour of the pure compounds

Sample	Onset temperature of DSC endotherms/°C	ΔH / J g^{-1}	ΔH / kJ mol^{-1}	Initial mass loss (50 to 110°C)
TPH	122±1	117±10	39±3	4.9±0.1
BCD	64±1	279±10	317±11	12.5±0.5
Glucose	158±1	190±10	34±2	–

The DSC curve for glucose (Fig. 6, curve (b)) shows a sharp endotherm (melting) with onset 158°C and ΔH = 190 J g^{-1}, which corresponds with the literature values [2].

The results characterizing the thermal behaviour of the individual compounds are summarized in Table 2 for later comparison with the thermal behaviour of mixtures

The thermal behaviours of binary physical mixtures of triprolidine hydrochloride, β-cyclodextrin and glucose

The DSC curves for the physical mixtures of glucose and BCD (not illustrated) show the features of the pure samples, although the glucose melting endotherm shows slight broadening. The lack of significant changes in the thermal behaviour on mixing indicates little if any interaction between glucose and BCD.

The DSC curves of the physical mixtures of TPH and BCD are shown in Fig. 4, together with the DSC curves for pure TPH and BCD. The endotherm associated with the melting of TPH disappears almost completely in the DSC curves of the mixtures. The dehydration endotherm of BCD is also decreased significantly in the DSC curve of the mixtures. The exotherm at above 200°C associated with TPH appears at slightly higher temperatures in the DSC curves for the mixtures.

The lack of a distinct melting endotherm for TPH in the DSC curves for both of the physical mixtures suggests that mixing has resulted in drug inclusion, or that the drug has been converted to an amorphous form by heating in the presence of BCD, as was observed in a study on nifedipine and randomly methylated-β-cyclodextrin [13,

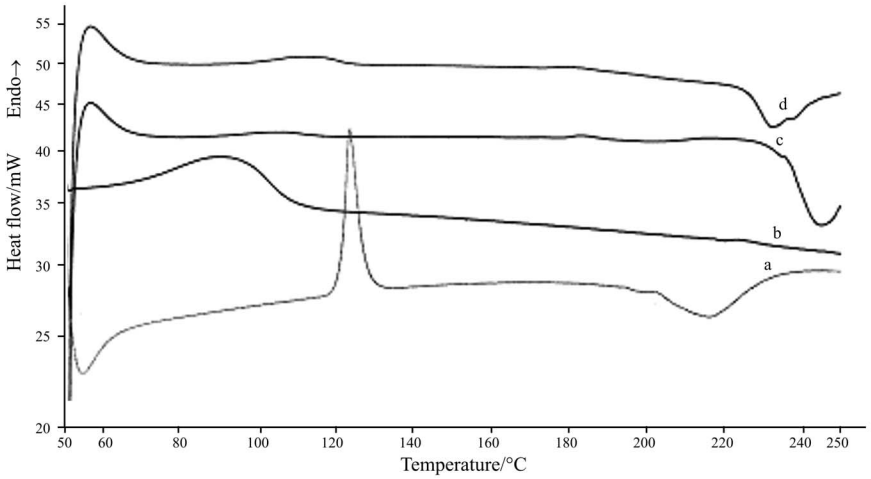

Fig. 4 DSC curves for a – TPH, b – BCD, c – a 1:1 mass ratio (equivalent to a 3.4:1.0 mole ratio) physical mixture of TPH and BCD and d – a 1:1 mole ratio physical mixture of TPH and BCD (heated at 10°C min^{-1}in flowing nitrogen)

14]. Inclusion complexation has been cited as the main reason for the unusual thermal behaviour of heated physical mixtures [15, 16]. The possibility of inclusion is supported by X-ray powder diffraction and molecular modelling (see below).

The TG curves of the physical mixtures of TPH and BCD are compared with those of pure TPH and BCD in Fig. 5. The 1:1 mass ratio physical mixture of TPH and BCD shows an initial mass loss of 8.3±0.1%, while for the 1:1 molar ratio mixture the mass loss is 10.0±0.1%, as expected for the higher content of BCD. Two further stages of mass loss are seen in the TG curves for both of the mixtures. These would correspond to the decomposition of the BCD followed by decomposition of the TPH at higher temperatures.

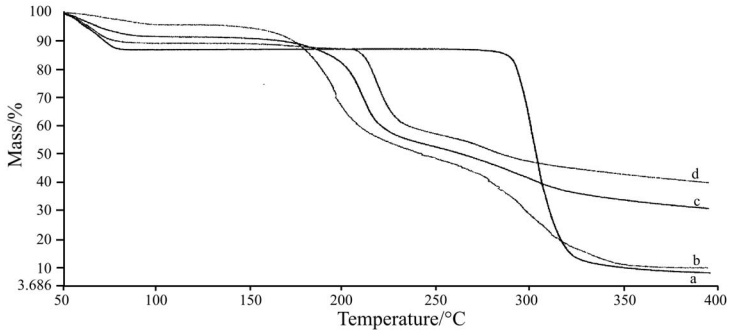

Fig. 5 TG curves for a – TPH, b – BCD, c – a 1:1 mass ratio (equivalent to a 3.4:1.0 mole ratio) physical mixture of TPH and BCD and d – a 1:1 mole ratio physical mixture of TPH and BCD, (heated at 10°C min^{-1} in flowing nitrogen using platinum pans)

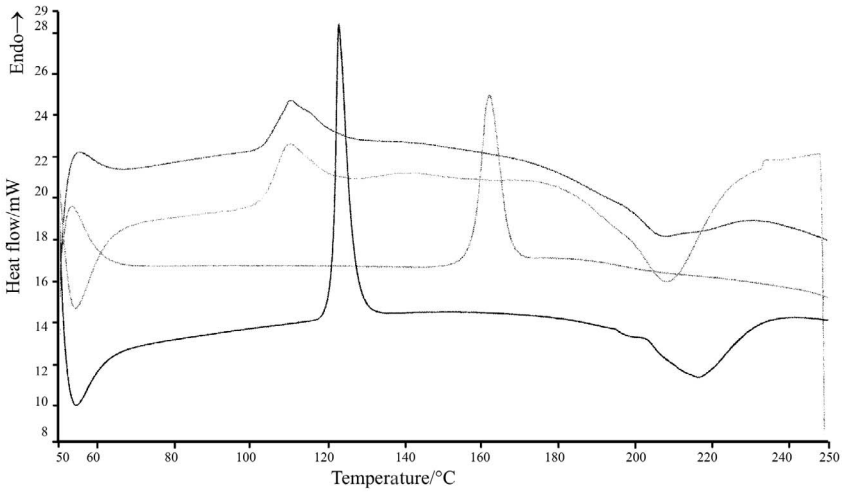

Fig. 6 DSC curves for a – TPH, b – glucose, c – a 1:1 mass ratio (equivalent to a 0.54:1 molar ratio) physical mixture of TPH and glucose and d – a 1:1 mole ratio physical mixture of TPH and glucose (heated at 10°C min^{-1} in nitrogen)

The DSC curves (Fig. 6) for physical mixtures of TPH and glucose show a broad endotherm at 105°C compared to the melting of TPH at 122°C and glucose at 157°C. The DSC curve for the 1:1 mole ratio mixture, i.e. with a higher mass proportion of TPH, shows similar lowering of the onset temperature of melting of TPH. Formation of eutectics or solid solutions is possible.

X-ray diffraction results

TPH, BCD and glucose all have distinctive crystalline X-ray powder diffraction patterns. The X-ray powder diffraction patterns of the physical mixtures of TPH and BCD in

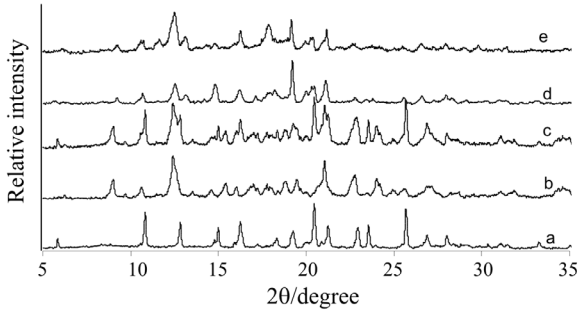

Fig. 7 X-ray powder diffraction patterns of a – TPH, b – BCD, c – addition of the individual XRD patterns of TPH and BCD, d – a 1:1 mass ratio (equivalent to a 3.4:1.0 molar ratio) physical mixture of TPH and BCD and e – a 1:1 molar ratio physical mixture of TPH and BCD

Fig. 7 show differences from the pure components. The most intense peaks of the pure compounds are absent from the patterns of both the mixtures, but the patterns of the mixtures still indicate significant crystallinity. These results support the indication of the thermal studies that interaction, possibly the formation of an inclusion complex, occurs even on physical mixing of TPH and BCD. The pattern (d) for the mixture with the higher TPH content is closer to that of TPH itself (a). Pattern (c), shows the addition, in the appropriate proportions, of the individual patterns of TPH and BCD. Patterns (d) and (e) for the mixtures differ from pattern (c) indicating that physical mixing produces a compound with a different, less-crystalline structure.

The X-ray powder diffraction patterns (Fig. 8) of the two physical mixtures of TPH and glucose differ from each other and some features of the glucose pattern are evident in the patterns of both mixtures. The more intense peaks of the TPH pattern are not evident in the patterns of the mixtures and patterns (d) and (e) do not resemble

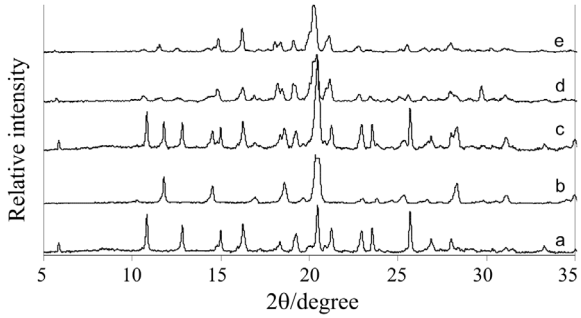

Fig. 8 X-ray powder diffraction patterns of a – TPH, b – glucose, c – the addition of the individual XRD patterns of TPH and glucose, d – a 1:1 mass ratio (equivalent to a 0.54:1.0 molar ratio) physical mixture of TPH and glucose and e – a 1:1 mole ratio physical mixture of TPH and glucose

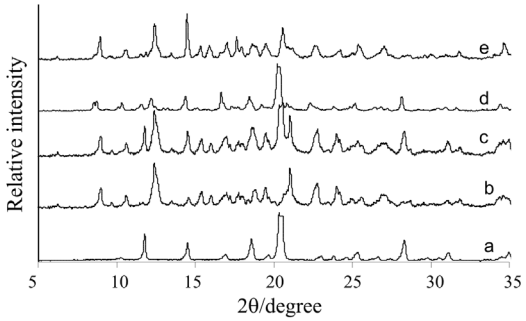

Fig. 9 X-ray powder diffraction patterns of a – glucose, b – BCD, c – the addition of the individual XRD patterns of glucose and of BCD, d – a 1:1 mass ratio (equivalent to a 0.16:1.00 mole ratio) physical mixture of glucose and BCD and e – a 1:1 mole ratio physical mixture of glucose and BCD

the added individual patterns of TPH and glucose (c). These results support the indications from the studies of the thermal behaviour that interaction, possibly eutectic or soild-solution formation, occurs between TPH and glucose.

Figure 9 shows the X-ray powder diffraction patterns of the physical mixtures of glucose and BCD. In the 1:1 mass ratio mixture (equivalent to a 0.16:1.00 mole ratio of glucose and BCD), the most intense peak of glucose is still evident, while in the 1:1 mole ratio physical mixture the glucose peak is not as intense, due to the higher proportion of BCD. These results support the thermal behaviour studies where indications are that glucose is not included in the BCD cavity.

Infrared results

Figure 10 shows the FTIR spectra of the physical mixtures of TPH and BCD compared with the spectra of the pure components. Infrared spectroscopy is often used to assess the interaction between guest and cyclodextrin molecules in the solid-state [17–19]. The characteristic absorption bands of cyclodextrins tend to be minimally affected by inclusion complexation and if the mass of the included drug component is less than about 25% of the complex, any changes in the absorption bands of the drug will be obscured by the host spectrum. These changes are most often shifts, decreas-

Fig. 10 Infrared spectra of samples of a – TPH, b – BCD, c – a 1:1 mass ratio (equivalent to a 3.4:1.0 mole ratio) physical mixture of TPH and BCD and d – a 1:1 mole ratio physical mixture of TPH and BCD

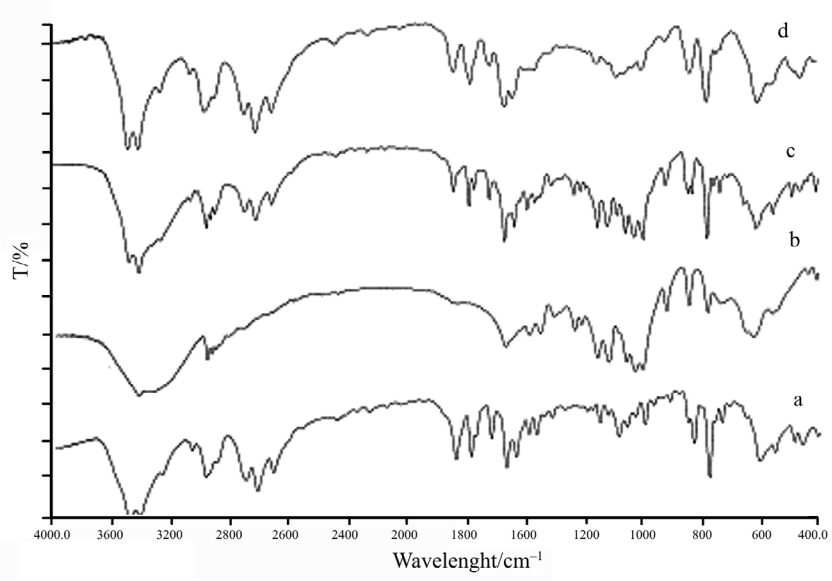

Fig. 11 Infrared spectra of samples of a – TPH, b – glucose, c – a 1:1 mass ratio (equivalent to a 0.54:1.0 mole ratio) physical mixture of TPH and glucose and d – a 1:1 mole ratio physical mixture of TPH and glucose

ing or broadening in intensity of characteristic absorption bands [20–22]. The most noticeable changes seen in the spectra in Fig. 10 are those connected with the water absorptions in the BCD spectrum. The broad band from 3800 to 3000 cm^{-1} and the slightly sharper band around 1680 cm^{-1} in spectrum (b) are not prominent in the spectra of the mixtures (c) and (d). This observation would support the replacement of water in the BCD cavity by TPH. An alternative explanation could be interaction between the HCl fragment of TPH and water from the BCD. There also appears to be a change in the intensity, broadening and shift of the –C=C– pyridine and other aromatic assignments suggesting a possible site for interaction between the TPH and BCD. The results thus support partial inclusion of TPH in the BCD cavity.

Figure 11 shows the IR spectra of the 1:1 mass ratio and 1:1 mole ratio physical mixtures of TPH and glucose, compared with the spectra of the pure components. The spectra of the mixtures seem to contain mainly the prominent features of the components.

Molecular modelling

Molecular modelling was used in a qualitative manner to investigate possible interactions, such as the formation of inclusion complexes [23, 24], between TPH and BCD and between glucose and BCD. Dynamic simulations were run using the Cerius2 software running on a Silicon Graphics O2 workstation. The starting conformer of the cyclodextrin used was obtained from the Cambridge Crystal Structure Database

[12]. The neutral triprolidine (TP) molecule was investigated first. Minimized structures of TP were used in a variety of starting orientations at a starting distance of approximately 0.7 nm from the centre of the cyclodextrin. Upon simulation these provided a variety of conformations for each of the three situations in which the toluene, pyridine, or pyrrolidine groups were included in the cyclodextrin cavity. The constant volume, constant energy equilibrium dynamics simulation was run at a temperature of 300 K for 10 000 steps, corresponding to a total simulation time of 10 ps. For each simulation, several of the lowest energy conformers obtained were examined and further minimized. Only the lowest energy conformers thus obtained were used for comparison. This provided three reasonable conformers corresponding to the three inclusion orientations.

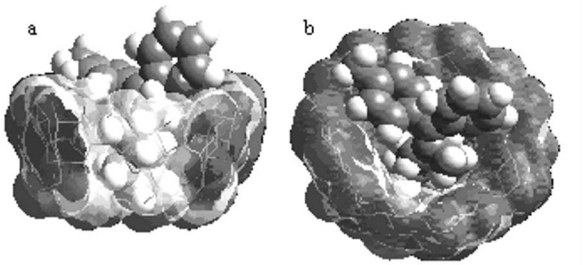

Fig. 12 Molecular modelling of *E*-TP (pyrrolidine)-β-cyclodextrin complexation
a – side view and b – bottom view

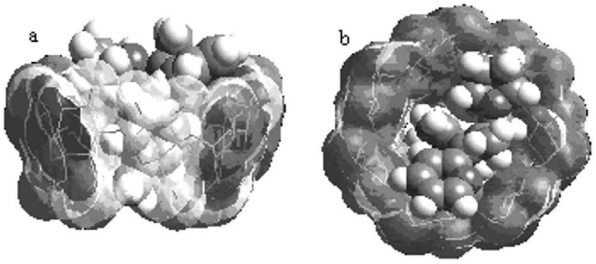

Fig. 13 Molecular modelling of *E*-TP (toluene)-β-cyclodextrin complexation
a – side view and b – bottom view

Figures 12 and 13 show the molecular structure of a possible inclusion complex of the *E*-isomer of TPH with BCD. The initial modelling of the *E*-isomer of TPH was based on the neutral triprolidine (TP) molecule and three different configurations were used for the approach of the TP molecule to the BCD cavity, namely with the pyridine, toluene or pyrrolidine groups. The minimum total energies calculated were: pyridine = 711 kJ mol^{-1}; toluene = 408 kJ mol^{-1}, and pyrrolidine = 416 kJ mol^{-1}. Therefore, on the basis of modelling only, the toluene group is most likely to be readily accommodated in the BCD cavity.

Molecular modelling can only indicate which molecular configurations are most likely on the basis of potential energies, and which configurations are highly unlikely. Other methods, such as spectroscopy and X-ray crystallography, are needed to determine whether such configurations actually occur. The results obtained here suggest that the neutral triprolidine molecule is most likely to be accommodated in the BCD cavity by preferential inclusion of the toluene portion of the molecule.

General discussion

The DSC curves for TPH show sharp melting at 122–123°C and a broad exotherm between 195 and 240°C, with the type of sample pan used affecting the curves obtained. The melting transition is not readily reversible and TG curves for TPH show that the onset of the first stage of the major mass loss occurs soon after the melting endotherm on the corresponding DSC curve. The mass loss may contain contributions from evaporation and decomposition of the liquid. By use of TG–FTIR, evolution of HCl from TPH was detected between 150 and 350°C, which is the temperature range of the overall mass loss in the TG curve.

The endotherm associated with the melting of TPH disappears almost completely in the DSC curves of the physical mixtures of TPH and BCD. Disappearance of the melting endotherm for the drug, in the DSC curves for drug/cyclodextrin mixtures, is generally regarded as an indication that the drug may have been included in the CD cavity [14], although other explanations are possible, such as that the drug has been converted to an amorphous form in the presence of the cyclodextrin [13, 14]. The possibility of inclusion is supported by the X-ray powder diffraction results and molecular modelling. The results of molecular modelling suggest that TPH is most likely to be accommodated in the BCD cavity as a neutral TP molecule, by inclusion of the toluene portion of the molecule.

The DSC curves for the physical mixtures of TPH and glucose show considerable lowering of the onset temperature of melting of TPH in the presence of glucose, possibly through the formation of eutectics or solid solutions.

The DSC curves for mixtures of glucose and BCD show the features of the pure samples, although the glucose melting endotherm shows slight broadening. The lack of significant changes indicates little if any interaction between glucose and BCD in the solid-state.

The X-ray powder diffraction patterns of the physical mixtures of TPH and BCD show differences from the pure components but still indicate significant crystallinity. These results support the possible formation of an inclusion complex on physical mixing of TPH and BCD.

The changes in the intensity, broadening and shift of the –C=C– pyridine and other aromatic assignments in the IR spectra, suggest that a possible site for interaction between the TPH and BCD could be the pyridine, toluene or pyrrolidine groups, and this has been supported by the molecular modelling.

Conclusions

Thermal studies of the solid TPH/BCD mixtures indicated that interaction between the components occurs and it is possible that the TPH molecule may be least partially accommodated in the cavity of the BCD host molecule. XRD results support this indication of inclusion. The results of molecular modelling suggest that TPH is most likely to be accommodated in the BCD cavity as a neutral triprolidine molecule with the toluene portion of the molecule preferentially included in the cavity.

The results obtained illustrate the general stability of TPH. The study has also shown TPH to be compatible with both glucose and BCD, which are potential excipients both in solid and liquid dosage forms. The presence of these excipients in dosage forms will thus not adversely affect the stability and the therapeutic efficacy of TPH.

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