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PHOTOSTABILITY 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.

Solid-state photostability studies of TPH were undertaken by irradiating TPH and its binary mixtures with β-cyclodextrin (BCD) and glucose, using an Atlas Suntest CPS$^+$ irradiation chamber and conditions according to the guidelines of the International Committee on Harmonization (ICH). HPLC analysis was used to determine the extent of photodegradation. XRD results showed that changes in the TPH crystal structure had occurred during irradiation and that these changes increased with the time of irradiation. Although the potential for isomerization under the influence of UV-light to the pharmaceutically inactive *Z*-isomer exists, results have proved that this transformation for solid-state TPH would require more extreme light conditions. The results of this study thus illustrate the general light stability of TPH in the solid-state.

Keywords: β-cyclodextrins, cyclodextrins, excipients, glucose, photostability, tripolidine, tripolidine hydrochloride

Introduction

Triprolidine hydrochloride, $C_{19}H_{22}N_2 \cdot HCl \cdot H_2O$ (TPH), a white, crystalline powder, is reported to be being photosensitive and as such requires storage in sealed, light-tight containers [1]. Triprolidine can exist as both the *Z*- and *E*-isomer (Fig. 1), but only the *E*-isomer [2], (E)-2-[3-(pyrrolidinyl)-1-*p*-tolylpropenyl] pyridine mono-hydrochloride [3] is pharmaceutically active as an antihistamine.

Thermal and XRD studies [5] of solid TPH/BCD mixtures indicated that interaction between the components occurs and it is possible that the TPH molecule may be at least partially accommodated in the cavity of the BCD host molecule. The results of molecular modelling [5] suggest that TPH is most likely to be partially included in the BCD cavity as a neutral triprolidine molecule with the toluene portion of the molecule preferentially accommodated in the cavity.

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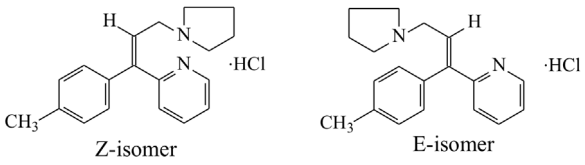

Fig. 1 Molecular structures of the *Z*- and *E*-isomers of triprolidine hydrochloride (TPH), $C_{19}H_{22}N_2 \cdot HCl$ [6]

Triprolidine hydrochloride is available as tablets containing 2.5 mg of the active drug and in an elixir containing 1 mg/4 mL [6]. Although triprolidine is not marketed as a racemic mixture, the United States Pharmacopoeia (USP) specifies a limit of not greater than 2% for the *Z*-isomer [7]. Many factors have been found to affect the stability of triprolidine hydrochloride in the liquid dosage form including temperature, water, pH, UV-light and some excipients [8]. It is thus important that certain conditions such as light and potential excipients are investigated in order to determine their ability to effect conversion of the *E*- to the inactive *Z*-isomer.

In this paper, results of photostability studies of TPH and its binary mixtures with β-cyclodextrin (BCD) and glucose, in the solid-state are reported.

Experimental

Materials

Samples of *E*-isomer of triprolidine hydrochloride (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. The behaviour of the irradiated samples, compared to the original samples, was evaluated using TG, DSC, XRD and IR using the methods described in [5].

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)

Photostability testing

Solid samples of TPH and its binary (1:1 by mass) physical mixtures [5] with BCD or glucose were irradiated using an Atlas Suntest CPS$^+$ irradiation cabinet at 550 Wh m^{-2} at 40°C for 20 h according to ICH guidelines. Samples were placed in

thin layers in petri-dishes and covered with polyethylene film. 'Dark control' samples were treated similarly but covered with aluminium foil.

High performance liquid chromatography (HPLC)

The main analytical technique used to monitor the effects of irradiation was HPLC. The modular HPLC system consisted of a Spectraseries P100 isocratic solvent pump (Spectra Physics, USA), a M7125 20 μL fixed-loop injector (Rheodyne Inc., CA, USA), a Lambda-Max M481 variable wavelength UV detector (Waters Assoc., Milford, MA, USA) and a Rikadenki flat-bed chart recorder (Kogyo Co. Ltd, Tokyo, Japan).

A stock solution containing 100 mg of triprolidine hydrochloride per 100 mL of 50/50% *v*/*v* ethanol and water was prepared to make up a final concentration of 0.01 mg mL^{-1} of TPH. The conditions used were: mobile phase – 15% by volume of aqueous 52 mM ammonium acetate (pH 7.2) and 85% of ethanol (95%) [7]; flow rate – 1.0 mL min^{-1}; column – Novapak® silica steel cartridge column (15 cm · 3.9 mm i.d., 4 μm); column temperature – ambient; detector setting – 254 nm; sensitivity – 2.0 AUFS, resulting in a retention time for TPH of 4.68 min.

The amount of drug present was quantified by the measurement of peak height [7, 9, 10]. This method for the analysis of TPH in the presence of the *Z*-isomer, photodegradation products, glucose and BCD was validated [11, 12] for accuracy and precision, linearity, specificity and limit of quantitation. The accuracy of the analytical method was assessed across a range of 80–120% of TPH, with the 100% recovery achieved at a concentration of 0.001 mg mL^{-1}. Linearity was confirmed over the concentration range of 50–150% of the expected TPH level, with a correlation coefficient of 0.998. Precision assessed under the same operating conditions over a short period of time (repeatability), resulted in an RSD < 0.5. The limit of quantitation was found to be $3.7 \cdot 10^{-4}$ mg mL, proving that TPH can be accurately quantitated to 4% of drug remaining. HPLC with photodiode-array detection was used to confirm the specificity of the method allowing the accurate quantitation of TPH in the presence of its photodegradants, the *Z*-isomer, and the excipients, glucose and BCD

Photodegradation of solid TPH and of physical mixtures of TPH and BCD and TPH and glucose

The results of the HPLC analyses of samples of solid TPH, irradiated for various times in a petri-dish covered with polyethylene film and 'dark control' samples covered with aluminium foil are plotted in Fig. 2.

Only about 10% of TPH is degraded under these light conditions. The dark control results suggest that some thermal degradation has also occurred. HPLC analyses of the irradiated physical mixtures of TPH and BCD are compared with results for TPH alone in Fig. 3.

Results for similar experiments on irradiated physical mixtures of TPH and glucose are compared with results for TPH alone in Fig. 4.

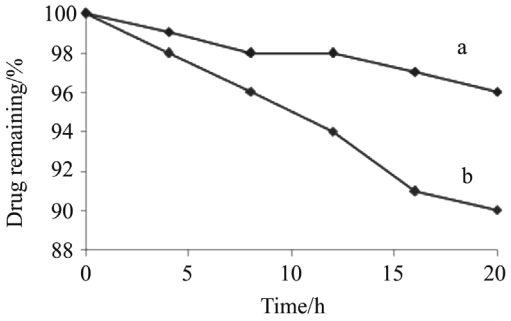

Fig. 2 Photodegradation of a – solid TPH after irradiation under condtitions specified, compared with b – *dark control* samples

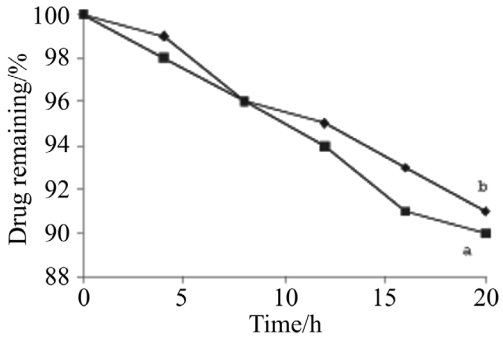

Fig. 3 Photodegradation of b – a 1:1 mass ratio physical mixture of TPH and BCD irradiated under the conditions specified, compared with a – the results for TPH alone. (Note: the points are joined for clarity.)

The results shown in Figs 3 and 4 show that neither the presence of BCD nor of glucose has a significant effect on the limited amount of photodegradation of TPH in the solid state (Fig. 2).

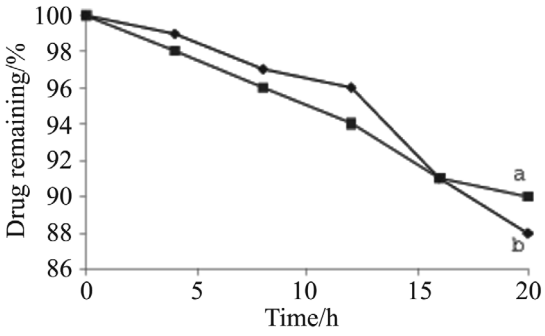

Fig. 4 Photodegradation of b – a 1:1 mass ratio physical mixture of TPH and glucose irradiated under the conditions specified compared with a – the results for TPH alone. (Note: the points are joined for clarity.)

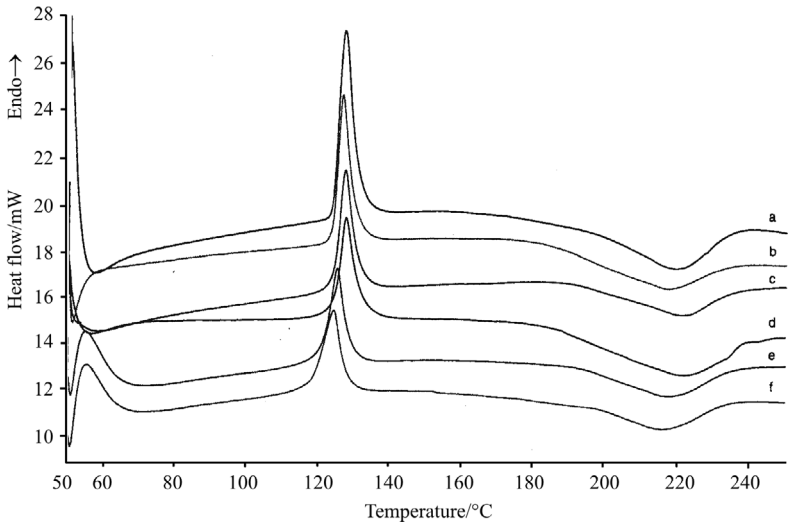

Fig. 5 DSC curves for a – original TPH and for samples of TPH irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h, (heated at 10°C min^{-1} in flowing nitrogen) using sealed pressure pans

DSC and TG results for irradiated TPH

The DSC curves for the original TPH and TPH samples irradiated for 4, 8, 12, 16 and 20 h (heated in flowing nitrogen at 10°C min^{-1} using sealed pressure pans) are shown in Fig. 5. Interpretation of the DSC curve of TPH has been discussed in [5]. The curves for TPH irradiated for 4 and 8 h show sharp endotherms (melting) at 122–123°C and the curves for TPH irradiated for 12, 16 and 20 h show broader endotherms with onsets 121 (d), 119 (e) and 117°C (f) respectively. This indicates that during irradiation some degradation has occurred, resulting in lowering of the melting point due to the possible presence of the degradants. TG curves for irradiated TPH (not illustrated) show only slight mass losses, confirming that the degradants are not significantly volatile.

X-ray powder diffraction patterns of irradiated TPH, BCD and glucose

The X-ray powder diffraction patterns of TPH and of samples of TPH irradiated for 4, 8, 12, 16 and 20 h are compared with those of pure TPH and the dark control sample, covered during irradiation with aluminium foil, in Figs 6 and 7.

The patterns for the irradiated samples (Fig. 6) show that changes of crystal structure from the original have occurred during irradiation and that these changes continue with increasing dose of irradiation. In Fig. 7, the patterns for the dark control samples

show that the temperature rise during irradiation has had an effect on the TPH even after 4 h. It is interesting that the XRD pattern of the dark control sample after irradiation for 20 h differs from that of the original TPH and also from that of the sample exposed to the irradiation for 20 h. These results indicate that thermal and photodegradation occur concurrently under these conditions confirming the HPLC results.

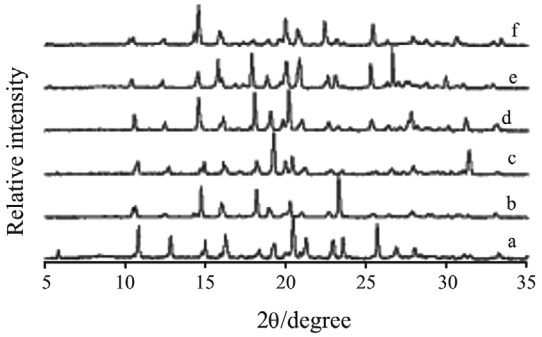

Fig. 6 X-ray powder diffraction patterns of a – TPH and of samples of TPH irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

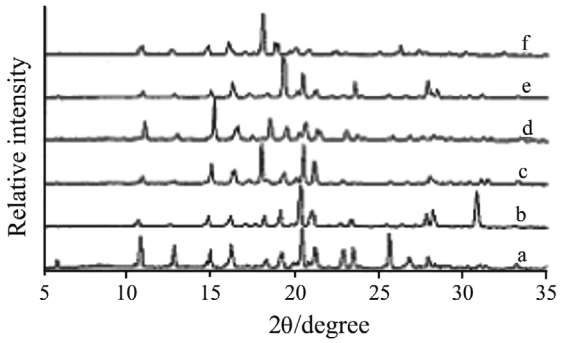

Fig. 7 X-ray powder diffraction patterns of a – TPH and of dark control samples of TPH irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

The X-ray powder diffraction patterns of the original BCD and of samples of BCD that had been irradiated for 4, 8, 12, 16 and 20 h are shown in Fig. 8 and the corresponding dark control samples of BCD in Fig. 9. Some slight changes in crystal structure are produced by irradiation and by the thermal effects during irradiation of BCD.

The patterns (not illustrated) for samples of glucose that had been irradiated for 4, 8, 12, 16 and 20 h and the corresponding dark control samples showed minimal changes from the original glucose.

The infrared spectra of samples of irradiated TPH (not illustrated) showed significant decreases in the absorption bands after irradiation. The spectra of samples of irradiated BCD and of irradiated glucose showed minimal changes.

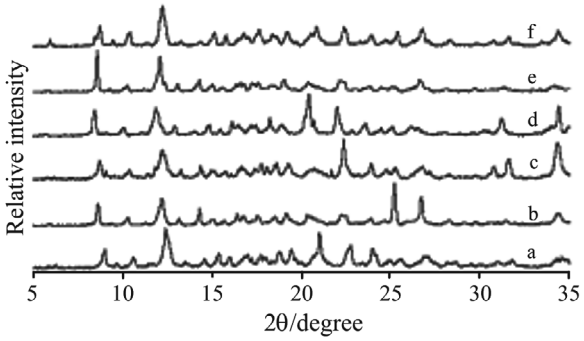

Fig. 8 The X-ray powder diffraction patterns of a – BCD and of samples of BCD irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

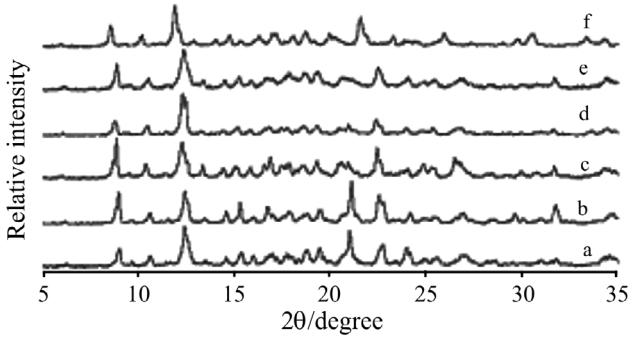

Fig. 9 The X-ray powder diffraction patterns of a – BCD and of dark control samples of BCD irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

DSC and TG results for irradiated mixtures of TPH and BCD

DSC curves for a sample of the original 1:1 molar ratio physical mixture of TPH and BCD and of samples that had been irradiated for various times are compared in Fig. 10. DSC curves for samples of the 1:1 mass ratio physical mixture of TPH and BCD after similar treatment are shown in Fig. 11.

No systematic changes in thermal behaviour were observable directly from the DSC curves of samples after irradiation. The variations seen could be due to the problems of sampling of solid mixtures, particularly after irradiation when surfaces have received the greatest dose.

Similar experiments were carried out on binary physical mixtures of TPH and glucose, and of glucose and BCD. The changes in onset temperatures for the TPH/glucose mixtures were much less than for the TPH/BCD mixtures above and no significant systematic changes in melting behaviour of glucose were observed after irradiation in the presence of BCD.

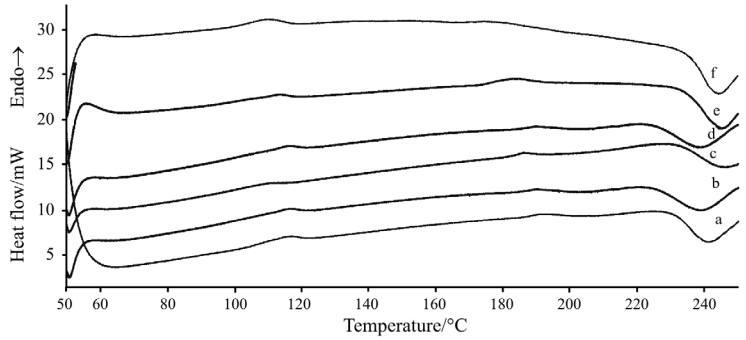

Fig. 10 DSC curves for a – a 1:1 molar ratio physical mixture of TPH/BCD and of samples of the mixture that had been irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h (heating rate 10°C min^{-1} in nitrogen)

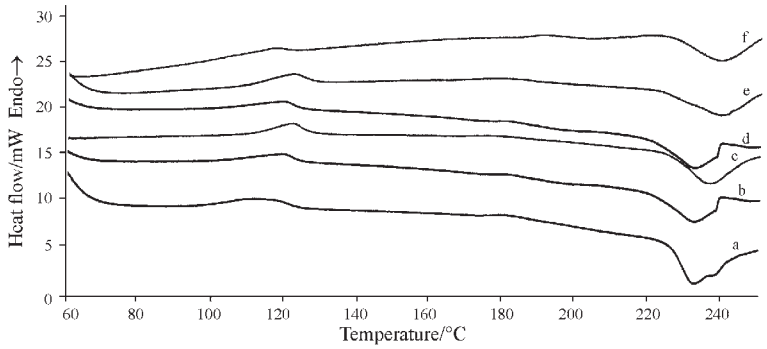

Fig. 11 DSC curves for a – a 1:1 mass ratio physical mixture of TPH/BCD and of samples of the mixture that had been irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h (heating rate 10°C min^{-1} in nitrogen)

X-ray powder diffraction patterns of irradiated mixtures of TPH

X-ray powder diffraction patterns of the original mixtures are reported in [5]. The patterns of irradiated mixtures of TPH and BCD are compared with those of the non irradiated mixtures in Figs 12 and 13.

Physical mixing produces a compound [5] with a different, less-crystalline structure than that of either TPH or BCD, represented by pattern (a) in Fig. 13. This diffraction pattern changes with irradiation dose and the appearance and disappearance of peaks indicates significant but complex changes in the crystal structure caused by irradiation. At the highest doses, in patterns (e) and (f), there is an indication of some deterioration in crystallinity.

The X-ray powder diffraction patterns of irradiated mixtures of TPH and glucose, shown in Figs 14 and 15, also indicate changes in crystal structure, although the intense peak of glucose is still evident in the irradiated mixtures. The changes increase with increasing time of irradiation.

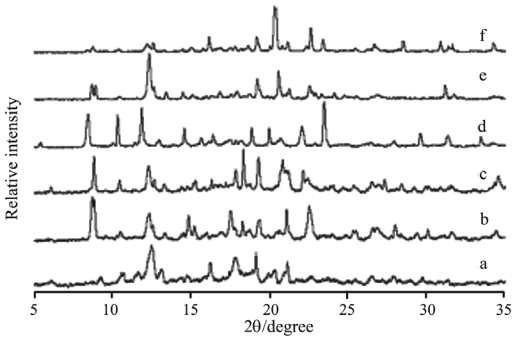

Fig. 12 X-ray powder diffraction patterns of a – a 1:1 mole ratio physical mixture of TPH and BCD and of samples of the mixture irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

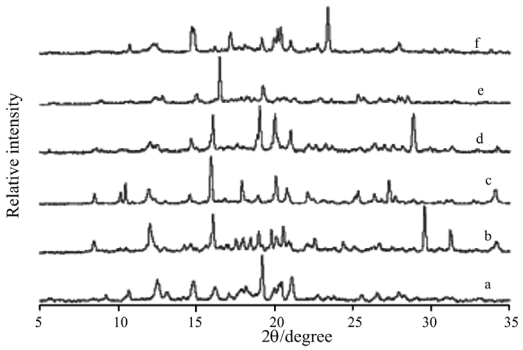

Fig. 13 X-ray powder diffraction patterns of a – a 1:1 mass ratio physical mixture of TPH and BCD (equivalent to a 3.4:1.0 mole ratio) and of samples of the mixture irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

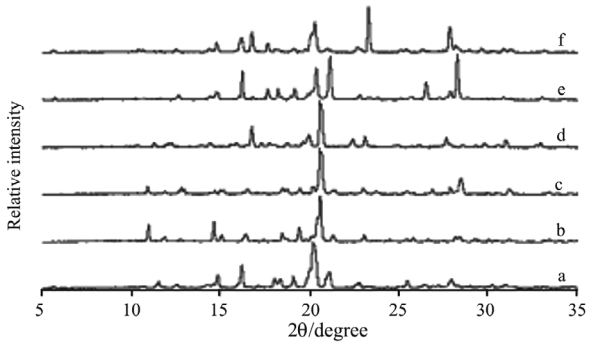

Fig. 14 X-ray powder diffraction patterns of a – a 1:1 mole ratio physical mixture of TPH and glucose and of samples of mixtures irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

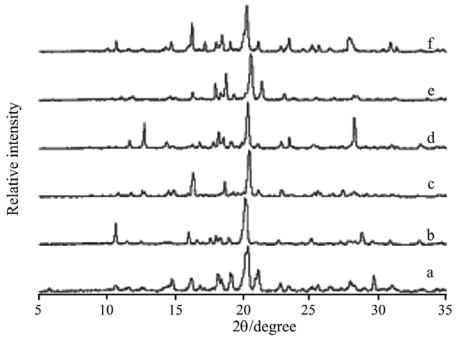

Fig. 15 X-ray powder diffraction patterns of a – a 1:1 mass ratio physical mixture of TPH and glucose (equivalent to a 0.54:1.00 mole ratio) and of samples of the mixture irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

The X-ray powder diffraction patterns of irradiated physical mixtures of glucose and BCD (not illustrated) do not show any marked changes in diffraction pattern with irradiation dose.

IR spectra of irradiated mixtures of TPH and BCD

Infrared spectroscopic studies of the original mixtures are reported in [5]. The infrared spectra of irradiated physical mixtures of TPH and BCD are compared with the spectra of the non irradiated mixtures in Figs 16 and 17.

The results show broadening of bands and decreased intensity, even disappearance of some IR bands, due to irradiation. The absorption bands at 3480, 1630 and 776 cm^{-1} which are attributed to O–H stretching, C=C stretching and 1-substituted pyridine, respectively, decreased significantly after irradiation indicating that some degradation had taken place.

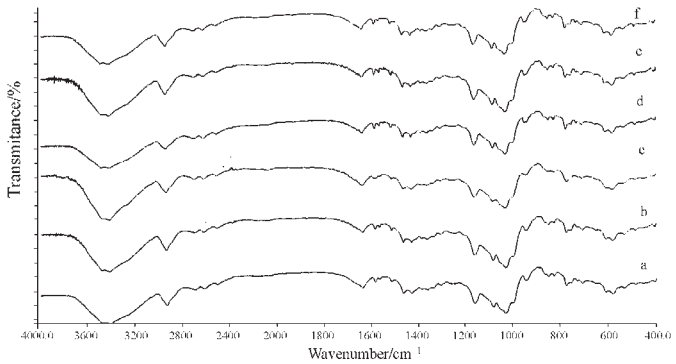

Fig. 16 Infrared spectra of a – a 1:1 mole ratio physical mixture of TPH and BCD and of samples of the mixture irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

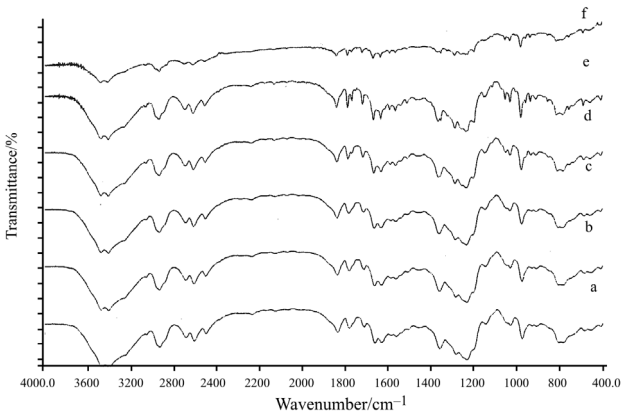

Fig. 17 Infrared spectra of a – a 1:1 mass ratio physical mixture of TPH and BCD (equivalent to a 3.4:1.0 mole ratio) and of samples of the mixture irradiated for b – 4, c – 8, d – 12, e – 16 and f – 20 h

Conclusions

In the solid-state, the amount of degradation under the conditions of irradiation used (Atlas Suntest lamp at 40°C at 550 W h m^{-2}) resulted in about 10% degradation after exposure for 20 h. Some of the degradation may be of thermal origin as indicated by the dark control results.

The HPLC analyses were the most sensitive means of detecting degradation. DSC studies were not sensitive enough to provide reliable information on any degradation of TPH that may have occurred during irradiation under the specified conditions. X-ray powder diffraction patterns were altered by irradiation, but the sequence of patterns with increasing irradiation dose did not show systematic changes in particular diffraction lines. This could indicate a complex solid-state degradation process or the difficulty of obtaining a representative sample after irradiation of the solid. The X-ray powder diffraction patterns of BCD and of glucose showed very much smaller changes during irradiation and these changes may have been caused by the temperature effects as shown by the dark control results.

The infrared spectra of samples of irradiated TPH showed significant decreases of absorption bands after irradiation. Similar treatment of samples of BCD and of glucose produced minimal changes in the FTIR spectra with irradiation dose. The changes detectable by thermal studies of irradiated physical mixtures of TPH and glucose and of glucose and BCD were minimal.

Physical mixing of TPH and BCD produces a compound with a different, less-crystalline structure than that of either TPH or BCD. This diffraction pattern changes with the irradiation dose, with the appearance and disappearance of peaks indicating significant but complex changes in crystal structure caused by irradiation. At the highest doses there is an indication of some deterioration in crystallinity.

The X-ray powder diffraction patterns of irradiated mixtures of TPH and glucose also indicated changes in crystal structure, although the intense peak of glucose is still evident in the irradiated mixtures. The changes increase with increasing time of irradiation. Changes in the X-ray powder diffraction patterns of irradiated physical mixtures of glucose and BCD are not very marked.

The above results illustrate the light stability of TPH, in the solid-state. Although the potential for isomerization to the pharmaceutically inactive *Z*-isomer exists, these findings have shown that this transformation would require more extreme light conditions than that required by the ICH and the Regulatory Authorities. 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 not adversely affect the stability in terms of isomerization to the inactive *Z*-isomer and thus the therapeutic efficacy of TPH.

References

1 British Pharmaceutical Codex, (1963) 867.
2 A. F. Casy, C. R. Ganellin, A. D. Mercer and C. Upton, J. Pharm. Pharmacol., 44 (1992) 791.
3 C. O. Wilson, O. G. Gisvaldo and R. F. Doerge, Textbook of Organic Medicinal and Pharmaceutical Chemistry, Raven-Lippincott, Philadelphia, 7th Edn, 1977, Chapter 18.
4 F. H. Metwally, J. Pharm. Biomed. Anal., 26 (2001) 265.
5 V. J. Ndlebe, M. E. Brown and B. D. Glass, J. Therm. Anal. Cal., 77 (2004) 445.
6 R. l. De Angelis, M. F. Kearney and R. M. Welch, J. Pharm. Sci., 66 (1977) 841.
7 United State Pharmacopoeia, 23 (1995) 1982.
8 Stability of triprolidine hydrochloride in liquid dosage form, S. M. Qassim, http://www.environment.gov.jo/triprolidine_stability.htm
9 E. Katz, (Ed.), Quantitative Analysis Using Chromatographic Techniques, John Wiley and Sons, New York, 1988, pp. 31–98.
10 D. R. Jenke, J. Liq. Chrom. Rel. Technol., 19 (1996) 1873.
11 C. P. Tonseth and J. Dohl, Guidelines for Validation of Analytical Methods, Analytical Sciences R&D, Nycomed Imaging, 1st Edn, 1993, pp. 35–57.
12 A. R. Buick, M. V. Doig, S. C. Jeal, G. S. Land and R. D. Mc Dowall, J. Pharm. Biomed. Anal., 8 (1990) 629.