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Preparation, characterisation and transformation of terfenadine polymorphic forms

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Abstract

Polymorphic modifications of terfenadine as well as solvates from various solvents have been prepared and characterised by X-ray powder diffraction (XRPD), infrared (IR) spectroscopy, differential scanning calorimetry (DSC) and thermogravimetric analysis. Crystallization of terfenadine from *n*-alkanols, except methanol and ethanol, resulted in the stable polymorph 1 (m.p. 151°C) while the iso-alkanols yielded the corresponding solvates. Water content, temperature of incubation and duration were found to have significant effect on transformation.

Keywords: Terfenadine; Polymorphic form; Preparation; Characterisation; Transformation

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Terfenadine is a relatively new H1-receptor antagonist, (Sorkin and Heel, 1985; Guill et al., 1986). The US Pharmacopeia XXII (1990) monograph indicates that the melting range of terfenadine is 145–151°C. Differential scanning colorimetry (DSC) of several commercial samples of terfenadine revealed that their melting peaks lies within the wide range specified in the officiacompendia (US Pharmacopeia XXII, 1990). However, deviation from symmetrical peaks shown by some of the samples suggested the existence of different polymorphic forms within the USP melting range specification. Three distinct polymorphs and two solvates were then identified and characterised (Badwan et al., 1990).

The aim of this study was to evaluate the effect of different proportions of water in alcohol–water mixtures, temperature, duration of incubation and homogenisation on transformation of unstable to the most stable polymorph and effect of position

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of hydroxyl group in a series of alkanols on formation of polymorphs and solvates.

Terfenadine (m.p. 151°C) was obtained from the Jordanian Pharmaceutical Manufacturing Co., Jordan. All solvents used in this study were obtained from May and Baker, Germany and propylene glycol from Dow Chemicals, USA. Polymorph 1 was obtained by dissolving commercial terfenadine in *n*-alkanols with aid of heating. The solution was filtered and cooled in a refrigerator. Polymorph 2 was obtained by cooling a solution of commercial terfenadine in propylene glycol for 3 days in a refrigerator and the glass form by rapid cooling of the melt. The thermograms of different crystalline modifications were obtained using Mettler TA 3000 DSC 20 unit (Mettler, Switzerland). The heating rate was 10°C/min and the sample size ranged between 4 and 10 mg.

To study the effect of water content in alcohol and the position of hydroxyl groups on the formation of polymorph and solvate, a different proportion of water and a series of *n*-alkanols and iso-alkanols were used. In addition, the effect of temperature, duration and homogenisation on transformation of the glass form as well as polymorph 2 was studied using DSC pattern.

DSC and X-ray diffraction (XRD) pattern of terfenadine polymorphs 1 and 2 were reported previously (Badwan et al., 1990). A single endothermic peak at 151.1°C (polymorph 1, stable form) and at 143.5°C (polymorph 2) indicated that no decomposition occurs at their melting points. X-ray diffractogram of the glass form indicated lack of crystallinity. The possibility of any chemical degradation was excluded after analysis by thin layer chromatography (TLC), high performance liquid chromatography (HPLC), IR spectroscopy and also by mass spectroscopy.

The melting point of terfenadine polymorphs and solvates crystallized from different solvents are as follows: terfenadine (starting material) 151.1, methanol (solvate) 149.3, methanol–water (50%) 150. Propylene glycol 143.5, ethanol (solvate) 152.3, ethanol–water (50%) 148.3, propanol 151.6, isopropanol (solvate) 150.0, butanol 152.0, isobutanol (solvate) 149.2, pentanol 153.4, 2-pentanol (solvate) 150.8 crystallization from pure methanol or ethanol yielded solvates. However, in the presence of water in these alcohols, polymorph 1 is readily formed. As the water content is increased in these mixtures (i.e. from 20 to 60% water) the desolvation peak in the DSC profile (87°C) starts to disappear. The material obtained from a mixture of 40% methanol and 60% water showed only one endothermic peak at 151°C corresponding to that of the stable polymorph. Thus, it appears that the proportion of water in these alcohol water mixtures is a crucial factor determining formation of solvate or the stable polymorph.

Methanol and ethanol yielded the corresponding solvates while *n*-propanol, *n*-butanol, *n*-pentanol, and *n*-octanol have led to the formation of the stable polymorph 1. However, the use of isopropanol and isobutanol always resulted in the formation of the metastable solvate as evidenced by the desolvation peak at 70, 85°C and an endothermic peak at 149.5°C (iso-propanol) and at 71, 100 and 149°C (iso-butanol). Allyl alcohol and tetrahydrofuran also yielded solvate peak in their DSC profile. Thus, it appears that in a series of alkanols, the iso-alkanols tends to favour formation of the solvate while the *n*-alcohols favour formation of stable polymorph 1. The solvate formed from isopropanol was shown to contain a stoichiometric amount of crystallisation solvent (1:1) by spectrophotometric estimation of terfenadine and by comparison with the theoretical amount for a (1:1) solvate.

Transformation of glass form of terfenadine was studied by incubating a water dispersion at 25°C. Fig. 1a shows the DSC profile of samples of glassy material at various time periods from 6 h to 15 days. The thermogram obtained at 6 h shows shoulder on the main peak at 147°C (metastable) which, by 24 h have clearly split into a second peak at 151°C. As the duration of incubation is increased, a steady increase in peak height at 151°C and the gradual disappearance of peak at 147°C is apparent. Homogenisation of the dispersion on the 14th day completed the transformation as shown by a single peak at 151°C.

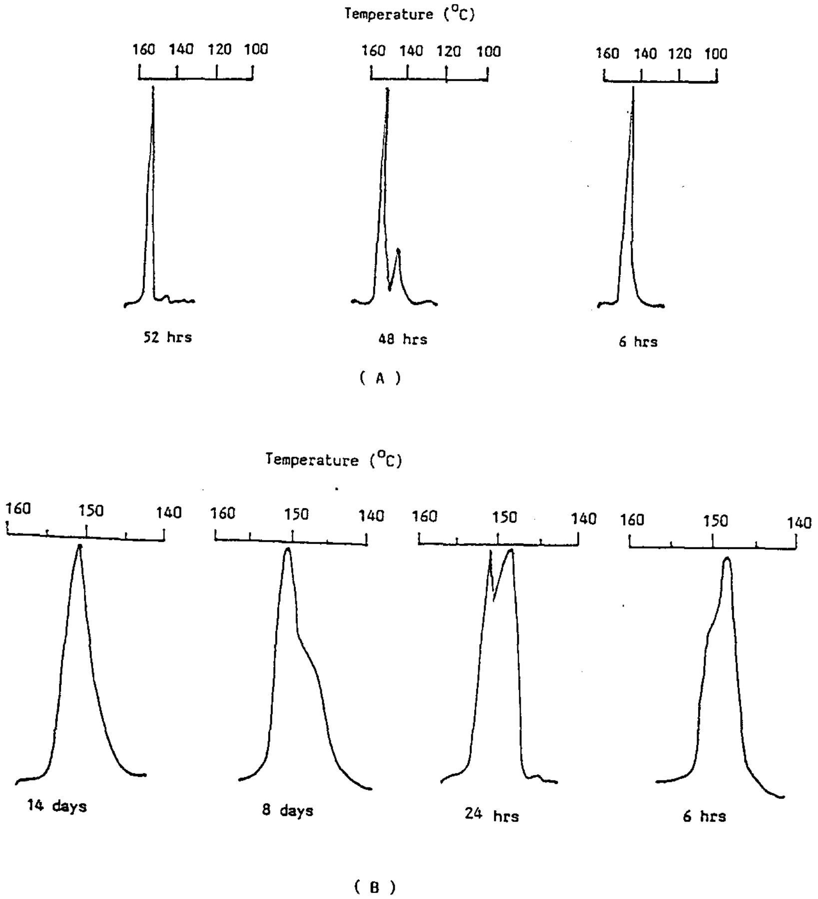

Fig. 1. DSC profile of transformation of (A) glass form of terfenadine with time at 25°C. (B) Polymorph 2 of terfenadine with time at 60°C.

The transformation of polymorph 2 by incubating a dispersion in water at 60°C for a period of 52 h is shown in Fig. 1b. A second peak in the thermogram corresponding to 151°C begins to appear alongside the main peak at 143°C and by 48 h, the proportion of the stable polymorph is increased significantly in the mixture. By 52 h, peak at 151°C with a small hump at 143°C indicated that the polymorph 2 is almost completely transformed into stable polymorph 1. Using an elevated temperature of 60°C has obviously accelerated the transformation to the stable form.

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