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DETERMINATION OF THE STABILITY OF OMEPRAZOLE BY MEANS OF DIFFERENTIAL SCANNING CALORIMETRY

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Abstract

Differential scanning calorimetry was used to study the stability of omeprazole in two forms: granules and powder. The drug was subjected to light, elevated temperature (40 and 60°C) and different pH values. The greatest alterations in stability were caused by pH, followed by light.

Keywords: differential scanning calorimetry, omeprazole, pH, stability

Introduction

Omeprazole is a substituted benzimidole (5-methoxy-2-[4-methoxy-3,5-dymethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole) used to treat gastric ulcers. This new antisecretory compound acts differently from anticholinergic or H_2 histamine antagonists: it is a gastric acid pump inhibitor that suppresses gastric acid secretion by specifically inhibiting the H^+/K^+ ATPase system at the secretory surface of the gastric parietal cell [1–3]. Omeprazole degrades very rapidly in aqueous solutions at low pH values [4]. Althoughs its therapeutic effects have been well characterized, few publications have centered on its technology and stability. The present study was therefore designed to characterize the stability of this drug under different experimental conditions.

Tests were performed with powdered and granulated (protected powder) forms of omeprazole. Stability was tested by subjecting samples to light and elevated temperature (40 and 60°C). Since pH appears to be a factor that markedly influences stability, the behavior of the drug at different pH values was also tested. Differential scanning calorimetry (DSC) was used to determine purity [5], kinetic properties [6], the behavior of solid dispersions [7] and stability [8].

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Materials and methods

Omeprazole in powdered and granulated forms was supplied by Schering-Plough SA (Madrid, Spain). Differential scanning calorimetry was performed with a Mettler FP89 apparatus for the range of temperatures from 30 to 300°C, at a heating rate of 5°C min^{-1}. Samples weighed 5–6 mg.

The effects of temperature were studied by placing the sample in an oven at 40 or 60°C. pH was tested in HCl and NaOH solutions to which the drug was added in different amounts to obtain a range of pH values from 2 to 11; these samples were then dried at room temperature for DSC. The effects of light were tested by exposing samples of powdered or granulated drug to sunlight for different periods of time.

Results and discussion

Figure 1 shows the DSC curves for powdered (A) and granulated omeprazole (B). The powdered form underment a clear endothermal transition at 156°C, followed by an exothermal transition at 164°C. This behavior may reflect recrystallization of the drug and the appearance of acetonitrile crystals [9]. In contrast, crystallization did not occur in the granulated form, and the stability was higher. The area under the exothermal peak represents the stability of the system. Physical stability was reflected by the absence of an exothermal peak under all conditions of time, pH, light and temperature. The coating used in the granulated form preserved its amorphous structure, and prevented crystallization. In a study of

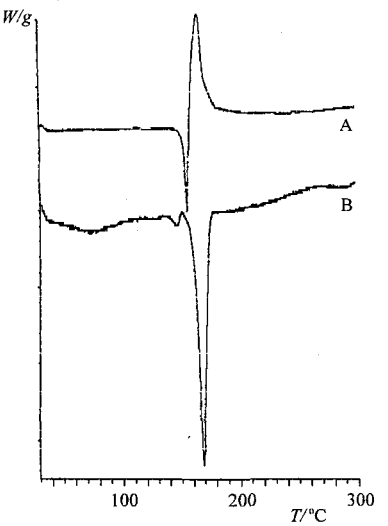

Fig. 1 DSC curves of omeprazole powdered (A) and omeprazole granulated (B)

microencapsulated sulfamethoxazole, Takenaka *et al.* [10] found a similar type of behavior; they suggested that hydrogen-bonds between the drug and polymer, and steric impedance induced by the polymer, restricted the intermolecular bonding of the drug, thereby impeding recrystallization.

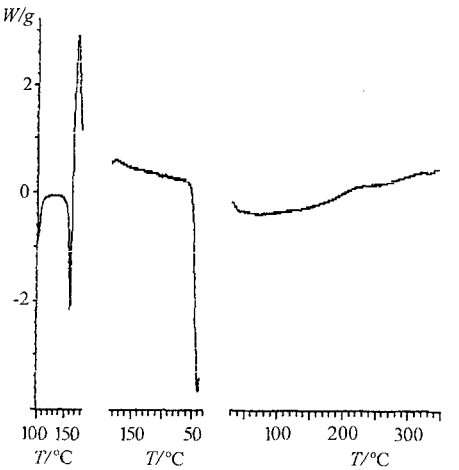

Fig. 2 Calorimetric behavior of omeprazole powdered

The effect of temperature on crystallization (Fig. 1A, powdered omeprazole) was tested by cooling the sample at the end of the exothermal transition, i.e. from 170 to 30°C. Figure 2 shows the resulting curve. No relationship was found between the results and the behavior of the drug during heating, and it is therefore suspected that omeprazole was destroyed at temperatures above 170°C.

Effects of temperature

DSC curves were recorded for powdered and granulated samples subjected to temperatures of 40 and 60°C for different periods. The results at the higher temperature are shown in Figs 3 (powder) and 4 (granules); the DSC curves obtained at 40°C were very similar and are not shown. The peaks found in the initial analyses appeared with only slight modifications, which were more noticeable at 60°C. After one month of exposure to an increased temperature, the area under the curve showed variations in enthalpy of −189 to −148 J g^{-1} for the endothermal transition and +283 to +324 J g^{-1} for the exothermal transition in powdered omeprazole, and −162 to −100 J g^{-1} for the endothermal transition in granulated omeprazole. These results suggest once again that the granulated form is the more stable of the two [11].

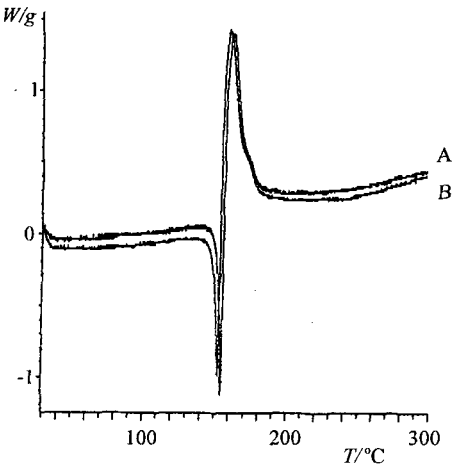

Fig. 3 DSC curves of omeprazole powdered at 60°C for 24 h (A) and 30 days (B)

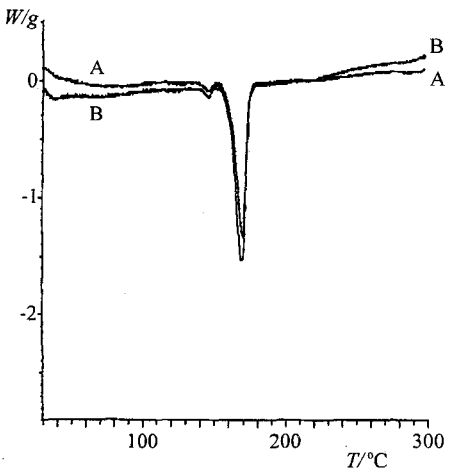

Fig. 4 DSC curves of omeprazole granulated at 60°C for 24 h (A) and 40 days (B)

Effects of light

Figures 5 and 6 show the effects of exposure to sunlight for 30 days on powdered and granulated omeprazole. The DSC curves obtained after exposure to light reveal that the stability was higher for the granulated than for the powdered drug. None the less, light caused a more marked degradation than did elevated temperature. This is not surprising in view of the chemical structure of the drug: susceptibility to the effects of light may reflect the presence of sulfur, or the resonance structure of the omeprazole molecule.

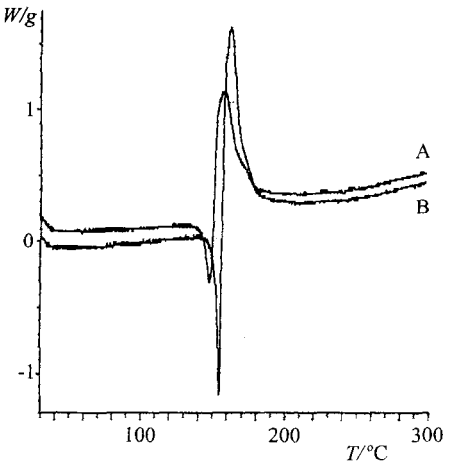

Fig. 5 DSC curves of omeprazole powdered obtained for exposure to sunlight for 24 h (A) and 30 days (B)

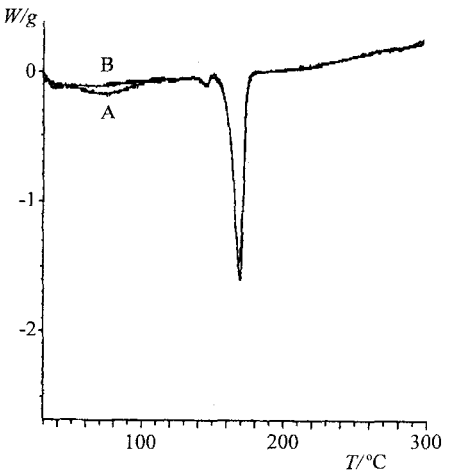

Fig. 6 DSC curves of omeprazole granulated obtained for exposure to sunlight for 24 h (A) and 30 days (B)

Effects of pH

The effects of pH were tested because omeprazole is hightly sensitive to acids. Initial tests were run on samples ranging in pH from 2 to 11; in physiological terms, values higher than 11 would have yielded no useful information. Figures 7 and 8 show the DSC curves obtained after treatment at different pH values. Slight variations were found in the endothermal transition both for the peak endother-

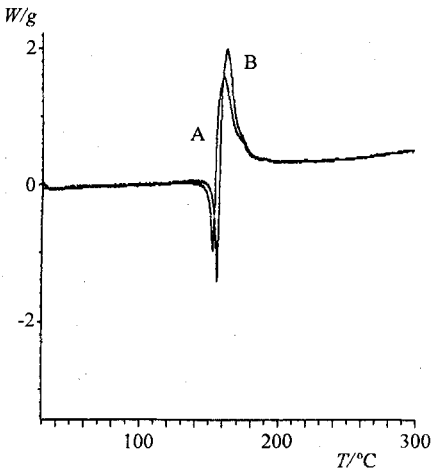

Fig. 7 DSC curves of omeprazole powdered obtained at pH 2(A) and pH 11(B)

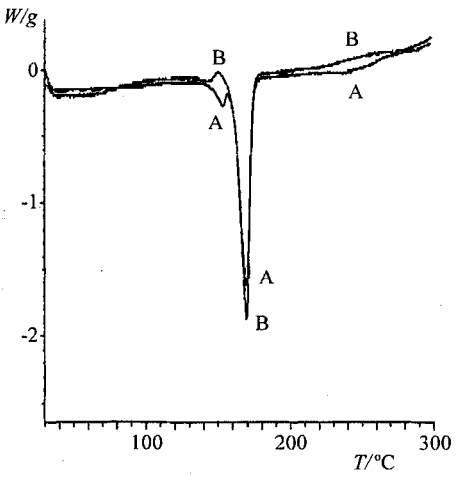

Fig. 8 DSC curves of omeprazole granulated obtained at pH 2(A) and pH 11(B)

mal and for the area under the curve. Acid pH media are known to degrade omeprazole rapidly. Mathew *et al.* [4] found that the degradation of omeprazole was more extensive in acid media, and became less severe as the pH increased.

In conclusion, DSC provided reliable data on the stability of omeprazole under different conditions of temperature, light and pH. The stability of the powdered form was affected most by pH. Both forms were relatively stable when dry, but were unstable in solution.

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