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Improvement of the in vitro dissolution characteristics of famotidine by inclusion in β-cyclodextrin

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Summary

An inclusion complex between famotidine and β-cyclodextrin was prepared by mixing the two components in a millimolar ratio in distilled water and heating under reflux for 1 h followed by stirring at room temperature for 5 days. Phase-solubility studies revealed the formation of a 1 : 1 complex of the AL type with a rate constant of 74.96 M^{-1}. The formation of the complex in the solid state was confirmed by infrared spectroscopy and differential scanning calorimetry. The inclusion complex was shown by X-ray powder diffraction to be significantly less crystalline than any of the pure components. More significantly, the dissolution rate of the complex from constant surface-area discs was determined to be about twice and six times higher than that of the physical mixture and the pure drug, respectively.

Introduction

Cyclodextrins have been extensively used to increase the solubility (Hamada et al., 1975; Glomot et al., 1988), dissolution rate (Corrigan and Stanley, 1982; Uekema et al., 1983) and bioavailability of poorly water soluble drugs (Nambu et al., 1978; Seo et al., 1983). The ability of cyclodextrins to modify these characteristics has been attributed to the formation of inclusion complexes between cyclodextrins and 'guest' drug molecules. Generally, this involves the entrapment of a single 'guest' molecule in the cavity of one host molecule without the formation of any chemical bond (Saenger, 1980).

Famotidine is a potent H_2-receptor antagonist which is effective in the treatment of gastric and duodenal ulcers and the Zollinger–Ellisone syndrome (Heinrich, 1986). It has a relatively low and variable bioavailability (Campeli-Richards and Clissold, 1986; Kromer and Klotz, 1987). This has been partly attributed to its low water solubility (Vincek, 1988) and its susceptibility to acid-catalyzed hydrolysis in the acidic environment of the stomach (Suleiman et al., 1989).

The purpose of this study is to improve the solubility and dissolution rate of famotidine in aqueous solutions and thereby improve its bioavailability. This was achieved through the formation of an inclusion complex with β-cyclodextrin. The formation of such complex was confirmed by

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a variety of techniques such as solubility determination, infrared spectrophotometry (IR), differential scanning calorimetry (DSC) and X-ray diffraction studies. The work also included the determination of the dissolution profile of the drug itself, the drug–cyclodextrin physical mix and the drug–cyclodextrin complex.

Materials and Methods

Materials

Famotidine, pharmaceutical grade, was kindly provided by Dar Al Dawa Development and Investment Company, Na'ur, Jordan. α- and β-Cyclodextrin were purchased from Sigma Chemical Co., St. Louis, U.S.A. and used without further treatment. Double distilled water from an all-glass still was used throughout this study.

Methods

Preparation of the inclusion complex. Famotidine (0.337 g, 1 mmol) and β-cyclodextrin (1.135 g, 1 mmol) were added to 25 ml of distilled water. The mixture was heated under reflux for 1 h and was then stirred at room temperature for 5 days. The solution was concentrated to 10 ml under vacuum using a rotary evaporator and then cooled in a refrigerator for 1 h. The precipitated product was filtered off and dried under vacuum at 50 °C. The product obtained was kept in a desiccator over silica gel until used.

Determination of the famotidine content of the inclusion complex. 10 mg of the product were dissolved in 100 ml of methanol. The amount of famotidine included by cyclodextrin was determined spectrophotometrically using a 240 Shimadzu spectrophotometer (Shimadzu, Kyoto, Japan) at a wavelength of 285 nm (β-cyclodextrin was not found to absorb at this wavelength). The amount of drug was found to be 2.317 ± 0.188 mg.

Preparation of famotidine–β-cyclodextrin physical mixture. The physical mixture was prepared by weighing 0.337 g of famotidine and 1.135 g of β-cyclodextrin and thoroughly mixing the two substances using the geometric dilution technique. The composition of the physical mixture was confirmed by spectrophotometry as outlined above.

Phase-solubility studies. Excess amounts of famotidine (100 mg) were weighed in to 25-ml glass-stoppered Erlenmeyer flasks, containing 10 ml of distilled water. Various amounts of β-cyclodextrin ($0–17.62 \times 10^{-3}$ M) were added and the flasks were agitated at 100 strokes/min in a thermostated shaking water-bath (Karl Kolb, Dreieich, F.R.G.) adjusted to 37 ± 0.5 °C. After 2 days, an aliquot was withdrawn and filtered through a 0.45 µm Millipore filter. The concentration of famotidine in each aliquot was determined spectrophotometrically at 285 nm with reference to a suitably constructed standard curve.

Dissolution rate studies. The dissolution rate studies from constant surface-area discs were carried out in a USP XX1 type 2 dissolution apparatus (DT-D6, Erweka, F.R.G.). Samples of the drug, drug–β-cyclodextrin physical mixture (1 : 1) and the inclusion complex were compressed under a pressure of 4000 kg/cm^2. The dissolution medium consisted of 500 ml of phosphate buffer (pH 7.4), stirred at 100 rpm and maintained at 37 ± 0.5 °C. At appropriate intervals 5-ml aliqouts were withdrawn and assayed spectrophotometrically for famotidine, as outlined above. A correction was applied for the cumulative dilution caused by replacement of the sample by equal volumes of fresh medium. Each experiment was carried out in triplicate and the standard deviation was below $\pm 5\%$.

Infrared spectroscopy (IR). The IR spectra of famotidine, β-cyclodextrin and the inclusion complex were recorded on an IR-435 Shimadzu spectrophotometer (Shimadzu, Kyoto, Japan). The products were dry-compressed in a KBr pellet using a Shimadzu hand press.

Differential scanning calorimetry (DSC). The DSC curves were recorded on a TA 3000 Mettler thermal analyzer, equipped with a DSC cell, under static conditions. Samples (2–4 mg) were placed in open aluminum crucibles and heated linearly at 10 °C/min from ambient temperature to 200 °C with an empty crucible as the reference.

X-ray diffractometry. The X-ray powder diffraction patterns were recorded on a Philips X-ray diffractometer. Operating conditions were as follows: X-ray, Ni-filtered Co-K_α radiation ($\lambda =$

1.79025 Å); voltage, 40 kV; current, 40 mA; slit width 0.5°; scale, 2000.

Results and Discussion

The phase solubility diagram obtained for famotidine with β-cyclodextrin is shown in Fig. 1, which shows that a linear relationship exists between the amount of drug solubilized and the concentration of β-cyclodextrin in solution. This indicates the formation of a soluble complex of the AL type which has a first-order dependence on the concentration of β-cyclodextrin (Higuchi and Connors, 1965). Based on Fig. 1 the stoichiometry of the inclusion complex is 1 : 1. The observed rate constant for the formation of the complex (K_c) was calculated according to the equation of Higuchi and Connors (1965) and was found to be 74.96 M^{-1}.

In contrast, no appreciable increase in solubility of famotidine was obtained with α-cyclodextrin. This might be due to the smaller cavity size of α-cyclodextrin (internal diameter 4.7–5.2 Å) which is composed of six molecules of α-cyclohexaamylose, as compared to the larger cavity size of β-cyclodextrin (internal diameter 6.0–6.4 Å) which is composed of seven molecules of β-cycloheptaamylose (Duchene et al., 1986). This would hinder the entry of the drug into the cavity of α-cyclodextrin.

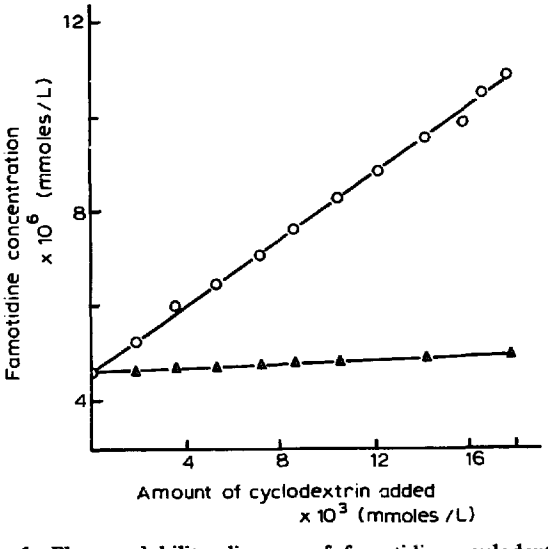

Fig. 1. Phase solubility diagram of famotidine–cyclodextrin systems in distilled water at 37°C. (○) β-cyclodextrin; (▲) α-cyclodextrin.

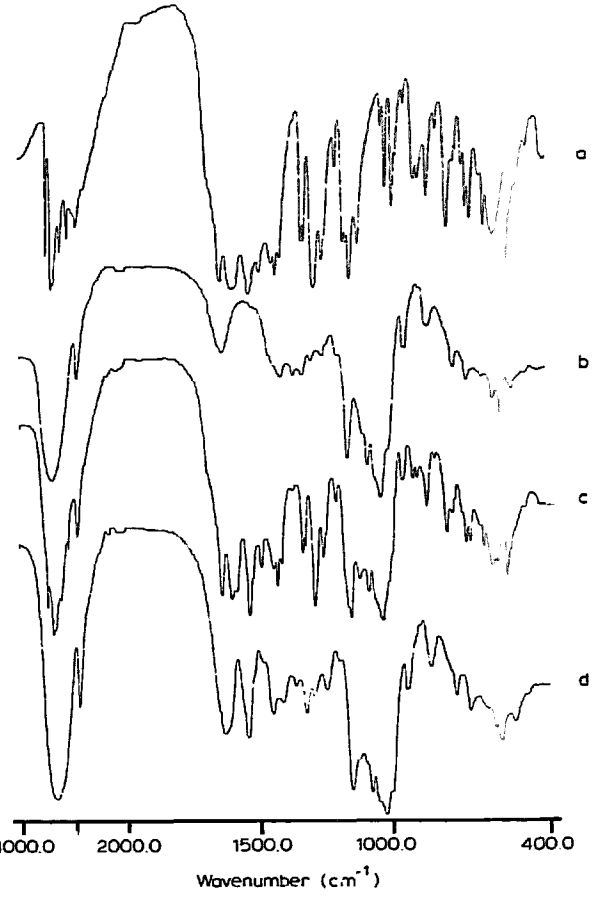

Fig. 2. IR spectra of: (a) famotidine; (b) β-cyclodextrin; (c) physical mixture; (d) inclusion complex.

The IR spectra of famotidine, β-cyclodextrin, the physical mixture and the inclusion complex are shown in Fig. 2. The IR spectrum of the physical mixture does not show any significant differences from the respective spectra of the pure components. However, the IR spectrum of the inclusion complex exhibits some significant differences. The absorption peaks characteristic of the amino groups of famotidine in the range 3220–3500 cm^{-1} have disappeared from the spectrum of the inclusion complex. Further, a shift in the position of the C = N stretching bands in the region of 1528–1636 cm^{-1} is observed in the IR spectrum of the complex. These spectral changes may have resulted from the inclusion of famoti-

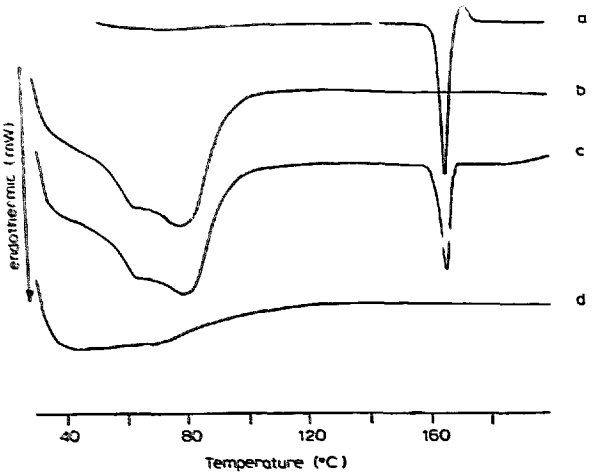

Fig. 3. DSC curves of: (a) famotidine; (b) β-cyclodextrin; (c) physical mixture; (d) inclusion complex.

dine within the cavity of β-cyclodextrin and the dissociation of the intramolecular hydrogen bonds of famotidine between the guanidino nitrogen and thiazole nitrogen through this complexation.

Supporting evidence for the complex formation was obtained from thermal analysis studies. The DSC thermal curves of the pure components, the physical mixture and the inclusion complex are presented in Fig. 3. The DSC trace of famotidine shows one endothermic peak at 164.5°C, corresponding to its melting point. Meanwhile, the DSC trace of β-cyclodextrin shows two shallow and broad endothermic peaks at 61.5°C and 79.5°C, which are attributed to the loss of the water content of β-cyclodextrin. This was confirmed by thermogravimetric studies (results not presented). On the other hand, the DSC curve of the physical mixture shows three endothermic peaks characteristic of the pure components. However, the DSC curve of the inclusion complex lacks the endothermic peak characteristic of pure famotidine. Further, the two endothermic peaks attibuted to β-cyclodextrin were highly distorted. The disappearance of the endothermic peak of famotidine and the distortion of the endothermic peaks of β-cyclodextrin provide a further indication of the formation of an inclusion complex between famotidine and β-cyclodextrin.

Further evidence of complex formation was obtained from X-ray powder diffraction studies. The X-ray powder diffractograms of the pure components, the physical mixture and the inclusion complex are shown in Fig. 4. The diffraction pattern of the physical mixture is simply the superposition of each component with the peaks having lower intensity. This may be attributed to reduction in particle size during the preparation of the physical mixture. On the other hand, the diffraction pattern of the complex shows only a very few peaks with very low intensity. This indicates that the inclusion complex is markedly less crystalline than the physical mixture or the pure components.

The dissolution rate profiles of drug, the physical mixture and the inclusion complex from constant surface-area discs are shown in Fig. 5. It is evident that both the complex and physical mixture demonstrate a faster dissolution rate than the free drug. At 30 min, the amount of famotidine

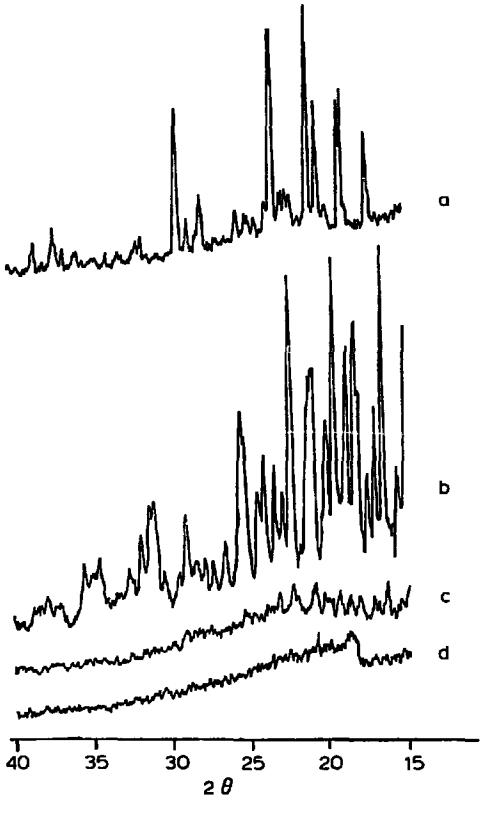

Fig. 4. X-ray diffraction patterns of: (a) famotidine; (b) β-cyclodextrin; (c) physical mixture; (d) inclusion complex.

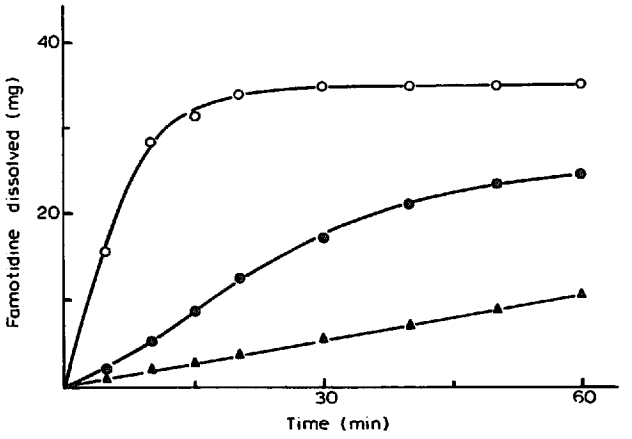

Fig. 5. Dissolution profiles of: (▲) famotidine; (●) physical mixture; (○) inclusion complex in phosphate buffer (pH 7.4).

dissolved was 87.6% from the inclusion complex compared to 43.5% and 14.2% from the physical mixture and the pure drug, respectively. The significant enhancement in the dissolution rate of the complex may be due to an increase in solubility and marked reduction in crystallinity. The leveling-off effect observed in the dissolution rate profile of the complex beyond 30 min is attributed to the disintegration of the disc and almost complete dissolution of the disintegrated particles.

The increase in the dissolution of famotidine when physically mixed with β-cyclodextrin is possibly due to a local solubilization action operating in the microenvironment or the hydrodynamic layer surrounding the drug particles in the early stages of the dissolution process as cyclodextrin dissolves in a short time thus improving the wettability, and hence dissolution, of the drug particles (Goldberg et al., 1966).

In conclusion, famotidine was found, by a variety of techniques, to form an inclusion complex with β-cyclodextrin. The complex was markedly less crystalline, and therefore more soluble, than the pure drug. Further, the dissolution rate of the complex was about six times higher than that of the pure drug. The impact of this appreciable improvement on the in vivo availability of famotidine from oral solid dosage forms is currently under investigation.

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