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International Journal of Pharmaceutics 142 (1996) 183–187

Preparation and evaluation of ketoconazole-β-cyclodextrin multicomponent complexes

M.T. Esclusa-Díaz, M. Gayo-Otero, M.B. Pérez-Marcos, J.L. Vila-Jato, J.J. Torres-Labandeira*

Laboratory of Pharmaceutical Technology, School of Pharmacy, University of Santiago de Compostela, Campus Universitario Sur, 15706 Santiago de Compostela, Spain

Received 27 June 1996; accepted 19 July 1996

Abstract

Increase in poor buffer pH 5 and 6 solubility of ketoconazole was studied. Two systems were used: binary complexes prepared with β-cyclodextrin and multicomponent systems (β-cyclodextrin and an acid compound), obtained by spray-drying. X-ray diffractometry and differential scanning calorimetry showed differences between ketoconazole/cyclodextrin complexes and their corresponding physical mixtures and individual components. The solubility of ketoconazole increased significantly with the cyclodextrin complexes. However, enhancement was better from the multicomponent systems.

Keywords: Ketoconazole; β-cyclodextrin complexes; Dissolution properties; Multicomponent systems; Solubility

1. Introduction

Ketoconazole (KET) is a imidazole antifungal agent suitable for the treatment of candidiasis and other systemic fungal infections. The major drawback in the therapeutic application and efficacy of KET as oral dosage forms is its very low aqueous solubility because of its hydrophobic structure. KET is a weak base and it can be solubilized only under extremely acidic conditions (Van der Meer et al., 1980).

Cyclodextrins have been used to improved the poor aqueous solubility of these drugs as well as the poor rate of dissolution from their formulations (Pedersen, 1994). Nevertheless, the usefulness of natural cyclodextrins has been limited by relatively low aqueous solubility particularly, β-cyclodextrin (BCD). Salt formation with different acids and cyclodextrins in the multicomponent complex has been studied to improve the solubil-

* Corresponding author. Tel.: +34 81 563100, ext. 15009; fax: +34 81 594595; e-mail: FFjuant@usc.es

PII S0378-5173(96)04666-2

ity of these base-type drugs and the solubility of classic binary complexes. Several papers have been published concerning the improvement of the solubility and bioavailability of imidazole derivatives through the formation of binary and multicomponent complexes with cyclodextrins (Szente et al., 1995; De Beule, 1996; Fenyvesi et al., 1996).

The aim of this study was to investigate the influence of the complexation of KET with BCD (either binary or multicomponent complexes) on its solubility in aqueous solutions pH 5 and 6. Phase solubility technique was used to analyze the complexation of KET with BCD in both dissolution media. Spray-dried method was employed to obtain solid complexes of KET and BCD in different molar ratio. X-ray diffractometry, differential scanning calorimetry (DSC) and dissolution studies were then used to investigate the interaction between KET, BCD and an acid compound (citric or hydrochloric acid, in the multicomponent systems) in buffer solutions and in solid state.

2. Materials and methods

2.1. Materials

Ketoconazole (*cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1H-imidazol-1-ylmethyl)-1,3 dioxolan-4-yl]methoxy]phenyl]piperazine) was supplied by Guinama (Valencia, Spain) and β-cyclodextrin by Cyclolab (Budapest, Hungary). All other materials and solvents were of analytical reagent grade.

2.2. Phase solubility studies

Solubility diagrams were obtained according to Higuchi and Connors (1965) in phosphate buffer solutions of pH 5 and 6. Excess KET was added to vials containing various concentrations of BCD. The vials were shaken in a water bath at 37°C until equilibrium was reached (7 days). The content of each vial was filtered (0.22 μm pore size) and the concentration of KET in the filtered solutions was measured by UV spectrophotometry at 225 nm.

The apparent stability constant of the KET-BCD complex, assuming 1:1 stoichiometry, were calculated from the slope of the initial straight portion of the phase solubility diagrams as

$$K_{1:1} = \text{slope}/S_0(1 - \text{slope})$$

where S_0 is the solubility of the pure drug (Higuchi and Connors, 1965). All the data are the average of three determinations.

2.3. Preparation and characterization of solid inclusion complexes and physical mixtures

The solid complexes of KET-BCD (1:1, 1:2, molar ratio) and KET-BCD with hydrochloric or citric acid (1:2:2, 1:2:1, molar ratio), were prepared using the spray-drying method as follows: KET and BCD in adequate molar ratio dissolved in ethanol and water, respectively, were mixed before spray-drying. Multicomponent complexes were obtained from an aqueous solution of KET, BCD and hydrochloric or citric acid.

Spray-drying was performed in a Büchi 190 apparatus under the following conditions: flow rate, around 4 ml/min; inlet temperature 85°C; outlet temperature 60°C; atomizing air pressure 3 kg/cm. The yield of this process was about 50%.

Physical mixtures of an appropriate amount of KET and BCD were obtained by pulverizing and thereafter mixing both solids in a Turbula T2C mixer (5 min at 30 rpm).

Powder X-ray diffraction patterns were carried out with a Philips X-ray diffractometer (PW 1710 BASED) using Cu-K_α radiation.

Thermal analysis was performed using a Shimadzu DSC-50 system with a differential scanning calorimeter equipped with a computerized data station (scanning rate 10°C/min).

2.4. Dissolution studies

Dissolution rates of KET, physical mixtures and the inclusion complexes were determined according to Nogami et al. (1969), in phosphate buffer solutions of pH 5 and 6 as the dissolution medium, at 37°C for 180 min. The samples, corresponding to 30 mg of KET, were placed in 100 ml of the dissolution medium and shaken at 500 rpm.

The concentration of the drug was determined by UV spectrophotometry at 225 nm. All samples were analyzed in triplicate. Dissolution efficiencies after 180 min were calculated according to Khan (1975). The effects of drug formulation on dissolution efficiency at each pH were investigated by one-way analysis of variance with the Scheffé test for multiple comparisons.

3. Results and discussion

3.1. Interaction between KET and BCD in aqueous media

Phase solubility profiles of KET with BCD are shown in Fig. 1. Both diagrams can be classified as A_L type according to Higuchi and Connors (1965). This indicates that the aqueous solubility of the drug increases linearly as a function of BCD concentration and a soluble complex is formed. Stability constants for the complex calculated from the slope of the initial straight portion of the solubility diagram were 1051.9 M^{-1} at pH 5 and 6959.3 M^{-1} at pH 6. From these values a different interaction in both media between the drug and the cyclodextrin can be deduced. The ionization of ketoconazole decrease with pH and, for this reason, the interaction with BCD is better at pH 6. Drug cyclodextrin complexation has been found to be better with unionized drug (Otero Espinar et al., 1989).

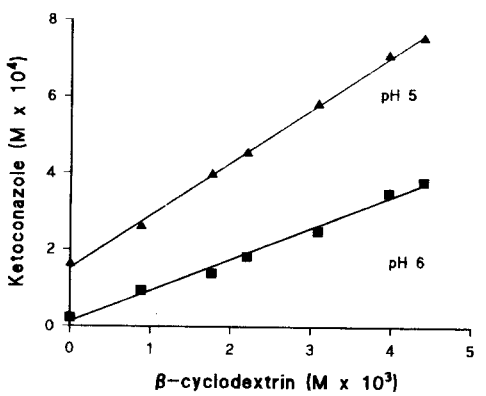

Fig. 1. Phase solubility diagrams of ketoconazole and β-cyclodextrin in buffer pH 5 and 6 at 37°C.

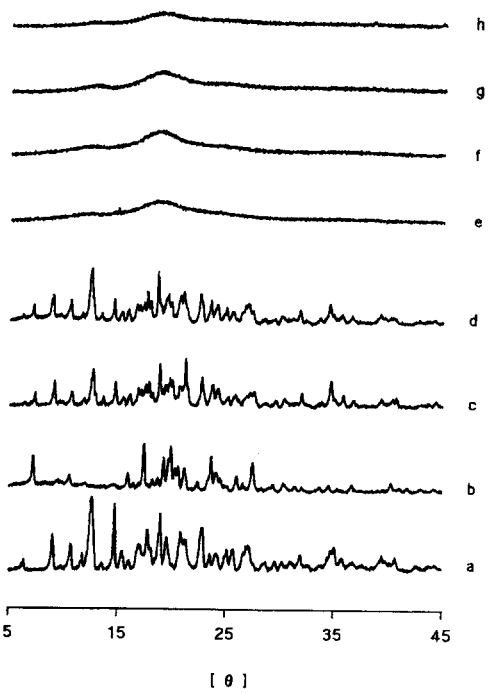

Fig. 2. Powder X-ray diffraction patterns of the different KET-BCD systems: (a) BCD; (b) KET; (c) physical mixture (1:1); (d) physical mixture (1:2); (e) KET-BCD (1:1) complex; (f) KET-BCD (1:2) complex; (g) KET-BCD-HCl (1:2:2) complex; (h) KET-BCD-Citric acid (1:2:1) complex.

3.2. Characterization of solid complexes

The X-ray diffractograms of KET-BCD binary and multicomponent complexes in comparison with the physical mixtures are shown in the Fig. 2. The diffraction patterns of the physical mixtures correspond to the superimposed diffractograms of KET and BCD, while those of the spray-dried complexes show fewer and less intense peaks. This indicates that all spray-dried compounds are markedly less crystalline than the physical mixtures or the pure components.

Fig. 3 shows the DSC thermograms of the physical mixtures of the KET and BCD as well as those of the solid binary and multicomponent complexes prepared by the spray-drying method. The physical mixtures show two endothermic peaks at 100°C (corresponding to the loss of the water content of BCD) and 149°C (due to melting of the drug). However, these peaks disappeared in

the case of all complexes prepared by spray-drying. These results can be explained on the basis of a better interaction among the drug and the cyclodextrin, indicating the complexation of KET with BCD.

X-ray and DSC studies indicate the formation of amorphous complexes between the cyclodextrin and the drug.

3.3. Effects of complexation on dissolution of the drug

Fig. 4 illustrates the dissolution profiles obtained with pure KET, physical mixtures and the inclusion complexes in buffer solution pH 5. One-way ANOVA in dissolution efficiency (0–180 min) reveals significant differences between the different formulations ($F_{(6,14)} = 2379.708$, $\alpha < 0.01$). The Sheffé test grouped the formulations as follows:

KET PM 1:1 PM 1:2 KET-BCD 1:1
KET-BCD 1:2 KET-BCD-HCl 1:2:2
KET-BCD-CITRIC ACID 1:2:1

Physical mixtures of KET with BCD showed a higher dissolution rate than pure KET and, this effect increases with the amount of BCD in the mixture. In the binary systems as the amount of BCD raises in the complexes, a better dissolution profile is shown.

Nevertheless, no differences were found among the binary system 1:2 and the multicomponent complexes, prepared with the same molar ratio of BCD. This fact is probably due to the ionization of the drug in this medium.

In buffer solution pH 6, the behavior of the prepared systems defers from the above at pH 5 (Fig. 5). The solubility of KET is lower because ionization decreases. For this reason, total amount of KET dissolved from all the preparations is lower than at pH 5. Therefore, in spite of the higher stability constant calculated at pH 6, the effect of cyclodextrins on drug solubility is lower than in the more acidic medium.

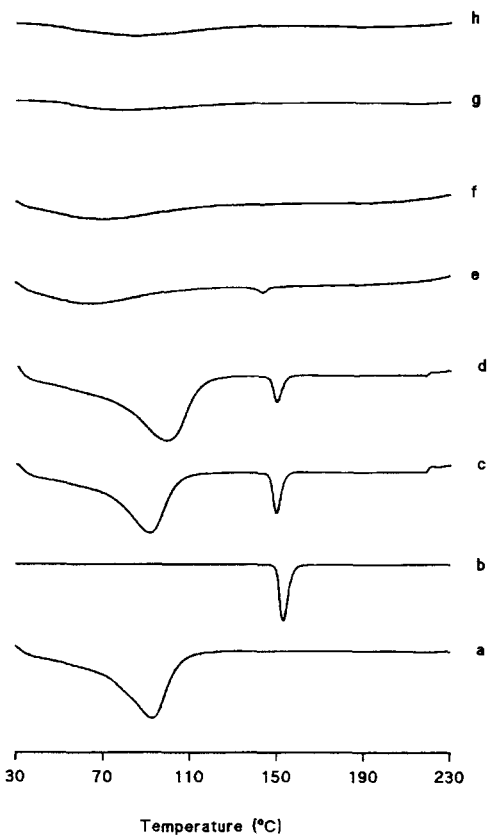

Fig. 3. Differential scanning calorimetry of the different KET-BCD systems: (a) BCD; (b) KET; (c) physical mixture (1:1); (d) physical mixture (1:2); (e) KET-BCD (1:1) complex; (f) KET-BCD (1:2) complex; (g) KET-BCD-HCl (1:2:2) complex; (h) KET-BCD-Citric acid (1:2:1) complex.

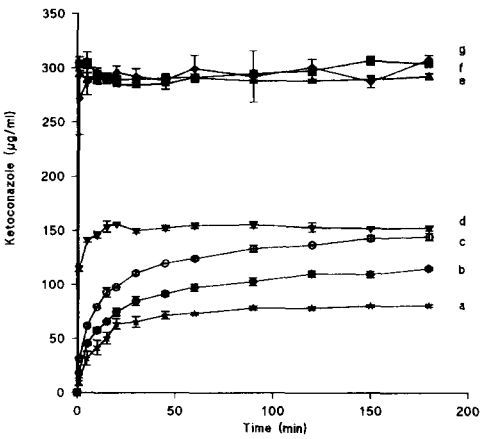

Fig. 4. Dissolution profiles of KET and its inclusion complexes at pH 5: (a) KET; (b) physical mixture (1:1); (c) physical mixture (1:2); (d) KET-BCD (1:1) complex; (e) KET-BCD (1:2) complex; (f) KET-BCD-HCl (1:2:2) complex; (g) KET-BCD-Citric acid (1:2:1) complex.

Analysis of variance indicates that the 'formulation' affects significantly 0–180-min dissolution efficiency ($F_{(6,14)} = 754.308$, $\alpha < 0.01$) and the Sheffé test grouped the systems as follows:

KET PM 1:1 PM 1:2 KET-BCD 1:1

KET-BCD 1:2 KET-BCD-HCl 1:2:2

KET-BCD-CITRIC ACID 1:2:1

The dissolution behavior of KET from the physical mixtures, and 1:1 complex is similar to the obtained at pH 5. From the binary system 1:2, it has been not possible to dissolve all the drug (around 80%) and after 30 min, the concentration decreased due to the recrystallization of KET in the medium (Szejtli, 1991).

Both multicomponent complexes show different dissolution profiles. The system prepared with citric acid reach a percentage close to 100% but after 90 min the concentration decreases as above, whereas that prepared with hydrochloric acid, 100% of the dose dissolved and remained in the solution all during the assay.

4. Conclusions

Binary and multicomponent inclusion complexes of ketoconazole and β-cyclodextrin can be obtained by spray-drying method. This confers improved drug solubility in both media studied. No differences were found between binary and multicomponent complexes prepared with the same molar ratio (1:2) at pH 5.

However, in buffer solution pH 6, inclusion complex formed in the presence of hydrochloric acid resulted in higher solubility enhancement for the drug.

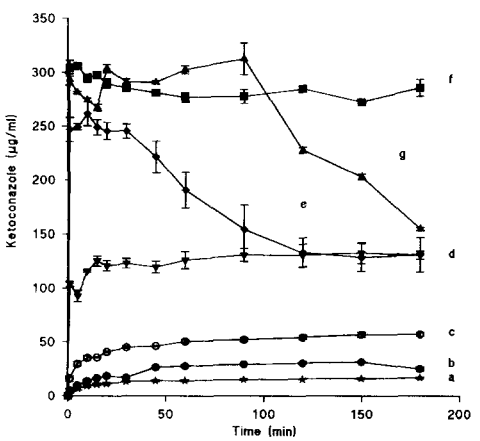

Fig. 5. Dissolution profiles of KET and its inclusion complexes at pH 6: (a) KET; (b) physical mixture (1:1); (c) physical mixture (1:2); (d) KET-BCD (1:1) complex; (e) KET-BCD (1:2) complex; (f) KET-BCD-HCl (1:2:2) complex; (g) KET-BCD-Citric acid (1:2:1) complex.

Acknowledgements

This work was supported by a research project from Xunta de Galicia XUGA20302A93.

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