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Short Communication

Study of the inclusion of gliclazide in α-cyclodextrin[1]

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1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides with the ability to encapsulate entirely, or at least partially, into their hydrophobic cavity, a wide variety of guest molecules, forming inclusion complexes. This inclusion processes leads to changes in the physicochemical properties of the guest, such as solubility, dissolution rate and bioavailability [1,2].

Gliclazide (GL) (Diamicron®) is a second-generation sulphonylurea, widely used for the treatment of non-insulin dependent diabetes mellitus. It has a low solubility in gastric fluids, which determines a low dissolution rate and hence interindividual variability on its bioavailability [3].

The objective of this work is the evaluation complexing ability of α-CD for the GL; also, a comparison of the results obtained for the α-CD with those obtained with β-CD, which demonstrated that it has a suitable cavity size to include the GL [4], will serve to study the influence of the CD cavity size.

2. Experimental

2.1. Materials

GL was supplied by Servier (E-Madrid) and α-CD was purchased from Ringdex (F-Paris). All other materials were of analytical reagent grade.

2.1.1. Elaboration of binary systems

α-CD was incorporated into GL by several methods: kneading, co-grinding and spray-drying, always in the same molar ratio (1:2 drug:CD).

(a) Kneading: α-CD (0.500 g) was kneaded in a mortar with a bit amount of purified water. Subsequently, GL (3.340 g) was added and kneaded for 45 min with the addition of some drops of water, when necessary. The final product was partially dehydrated at 37°C for 24 h (Selecta, mod. 204).

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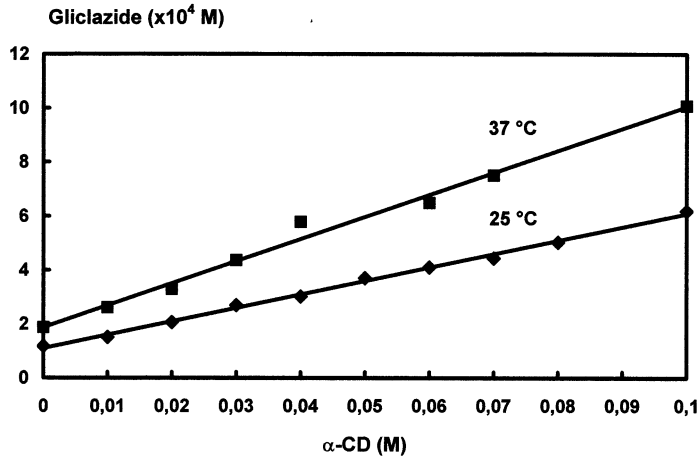

Fig. 1. Phase solubility diagram for the GL-α-CD system at 25 and 37°C.

(b) Co-grinding: A physical mixture of the two components was introduced in an oscillatory mill (Herzog HSM 100). The milling process lasted 5 min.

(c) Spray-drying: GL (0.500 g) and α-CD (3.340 g) were dissolved in 400 ml of 96% EtOH and 300 ml of purified water, respectively. Both solutions were mixed by sonication for 20 min and spray-dried (Büchi 190M miniSpray-Dryer). The conditions were as follows: flow rate: 800 ml h^{-1}, inlet temperature: 152°C, outlet temperature: 85°C, air flow rate: 400 $Nl \cdot h^{-1}$.

2.2. Characterization techniques

2.2.1. Phase solubility studies

The solubility isotherms of the GL-PMCD system were obtained at 25 and 37°C using the technique proposed by Higuchi and Connors [6]. The solubilized drug was quantified by UV spectroscopy using a Hitachi U-2000 apparatus ($\lambda_{max} = 228$ nm).

2.3. DSC

DSC determinations were carried out in a Mettler TA 4000 equipped with a Mettler DSC 25 furnace. The samples were weighed in a Mettler M3 microbalance in open aluminium pans (weight 4–7 mg). Samples were previously treated by heating from 40 to 80°C at $10°C \cdot min^{-1}$, further isotherm at 80°C for 10 min, and final cooling from 80 to 40°C at $10°C \cdot min^{-1}$, in order to dehydrate the CD of the sample. This treatment was immediately followed by heating from 40 to 250°C, at $10°C \cdot min^{-1}$ in static air atmosphere.

2.4. X-ray diffraction (XRD)

The diffractograms of the systems under study were obtained by means of a Siemens Kristallofex D-500 equipment. The conditions were Ni-filtered CuKα radiation, 50 kV voltage, 30 mA current, 1° $(2\theta) \cdot min^{-1}$ scanning speed and a range of exploration from 2 to 65° (2θ).

2.5. Fourier-transform infrared spectroscopy (FTIR)

The infrared spectra of the samples under study were obtained by using a Bomem M-120 IR instrument. The samples were mixed with KBr and compressed as disks. The selected wavenumber ranged between 600 and 4000 cm^{-1}, being the spectra resolution of 4 cm^{-1} and 10 being the number of scans.

Table 1
Thermodynamic parameters calculated from solubility studies at different temperatures

Temperature (K)	Slope	r	K_c (M^{-1})	ΔG ($kJ \cdot mol^{-1}$)	ΔH ($kJ \cdot mol^{-1}$)	ΔS ($J \cdot mol^{-1} \cdot K^{-1}$)
298	0.00498	0.994	44	−9.376	11.090	5.8
310	0.00187	0.998	37	9.306	11.090	5.8

3. Results and discussion

The phase solubility diagrams corresponding to the GL-α-CD system are reported in Fig. 1. GL presents A_L type solubility curve with α-CD at the two temperatures under assay, indicating the formation of 1:1 soluble complexes. The value of the association constant at 25°C (K_c), was calculated according the Higuchi-Connors equation [5] ($K_c = 44\ M^{-1}$). Considering that the K_c value for β-CD (1094 M^{-1}) [4] is much higher, this low value indicates an inadequate size of the CD cavity for the entrance of the GL groups.

The thermodynamic parameters of the complex obtained from the temperature dependence have been calculated and reported in Table 1. The negative values of the free energy and enthalpy indicate that the interaction of GL with α-CD would involve the substitution of an unfavourable polar–apolar interaction between the included water and the hydrophobic α-CD cavity by the more energetically favoured apolar–apolar interaction between GL and α-CD cavity [6]. However, the unfavourable entropy variation reveals a smaller disorder of the displaced water molecules, which are released from GL and α-CD, and hence the low extent of the complexation process.

The DSC scans of the systems under study are reported in Fig. 2. Normally, the α-CD has three endotherms at 62, 89 and 105°C related with the loss of water molecules [7]. In this case, due to the previous heating treatment, a partial dehydration was produced appearing at only two endothermic peaks about 85 and 100°C (Fig. 2(a)), corresponding to the stronger bonded water molecules of the α-CD. The physical mixture (Fig. 2(b)) shows two endothermic peaks. The first one, about 90°C, corresponds to the loss of the water content of the α-CD, and the second one, about 170°C, to the melting of the drug. The peak attributed to the fusion of the drug is already visible in the samples prepared by kneading (Fig. 2(c)) and spray-drying (Fig. 2(d)). However, the feasibility of a possible complexation of the drug into the CD is reflected by the reduction of the heat of fusion of this endotherm, in comparison with the physical mixture. On the contrary, this peak disappears in the case of the sample prepared by co-grinding (Fig. 2(e)). At this point, a thermal evaluation was carried out for pure GL (peak temperature in degrees (P.T.): 169.4 and fusion enthalpy in J/g (ΔH_f): 121.0) and GL treated separately by knead-

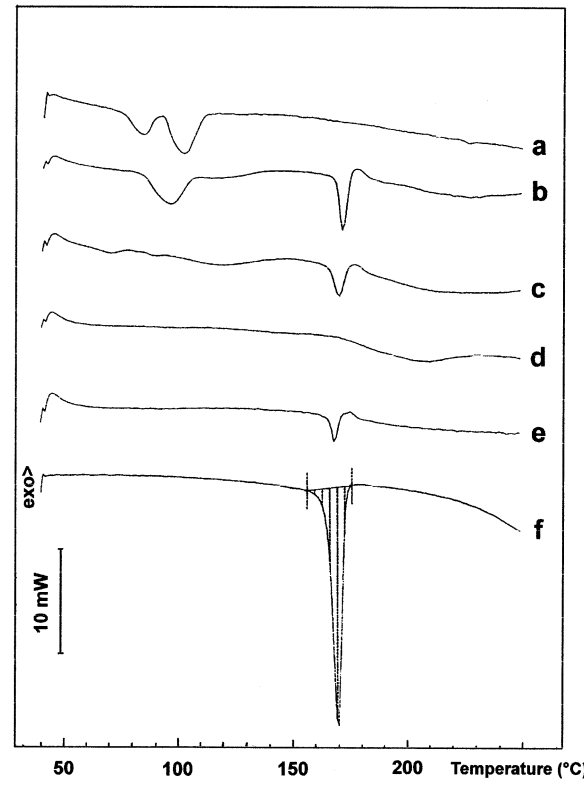

Fig. 2. DSC curves of: (a) α-CD; (b) physical mixture; (c) kneaded mixture; (d) co-ground; (e) spray-dried; and (f) GL.

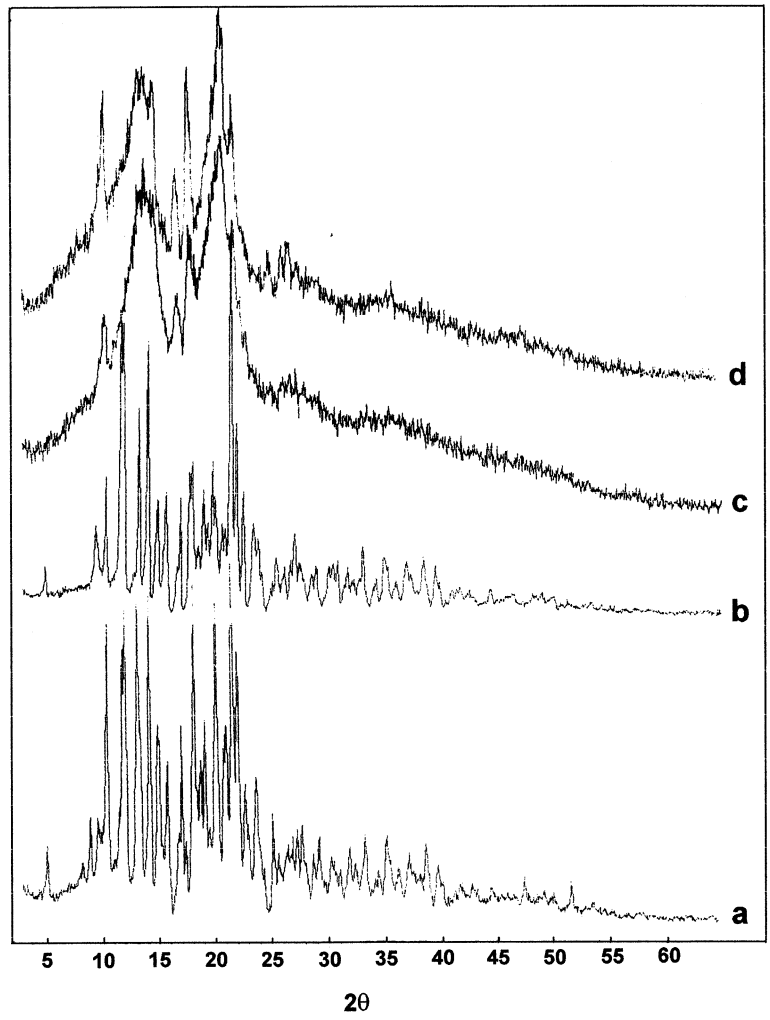

Fig. 3. X-ray diffraction patterns corresponding to the following products: (a) physical mixture; (b) kneaded mixture; (c) co-ground; and (d) spray-dried.

ing (P.T./ΔH_f: 168.8/116.3), co-grinding (P.T./ΔH_f: 166.8/107.6) and spray-drying (P.T./ΔH_f: 165.9/117.0). The estimated amorphous fraction in the samples were calculated by the expression:

$$\%\ \text{Amorphous} = 100 - \left(\frac{\Delta H_f\ \text{sample}}{\Delta H_f\ \text{commerical}}\right) \cdot 100$$

The higher amorphous percentages were obtained for the co-grinding and spray dried systems (11.4 and 11.6%, respectively), indicating that the processing technique do not affects significantly the crystallinity of the drug. Only the presence of CD leads to the disappearance of the fusion phenomenon, which would be attributed to the total complexation of the drug in the case of a co-ground sample, but also in the presence of an amorphous dispersed mixture GL-α-CD.

The X-ray spectra of the systems under study are represented in Fig. 3. It is observed that a kneaded system has a crystalline structure, similar to the superposition of the spectra of the single components as well for the physical mixture. The co-ground and spray-dried products showed patterns typical of amorphous samples, the study of

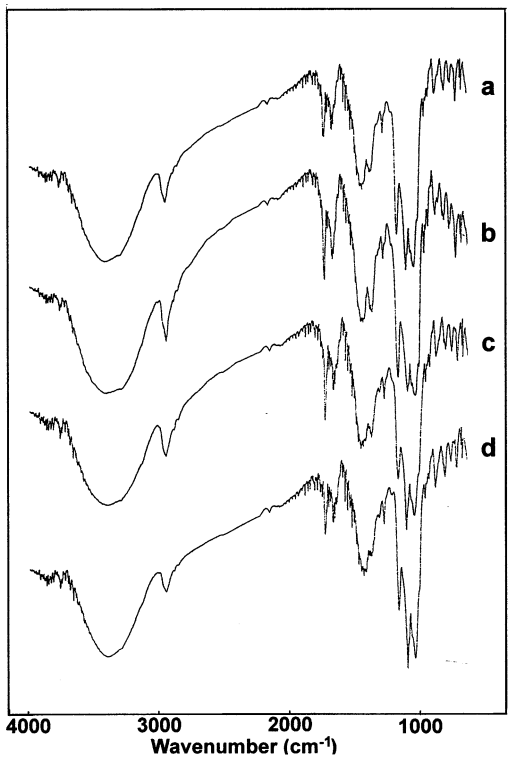

Fig. 4. FTIR spectra of GL-α-CD systems: (a) physical mixture; (b) kneaded mixture; (c) co-ground; and (d) spray-dried.

the presence of differential peaks attributed to a hypothetical complex GL-α-CD being difficult. For this reason, this technique does not present utility in our case as an aid to elucidate the presence of inclusion complexes, confirming only the amorphous features for the co-ground sample, in agreement with DSC data.

Fig. 4 shows the IR spectra of the GL-α-CD systems. For these, the study was focused on the behaviour of the carbonyl-stretching band, situated at 1709 cm^{-1}. This band is not significantly modified in the different systems, indicating only the presence of a dispersion of the GL in the carrier. No interaction between the drug and CD exists, discarding the existence of a true inclusion complex in any case.

4. Conclusions

The cavity size of α-CD seems to be insufficient to allow the entrance of the GL rings, the formation of a complex not being possible, which would modify the physicochemical characteristics of the free drug or a simple drug-carrier mixture. Only an amorphous dispersion was reached by co-grinding and spray-drying procedures, which cannot be considered as true inclusion complexes, as demonstrated by the characterisation techniques described above, where no modification of the physicochemical behaviour were observed, particularly in the IR studies.

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