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Solid-state characterization and dissolution characteristics of gliclazide-β-cyclodextrin inclusion complexes

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Abstract

Solid complexes between gliclazide and β-cyclodextrin (β-CD) were prepared by kneading, coprecipitation, neutralization, co-grinding and spray-drying. Characterization of gliclazide-β-CD inclusion complexes was performed using X-ray diffractometry and cross polarizing/magic angle spinning ^{13}C-nuclear magnetic resonance spectroscopy. These techniques have clearly demonstrated the existence of solid-state inclusion compound formation. The complexes, obtained by neutralization and spray-drying methods, showed enhanced dissolution rates of gliclazide. © 1997 Elsevier Science B.V.

Keywords: Gliclazide; β-Cyclodextrin; XRD; CP/MAS; ^{13}C-NMR; Dissolution rate

1. Introduction

Complexation phenomena involving cyclodextrins (CD) and their application for the improvement of physicochemical and biopharmaceutical characteristics of many drugs, such as solubility, dissolution rate, chemical stability and bioavailability have been extensively investigated in the last years (Bekers et al., 1991; Fromming and Szejtli, 1994).

Gliclazide (GL) [1-(1-azabicyclo(3,3,0)octyl)-3-(*p*-tolylsulphonylurea)] is a second-generation sulphonylurea, characterized by poor solubility and, hence, by low dissolution rate in water. This causes interindividual variations of its bioavailability (Palmer and Brogden, 1993). The CD complexation may be expected to overcome these disadvantages.

The present paper is orientated to the investigation of the inclusion mode between GL and β-CD in the solid state using X-ray diffractometry (XRD) and cross-polarization/magic angle spinning ^{13}C-nuclear magnetic resonance spectroscopy

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(CP/MAS ^{13}C-NMR). In addition, the methods used for the preparation of the inclusion complex were evaluated in terms of their ability of increasing the dissolution rate of GL.

2. Experimental

2.1. Materials

GL was kindly supplied by Servier (E-Madrid) and β-CD was purchased from Roquette (F-Lestrem). All other materials were of analytical reagent grade.

2.2. Preparation of solid complexes

The preparation of solid complexes GL-β-CD was performed by different techniques, which are described below in detail. The molar ratio was 1:2, based on previous studies (Moyano et al., 1997). The products obtained were milled and sieved (50–200 μm).

2.2.1. Kneading

β-CD was put in a mortar and wetted with a few drops of purified water and then kneaded. The drug was added slowly and kneaded with the addition of few drops of water. This process was continued for 45 min and the product was dried at 37°C for 24 h (Selecta, mod. 204).

2.2.2. Coprecipitation

The preparation of the inclusion complex was carried out by addition of 0.1940 g of GL to 100 ml of a 0.012 M solution of β-CD. The system was kept under magnetic agitation for 1 week at room temperature and protected from the light, due to the GL photolability. The formed precipitate was separated by vacuum filtration and dried at room temperature, in order to avoid the loss of the structure water from the inclusion complex.

2.2.3. Neutralization

For this technique, a 0.012 M solution of β-CD (100 ml) was prepared. This solution was alkalinized by adding a small quantity of ammonium hydroxide solution (25% w/w), in order to dissolve the joined GL (0.1940 g). The clear solution obtained after few seconds under magnetic agitation was neutralized using a 1 N hydrochloric acid solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The separation process of the precipitate was the same as that used for the coprecipitation method.

2.2.4. Co-grinding

The two components were mixed for 15 min, and the physical mixture was introduced in an oscillatory mill (Herzog HSM 100). The grinding process was continued for 5 min.

2.2.5. Spray-drying method

Spray-drying was performed in a Büchi 190M mini-Spray-Dryer. GL (0.500 g) was dissolved in 400 ml of 96% ethanol. The required stoichiometric amount of β-CD was dissolved in 300 ml of purified water. Solutions were mixed by sonication for 20 min to produce a clear solution, which was then spray-dried. The conditions were: flow rate, 800 $\mathrm{ml \cdot h^{-1}}$; inlet temperature, 152°C; outlet temperature, 85°C; air flow rate, 400 $\mathrm{NL \cdot h^{-1}}$.

2.3. X-ray diffraction studies

The diffractograms of the different samples were obtained by a Philips PW 1800 equipment. Conditions: Ni-filtered CuKα radiation, voltage 50 kV, current 30 mA, scanning speed 1° $(2\Theta) \cdot \mathrm{min}^{-1}$, investigating the samples in the 2Θ range 2–50°.

2.4. CP/MAS ^{13}C-NMR

The solid-state ^{13}C-NMR spectra of the samples were recorded by using a Bruker CXP-300, operating under cross polarizing and magic-angle spinning. The magnetic field was 7.04 T, at a frequency of 75.47 MHz for the carbon nuclei. The pulse angle was of 3.1 μs, being the time contact for the Hartmann-Hann conditions of 1 ms. The acquisition time was 23 ms, the same value for the decoupling time, being the time domain of 1 K. All the spectra were processed

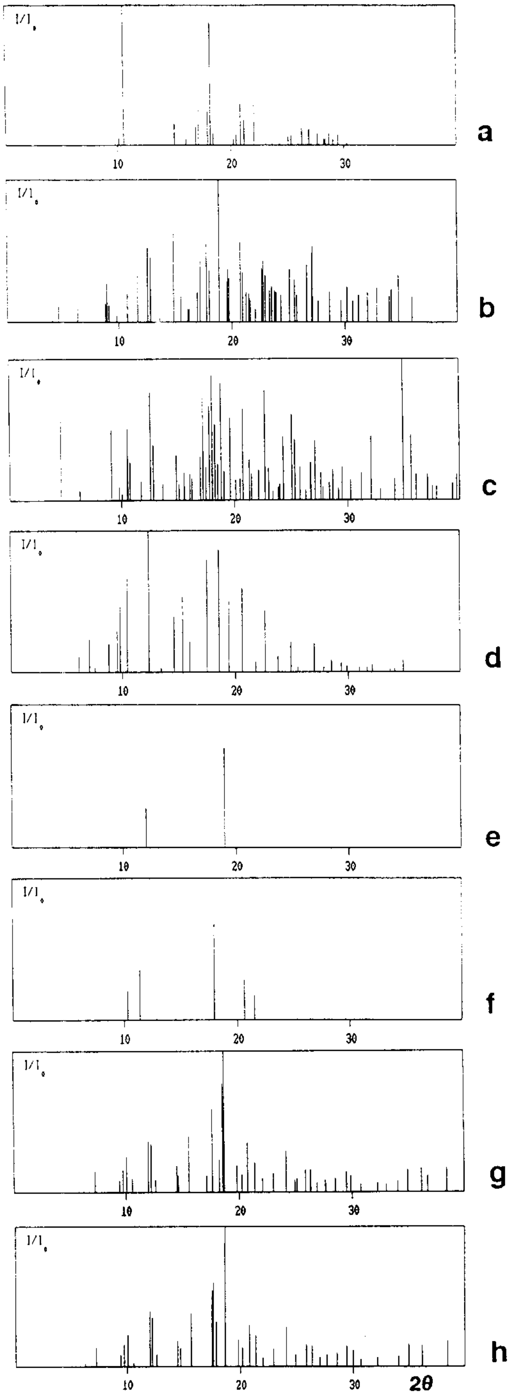


Fig. 1. X-ray diffraction patterns for the following products: (a) GL; (b) β-CD; (c) physical mixture; (d) kneaded mixture; (e) co-ground; (f) spray-dried; (g) coprecipitated, and (h) neutralized.

with a size of 8 K. The spectral width was 22 000 Hz. The chemical shifts were referred to the tetramethylsilane as standard. Two spectra at different rotation speeds (3.9 and 4.5 kHz) were collected for the GL sample, with the aim of identifying the mirror peaks due to the rotation (sidebands). All other spectra were registered at 4.5 kHz. The scan number was variable, depending on the sample nature.

2.5. SEM

SEM micrographs of the different samples were obtained by means of a Philips XL30 electron microscope. Samples were previously coated by a treatment with graphite, in order to make them conductors.

2.6. Dissolution rate studies

The dissolution rate studies were performed according to the USP XXIII rotating basket method (Turu Grau mod. D-6). The samples, corresponding to 10 mg of GL, were placed into hard gelatin capsules. Dissolution medium was artificial gastric juice without enzymes (pH 1.2). The stirring speed was 50 rpm and the temperature was maintained at 37 ± 0.5°C. Three ml samples were withdrawn at settled time intervals using a syringe and analyzed spectrophotometrically at 228 nm.

3. Results and discussion

3.1. XRD

The XRD patterns of the GL-β-CD systems are represented in Fig. 1. The diffractograms of GL and β-CD exhibit a series of intense lines, which are indicative of their crystallinity. The spectra relevant to the physical mixture and the kneaded system are constituted practically by the superposition of the spectra of the single components, although in the second system a remarkable decrease of crystallinity is evident. The spectra of coprecipitated and neutralized samples (which are identical) showed with respect to the components the disappearance of important spectral lines situ-

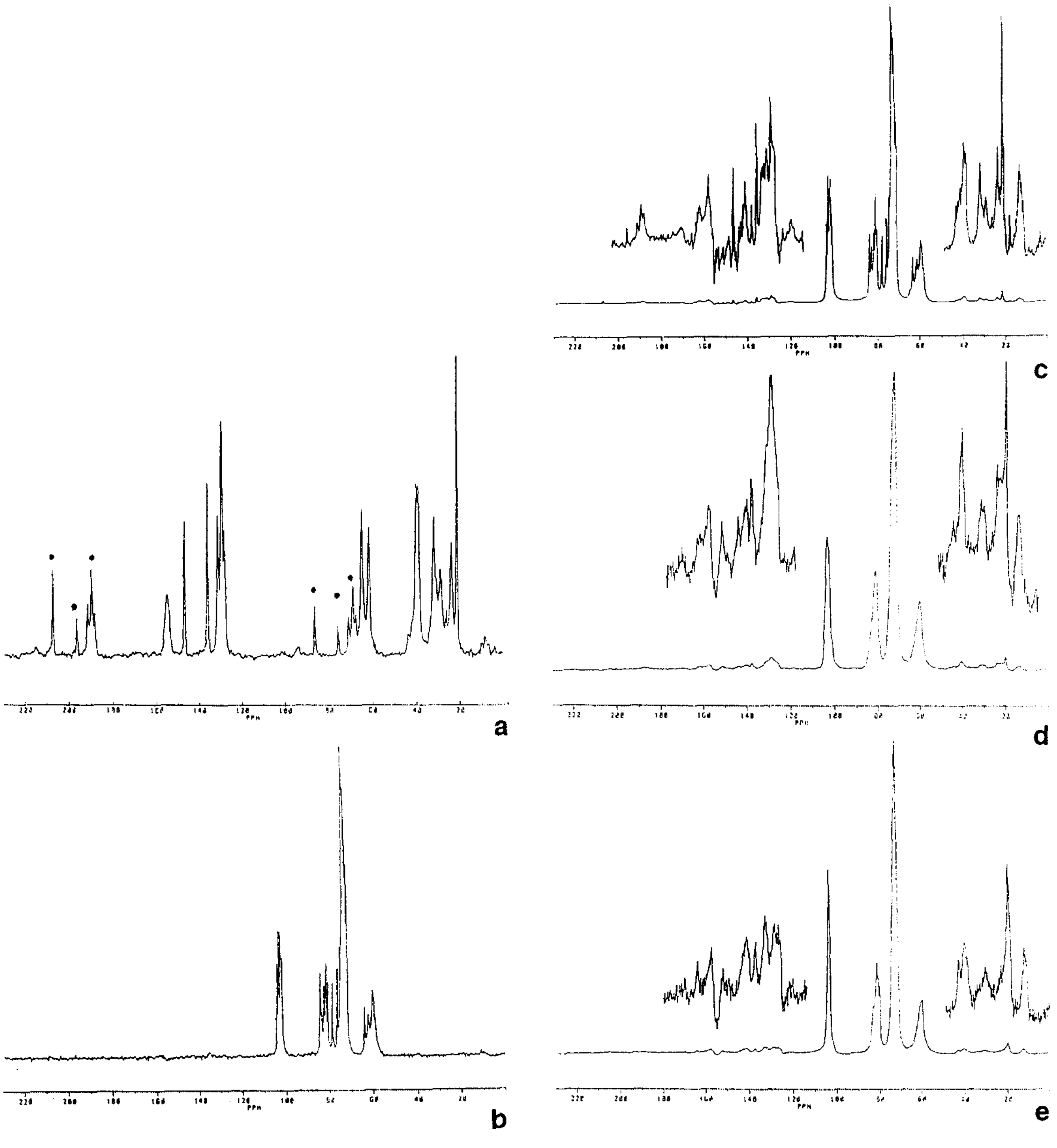


Fig. 2. CP/MAS ^{13}C-NMR spectra for: (a) GL; (b) β-CD; (c) physical mixture; (d) coprecipitated, and (e) neutralized.

ated at 10.590, 14.985, 17.100, 18.150 and 22.075° (2θ) for GL and at 4.570, 6.290, 8.950, 10.725, 18.865, 22.620, 27.040, 27.135, 32.045 and 34.875° (2θ) for β-CD. On the other hand, the appearance of new peaks at 7.230, 11.930, 11.980, 12.195 and 28.650° (2θ) was observed, indicating the presence of new solid crystalline phases, corresponding to inclusion complexes of the same nature. It is important also to remark that the peak intensities are diminished with respect to the spectra of the starting materials, indicating a lower degree of crystallinity for these complexes. This fact may be attributed to the very rapid precipitation of the complexes during their preparation,

Fig. 3. SEM photomicrograph of pure GL.

insufficient for a regular crystal growth and spatial order at higher ranges. The co-ground and spray-dried products showed a halo pattern, typical of amorphous samples, with three hillocks in the 12°–18° (2θ) range. The spray-dried sample seems to be more crystalline than the co-ground one, in good agreement with DSC studies (Moyano et al., 1996), where it exhibited the permanence of the melting peak of GL. In these two cases, the formation of an amorphous inclusion complex is very probable.

3.2. CP/MAS ^{13}C-NMR

CP/MAS ^{13}C NMR spectra of β-CD and its inclusion complexes with GL are shown in Fig. 2. The sidebands of GL are labelled in Fig. 2a. Due to the sensibility to the crystallinity of the sample, this technique has been applied only on crystalline systems. The ^{13}C signals from guest molecules in the binary systems are masked because the amount of GL is low (about 11% w/w) compared with the carrier. A similar case was observed by other authors (Acartürk et al., 1993). It is appreciated that a certain amorphization was produced for the coprecipitated and neutralized samples, as observed by the diminution of the β-CD signal intensities, in good agreement with the XRD studies. Moreover, this fact may suggest a distortion of the macrocyclic structure of the CD, with a variation of the dihedral angles values of the glycosidic linkages, closely related with the C_1 and C_4 signals, as a consequence of the complexation process. For the GL signals, the study reveals a

Fig. 5. SEM photomicrograph GL-β-CD co-ground.

Fig. 4. SEM photomicrograph GL-β-CD kneaded mixture.

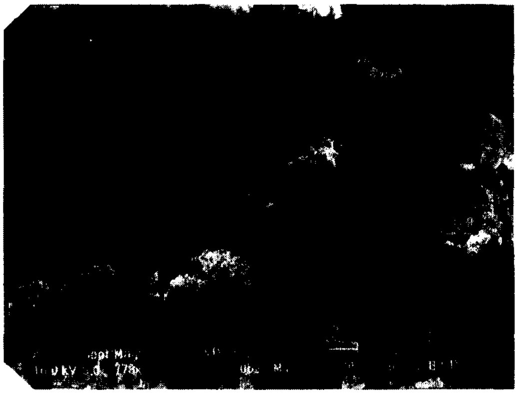


Fig. 6. SEM photomicrograph GL-β-CD spray-dried.

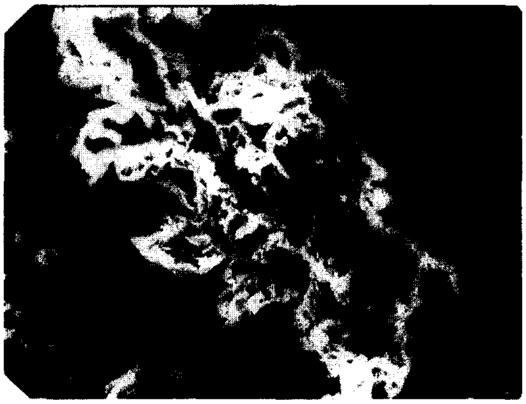


Fig. 7. SEM photomicrograph GL-β-CD coprecipitated.

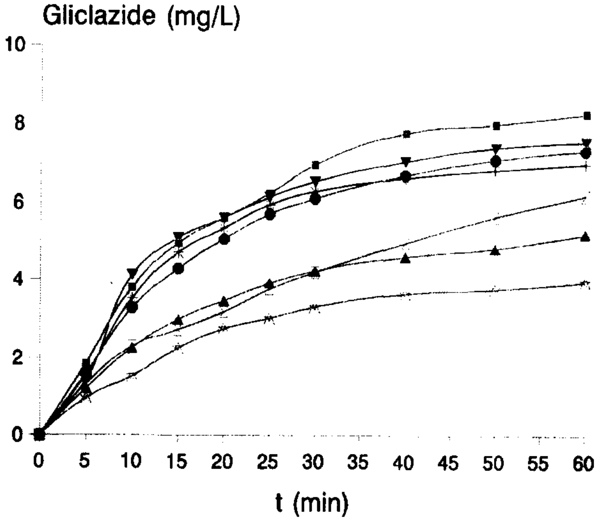
modification of these ones for the complexes, indicating the existence of a solid-state complex, being involved both azabicyclooctyl and tolyl functions of GL in this process.

3.3. SEM

The SEM photomicrographs of GL-β-CD systems are reported in Figs. 3-7. GL product is characterized by the presence of irregular-shaped crystals. The kneaded product is constituted by relative bulky particles, with other small ones adhered on its surface. Spray-dried and co-ground samples showed the typical features of amorphous products. In the case of co-ground sample, the particles are characterized by the presence of a smooth surface, with good definite edges, but not exhibiting a regular shape. This fact is due to the elaboration technique, which lead to the friction between the particles, being impossible the distinction between both components. For the spray-dried system, it is clear the presence of spherical small-size particles tending to aggregation. This observation, although scarcely conclusive, lead us to estimate the existence of a single phase in these two last preparations (Szejtli, 1988). The coprecipitated and neutralized systems present a similar aspect, showing the presence of agglomerates of small-size crystals, which are different from those of the raw materials, indicating the presence of a new solid phase, thus corroborating the XRD observations.

3.4. Dissolution rate studies

The dissolution profiles of GL and GL-β-CD systems are reported in Fig. 8. It is evident that the coprecipitated, neutralized, spray-dried and co-ground systems exhibit a higher dissolution



	DE_{60}	DP_{60}
☆	0.2913	38.65
I	0.4036	58.74
*	0.5233	68.17
□	0.5914	76.64
●	0.5115	68.45
▼	0.5692	72.27
Δ	0.3177	46.39

Fig. 8. Dissolution curves and DE_{60} and DP_{60} parameters of GL-β-CD binary systems (☆, physical mixture; □, kneaded; *, co-ground; □, spray-dried; ●, coprecipitated; ▼, neutralized; △, gliclazide).

rates than the physical mixture, the kneaded product and the pure drug. The dissolution profiles are evaluated by the dissolution efficiency (DE) parameter (Khan, 1975) at 60 min and the dissolved percentage (DP) at 60 min. The extent of the enhancement of the dissolution rate was found to be dependent on the preparation method, since the spray-dried and neutralized exhibit the highest dissolution rates. This enhancement has been attributed in all these cases both to the formation of an inclusion complex in the solid state and to the reduction of the crystallinity of the products, as confirmed by XRD studies. The small dissolution rate increase reached for the physical and kneaded mixtures is only due to the wetting effect of the CD: in fact, this effect is more evident for the kneaded product, where the mixing process between the two components is more intensive.

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