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Note

Study of the complexation behaviour of gliclazide with partially methylated β-cyclodextrin in solution and solid state

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Abstract

The complexation of Gliclazide (GL) with a partially methylated β-cyclodextrin was studied. Phase-solubility and ^{1}H NMR spectroscopy were employed to investigate the complexation behaviour in solution and to demonstrate the complexation in liquid medium with the participation of both azabicyclooctyl and tolyl moieties of GL in the inclusion process. Solid systems prepared by kneading, co-grinding and spray drying have also been checked, using DSC and HSM, for assessing the formation of the inclusion compound. Experimental evidence of the complexation between drug and cyclodextrin was reported for the co-ground and spray-dried systems. © 1997 Elsevier Science B.V.

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Gliclazide (GL) [1-(1-azabicyclo (3,3,0)octyl)-3-(*p*-tolylsulphonylurea)] is an oral hypoglycemic sulphonylurea, characterised by a very low solubility in water (≈ 55 mg l^{-1})—a common characteristic of this group (Ghandi and Karara, 1988; Betageri and Makarla, 1995).

In this work experimental data is reported concerning the preparation and characterisation of complexes between GL and partially methylated β-cyclodextrin (PMCD), an amorphous β-CD derivative obtained from a non-selective methylation process.

GL was supplied by courtesy of Servier (E-Madrid) and PMCD (average substitution degree (DS): 2.07) was provided by Ringdex (F-Paris). All other materials were of analytical reagent grade.

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Solid complexes were prepared by kneading, co-grinding and spray-drying in 1:2 drug:CD molar ratio, as previously assessed (Moyano et al., 1997a). The final products were pulverised and sieved (50–200 μm).

Solubility isotherms of the GL-PMCD system were obtained at 25 and 37°C using the technique proposed by Higuchi and Connors (Higuchi and Connors, 1965), in unbuffered aqueous solutions. The solubilized drug was quantified spectrophotometrically (Hitachi U-2000) at $\lambda = 228$ nm.

NMR studies were carried out using a Bruker ACF-200 spectrometer operating at 200 MHz. Chemical shifts were referred to external sodium trimethylsilylpropionate, sodium salt (TSP) at 0 ppm. The solvent employed to dissolve the drug was a 0.2 N NaOD solution in D_2O (Merck). The conditions were: acquisition time, 3.49 μs; pulse width, 2 μs; time domain, 16 K; Fourier number, 16 K; spectral width, 2347 Hz and temperature 37°C.

DSC determinations were carried out in a Mettler TA 4000 equipped with a Mettler DSC 25 furnace. A previous heating from 40-80°C (heating rate 10°C min^{-1}), followed by an isotherm at 80°C over 10 min and final cooling to 40°C was carried out for the dehydration of the CD in the samples, for a good evaluation of the melting peak of GL. This treatment was continued by heating in the temperature range of 40–250°C, at a rate of 10°C min^{-1} in static air atmosphere.

HSM studies were carried out using a Mettler FP 82HT hot-stage, linked to an Olympus BH-2 microscope. The heating conditions were adjusted by a Mettler FP 80HT control unit: temperature range 30–220 °C and heating rate 5°C min^{-1}.

The solubility diagram of the GL-PMCD system at 25°C in water is represented in Fig. 1. It corresponds to an A_L type of Higuchi. The association constant (K_c), considering the formation of a 1:1 complex, was calculated as $K_c = 895$ M^{-1}. This relatively high K_c value is lower than the obtained with β-CD (1094 M^{-1}) (Moyano et al., 1997a), probably due to steric hindrance of methoxyl groups of PMCD, which hamper the entry of the drug within the cavity. A 7-fold increase of the apparent solubility of GL in 0.01 M PMCD clearly underlines the effect of complexation in the liquid state.

The thermodynamic parameters of the inclusion were calculated from the K_c values at two temperatures (895 and 607 M^{-1} at 25 and 37°C, respectively), using the following equations (Bloch et al., 1982):

$$\ln \frac{K_2}{K_1} = \frac{\Delta H}{R} \frac{T_2 - T_1}{T_2 \cdot T_1} \quad (1)$$

$$\Delta G_i = -RT_i \ln K_i \quad (2)$$

$$\Delta S_i = \frac{\Delta H_i - \Delta G_i}{T_i} \quad (3)$$

K_1 and K_2 are the association constants at 25 and 37°C, respectively, R is the gas constant (8.28 J mol^{-1} K^{-1}), being T_1 and T_2 in Kelvin. The results indicate that the binding process is spontaneous ($\Delta G = -16\,451$ J mol^{-1} at 298 K and $-16\,771$ J mol^{-1} at 310 K), joined however, to a negative ΔS (-26.63 J mol^{-1} K^{-1} at both temperatures). Negative ΔH ($-24\,705$ J mol^{-1}) is associated with the presence of dipolar interactions and hydrogen bonds in the complex formation (Uekama et al., 1978), whereas the negative entropy indicates greater order after complexation. It is mainly due to the loss of rotational and translational freedom degrees of the molecules implicated in the complexation process.

The GL protons chemical shifts from the NMR spectra of pure GL and the binary system are

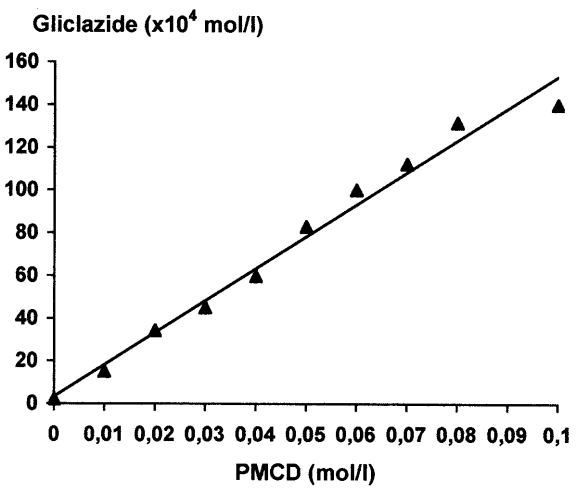
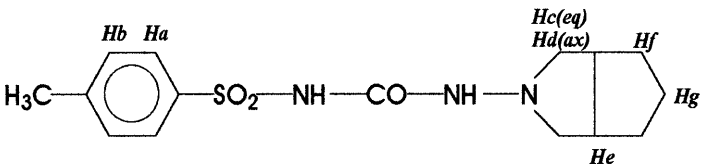


Fig. 1. Phase solubility diagram for the GL-PMCD system at 25°C.

Table 1
Chemical shifts corresponding to GL protons, in absence and presence of PMCD



	δ_{free}	$\delta_{complex}$	$\Delta\delta$ (ppm)
H_a	7.700	7.718	0.018
H_b	7.360	7.335	−0.025
$H_{c(eq)}$	3.100	3.232	0.132
$H_{d(ax)}$	2.190	2.331	−0.141
H_e	2.530	2.615	0.085
H_f	1.550	1.598	0.048
H_g	1.402	—	—
Methyl	2.390	2.400	0.010

reported in Table 1. This latter spectrum is characterised by the low-field shift of the GL proton signals, especially those of the azabicyclooctyl moiety, indicating that the complexation in liquid medium is preferentially performed in this way. On the other hand, the $\Delta\delta$ values for the aromatic group also indicate its participation in the complexation phenomenon, although in lower extension that the azabicyclooctyl one. This would be due to the high pD of the medium, that ionises the tolylsulfonamide group, thus diminishing its affinity for the CD cavity.

The DSC curves are presented in Fig. 2. Pure GL (Fig. 2f) is characterised by the presence of a sharp endothermic effect (peak temperature at 169.4°C), assigned to its melting. The PMCD (Fig. 2a) displays a wide and weak endothermic effect in the 150–200°C interval, which may be ascribed to fusion. The physical mixture (Fig. 2b) and the kneaded product (Fig. 2c) do not show the endothermic effect of GL, which is masked by the fusion of PMCD, as demonstrated the HSM studies. On the other hand, the co-ground product (Fig. 2d), is characterised by the presence of an intense exothermic effect at 142.1°C ($\Delta H_f = 8.6$ J g^{-1}), not observed for the raw materials separately treated, and ascribed to the recrystallisation of the amorphous complex. Similar results have been reported also by other authors (Ahmed et al., 1990; Hanawa et al., 1993). Also, an endotherm at 194.9°C ($\Delta H_f = 10.5$ J g^{-1}) was observed and may be ascribed to the melt of this recrystallised complex. A similar process was found for the spray-dried product (Fig. 2e), although, in this case, without melting, only an exothermal effect is observed at 120°C, again ascribed to a recrystallisation of the formed complex. Similar situations have been described by different authors, during the study of the interactions between methylated CDs and diverse drugs (Moyano et al., 1997b; El-Gendy and El-Gendy, 1993).

HSM studies revealed that PMCD appears as irregular particles at room temperature. At 160°C, it is possible to observe the glass transition of PMCD, while GL is not affected. At higher temperatures, a homogeneous liquid can only be appreciated. As a common feature the prolonged endothermic effect of PMCD covers the GL endotherm, which is in low weight proportion in the mixture. On the other hand, the low energetic endotherm of PMCD can be ascribed to its amorphous nature. Finally, HSM studies were not conclusive in the study of the nature of the

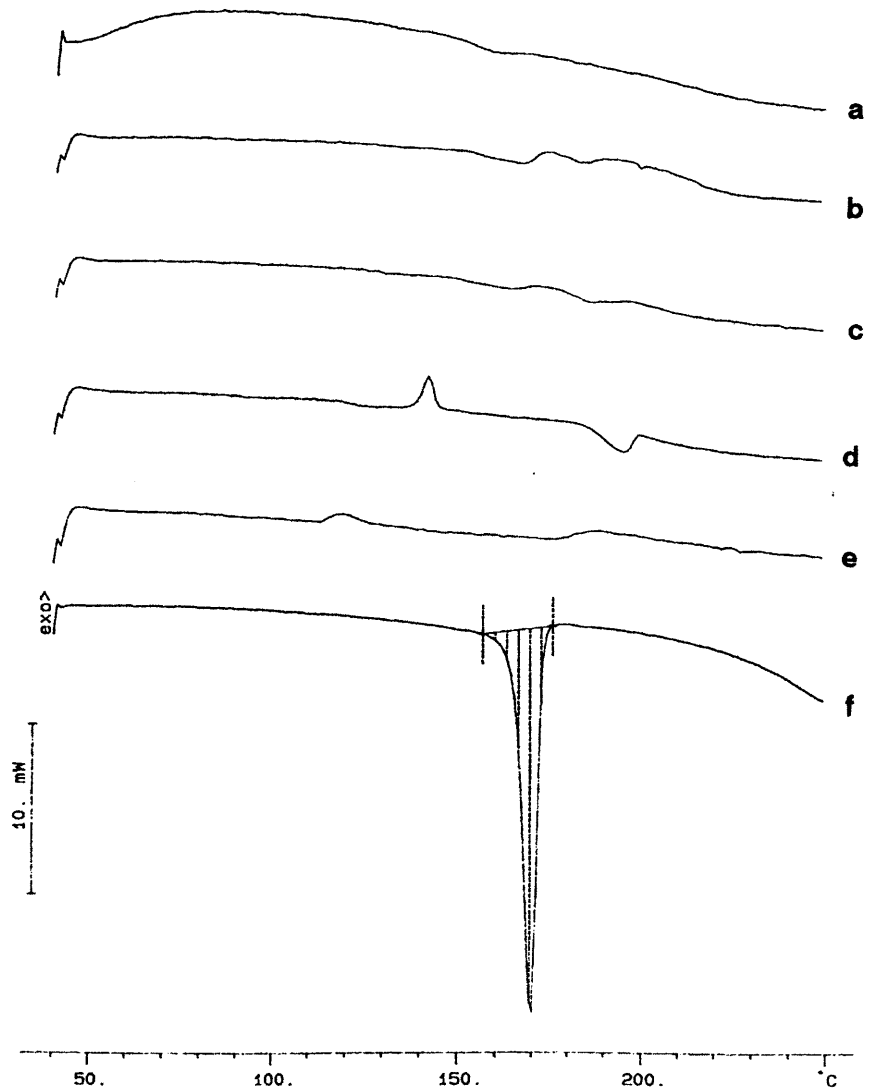


Fig. 2. DSC curves for: (a) PMCD; (b) physical mixture; (c) kneaded mixture; (d) co-ground; (e) spray-dried and (f) GL.

exothermal of co-ground and the spray dried products, being these effects not related with morphological changes.

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