STUDY OF COMPLEXATION OF GLICLAZIDE WITH ß-CYCLODEXTRIN IN SOLUTION BY NMR TECHNIQUES

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ABSTRACT

The study of complexation between GL and ß-CD in liquid medium has been carried out by phase-solubility, ^{1}H and ^{13}C NMR studies. A formation complex is observed from the phase solubility diagram, being the average association constant of 1094 M^{-1}. The NMR studies revealed the preferent complexation of the aliphatic moiety of GL. The aromatic moiety is also entrapped, but in minor extent, by the CD molecules.

1. INTRODUCTION

Gliclazide (GL) (see Figure 1 for its structure) is an orally active hypoglycemic agent, included in the second generation sulphonylurea group. It is characterized by a poor solubility in water and gastrointestinal fluids, which yields an absorption process limited by its dissolution rate and interindividual variability on its bioavailability [1].The aim of this work is the study of complexation of GL with the ß-CD in liquid medium, in order to evaluate this CD as an adequate complexant agent for our objectives. Phase-solubility and ^{1}H and ^{13}C NMR studies were used to evidence the inclusion process.

2. MATERIALS AND METHODS

GL was kindly supplied by Servier (E-Madrid) and β-CD was purchased from Roquette (F-Lestrem). D_2O and deuterated sodium hydroxide were purchased from Merck (E-Barcelona). The solubility studies have been carried out by the Higuchi and Connors technique at 298 K. ^{1}H and ^{13}C NMR spectra recorded at 310K using a Bruker ACF 200 spectrometer operating at 200.13 and 50.3 MHz, respectively. The chemical shifts

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were referred to an external sodium trimethylsilylpropionate (TSP) at 0 ppm. The solvent employed was a 0.2 N solution of NaOD in D_2O. The nOe measurements were made during *steady-state* experiments, by irradiation of the H3 signal of the β-CD, at a temperature of 310 K.

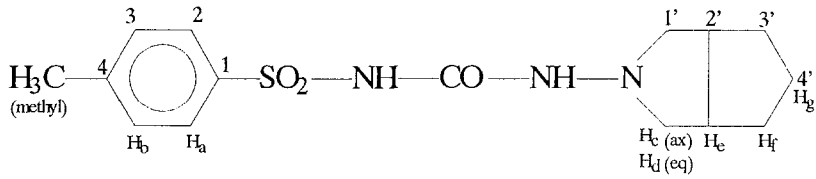

Figure 1. Structure of GL.

3. RESULTS AND DISCUSSION

3.1. Phase-solubility studies

The studies revealed that GL shows a typical Bs solubility curve in presence of ß-CD (Figure 1), with the apparition of a precipitate, corresponding to a complex GL-ß-CD. The apparent 1:1 stability constant value, calculated from the first straight line portion of the solubility diagram, appears to be 1094 M^{-1}. By the other hand, the stoichiometry of the complex formed, calculated from the plateau region of the diagram, was of 1:2 drug:CD.

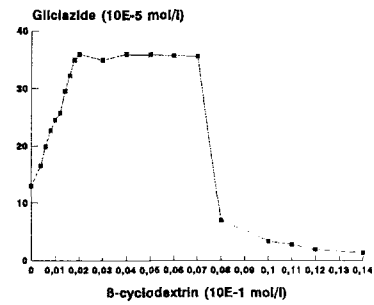

Figure 2. Phase-solubility diagram GL-β-CD.

3.2 ^{1}H NMR spectroscopy

The chemical shifts for the GL and β-CD protons are summarized in Tables 1 and 2, respectively. The GL is characterized by the presence of two groups (azabicyclooctyl and tolyl) which potentially may interact with the CD cavity. For them, it is observed

that the protons of the azabicyclooctyl group showed the higher chemical shifts variations, indicating the preferential complexation of this radical compared with the aromatic one.

For the β-CD, the presence of GL is related to an upfield shift of its H3 proton and the apparition of the H5 proton signal, which is overlapped with the H6 signal, indicating also an upfield shift of this one, which is ascribed to the GL complexation. In our case, they are not observed stronger changes of the chemical shifts of H3 and H5 signals. This fact also indicates a preferential complexation of the aliphatic moieity, which does not induces an strong anisotropic effect such as a ring current of the π electrons of an aromatic group.

TABLE 1. ^{1}H chemical shifts corresponding to the Gl, in absence and presence of β-CD.

Gl protons	δ_{Free}	$\delta_{Complex}$	$\Delta\delta$ (ppm)
Ha	7.700	7.710	0.010
Hb	7.360	7.360	0
Hc (eq)	3.100	3.220	0.120
Hd (ax)	2.190	2.060	-0.130
He	2.530	2.600	0.070
Hf	1.550	1.620	0.070
Hg	1.402	1.500	0.098
Methyl	2.390	2.390	0

TABLE 2. ^{1}H chemical shifts corresponding to the β-CD, in presence and absence of Gl.

β-CD protons	δ_{Free}	$\delta_{Complex}$	$\Delta\delta$ (ppm)
H1	4.940	4.940	0
H2	3.490	3.495	0.005
H3	3.860	3.840	-0.020
H4	3.420	3.420	0
H5	-	3.780	-
H6	3.820	-	-

3.3. **NOE studies**

For these experiments, a significant nOe effect is observed between the protons of the azabicyclooctyl group and the H3 protons, principally for the Hc (1.17 %) and He (2.08 %), indicating the complexation of this one on the CD cavity. For the tolyl group, is also registered a significant signal enhancement of their protons signals (0.78 %), as well indicating the complexation of this group, but in minor extent that the aliphatic ring. All the above mentioned observations may conclude in two posibilities: a) the presence of a bimodal complexation [2] (i.e., the existence of two 1:1 complexes), with a formation of a 1:2 complex at high concentrations of β-CD or b) the direct formation of an 1:2 inclusion compound. This matter will be treated in future studies.

3.4. ^{13}C NMR spectroscopy

The ^{13}C NMR asignments signals for the pure components and the complex are reported in Tables 3 and 4. The most shifted ^{13}C NMR signals for the drug molecule corresponded to the azabicyclooctyl moiety, being these results in good agreeement with the ^{1}H NMR studies. By the other hand, the GL-induced large shifts of the C3 and C5 carbons of the β-CD indicate the formation of an inclusion complex, because these carbons are situated in the CD cavity.

TABLE 3. ^{13}C chemical shifts corresponding to the GL, in absence and presence of β-CD.

Gl carbons	δ_{Free}	$\delta_{Complex}$	$\Delta\delta$ (ppm)
C1	145.540	145.483	-0.057
C2	128.623	128.651	0.028
C3	132.022	131.948	-0.074
C4	142.480	142.605	0.125
Methyl	23.193	23.258	0.065
C1'	64.825	65.444	0.619
C2'	42.540	42.751	0.211
C3'	33.712	34.062	0.350
C4'	27.053	27.077	0.024

TABLE 4. ^{13}C chemical shifts corresponding to the β-CD, in presence and absence of Gl.

β-CD protons	δ_{Free}	$\delta_{Complex}$	$\Delta\delta$ (ppm)
C1	105.673	105.750	0.077
C2	75.935	76.009	0.071
C3	76.742	76.834	-0.092
C4	84.598	84.608	0.010
C5	74.583	74.684	0.101
C6	63.187	63.104	-0.083

CONCLUSIONS

From these studies, it is clearly observed the complexation of GL with β-CD in aqueous medium. Under these conditions (0.2 N in NaOD), the NMR studies evidenced the preferential complexation of the azabicyclooctyl moiety, but the phase solubility diagram revealed the formation of a 1:2 compound, indicating also the participitation of the tolyl moiety.

REFERENCES

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