Preparation and Characterization of Solid Complexes of Naphtoquinone and Hydroxypropyl-β-Cyclodextrin

Marcela Linares, María Martínez de Bertorello and Marcela Longhi*

Departamento de Farmacia, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba. Ciudad Universitaria , 5000 Córdoba, Argentina
Fax: 54-351-433-4163, E-mail: mrlcor@dqo.fcq.unc.edu.ar

* Author to whom correspondence should be addressed.

Abstract*:* The formation of an inclusion compound between a naphthoquinone derivative (**I**) and HP-ß-CD was studied in solid state by X-ray diffractometry, DSC, and IR.

Introduction

The formation of inclusion complexes with cyclodextrins constitutes a widely used strategy to increase the aqueous solubility and to decrease the countereffects of many drugs. Isoxazolylnaphthoquinones belong to a family of compounds with bacterial and tripanocidal activity [1,2], as well as with very low solubility in water. In previous studies in our laboratory, we demonstrated that their hydrophilic capacity increases markedly through complexation with hydroxypropyl-ß-cyclodextrin (HP-ß-CD) in aqueous solution [3].

In this study we investigate the formation of complexes between 2-hydroxy-N-(3,4-dimethyl-5-isoxazolyl)-1,4-naphthoquinone-4-imine (**I**) and HP-ß-CD in solid state. Thermoanalytic techniques, X-ray diffraction and IR spectroscopy were performed [4].

Experimental

1. Materials

The synthesis and identification procedures for **I** have been described previously. HP-β-CD (MW = 1326 - 1400; degree of molar substitution, 7.0) was a gift from CERESTAR USA Inc. (Hammond, IN). All other materials and solvents were of analytical reagent grade.

2. Methods

2.1 Preparation of inclusion complexes

Formation of solid complexes: aqueous solutions were prepared between **I** and HP-ß-CD in concentrations of 1:0,5; 1:1 and 1:2, respectively. The solutions were then placed in a thermostat bath at 25ºC for 72 hours and subsequently filtered by using nylon membranes 0.45 μm pores. The solid complexes were obtained after water removal. The freeze drying technique (LABCONCO, Freeze Dry System) was used to prepare inclusion complexes of **I** and cyclodextrin in solid state. Physical mixtures were prepared in parallel by mixing the powders employing the same molar ratios of **I** and HP-ß-CD.

2.2 Characterization of inclusion complexes

2.2.1 Fourier Transformed Infra Red (FTIR) Spectral Studies

The spectra of **I,** physical mixtures and inclusion complexes were recorded in a KBr pellet using a NICOLET FT / IR 5-SXC Spectrophotometer.

2.2.2 Differential Scanning Calorimetry (DSC) Studies

The samples were subjected to DSC studies using a Shimadzu DSC-50 model. In , Sn, Pb and Zn were used as reference materials. The samples were scanned at the rate of 6^{o}C / min.

2.2.3 *Powder X-ray diffraction (XRD) Studies*

The XRD patterns were recorded using a Philips X-ray generator (PW 1010), using Cu-K_{α} radiation.

Results and Discussion

Differential Scanning Calorimetry (DSC) Studies

The appearance of two endothermal peaks corresponding to the melting of compound **I** and to the dehydration of HP-β-CD is clearly observed in the thermogram corresponding to the physical mixture. It can also be observed the disappearance of the melting point at 223,6^{o}C corresponding to compound **I** in the thermogram of the inclusion complex 1:1.

Powder X-ray diffraction (XRD) Studies

The XR model corresponding to the physical mixture resulted from the simple overlapping of the diffractograms of compound **I** in its crystalline form and of the amorphous diffractogram of HP-β-CD. The diffractograms corresponding to the inclusion complexes were free of interference due to the amorphous state of the product obtained after the liophilic process.

Fourier Transformed Infra Red (FTIR) Spectral Studies

No significant variations were observed in the absorption spectra corresponding to the physical mixtures which resulted from the overlapping of the simple spectra (compound **I** and HP-β-CD). On the other hand, a shift and attenuation in the absorption band corresponding to the carbonyl of compound **I** were observed when the complex is formed by liophilization.

Conclusions

The FTIR, DSC and XRD studies for the complexes showed significant evidence of complexation 1:1 when the complexes are prepared by the freeze drying technique. The results demonstrate the capacity of HP-β-CD to interact with compound **I**.

When the complex was prepared by mixing the powders, it was evident in all cases that there was no true inclusion taking into account a simple physical mixture of both compound **I** and HP-β-CD.

References and Notes

1. Bogdanov, P.; de Bertorello, M.M.; Albesa, I. Oxidative Stress in Staphylococcus aureus Associated to the Cleavage of an Isoxazolylnaphthoquinoneimine with Antibacterial Capacity. *Biochem. and Biophysical Res. Comm.* **1998**, *244*, 561.
2. Schwarcz, M.; Goijman, S.; Molina, M.; Stoppani A. Effects of Isoxazolyl-naphthoquinoneimines on Growth and Oxygen Radical Production in *Trypanosoma cruzi* and *Crithidia fasciculata*. *Experientia* **1990**, *46*, 502.
3. Linares, M.; de Bertorello, M.; Longhi, M. Effect of Hydroxypropyl-β-cyclodextrin on the Solubility of a Naphthoquinone-imine. *Int. J. Pharm*. **1997**, *159*, 13.
4. Proceeding of the Ninth International Sympossium on Cyclodextrins, Santiago de Compostela, España; 1998.