Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 350 (2008) 155–165
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Theoretical and experimental vibrational study of miconazole and its dimers with organic acids: Application to the IR characterization of its inclusion complexes with cyclodextrins

Valéry Barillaro [a,*,1], Georges Dive [b,1], Eric Ziémons [c], Pascal Bertholet [a], Brigitte Evrard [a], Luc Delattre [a], Geraldine Piel [a]

[a] *Laboratory of Pharmaceutical Technology, Department of Pharmacy, University of Liege, CHU-Tour 4, Bât. B36, Avenue de l'Hôpital, 1, B-4000 Liège, Belgium*
[b] *Center for Protein Engineering, Chemical Department, University of Liege, Bât B6, Allée de la Chimie, 3, B-4000 Liège, Belgium*
[c] *Laboratory of Analytical Chemistry, Department of Pharmacy, University of Liege, CHU-Tour 4, Bât. B36, Avenue de l'Hôpital, 1, B-4000 Liège, Belgium*

Received 6 July 2007; received in revised form 22 August 2007; accepted 24 August 2007
Available online 4 September 2007

Abstract

The geometry, frequency and intensity of the vibrational bands of miconazole were derived from the density functional theory (DFT) calculations with the hybrid functional B3LYP and the 6-31G(d) basis set. Starting from the fully AM1 optimized geometries of miconazole/βCD/acids complexes, the miconazole/acid dimers were reoptimized at the B3LYP/6-31G(d) level. Three acids were studied: maleic, fumaric and L-tartaric acids. To begin with the vibrational spectral data obtained from solid phase in mid FT-IR spectrum of miconazole and its dimers are assigned based on the results of the normal modes calculations. All the observed spectra and the calculated ones are found to be in good agreement. In a second step, theoretical results allowed the assignment of FT-IR spectrum for the miconazole/HPγCD inclusion complex produced by supercritical carbon dioxide treatment and confirmed the inclusion of miconazole. The experimental spectra for the miconazole/HPγCD/acids complexes prepared by supercritical carbon dioxide processing were also assigned using theoretical results. The results confirmed the presence of a genuine inclusion complex and also the interaction between miconazole and the acid.

Keywords: Miconazole; Molecular modeling; Density functional theory; Normal mode; Miconazole/acid dimer; Cyclodextrin inclusion complexes

1. Introduction

Miconazole (1-2-((2,4-dichlorophenyl)-2-(2,4-dichlorophenyl)-methoxy)ethyl)-1-imidazole) is an antifungal drug with poor water solubility. For many years, authors have studied its interactions with cyclodextrins (CDs), a family of cyclic oligosaccharides consisting of 6-8 D-glucopyranosyl units linked by $\alpha_{(1\rightarrow4)}$-glycosylic bonds and presenting an apolar cavity. Depending on their shape, CDs can accommodate molecules inside their cavity to form inclusion compounds which modify the physico-chemical properties of the guest as its water solubility (Frömming and Szejtli, 1994). So, CDs are mainly used as excipients which can enhance aqueous solubility of sparingly soluble drugs (Loftsson and Brewster, 1996).

Infrared spectroscopy is a standard tool for structural characterization of chemical entities. The infrared assignments of miconazole have not yet been reported. For large molecules, quantum chemical calculations predicting harmonic frequencies and spectral intensities are essential when interpreting experimental infrared spectra. In the theoretical prediction of molecular vibrational properties, density-functional theory (DFT) has been demonstrated to be a cost-effective alternative to conventional *ab initio* approaches, more efficient than Hartree–Fock approach and second-order Møller–Plesset perturbation theory (MP2) (Johnson et al., 1993; Scott and Radom,

* Corresponding author. Tel.: +32 4 366 43 01; fax: +32 4 366 43 02.
E-mail address: v.barillaro@gmail.com (V. Barillaro).
[1] Equal contributors to this study.

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.08.048

1996; Wong, 1996). The DFT calculations with the hybrid exchange-correlation functional B3LYP (Beecke's three parameters (B3) exchange in conjunction with the Lee–Yang–Parr's (LYP) correlation functional) have been proved to be very effective for vibrational studies on several systems (Giese and McNaughton, 2002; Fu et al., 2003; Arici et al., 2005).

In our previous paper (Barillaro et al., 2007), we investigated the molecular structures of the miconazole/CD/acids complexes using the semiempirical Austin Model 1 (AM1) method developed by Dewar et al. (1985). The fully optimized geometries and the energetic outcomes of the complexes were determined. The role of the acid during the complexation of miconazole into cyclodextrins has been evidenced.

In another paper, we have shown that, after supercritical processing and in presence of cyclodextrins and of acids, the miconazole infrared spectrum is modified (Barillaro et al., 2004). The aim of the present work is to compute the equilibrium geometry, vibrational frequencies and infrared intensities for miconazole and miconazole/acids dimers using hydrid DFT and medium basis set. These calculations enable the assignment of the bands in the experimental pellet infrared spectra for both miconazole and miconazole/acids dimers. Then, the miconazole/CD(/acids) complexes infrared spectra were analyzed with the help of the theoretical results in order to point out interaction between the compounds and to confirm the presence of genuine inclusion complexes.

2. Materials and methods

2.1. Materials

Miconazole base ((1-2-((2,4-dichlorophenyl)-2-(2,4-dichlorophenyl)-methoxy)ethyl)-1-imidazole) was obtained from Janssen Pharmaceutica (Beerse, Belgium). Hydroxypropyl-γ-CD (HPγCD) (Cavasol® W8 HP, MS 0.58, 1.62% H_2O) was obtained from Wacker Chemie GmbH (Munich, Germany). Fumaric acid was from Fluka (Buchs, Switzerland), maleic acid from Acros (New Jersey, USA) and L-tartaric acid (Eur Ph. 4th Edition) from Merck (Damstadt, Germany).

CO_2 was of N48 quality (99.998%) from Air Liquide (Liège, Belgium). All the products were used as received.

2.2. Methods

2.2.1. Preparation of the physical mixtures

All the physical mixtures were prepared by gently grinding, in a mortar, the calculated and exactly weighed amounts of compounds in equimolar ratio.

2.2.2. Experimental preparation of the miconazole/acid associations

The miconazole/acid associations were prepared as follow: the miconazole/acid physical mixtures were left in an oven at 125 °C for 60 min, these conditions simulating temperature conditions in the supercritical carbon dioxide experiments.

2.2.3. Experimental preparation of the inclusion compounds using supercritical carbon dioxide processing

The inclusion complexes were produced using supercritical carbon dioxide ($SCCO_2$) following a procedure and using an experimental set-up previously described (Barillaro et al., 2004). Miconazole/HPγCD 1:1 (mol:mol) and miconazole/HPγCD/acids 1:1:1 (mol:mol:mol) physical mixtures were processed by supercritical carbon dioxide in a static mode at 30 MPa, 125 °C during 60 min. At the end of the experiment, the vessel was depressurized within 15 s. The vessel content, in the form of a compact solid, was emptied, ground and homogenized in a mortar before further analysis.

2.2.4. FT-IR spectrum

The transmission IR spectra were recorded from isotopically dispersed products in KBr. The FT-IR spectra were collected over the spectral region 4000–600 cm^{-1} at a resolution of 0.5 cm^{-1} on a computer interfaced Bruker Tensor 27 FT-IR spectrophotometer equipped with a N_2-cooled MCT detector. The number of scans was 64.

2.2.5. Normal modes analysis

A fully unconstrained geometry optimisation was performed at the DFT level using the 6-31G(d) basis set and gradient techniques with the help of the Gaussian 98 software (Frisch et al., 1998). The DFT level is the B3LYP functional which uses the three-parameter functional of Beecke (Becke, 1988; Becke, 1993) and the exchange-correlation term of Lee–Yang–Parr (Lee et al., 1988). For all the studied systems, all the degrees of freedom are optimized thus requiring a significant amount of computational time.

Starting from the AM1 optimized geometries for the miconazole/βCD/acid complexes (Barillaro et al., 2007), the βCD was removed and the DFT geometry optimizations were carried out without constraints. As two docking modes have been studied (dock1 and dock2), the B3LYP optimisations give rise to two different thermodynamically stable geometries for each miconazole/acid dimer.

To visualize the normal modes, the Molden® v. 3.5 software for Windows® was used (Schaftenaar and Noordik, 2000). For comparison with the experimental results, simulated IR spectra were calculated using the Swizard program revision 4.1 (Gorelsky, 2005) using the lorentzian model. The half-bandwidths (Δ1/2,I) were taken to be equal to 10 cm^{-1}. To facilitate the analysis of the results, only the mid wavenumber region (*ca.* 1700–1400 cm^{-1}) is considered.

3. Results

3.1. Normal modes analysis

Normal mode vibrational analyses at the B3LYP level were performed at the local energy minima characterized by all positive frequencies.

3.1.1. Miconazole

Miconazole is made of 39 atoms giving rise to 111 vibrational degrees of freedom. To allow the interpretation of the