The Pressure-Induced Polymorphic Transformations in Fluconazole

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ABSTRACT: The structural properties and Raman spectra of fluconazole have been studied by means of X-ray diffraction and Raman spectroscopy at pressures up to 2.5 and 5.5 GPa, respectively. At a pressure of 0.8 GPa, a polymorphic phase transition from the initial form I to a new triclinic form VIII has been observed. At higher pressure of $P = 3.2$ GPa, possible transformation into another new polymorphic form IX has been detected. The unit cell parameters and volumes, and vibration modes as functions of pressure have been obtained for the different forms of fluconazole. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:4164–4169, 2015

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INTRODUCTION

Fluconazole [2-(2,4-difluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl) propan-2-ol], an imidazole derivative, is an essentially active antifungal agent.[1,2] Two major advantages of fluconazole over other antifungal agents are the possibility to cross the blood–brain barrier and efficiency against *Cryptococcus neoformans*.[3–6] As active pharmaceutical ingredient (API), fluconazole crystallizes in more than one solid polymorphs.[7–9] The occurrence of polymorphism in an API and its impact on physicochemical and pharmaceutical properties can result in changes in the solubility, stability, dissolution, bioavailability, and efficacy of a drugs. This problem is well documented in the pharmaceutical literature.[10–13] However, during a pharmaceutical manufacturing, the initial compound purity can degrade as a result of stresses and other factors leading to the irreproducible transformations.[10,14–16] To understand the nature of these effects, the detailed characterization of the various forms of pharmacological compounds, such as polymorphs, solvates, or complexes, and their mechanisms of formation is a necessity.[17] Because of this, a large number of research groups have been engaged in various investigations aiming to generate and describe new polymorphs of pharmaceuticals to study their biomedical applications or to preserve the purity of the initial forms.[18–20] As an example, recently, it was found that the physical and chemical properties of fluconazole are changed under ionizing irradiations,[21] which is leading to the formation of radiolysis products with subsequent lowering of the concentration of the pure fluconazole.

The two forms of fluconazole named as polymorphic forms I and II were explored well by means of an X-ray diffraction, Raman spectroscopy, and differential scanning calorimetry.[7,8,12] Prior to the melting of fluconazole form I, a transition into a glassy state was found,[8] which is subsequently transformed to a stable polymorphic form II after cooling.[7] The following detailed studies of a fluconazole crystallization and recrystallization processes resulted in the discovering of fluconazole form III.[22,23] Structural and vibration spectra data for this phase are still contradictory and debatable.

A comprehensive review of the fluconazole polymorphs, solvates, and salts and some attempts of their classification were reported previously.[7] In addition, the crystal structure and vibration spectra of new four polymorphs of the fluconazole have been reported. In particular, fluconazole form IV was formed by cocrystallization of fluconazole with saccharin and its crystal structure have been described as the monoclinic symmetry, space group $P2_1/n$. Forms V and VI crystallize in the orthorhombic Pbca and monoclinic $C2/c$ space group, respectively. Fluconazole polymorph VII has orthorhombic symmetry with two molecules in the asymmetric unit.[7]

It should be noted that the features of the crystal structures of the fluconazole are governed by the dominant role of intermolecular hydrogen bonding as well as the versatility of the molecules in assembling within the complex geometry of hydrogen bonds.[24,25] Application of pressure can change the hydrogen bonds array dramatically, and could add an instability into the initial pharmaceutical polymorph.[14,24] High-pressure measurements can give us an important insight into the pressure-induced polymorphic transformations to reveal and understand the mechanisms of the polymorphic phase transitions. However, until now, the pressure effects on the fluconazole crystal were not addressed.

In order to study the pressure effects on the crystal structure and vibrational spectra of fluconazole, we conducted energy-dispersive X-ray diffraction and Raman spectroscopy experiments at pressures up to 2.5 and 5.5 GPa, respectively.

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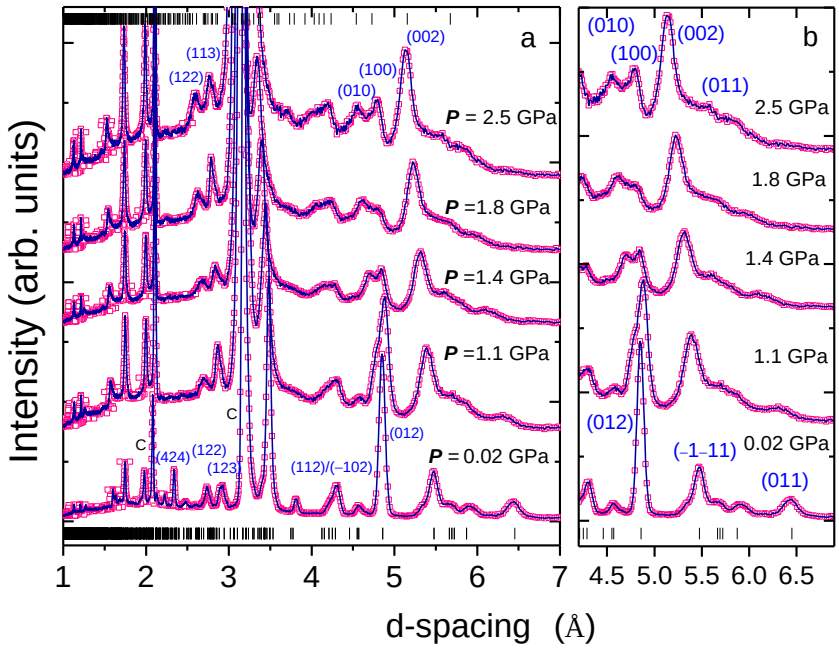

Figure 1. (a) The energy-dispersive X-ray diffraction patterns of the fluconazole measured at selected pressures and room temperature, and refined by the profile matching method. The experimental points and calculated profiles are shown. The ticks at the bottom and top indicates the calculated positions of a diffraction peaks for the initial form I of the fluconazole at ambient pressure and for the pressure-induced form VIII (at $P = 2.5$ GPa). (b) The enlarged parts of the X-ray diffraction patterns of the fluconazole. The selected diffraction reflections for forms I and VIII are marked.

EXPERIMENTAL

The initial sample of fluconazole was obtained from Sigma Chemical Company (St. Louis, Missouri) and used as received.

The energy-dispersive X-ray diffraction experiments at pressures up to 2.5 GPa were carried out at the beamline F2.1 (HASYLAB-DESY, Hamburg, Germany) using the multianvil X-ray system MAX80.[26] The sample was placed in the cylindrical boron nitride container with an internal diameter of 1 mm. The upper half was filled with the sample; the lower half contained sodium chloride powder for *in situ* pressure calibration. The cubic boron-epoxy chamber with sample container was compressed by six tungsten carbide anvils in a large hydraulic press. Diffraction spectra were recorded in an energy-dispersive mode using white synchrotron X-rays beam from the storage ring DORIS III. The ring operated at 4.5 GeV and a positron current of 80–150 mA. The incident X-ray beam was collimated to $100 \times 100\ \mu m^2$ with a divergence smaller than 0.3 mrad. Spectra were recorded by a Ge solid-state detector with a resolution of 155 eV at 5.9 keV and 500 eV at 122 keV resulting in a resolution of diffraction patterns of $\Delta d/d \approx 1\%$. The Bragg angle 2θ was fixed at 9.089°, counting times for each diffraction pattern were about 10 min. The refinement of powder diffraction patterns was made by means of Fullprof program.[27]

The Raman data at room temperature and pressures up to 5.5 GPa were obtained using a LabRam spectrometer (NeHe excitation laser) with a wavelength of 632.8 nm, 1800 grating, confocal hole of 1100 μm, and a 50 × objective. The BX90 type diamond anvil cell[28] was used for Raman experiments. The sample was loaded into the hole of the 120-μm diameter made in the Re gasket intended to about 30 μm thickness. The pressure was determined by the ruby fluorescence technique.[29] The fluconazole sample is very soft and it reacts with most of the commonly used pressure transmitting substances; as a result, experiments were performed without pressure transmitting medium.

RESULTS AND DISCUSSION

Energy-Dispersive X-Ray Diffraction

The energy-dispersive X-ray diffraction spectra of fluconazole measured at different pressures are illustrated in Figure 1. At ambient pressure, the triclinic phase with space group $P\bar{1}$ was evidenced. The calculated unit cell parameters were $a = 7.502(4)$ Å, $b = 7.705(5)$ Å, $c = 11.981(5)$ Å, $\alpha = 85.1(1)$, $\beta = 84.5(2)$, $\gamma = 75.9(3)^0$ consistent with the previous studies.[7,8]

At pressure of $P \sim 0.8$ GPa, numerous changes in X-ray diffraction patterns were observed, as illustrated in Figure 1. The diffraction peaks indexed as (011) at $d_{hkl} \approx 6.5$ Å and (424)/(0$\bar{1}$7) at $d_{hkl} \approx 2.3$ Å disappeared. The initially narrow reflection (012) at $d_{hkl} \sim 4.8$ Å became split. In addition, a drastic change in the relative intensities of the diffraction peaks (122)/(123) located around 2.8 Å was detected (Fig. 1). Changes in the diffraction data clearly evidence a structural phase transformation in the fluconazole. The structural models for different polymorphic phases of fluconazole[7] were tested during diffraction data refinement. Successful indexing and better fitting of diffraction patterns were obtained with the triclinic $P\bar{1}$ symmetry but with the lattice parameters different from the initial form I of fluconazole. We introduce the notation "form VIII" for this new phase of fluconazole in terms of classification introduced in references.[1,7,8] The refined unit cell parameters of the fluconazole form VIII (at pressure $P = 1.4$ GPa) are $a = 4.959(2)$ Å, $b = 7.281(3)$ Å, $c = 10.919(5)$ Å, $\alpha = 95.3(2)$, $\beta = 82.1(1)$, $\gamma = 83.1(2)^0$.