Journal of Molecular Structure 1118 (2016) 288–292

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

X-Ray diffraction, spectroscopy and thermochemical characterization of the pharmaceutical paroxetine nitrate salt

Paulo S. Carvalho Jr. [a], Cristiane C. de Melo [a, b], Alejandro P. Ayala [b], Javier Ellena [a, *]

[a] Instituto de Física de São Carlos, Universidade de São Paulo, CP 369, 13560-970, São Carlos, SP, Brazil
[b] Departamento de Física, Universidade Federal do Ceará, CP 6030, Fortaleza, Ceará 60455–970, Brazil

ARTICLE INFO

Article history:
Received 4 March 2016
Received in revised form
5 April 2016
Accepted 6 April 2016
Available online 14 April 2016

Keywords:
Antidepressant
Paroxetine nitrate
Solid state
DSC/TGA
Infrared spectra

ABSTRACT

A comprehensive solid state study of Paroxetine nitrate hydrate, $(PRX^{+}\cdot NO_3^{-})H_2O$, is reported. This salt was characterized by a combination of methods, including Single crystal X-ray diffraction, Thermal analysis, Fourier transform infrared spectroscopy (FTIR) and Solubility measurements. $(PRX^{+}\cdot NO_3^{-})H_2O$ crystallizes in the monoclinic C2 space group ($Z' = 1$) and its packing was analyzed in details, showing that the main supramolecular motif consists in a $C_2^2(4)$ chain formed by charge-assisted N^{+}-H···O^{-} hydrogen bonds. The salt formation and conformation features were also accuracy established *via* FTIR spectra. In comparison with the pharmaceutical approved $(PRX^{+}\cdot Cl^{-})\cdot 0.5H_2O$, $(PRX^{+}\cdot NO_3^{-})\cdot H_2O$ showed a decrease of 24 °C in the drug melting peak and a slight reduction in its water solubility value.

1. Introduction

Paroxetine (PRX), [(3S-trans)-3-[(1,3-benzodioxol-5-yloxy) methyl]-4-(4-fluorophenyl)-piperidine (Scheme 1), is the most potent inhibitor of the neuronal reuptake of serotonin (5-hydroxytryptamine, 5-HT) [1] and is clinically approved for the treatment of major depression, obsessive compulsive disorder, generalized anxiety and social phobia [1–7]. Furthermore, PRX is well tolerated and effective in the depression/anxiety treatment of young and elders [2], being one of the most widely prescription drugs in the world [8]. PRX has been pharmaceutically administered as a hydrochloride salt. Two polymorphic forms are recognized for this salt: a stoichiometric hydrate, $(PRX^{+}Cl^{-})H_2O$, and a hemihydrate form, $(PRX^{+}Cl^{-})0.5H_2O$; in which the latter is the thermodynamically most stable. Additionally, anhydrate [9] and solvate salts containing propan-2-ol (isopropyl alcohol) [10] has been reported. Recently, Paroxetine bromide hemihydrate, $(PRX^{+}Br^{-})0.5H_2O$ and its corresponding dehydrate phase have been reported for us, as a part of our studies on designing of better antidepressant solid forms [11]. Beyond these structures, novel PRX salts with improved solubility and stability are still requested to provide a better manufacturing and pharmaceutical performance of this drug.

Salt selection is a common strategy applied to improve pharmaceutical properties of ionic APIs. In general, the salt confers valuable attributes such as the increasing of chemical stability, aqueous solubility and bioavailability [12–15]. For this purpose, there are a wide variety of salt formers included into the GRAS list with different chemical properties (pK_a, molecular weight, solubility) that can be combined with PRX to achieve a salt. Within this context, we have been rationally prepared the paroxetine nitrate hydrate salt, $(PRX^{+}\cdot NO_3^{-})H_2O$, following a supramolecular approach based on the establishment of charge-assisted hydrogen bonds (CAHBs). Structural correlations between $(PRX^{+}\cdot NO_3^{-})H_2O$, $(PRX^{+}Cl^{-})H_2O$ and $(PRX^{+}Cl^{-})0.5H_2O$ salts were also accuracy established. Furthermore, thermal behavior, spectroscopy properties and solubility measurements were performed for supporting the crystallographic results.

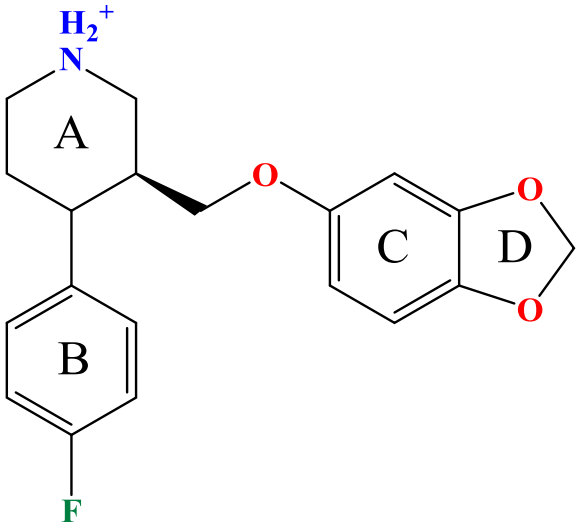
2. Experimental details

2.1. Preparation of paroxetine nitrate salt

Paroxetine chloride hemihydrate, $(PRX^{+}Cl^{-})0.5H_2O$, was used as a precursor for the synthesis of the nitrate salt. Chemicals and solvents, such as sodium hydroxide, sodium sulfate anhydrous,

* Corresponding author.
E-mail address: javiere@ifsc.usp.br (J. Ellena).

http://dx.doi.org/10.1016/j.molstruc.2016.04.014
0022-2860/



Scheme 1. Structure of Paroxetine cation (PRX^+). The N1–C1→C5, C7→C12, C14→C19 and C10–C11–O5–C13–O6 are designed A, B, C and D rings, respectively.

nitric acid, ethanol 95%, ethyl ether were of reagent grade quality and used without further purification. Paroxetine free base was obtained after deprotonation of $(PRX^+Cl^-)0.5H_2O$, following a protocol previously reported for us [11]. $(PRX^+NO_3^-)H_2O$ was prepared though the reaction of PRX free base and HNO_3 acid. Single crystals were growth from an ethanol solution 95%(v/v).

2.2. Single-crystal X-ray diffraction (SCXRD)

X-ray data of $(PRX^+NO_3^-)H_2O$ were acquired at 120 K (Cryostream, Oxford Cryosystems) on a Bruker D8 VENTURE diffractometer with PHOTON 100 CMOS detector system, using Cu Kα radiation. The data were integrated and processed *via* SAINT [16] and SADABS [17] softwares. The structure was determined using the Olex2 [18] program as a graphical interface together with the SHELXS and SHELXL programs [19], in order to solve and refine the structure, respectively. Hydrogen atoms were placed in geometric positions and refined with fixed individual displacement parameters [$U_{iso}(H) = 1.2U_{eq}$ or $1.5U_{eq}$] according to the riding model (C-H bond lengths of 0.97 Å and 0.96 Å, for methylene and methyl groups, respectively). Molecular representations, tables and pictures were generated by Olex2 [18] and MERCURY 3.2 [20] programs. The crystallographic data were deposited at the Cambridge Crystallographic Data Center under the numbers CCDC 1456602. Copies of the data can be obtained, free of charge, *via* www.ccdc.cam.ac.uk.

2.3. Vibrational spectroscopies

Middle infrared spectrum (4000-400 cm^{-1}) was recorded for $(PRX^+NO_3^-)H_2O$ and $(PRX^+Cl^-)H_2O$ salts as KBr pellets on a Shimadzu IR Prestige FTIR Spectrometer. The spectra were acquired under 64 scans of accumulation and at 4 cm^{-1} of resolution.

2.4. Thermal analysis

Differential Scanning Calorimetric measurements (DSC) were carried out on a Shimadzu DSC-60 instrument. Samples (2.5 ± 0.5 mg) were sealed in a crimped aluminum pan and heated under a flow of 5% O_2-N_2 from 25 to 300 °C at a heating rate of 10 °C/min. Thermogravimetric analyses (TGA) were performed on a Shimadzu TGA-60 thermobalance. Approximately 2.5 mg of sample were placed on an alumina pan and heated under a flow of 5% O_2-N_2 from 25 to 300 °C at a heating rate of 10 °C/min. All data were processed using the Shimadzu TA-60 thermal data analysis software.

2.5. Hot-stage microscopy (HSM)

Hot-stage (HS) microscopy was performed using a Linkam T95-PE device coupled to an optical microscope Leica DM2500 P. The $(PRX^+NO_3^-)H_2O$ crystal was heated at a constant rate of 10 °C/min from 25 °C to 150 °C, with this process being stopped after the melting of the compound. Images were recorded by a CCD camera attached to the microscope in time intervals of 10 s *via* the software Linksys 32.

2.6. Solubility

Aqueous solubility of $(PRX^+NO_3^-)H_2O$ was determined by the classical saturation shake-flask method at 20 °C in deionized water [21]. A saturated solution of $(PRX^+NO_3^-)H_2O$ was obtained stirring an excess amount of $(PRX^+NO_3^-)H_2O$ salt (30 mg) in 600 μL of water for 48 h. After this time, an aliquot of the saturated solution was removed, filtered through a 0.45 mm filter (Millipore), diluted 100-fold in water and its concentration measured by UV spectroscopy at $\lambda_{max} = 293$ nm. The standard solutions used to generate the calibration curve were prepared using $(PRX^+Cl^-)0.5H_2O$ salt. The concentration of PRX^+ in the saturated aliquots was quantified by interpolating of spectroscopic measurements in a calibration curve whose concentrations ranged from 0.005 to 0.2 mg mL^{-1}. This experiment was run in triplicate.

3. Results and discussion

3.1. Crystal structure of paroxetine nitrate hydrate

Considering the strong tendency of PRX to form salts ($pK_a = 9.9$ of piperidine N), and the dominance of CAHBs in the crystal packing of chloride and bromide PRX forms [10,11,22], a stoichiometric paroxetine nitrate hydrate salt was prepared, $(PRX^+ NO_3^-)H_2O$. This salt crystallizes in the monoclinic Sohncke space group C2 in a needle-shaped morphology. The C-centered unit cell shows a very long *a* axis compared to *b* and *c*-axis. Details of the structure determination and the refinement parameters are presented in Table 1. The asymmetric unit encloses a protonated PRX^+ molecule, a NO_3^- anion and a H_2O molecule. The water molecule lies on the crystallographic 2-fold axis and had its H atoms refined with 0.5 of occupancy. A view of crystallographic asymmetric unit is shown in Fig. 1.

PRX^+ is a six-membered piperidinium ring in the usual chair conformation (puckering parameters [23]: $q_2 = 0.0284(3)$, $q_3 = -0.5705(3)$, $Q_T = 0.5713(3)$, $\varphi_2 = -52.69(5.10)$ and $\theta_2 = 177.15(3)^o$) with the ethoxyl-benzodioxole and fluorophenyl substituents in the equatorial position. The geometric parameters of PRX^+ are listed in Table S1. Due to protonation, the sp^3 hybridized N1 atom bears a positive charge and assumes a tetrahedral configuration. In the present structure, the ethoxyl bridge between the piperidine ring and benzodioxolo group (C + D ring) has an antiperiplanar conformation with C5-C6-O4-C7 of 172.2(3)° (Table S1, support information). As reported previously, the conformational flexibility of PRX^+ is related to the rotation freedom about C6-O4 bond. Additionally, the C6-O4-C7-C12 torsion angle that defines the orientation of benzodioxole groups with respect to C5-C6-O4 mean plane assumes the value of −169.2(3)°. Although the conformation of PRX^+ in $(PRX^+ NO_3^-)H_2O$ salt differs from those reported in $(PRX^+ Cl^-)0.5H_2O$ [10,22] and $(PRX^+ Br-)0.5H_2O$