Crystal Chemistry of Sibutramine: Thermal, Diffractometric and Spectroscopic Characterization

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ABSTRACT: Monohydrated sibutramine hydrochloride is a widely used active ingredient for the treatment of obesity. An anhydrous form of sibutramine hydrochloride was prepared starting from its monohydrate form upon heating it at 140°C for 15 min. This dehydration process was monitored using conventional TG/DSC methods. Heated above 190°C, sibutramine hydrochloride sublimes and recrystallizes on the cold walls of the test tube, giving platelet shaped crystals suitable for single crystal X-ray diffraction analysis: monoclinic, $P2_1/n$, $a = 7.321(2)$ Å, $b = 25.456(5)$ Å, $c = 9.750(3)$ Å, $\beta = 101.60(2)°$, $V = 1779.9(8)$ Å^3, $Z = 4$. At variance, sibutramine free base was typically recovered as a viscous oily material, upon treatment of its hydrochloride salt in ethyl acetate solution. Recrystallization from hexane yielded a white polycrystalline powder, the structure of which was determined by unconventional *ab initio* X-ray powder diffraction analysis: triclinic, $P\text{-}1$, $a = 8.6578(3)$ Å, $b = 9.3318(3)$ Å, $c = 11.1224(4)$ Å, $\alpha = 110.434(3)°$, $\beta = 100.159(3)°$, $\gamma = 89.201(2)°$, $V = 827.76(5)$ Å^3, $Z = 2$. Sibutramine, in its different crystalline environments, was also fully characterized by solid state ^{13}C NMR analyses. Additional spectral information was obtained by collecting spectra of a metastable, oily sample, before it slowly recrystallizes (within hours). © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:5229–5239, 2008

Keywords: sibutramine; crystal and molecular structure; powder diffraction; solid state NMR

INTRODUCTION

Racemic sibutramine hydrochloride belongs to a new generation of active ingredients in drugs for the treatment of different diseases, mainly obesity and more rarely, for depression and Parkinson's disease.[1,2] It is a neuronal monoamine reuptake inhibitor of the norepinephrine, dopamine and, to a lesser extent, serotonin.[3–5] As reported in the patent literature,[2,6,7] sibutramine (hereafter, **S**) has been prepared in different crystalline forms, that is, as free base or in a number of salts, such as anhydrous hydrochloride, monohydrate hydrochloride, hemihydrate methanesulfonate and anhydrous malate.[8] According to the cited patents, the hemihydrate methanesulfonate and anhydrous malate forms are highly soluble in water over a broad pH range, with solubilities >700 g L^{-1} at pH values from 1.2 to 7.4. Differently, the monohydrate hydrochloride form (**S · HCl · H$_2$O**) is much less soluble in water (solubility = 2.9 g L^{-1} at pH = 5.2 and 30.6 g L^{-1} at pH = 7.4[9]), while the anhydrous hydrochloride form (**S · HCl**) is highly hygroscopic, thus making

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it less appropriate for formulation and therapeutic use. The monohydrate hydrochloride form is presently commercialized for clinical treatments under the trade names of Meridia® (in the USA) or Reductil® (in Europe).

Only very recently, the structural model of the (**S · HCl · H$_2$O**) form was reported.[10] In addition, a few single-crystal structural models for more complex sibutramine derivatives have been proposed.[11–13] However, to our knowledge, no report on the physical properties of the *hydrated* commercialized crystalline form, highlighting the role of the lattice water molecules, has ever been presented. Thus, aiming at addressing the relative stability of the hydrated and anhydrous species (also in view of preparing different drug formulations), a series of experiments were carried out. Accordingly, in the following sections, our studies on the anhydrous (**S · HCl**) and free base (**S**) forms are reported, which combine diffraction, thermal and NMR analyses, in conjunction with an extended characterization of the **S · HCl · H$_2$O** form and of their mutual transformation paths.

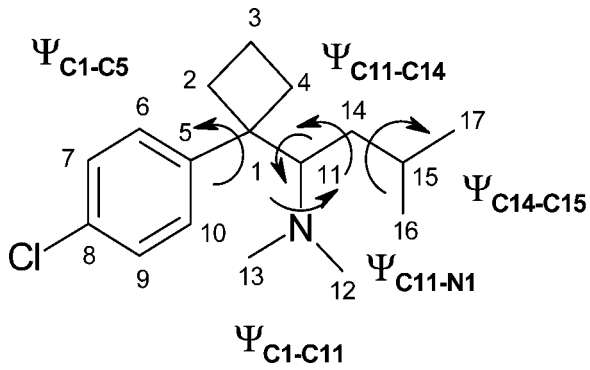
The structural results and spectroscopic assignments discussed hereafter will refer to the molecular structure and numbering scheme exemplified for the free base molecular sketch depicted in Scheme 1, where a number of torsion angles (Ψ_{i-j}), relevant in addressing its conformational freedom and later collected in Table 2, are also shown.

EXPERIMENTAL

Materials and Methods

The synthesis of the monohydrate sibutramine hydrochloride form (**S · HCl · H$_2$O**) was carried out according to literature methods.[7] Heating this material above 140°C for about 15 min allows the preparation of the anhydrous species in quantitative yields. Single crystals of anhydrous sibutramine hydrochloride were obtained by sublimation/decomposition (see below) of the monohydrate form at 190°C for an hour, allowing deposition of 100% pure **S · HCl** on the cold walls of a test tube, maintained near room temperature. This material was fully characterized by X-ray single-crystal and powder diffraction methods, as well as by solid state ^{13}C NMR. Thermal analyses were performed using a Perkin Elmer DSC-7 operated on *ca*. 3.0 mg of samples and at scanning rate of 10°C/min from 40 to 220°C.

Solid state ^{13}C measurements were performed on a Bruker AVANCE 400 spectrometer operating at 100.63 MHz for carbon, equipped with a 4 mm double bearing MAS probe. The cross-polarization magic-angle-spinning (CPMAS) spectra were recorded at room temperature using 90° pulse lengths of 4–5 μs, recycle time of 20 s, contact time of 1 ms, high power proton decoupling of 110 kHz, spinning rate of 7.5 kHz and were transformed using an exponential line broadening of 20 Hz. Single pulse excitation (SPE) experiments with high power proton decoupling (70 kHz) were recorded with a recycle times of 5 s, so as to select carbons belonging to the most mobile moieties. The SPE spectrum of **molten S** was recorded without spinning. When **molten S** resolidified (within hours), a CPMAS was acquired. The spectra were referenced to tetramethylsilane (TMS) as indirect standard.



Scheme 1.

Single Crystal X-Ray Diffraction Structural Analysis

Single crystal X-ray measurements for sibutramine hydrochloride (anhydrous form) **S · HCl** were performed on a Enraf Nonius CAD4 diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å), using the ω scan technique. Unit cell parameters were determined using 25 reflections in the $9 \leq 2\theta \leq 15°$ range, a total of 3384 reflections (3226 unique) were collected, at room temperature, up to 50.6° in 2θ and index range: $-8 \leq h \leq 8$, $0 \leq k \leq 30$, $0 \leq l \leq 11$. Intensity decay of about 6% was observed during data collection. The structure was solved by direct methods using the SHELX97 suite of programs and refined on F^2 by full-matrix least-squares procedure,[14] with anisotropic temperature factors for non-H atoms. H atoms were treated isotropically as riding on their pertinent C (or N) atoms.