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Short communication

Structures from powders: Bupropion hydrochloride

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ABSTRACT

The crystal structure of bupropion hydrochloride, **1**, was fully characterized from powdered crystalline samples, using the *ab-initio* XRPD technique and a global optimization strategy (simulated annealing), adopting, as starting model, the already known molecular structure of its ethanol solvate, **2**. Bupropion hydrochloride crystallizes as a racemate in monoclinic system, space group $P2_1/c$ with $Z = 4$, $a = 14.3406(3)$ Å, $b = 8.7564(2)$ Å, $c = 11.8801(2)$ Å, $\beta = 78.025(2)^\circ$, $V = 1459.34(5)$ Å^3. In the crystals of **1** the molecules interact *via* strong NH···Cl contacts, generating dimeric entities with μ-Cl ions. Further stabilizing contacts, of the CH···O are at work, but differently organized in the **1** and **2** phases. The thermal behaviour of the product was assessed by differential scanning calorimetry.

1. Introduction

Bupropion hydrochloride, (±)1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)amino]-1-propanone hydrochloride, belongs to the chemical class of aminoketones and it is known also with the generic name of amfebutamone hydrochloride. It is a second generation antidepressant approved in US and in some European countries, but its exact mechanism of action is not completely clear. With respect to the first generation antidepressants, which act at different sites in the brain, second generation drugs act at specific neurotransmitter receptor sites. In particular, bupropion hydrochloride seems to act as a dopamine norepinephrine reuptake inhibitor and it is used also in smoking cessation and for treatment of seasonal affective disorders [1]. Pure bupropion enantiomers were successfully synthesised but they give rise to a rapid racemization [2]. Additionally, in patent literature the pharmaceutical uses of the pure enantiomers of bupropion, (+) and (−)-bupropion are reported [3]. However, this dug is preferably used as a racemate. In fact, racemic bupropion is the Active Pharmaceutical Ingredient (API) of Wellbutrin® and Zyban® (marketed by Glaxo Smith Kline). In literature a crystal structure of an ethanol hemisolvate bupropion derivative, obtained from single-crystal X-ray analysis, is reported [4] while the patent literature includes the characterization by X-ray powder diffraction and DSC analyses of three polymorphic forms of the more stable bupropion hydrobromide.[1] Standard solution ^{1}H and ^{13}C NMR analyses of bupropion free base and bupropion hydrochloride have been also carried out [5]. Nevertheless, a complete characterization of pure solid bupropion hydrochloride is still absent.

Nowadays, pharmaceutical companies often require the complete and exact determination of the solid-state structure of API's, since many different polymorphic forms may occur during their preparation, processing or even storage. Since different crystal arrangement induce different physicochemical properties [6], the same API, in different crystal forms, may show different activity, solubility, bioavailability, permeability and adsorption from the tissues or biological membranes, thus heavily influencing the efficiency (and toxicity) of the pharmaceutical formulation. Accordingly, in the past few years, we have started a project, in collaboration with some Italian Pharmaceutical Industries, on the structural characterization of APIs [7]. Following our experience in solving structure from polycrystalline samples [8], we present here the complete molecular and crystal characterization by X-ray powder diffraction analysis of bupropion hydrochloride, **1**, coupled with the additional information obtained from thermal analysis.

2. Experimental

2.1. Materials and methods

Thermal analyses were performed on a Perkin Elmer DSC7 machine. The sample weighting (3.30 mg) was heated in an opened

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[1] Bupropion hydrobromide is more stable to degradation than equivalent bupropion hydrochloride compositions when stored for at least 3 or 6 months in accelerated storage conditions: 40 °C and 75% relative humidity. See: W. Oberegger, F. Zhou, P. Maes, S. Turchetta, G. Jackson, P. Massardo, Modified release formulations of a bupropion salt, WO2007/002597, 2007.

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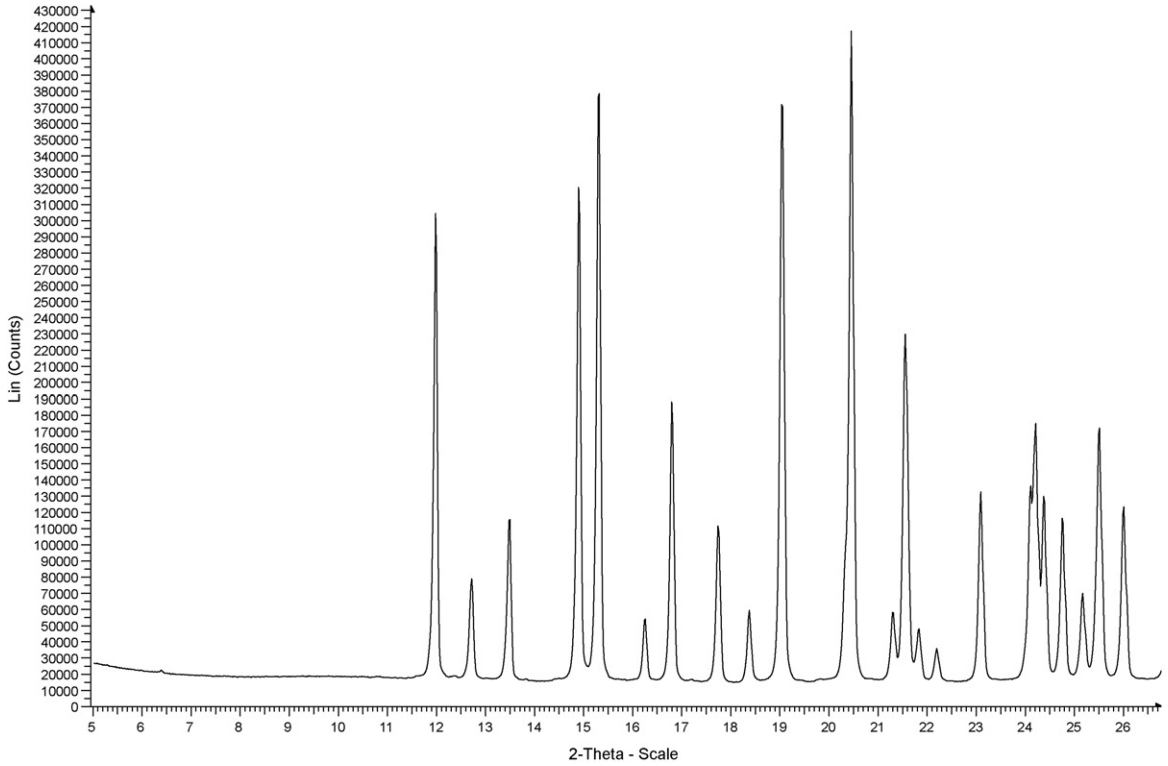


Fig. 1. Low angle portion ($5 < 2\theta < 27^\circ$) of the X-ray powder diffraction trace of bupropion hydrochloride.

aluminium pan at a scanning rate of 10 °C min^{-1}. NMR experiments were performed on a Bruker AVANCE 400 spectrometer operating at 400.16 MHz for ^{1}H and at 100.63 MHz for ^{13}C, respectively. IR experiments were performed on a FTIR Shimadzu 21 Prestige on Nujol mulls.

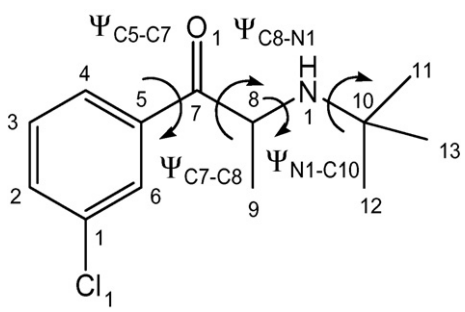
2.2. X-ray powder diffraction analysis

A strictly monophasic sample of bupropion hydrochloride was gently ground in an agate mortar, and then deposited in the hollow of a 0.2 mm deep aluminum sample holder, equipped with a quartz monocrystal zero background plate (supplied by *The Gem Dugout*, State College, PA). Diffraction data were collected in the 5–105° 2θ range (no significant peaks being observed at high angles), sampling at 0.02°, on a θ:θ vertical scan Bruker AXS D8 Advance diffractometer, equipped with a linear Lynxeye position sensitive detector, set at 300 mm from the sample (Ni-filtered Cu K$\alpha_{1,2}$ radiation). Fig. 1 contains the low angle portion of the raw data. Standard peak search methods, followed by indexing by TOPAS-R, allowed the determination of approximate cell parameters: a = 14.32 Å, b = 8.77 Å, c = 11.90 Å, β = 101, 90°, V = 1462 Å^3, in the monoclinic $P2_1/c$ space group, GOF(23) = 36.4. The structure solution was initiated by employing a semi-rigid molecular fragment [flexible about a few torsion angles (see Scheme 1)] taken from the known single-crystal structure of the ethanol hemisolvate derivative (**2**, CCDC code NUFSOW), removing the solvent molecule. Simulated annealing, using the default parameters set in TOPAS-R and 1,000,000 iterations, allowed the location and orientation of the used fragments, later refined by the Rietveld method. All computations were performed using TOPAS-R, accounting for the full α_1–α_2 doublet. No antibump or distance restraints were introduced in the final refinement cycles, apart from the rigid-body description of the molecular fragment cited above. The fundamental parameters approach in describing the peak shapes was employed, the background contribution was modeled by a polynomial fit (4th order Chebyshev model), and preferred orientation correction for [1 0 0] pole was described by the March–Dollase formulation [final magnitude r = 0.931(2)]. Fig. 2 shows the final Rietveld refinement plot. Crystal data: $C_{13}H_{19}NOCl_2$, 293 K, λ (Å) = 1.5418, monoclinic space group $P2_1/c$, a = 14.3406(3) Å, b = 8.7564(2) Å, c = 11.8801(2) Å, β = 78.025(2)°, V = 1459.34(5) Å^3, Z = 4, ρ_{calc}, 1.257 g cm^{-3}, μ (Cu Kα) = 3.876 mm^{-1}, R_{wp} = 0.163, R_p = 0.076, R_{Bragg} = 0.056, 2θ range 5–105°. Fractional atomic coordinates have been deposited as CIF file within the Cambridge Crystallographic Database as publication No 710556.

3. Result and discussion

3.1. Thermal properties

The DSC trace recorded for bupropion hydrochloride sample (not shown here) shows a sharp endotermic peak at about 246 °C (T_{onset} at *ca.* 244 °C) corresponding to the melting point of bupropion HCl. Previously, in patent literature a much lower melting point (233 °C) was reported [9]. The presence of a unique endothermic peak assesses the purity of the compound and the absence of resid-



Scheme 1.

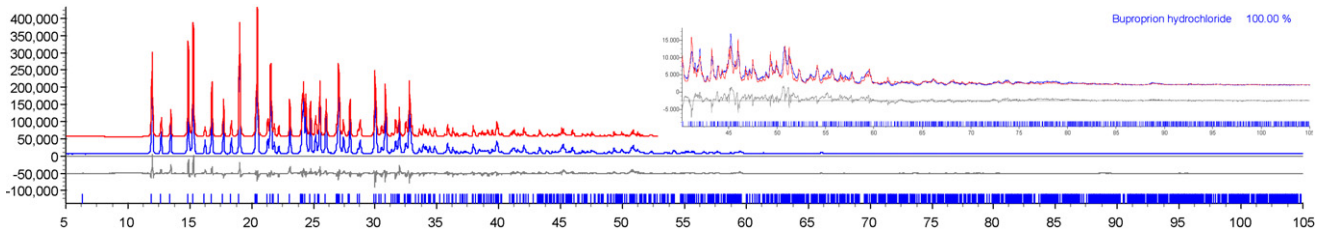


Fig. 2. Final Rietveld refinement plot for bupropion hydrochloride, with peak markers and difference plot ($y_{obs} - y_{calc}$) at the bottom. Blue: observed data (y_{obs}); red: calculated data (y_{calc}, shifted along the y coordinate for sake of graphical comparison). The insert shows the high angle region ($2\theta > 40^\circ$) and a magnified scale (12×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

ual crystallization solvent. The transition from the solid-state to the liquid state involves an enthalpy change of about 26 kJ mol^{-1}. After the melting event, this compound appears to undergo degradation and/or decomposition.

3.2. IR and NMR spectroscopy

The IR, ^{1}H and ^{13}C NMR spectra of bupropion hydrochloride were already reported in literature [5]; our measurements confirm the identity of these spectral features, and, additionally, witness, through comparison of the IR spectrum (collected by Perrine et al., as in Ref. [5], on a solid sample in Nujol mulls), that a unique crystal phase (not a – still unknown – polymorph) is present. The presence of a strong N–H···Cl hydrogen bond (see the structural description) is also evident from the lowering of the (υ N–H) band, down to 2671 cm^{-1}.

3.3. X-ray powder diffraction

The diffraction pattern of a product, a fingerprint of its crystalline state, can be used to identify the crystal form of any drug. Fig. 2 shows the XRPD spectrum of bupropion hydrochloride. The most intense XRPD peaks have the 2θ angle positions at the following values (°): 6.36; 11.96; 12.69; 13.47; 14.88; 15.27; 16.26; 16.80; 17.74; 18.34; 19.05; 20.45; 21.30; 21.57; 21.83; 22.19; 23.07; 24.10; 24.22; 24.38; 24.75; 25.18; 25.49.

3.4. Crystal and molecular structures of bupropion hydrochloride

A view of the molecule, with the conformation derived by our structural analysis is depicted in Fig. 3a (for the atomic labeling see Scheme 1). The lateral branch, connected to the phenolic atom C5, is flexible around four torsion angles which were freely refined during the structural analysis. The values obtained in the final refinement are reported in Table 1, where a comparison with the geometrical parameters of the ethanol hemisolvate, **2**, is also shown [4].

In the structure of pure bupropion hydrochloride, **1**, the organic molecule shows a molecular conformation similar (but not equal) to that of the ethanol hemisolvate derivative, **2** (see Table 1). Fig. 3a and b highlights the relative stereochemical differences, mostly related to the *ca.* 37° difference in the C6–C5–C7–C8 torsional angle.

Table 1
Selection of the relevant conformational parameters of the bupropion hydrochloride and of the ethanol hemisolvate derivative (CCDC code: NUFSOW).

	Torsion angle	Bupropion hydrochloride	Bupropion hydrochloride ethanol hemisolvate [4]
C6–C5–C7–C8, °	Ψ_{C5-C7}	−154.8(2)	169.9
C5–C7–C8–N1, °	Ψ_{C7-C8}	−148.2(1)	−146.6
C7–C8–N1–C10, °	Ψ_{C8-N1}	79.9(3)	81.2
C8–N1–C10–C11, °	Ψ_{N1-C10}	179.0(3)	−171.98[a]

[a] In NUFSOW the C13 atom of the *t*-butyl residue has been used.

In both species, the molecules are linked by H-bond interactions to chloride anions (NH···Cl 3.14 and 3.22 Å in **1** and **2**, respectively); in both cases, NH···Cl interactions generate centrosymmetric dimers (see Fig. 4) in which two Cl$^-$ ions bridge the $NH_2\cdots NH_2$ contact (above 4.2 Å). These crystalline species are further stabilized by weaker C—H···O contacts [10]: C4···O1 = 3.31 Å in **1** and C2···O2 = 3.50 Å in **2**. Obviously, ethanol in **2** is a non-innocent molecule, as, interacting with the chlorides through evident OH···Cl bonds (3.39 Å), it does not act merely as a space filling moiety.

The (computed or measured) X-ray powder diffraction traces of **1** and **2** are very distinct; but, as evidenced by the seminal work

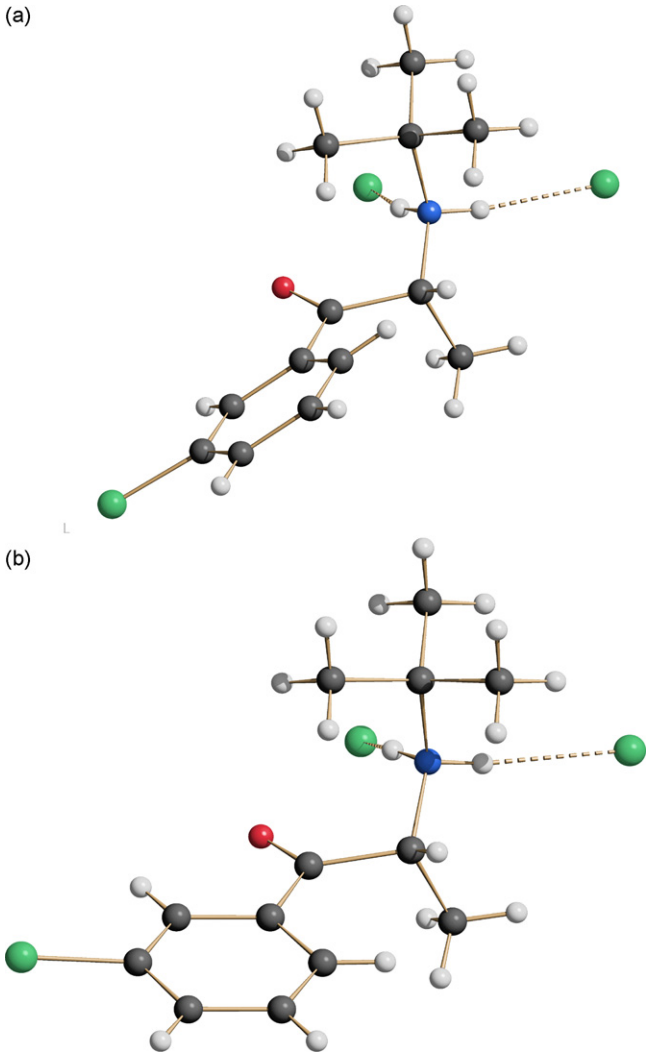


Fig. 3. Schematic drawing of the molecular conformations of bupropion hydrochloride in **1** (a) and in the solvated phase **2** (b). Intermolecular hydrogen bonds are shown with fragmented lines.

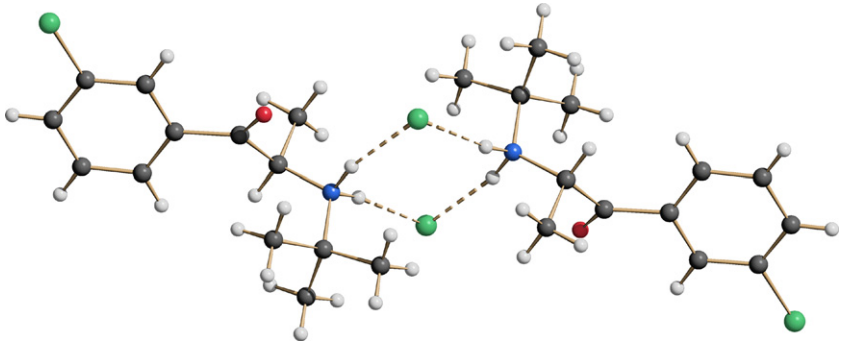


Fig. 4. Schematic drawing of the molecular conformation of bupropion hydrochloride dimers. Intermolecular hydrogen contacts (NH···Cl) with μ_2-bridging chlorides are shown with fragmented lines.

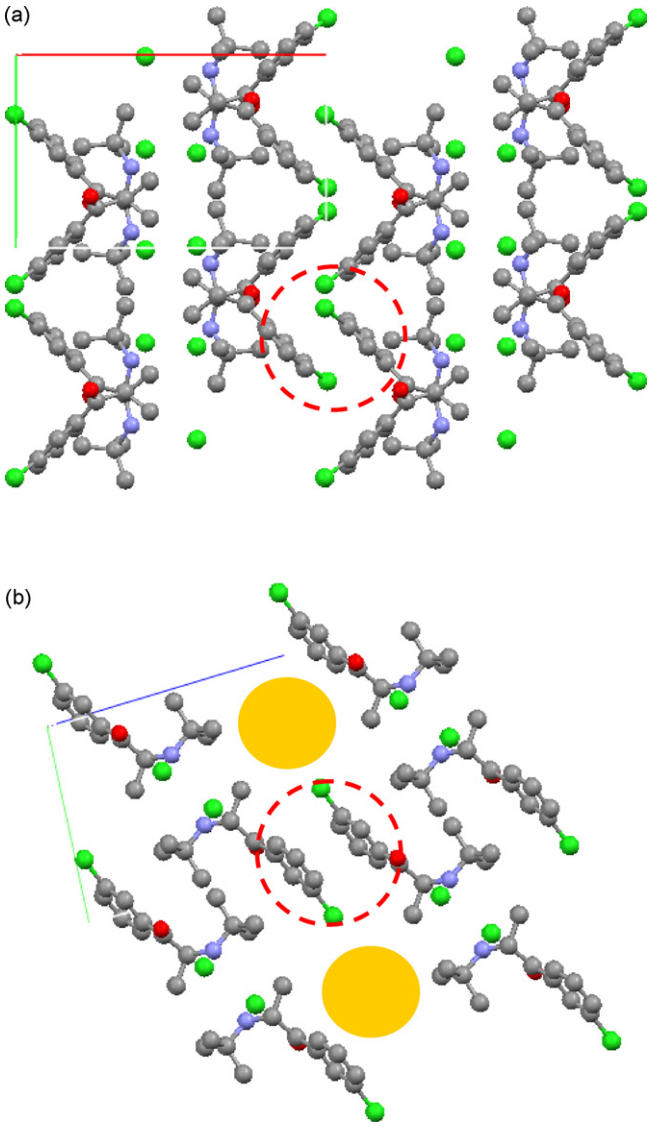


Fig. 5. Schematic drawing of the crystal packing of bupropion hydrochloride in **1**, viewed down [0 0 1] (a) and in the solvated phase **2**, viewed down [1 0 0] (b). In (a) horizontal axis is *a*; in (b) the (nearly) horizontal axis is *c*. Apparently facing chlorophenyl rings are isooriented in the two drawings and highlighted by dashed circles. In (b), solid circles indicate the location of the ethanol molecules (here removed for sake of clarity).

of Gelbrich and Hursthouse [11] this fact alone cannot be taken as a direct proof for significant packing differences. However, the supramolecular arrangements of bupropion hydrochloride, in **1** and **2**, are definitely distinct, as it can be easily seen by comparing the crystal packing diagrams of both structures (Fig. 5). As a consequence, the presence of a (disordered) ethanol molecule within the lattice of **2**, generates a crystal packing *not* related to that of **1**. Even if not experimentally proved here, this might suggest that the **2** → **1** interconversion may need the intermediacy of an amorphous phase before crystallization to the unsolvated form occurs.

4. Conclusions

The crystal structure of bupropion hydrochloride, **1**, was determined uniquely from laboratory X-ray powder diffraction data using as starting model the already known molecular structure of its ethanol solvate **2**, adding structural flexibility with the aid of a few freed torsional angles. The molecular geometry was fully determined and the molecular packing was investigated in order to clarify the stabilizing effects in the solid-state. In the crystals of **1** the molecules interact *via* strong NH···Cl contacts, generating, as in **2**, dimeric entities with μ-Cl ions. Further stabilizing contacts, of the CH···O are at work, but differently organized in the **1** and **2** phases. In the latter, evident ethanol-Cl^- contacts are present, thus demonstrating the non-innocent nature of the clathrated molecules, causing a complete scrambling of the supramolecular features on passing from **1** to **2**, as witnessed by the extremely different powder diffraction traces. The thermal analysis of **1** shows a melting point of about 246 °C and degradation of the molecule at higher temperatures.

Finally, we have proved, once again, that, in the absence of suitable single-crystals, state-of-the-art powder diffraction methods and *laboratory data* can be successfully employed in unravelling the main structural features of molecular crystals of moderate complexity.

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