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Investigation of intermolecular interactions in finasteride drug crystals in view of X-ray and Hirshfeld surface analysis

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ABSTRACT

The *N,N*-dimethylformamide (DMF) solvate hemihydrate (**1**) of finasteride, has been structurally characterized by single-crystal X-ray diffraction at 100 K and compared with previously reported finasteride crystalline forms. In addition, in order to resolve ambiguity concerning H-bond interactions, the crystal structure of finasteride hemihydrate, (**2**), originally reported by Schultheiss et al. in 2009, has been redetermined with higher precision. The (1) and (2) pseudopolymorphs of finasteride crystallize as orthorhombic in chiral $P2_12_12_1$ space group with two very similar host molecules in the asymmetric unit. The conformation of fused 6-membered rings are screw-boat, chair and chair for both molecules, while 5-membered rings assume chair in (1), and half-chair in (2). There is a fairly close resemblance of the molecular geometry for all analyzed compounds, arising due to the rigid host molecule. Inter- and intramolecular host–host, host–guest strong O–H···O, N–H···O hydrogen bonds and weak C–H···O interactions form 3D net conferring stability to the crystal packing. Finasterides can be classified as synthon pseudopolymorphs. Isostructural solvates crystallizing in the orthorhombic space group $P2_12_12_1$, with $Z' = 2$, exhibit $R^2_2(8)C^2_2(15)$ network, monoclinic solvate ($Z' = 1$) possess $D^1_1(2)$, while both orthorhombic and monoclinic polymorphs have $C(4)$ motifs, respectively. The structural similarities and subtle differences have been interpreted in view of the 3D Hirshfeld surface analysis and associated 2D fingerprint plots, which enabled detailed qualitative and quantitative insight into the intermolecular interactions. The 97–100% of Hirshfeld surface areas are due to H···H, O···H/H···O, C···H/H···C and N···H/H···N contacts. Furthermore, the electrostatic potential has been mapped over the Hirshfeld surfaces to decode the electrostatic complementarities, which exist in the crystal packing.

1. Introduction

Finasteride, [*N*-(1,1-di-methylethyl)-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide], presented in Scheme 1, is a synthetic 4-*aza*-steroid, well-known as the most potent 5α-reductase inhibitor [1], that interferes with the effects of certain male hormones (e.g. androgens) [2]. It is used in treatment for male hair loss (marketed under the brand name *Propecia,* since 1992) and in treatment for benign prostatic hypertrophy (*Proscar*) [3,4]. Finasteride was developed in the 1970's and has been known so far in various crystalline modifications. In the literature [5–9] the finasteride has been reported as two main polymorphs (I and II forms). Their crystal structures appear in the crystallographic Cambridge Crystal Structure Database (CSD, version 5.36 with updates of February 2015) [10] under the refcodes: WOLXOK01 [6] and WOLXOK02 [5] for orthorhombic form I and WOLXOK [6], WOLXOK03 [5] for monoclinic form II. The other three polymorphic forms were described only in the patent literature [11–13]. Furthermore, over the years, the crystal structures a variety of solvates of finasteride have been determined. Six solvates have been reported so far, and their crystal structures appear in the CSD, such as – acetic acid (WOLXEA) [6], *p*-dioxane solvate hemihydrate (TIPGUV) [14], isopropanol solvate hemihydrate (TIJKON) [14], hemihydrate (APUYUG) [3], tetrahydrofuran solvate hemihydrate (TIPHAC), Othman et al. [14], ethyl acetate clathrate monohydrate (WOLXIE), Wawrzycka et al. [6].

It is important to note that some crystals are supramolecular systems. Then, their structural features can be described through supramolecular synthons, the smallest structural units generated by the intermolecular interactions. Combination of different synthons in supramolecular architecture plays a significant role in crystal engineering [15]. The main aim of crystal engineering is the

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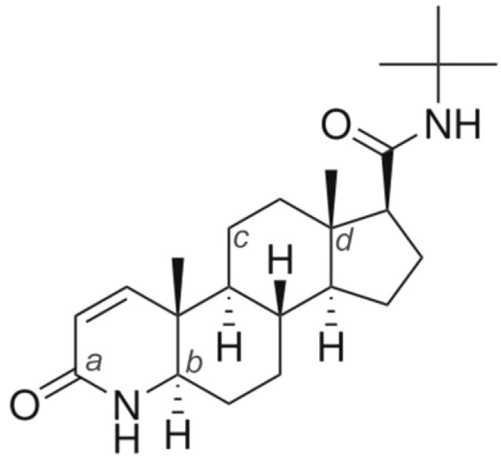

Scheme 1. Chemical diagram of finasteride.

understanding of intermolecular interactions and their application in the design of novel compounds with specific architectures and improved properties. Nevertheless, a major difficulty is the fact that the interactions, which control crystal structures are numerous [16–20]. It seems therefore, that the crystal engineering can become a useful tool for optimize the physic-chemical properties of Active Pharmaceutical Ingredient (API) in the solid state. According to Jetti et al. [21] and Sreekanth et al. [22] different crystal structures of the same compound with different hydrogen bonding or supramolecular synthons can be classified as synthon polymorphs or pseudopolymorphs.

In view of the importance of the mentioned above, the main scientific goal of this study is the comprehensive comparison of structural differences and similarities of all known finasterides (presented in the Table S1, in Supporting Information), including both qualitative and quantitative investigation of the intermolecular interactions nature and crystal packing behavior, in view of Hirshfeld surface analysis. An additional goal is to determine the crystal structure of new crystalline form of this class drugs, finasteride *N,N*-dimethylformamide (DMF) solvate hemihydrate (**1**), and a redetermination of the crystal structure of finasteride hemihydrate (**2**) (CSD refcode: APUYUG, [3]) with high precision. The structure of (**2**) was refined to $R = 4.3\%$ for 7886 Fo > 4sig(Fo) ($R_{int} = 2.7\%$), while the structure determined previously refined to $R = 9.3\%$. The reason for undertaking such study was resolving ambiguity concerning hydrogen bond interactions.

2. Experimental

2.1. Crystallization

Starting materials (finasteride and solvents) used in this work were obtained from commercial sources (Sigma–Aldrich Co.). Colorless, block-formed monocrystals of (**1**) were grown by slow evaporation from *N,N*-dimethylformamide (DMF) – water mixture (50:50 v/v) after several weeks at room temperature. Colourless, needle-formed single crystals of (**2**) were obtained from the ethanol/water solution.

2.2. Single crystal X-Ray diffraction

Crystallographic data for (**1**) and (**2**), were recordered on the Bruker SMART APEXII CCD diffractometer at 100 K (liquid nitrogen) using Cu-*Kα* (λ = 1.54184 Å) radiation. The absorption correction was applied using semi-empirical methods of SADABS program [23] in both cases. Cell refinement, indexing and scaling of the data set were done with SMART and SAINT-PLUS programs [24]. The structures were solved by direct methods using SHELXS97 [25] and all of the non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using SHELXL97 [26]. Positions of all hydrogen atoms were located in difference electron density map. Hydrogen atoms, bonded to carbon and nitrogen, were positioned geometrically and allowed to ride on their parent atoms, with $U_{iso}(H) = 1.2U_{eq}(C, N)$ or $1.5U_{eq}(C_{methyl})$. In the case of water molecules, H atoms were treated with O–H = 0.86 Å. In (**1**) DMF molecule and *tert*-butyl groups are disordered. The application a model with split atom positions did not improve *R* values. In this respect, using large ADP ellipsoids is the best description of the disorder. To handle disordered solvent regions and the contribution of solvents to the diffraction intensities the squeeze procedure [27] in PLATON program [28] was used. The experimental details, including crystal data, data collection and structure refinement details of (**1**) and (**2**) are summarized in Table 1. For preparing figures and the geometrical calculations, Mercury [29] and PLATON [28] programs were used.

2.3. Hirshfeld surface (HS) analysis

The HS analysis, provides information about all existing interactions in the structure and help to understand the overall crystal packing. The HS images external contour of the space, which a molecule or an atom uses in a crystalline environment. It is constructed on d_e and d_i (distances from the nearest nucleus external and internal to the HS) and the van der Waals (vdW) radii of the atom, enabling identification based on the electron distribution calculated as the sum of spherical atom electron densities. The normalized contact distance, d_{norm}, is based on both d_e and d_i, and the vdW radii of the atom, given by the Eq. (1) and is graphically displayed using a red (negative, hollows) and blue (positive regions, bumps) colors for contacts shorter and greater than vdW separations.

$$d_{norm} = \frac{d_i - r_i^{vdw}}{r_i^{vdw}} + \frac{d_e - r_e^{vdw}}{r_e^{vdw}} \quad (1)$$

The 2-D fingerprint plot (FP) format is generated by the combination of d_e and d_i. The 3D HS and corresponding 2-D fingerprints were prepared for all known finasteride structures using the program CrystalExplorer (Ver. 3.1) [30–32]. Bond lengths of hydrogen atoms were normalized to standard neutron values (C–H = 1.083 Å, O–H = 0.983 Å, N–H = 1.009 Å). It is worth to mention that hydrogen atoms in WOLXOK01, WOLXEA and WOLXIE were firstly placed in idealized positions using Mercury program. Furthermore, the calculations of electrostatic potential (EP) were performed with the Gaussian 03 [33] package using the implemented B3LYP methodology with standard 6–311++G (d, p) basis set.

3. Results and discussion

3.1. Structural description

The crystallographic asymmetric unit of the (**1**) contains three different species, such as: two discrete finasteride (host), one water and 0.35 DMF molecules (guests). A view of the molecular structure of (**1**) with atom numbering schemes is depicted in Fig. 1 [ORTEP plot of (**2**) is presented in the Fig. S1 in Supporting information].

The stereogenic sites of host molecules (**1**) and (**2**) display the following chirality: *R* at C4/C27, and *S* at C7/C30, C8/C31, C9/C32, C12/C35, C13/C36, C16/C39 atoms, respectively. The core of the