Crystal Structure and Desolvation Behaviour of the Tadalafil Monosolvates with Acetone and Methyl Ethyl Ketone

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ABSTRACT: Crystal structures of Tadalafil (TDF) monosolvated forms with acetone (ACE) and methyl ethyl ketone (MEK) were determined by single-crystal X-ray diffraction in which same persistent chains of TDF molecules are present as in the reported structures. The solvates crystallize in a higher orthorhombic symmetry than the known forms with monoclinic structures. Weak interactions between TDF and solvent molecules are present in both solvates, leading to slight conformational distortions of TDF molecules. The MEK solvate showed slightly higher stability than the ACE solvate, regardless of their highly similar molecular conformations and crystal packing. Desolvation into anhydrous TDF was achieved by heating, exposure to temperature and relative humidity and by mechanical stress. The high solubility of TDF in ACE and MEK solvents combined with the ease of desolvation of the resulting solvated forms indicates the viability of the solvates use as intermediates in the TDF crystallization process. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:3782–3788, 2015

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INTRODUCTION

The solid form landscape of active pharmaceutical ingredients (APIs) encompasses polymorphs, solvates, salt, and co-crystal forms, which can profoundly impact the physicochemical properties of the final drug. Different solid forms of an API may have different physicochemical properties, particularly solubility and dissolution rate having possible effect on their bioavailability.[1,2] In addition, properties like melting point, thermal stability, hygroscopicity, compressibility, and powder flow are essential in developing a successful drug product.[3,4]

Polymorphism is common in pharmaceutical compounds and it must be controlled, in order to prevent possible ineffective therapy and improper dosage regimen. Unlike polymorphs, the use of solvated forms in drug products is strongly limited by the toxicity of the solvents. In the context of industrial crystallization, residual solvents need to be present below acceptable levels because of their potential hazard to human health and to the environment.[5–7]

The most important technical and industrial applications of solvates[8] are related to purification,[9] use as precursors of desired polymorphs,[10–12] or particle size control. Notably, the particle size and morphology can be controlled through the desolvation process while at the same time obtaining the original target anhydrous polymorph.[13]

In some cases, there is a strong tendency of the pharmaceutical compounds to form solvates and therefore, the knowledge of the desolvation process becomes important in obtaining the desired polymorph.[14–16]

Tadalafil (TDF; Fig. 1) is a cyclic guanosine monophosphate-specific type V phosphodiesterase inhibitor[17] used for the treatment of erectile dysfunction (ED),[18] benign prostatic hyperplasia,[19] and for the treatment of pulmonary arterial hypertension.[20] TDF is the active ingredient of Cialis® approved by United States Food Drug and Administration (US FDA) in 2003 for the treatment of ED and in 2011 for the treatment of benign prostatic hyperplasia or/and ED, and of Adcirca® approved by US FDA in 2009 for the treatment of pulmonary arterial hypertension.

According to the Biopharmaceutics Classification System, TDF is a class II drug, practically insoluble in water,[21] which has a negative influence on its bioavailability.[18] To enhance the dissolution rate and bioavailability of TDF, several formulation approaches have been reported, including nanosuspensions and solid dispersions,[22] inclusion complexes with beta-cyclodextrin,[23] or conversion into the amorphous form.[24]

In addition, studies focused on the discovery of new solid forms of TDF (including polymorphs, solvates, and co-crystals) have been undertaken. In the US 2006/0111571A1 patent application,[25] eight solid forms of TDF have been reported[25] and recently a number of co-crystals were discovered.[26,27] Despite of the rich crystal form landscape, only the crystal structure of anhydrous TDF (refcode: IQUMAI),[28] identified as form I,[25] and three co-crystals with methylparaben, propylparaben, and hydrocinnamic acid have been reported[26] in the Cambridge Structural Database (CSD).[29]

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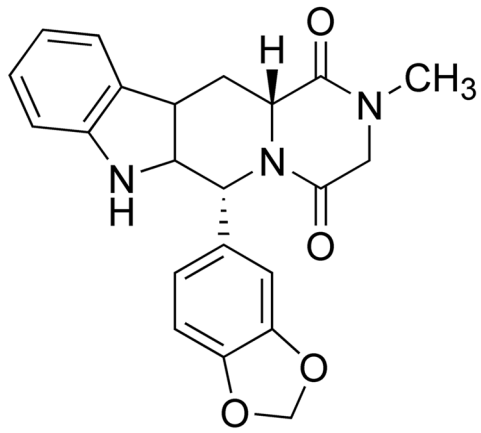

Figure 1. Molecular structure of Tadalafil (TDF).

In order to obtain different solid forms of TDF, we carried out crystallization experiments from various organic solvents. Our experiments showed that TDF has poor solubility in a large number of organic solvents, which is not desirable for the development of a viable crystallization process. However, in the crystallization experiments with acetone (ACE) and methyl ethyl ketone (MEK), higher TDF concentrations were achieved (>20 mg/mL). These experiments led to the identification of two solvated forms, with ACE and MEK[25] labeled by us TDF-(ACE) and TDF-(MEK). As it was possible to obtain single-crystals of these solvates, herein we report their crystal structures as determined by single-crystal X-ray diffraction together with their comprehensive characterization by solid-state nuclear magnetic resonance (ss-NMR) spectroscopy, molecular modeling, thermal analysis, stability, and desolvation studies.

EXPERIMENTAL

Materials

Tadalafil ((6*R-trans*)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-pyrazino [1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione) was purchased from HANGZHOU DAYANGCHEM Company, Ltd. The solvents were supplied by Sigma–Aldrich (Bucharest, Romania) and were of reagent grade.

Solvent Screening Studies

The solvent screening experiments of TDF (Supporting Information, Table S1) were performed by cooling crystallization method from a range of 27 organic solvents by suspending 15–20 mg TDF in 1 mL organic solvent. The vials were heated up to 60°C, slowly cooled to 15°C and further aged at 4°C. After 2 days, the experiments with ACE and MEK led to colorless single-crystals with needle shape, which were analyzed by single-crystal diffraction. All solids obtained by cooling and slow evaporation were examined using X-ray powder diffraction (XRPD).

X-Ray Crystallography

Single-crystal diffraction data were collected on an Oxford Diffraction SuperNova dual wavelength diffractometer with operating mirror monochromated CuKα radiation mode (λ = 1.5418 Å). X-ray data collection was monitored and all the data were corrected for Lorentzian, polarization and absorption effects using CrysAlisPro program.[30] Olex2 program was used for the crystal structures solution and refinement[31]: SHELXS97 was used for structure solution[32] and SHELXL was used for full matrix least-squares refinement on F2.[33]

X-ray powder diffraction patterns were obtained on a D8 Advance Bruker AXS θ-2θ diffractometer with CuKα radiation (40 kV, 30 mA). The measurements were performed in the 3°–40° range in steps of 0.02°.

Solid-State NMR

^{13}C ss-NMR spectra were obtained on a Bruker Avance III 500 MHz wide-bore NMR spectrometer operating at ambient probe temperature (ca. 20°C). Standard RAMP CP-MAS spectra were acquired at 14 kHz spinning frequencies, 2 ms contact times, and proton decoupling under TPPM. The acquisition parameters were optimized to following values of relaxation delay/number of scans: 20 s/ 4000 scans for TDF, 20 s/1000 scans for TDF-(ACE), 10 s/3000 scans for TDF-(MEK). The recorded spectra are calibrated relative to the CH_3 line in TMS (tetramethylsilane), through an indirect procedure which uses the α form of L-glycine as external standard (C=O of Glycine at 176.5 ppm).

Thermal Analysis

Thermogravimetric (TG) and differential scanning calorimetry (DSC) analyses were performed with a simultaneous TG/DSC Q600 system from TA Instruments. The instrument was calibrated using standard weights for TG and sapphire for DSC. The 3–4 mg amounts of sample were heated in the 30°C–400°C temperature range at a constant heating rate of 10°C/min in alumina crucibles and nitrogen as purge gas flowing at 100 mL min^{-1}.

Quantum Chemistry Calculations

First-principle geometry optimization and NMR chemical-shift calculations were performed using the CASTEP and NMR CASTEP tools within the Materials Studio® suite.[34] CASTEP[35] implements density functional theory (DFT) within a generalized gradient approximation and the plane wave pseudopotential approach. All geometry optimizations and NMR chemical shift calculations used the PBE exchange-correlation functional, with ultrasoft pseudopotentials, and a basis set cut-off energy of 900 eV. Forces, energies, and displacements were converged better than 0.01 eV/Å, 0.000005 eV, and 0.0005 Å, respectively. Initial geometry optimization of TDF was performed starting from the CSD crystal structure, refcode IQUMAI,[28] $Z = 2$, space group $P2_1$, temperature 293 K. The crystal structures of TDF-(ACE) and TDF-(MEK) were determined from single-crystal XRD data. All these three crystal structures solutions have been optimized (with the unit cell parameters and heavy atoms positions considered fixed at their diffraction derived values) prior to chemical shielding calculations.

Nuclear magnetic resonance chemical shift calculations employed the GIPAW method[36,37] to determine the shielding tensor for each nucleus in the crystal structure. The calculations used a plane wave basis set with a maximum cut-off energy of 900 eV, ultrasoft pseudopotentials generated on the fly, and integrals taken over the Brillouin zone by using a Monkhorst-Pack grid of minimum sample spacing $0.04 \times 2\pi$ $Å^{-1}$. To compare the results directly with experimentally measured