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Solid-State Insight Into the Action of a Pharmaceutical Solvate: Structural, Thermal, and Dissolution Analysis of Indinavir Sulfate Ethanolate

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ABSTRACT

The crystal structure of indinavir sulfate, a pharmaceutical administered as an ethanol solvate, is presented, revealing a unique channel/ionic solvate structure to be characteristic of the compound. The properties of the material with regard to thermal treatment and water adsorption follow closely from the structure. The *in situ* amorphization of the pharmaceutical upon contacting liquid water is observed and highlights the unique dissolution enhancement of marketing the crystalline solvate dosage. Through survey of published crystal structures, an ambiguous sulfate/bisulfate ionization state is also observed in the crystal, which challenges the general understanding of the pharmaceutical. This study provides a solid-state insight into the function of a special multicomponent crystalline pharmaceutical form.

Introduction

Active pharmaceutical ingredients (APIs) are commonly developed into dosages as crystalline solid forms.[1] Single component forms, those that only contain the drug molecules, are commonly used although APIs can also be administered as multicomponent solid forms such as salts, cocrystals, and solvates to obtain optimal properties.[2] The formation of solvates is commonly observed during solution-based crystallization of APIs in various media including water and organic solvents.[3,4] However, solvates besides hydrates are not frequently administered in pharmaceutical products, mainly due to concerns about the toxicity of the solvents.[5-8] The stability issues associated with using high volatility solvents also demand thorough solid form property studies of these solvates to assess their susceptibility to desolvation.[9] These analyses are crucial for the validation of the consistency and reliability of the expected efficacy of the solvates. We are aware of only 7 pharmaceuticals marketed as solvates: trametinib,[10] dapagliflozin,[11] cabazitaxel,[12] darunavir,[13] doxycycline,[14] indinavir sulfate,[15] and warfarin sodium.[16] Among these pharmaceuticals, indinavir, darunavir, and doxycycline are dosed as ethanol solvates (ethanolates).

Indinavir sulfate is used as an inhibitor of HIV protease and is marketed by Merck as Crixivan (Fig. 1a).[17] It is the only pharmaceutical that is formulated simultaneously as a sulfate salt and an ethanol solvate because of its superior solubility (more than 25,000 times higher) and oral pharmacokinetics compared to the neutral monohydrate form.[18,19] The solvate form has also demonstrated satisfactory shelf stability as long as 2 years.[20] However, the crystal structure of indinavir sulfate ethanolate has not been reported; therefore, the solid-state basis for these properties is unknown. Herein, we report the crystal structure of indinavir sulfate ethanolate and interpret the structural data to enable better understanding of the physicochemical properties observed for this solid form. The ionization state, which is more complex than previously thought, is determined and interpreted in the context of data culled from the Cambridge Structural Database (CSD) on structurally related compounds. Thermal stability of the pharmaceutical is evaluated by relating the thermal analysis of the desolvation process to the bonding interactions and packing arrangements observed in the crystal structure. Finally, a chemical basis for the known amorphization of this solid form is proposed.

Abbreviations used: API, active pharmaceutical ingredient; CSD, Cambridge structural database; PXRD, powder X-ray diffraction.

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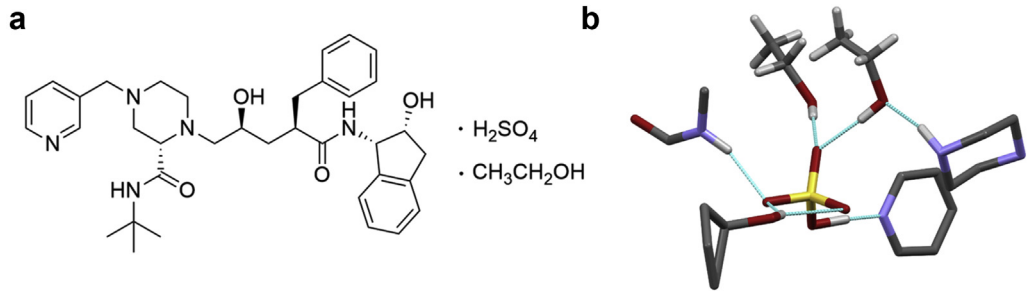

Figure 1. (a) Chemical structure of indinavir sulfate ethanolate (Crixivan). (b) Illustration of hydrogen bonding interactions in the crystal structure of indinavir sulfate/bisulfate ethanolate revolving around the sulfate/bisulfate ion; only fragments of indinavir molecules are shown. White = hydrogen, gray = carbon, blue = nitrogen, red = oxygen, yellow = sulfur.

Methods

Single Crystal X-Ray Diffraction

Colorless plates of indinavir sulfate ethanolate (98%; Cayman Chemical Co., Ann Arbor, MI) were grown by completely dissolving 10.0 mg of the compound in 1.0 mL of ethanol at 80°C and cooling to room temperature. The crystals were collected and immediately analyzed without drying. A crystal of dimensions 0.17 × 0.09 × 0.02 mm was mounted on a Rigaku AFC10K Saturn 944+ CCD-based X-ray diffractometer equipped with a low temperature device and Micromax-007HF Cu-target microfocus rotating anode (λ = 1.54187 Å) operated at 1.2 kW power (40 kV, 30 mA). The detailed structural analysis procedure is included in the Supplementary Material.

The CSD Survey

The CSD searches employed ConQuest, version 1.18.[21] Pyridine/pyridinium and sulfate/bisulfate moieties were drawn and searched with the following filters used as criteria: the hits must have determined 3D coordinates and a R factor <0.05 with no disorder or errors. Organometallic structures and polymeric structures and structures determined from powder X-ray diffraction (PXRD) were also excluded from the results.

Results and Discussion

Ionization State Analysis

According to the patent and the analysis published by Merck, the chemical composition of the pharmaceutical Crixivan is indinavir monosulfate ethanolate.[17,22] The molecule contains 3 basic nitrogen atoms (2 tertiary amine nitrogen atoms and 1 pyridine) (Fig. 1b) capable of accepting protons from the incorporated sulfuric acid. As illustrated in the determined crystal structure of indinavir sulfate, one of the 2 tertiary amine nitrogen atoms is clearly protonated, whereas the case associated with the protonation of the pyridine nitrogen is more complicated. It is often observed that in the solid state when an acid-base pair is present, a Δp*K*a value (Δp*K*a = p*K*a of the protonated base − p*K*a of the acid) greater than 3 will result in salt formation[23,24]; however, proton transfer is also dependent on the specific molecular environment in the crystal structure.[25-27] Based on the empirical rule, the Δp*K*a of a pyridine/bisulfate pair is equal to ~3.2,[28] which predicts the favorable formation of a pyridinium cation and sulfate anion. It should be noted that pharmaceuticals administered as bisulfate are relatively rare. The Food and Drug Administration Orange Book Database, as of June 2017, shows the presence of 41 approved sulfate drug products with therapeutic equivalence evaluations, but only one bisulfate drug, clopidogrel bisulfate.[29] However, the crystal structure determination of indinavir demonstrates the presence of a more ambiguous ionization state between sulfate and bisulfate. The proton placement derived directly from the diffraction data shows the presence of a bisulfate OH bond, albeit with an unusually long O-H bond distance of 1.13(7) Å.

Analysis of the CSD was undertaken to elucidate the ambiguous proton assignment by assessing the resemblance between the structural features of the determined indinavir structure and those of the existing structures in the database. An unconventional bisulfate O-S bonding distance (1.523(3) Å) and pyridine C-N-C angle (119.2(4)°) in the determined structure corresponding to an intermediate state between sulfate ion and bisulfate ion were

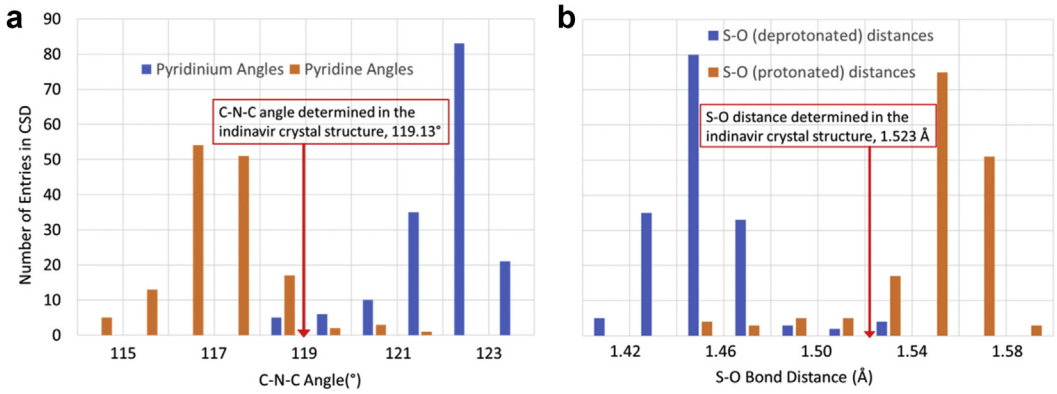

Figure 2. Statistical analysis of C-N-C bond angles in structures containing pyridine/pyridinium (a) and O-S bond distances (b) in structures containing sulfate/bisulfate collected from the CSD.