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Single crystal structure, solid state characterization and dissolution rate of terbinafine hydrochloride

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ABSTRACT

Terbinafine hydrochloride (TH), a poorly water soluble antifungal agent, was characterized by solid state techniques including differential scanning calorimetry, thermogravimetry, X-ray powder diffraction, optical and electron microscopies, Fourier transform infrared, Raman and solid-state nuclear magnetic resonance spectroscopies and intrinsic dissolution rate (IDR). A colorless single crystal of TH was grown from an ethanol:water solution and its crystalline structure was determined through X-ray single crystal diffraction. Also, a new crystal habit of TH was obtained through the slow solvent evaporation technique revealing a needle-like shape. A comparison between the IDR results for the TH raw material and TH needle-like crystal revealed lower values for the new crystal habit, which can be attributed to the preferential orientation of the crystals in the compressed disks.

1. Introduction

The solid state characterization of active pharmaceutical ingredients (APIs) plays an important role in drug development due to its implications in terms of the physicochemical and biopharmaceutical properties, such as solubility, dissolution rate, bioavailability and stability [1–5]. The characterization and an understanding of solid properties are essential for quality control and regulatory purposes [6,7]. The polymorphism of APIs is routinely controlled since its influence on several solid state properties is a well-established [8]. In some cases, it is also of interest to control the crystal habits and/or morphology of the particles. Recently, researchers in the pharmaceutical industry have demonstrated considerable interest in the possibility of predicting the crystal morphology to optimize drug manufacturing [9]. Regarding the crystal habit, the main differences between solids of different morphologies include the dissolution rate, compaction behavior and powder flow properties [10–12].

The obtainment of distinct crystal habits is greatly influenced by the solvent recrystallization since the morphology is defined by the solute-solvent interaction at various crystal faces [13]. As it occurs with polymorphism, depending on the crystallization conditions (solvent, cooling rate, evaporation rate, final temperature, solution concentration, etc.), several polymorphic forms can be crystallized. The crystal habit or morphology is also dependent on the crystallization conditions. The crystal habit influences the solid state properties, such as fluidity, apparent density, dissolution rate and stability APIs, such as ibuprofen, dipyridamole and phenytoin, which presented distinct morphologies, differ in terms of their physicochemical and/or mechanical properties [13–17].

Terbinafine hydrochloride, (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalene ethanamine hydrochloride (TH) (Fig. 1), is a potent antifungal agent of the allylamine class. The FDA recommends its use in superficial skin and nail fungal infections since it has a broad spectrum of activity against yeasts, dimorphic fungi and dermatophytes [18–20]. The mechanism of action involves irreversible inhibition of the enzyme squalene epoxidase in fungal ergosterol biosynthesis, promoting intracellular squalene accumulation, which compromises the cell wall integrity [21,22].

This compound is currently marketed in solid state as tablets, capsules and oral granules [18,22] and presents poor solubility in

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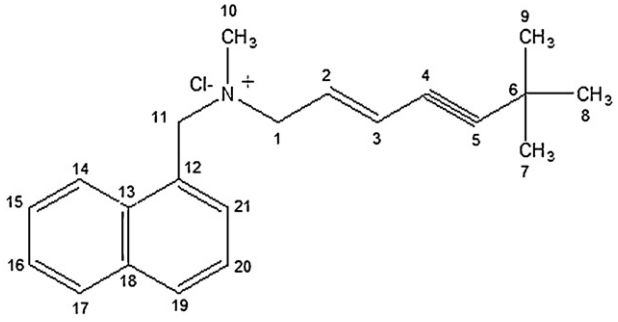

Fig. 1. Chemical structure of TH.

water [23]. However, the data available on the solid state characterization and crystallographic characteristics of TH are incomplete. Detailed searches in the literature and in the Cambridge Structural Database revealed one only crystal structure reported in 2002 by Tedesco, Giron and Pfeffer [24] obtained from synchrotron X-ray powder diffraction data. The authors identified the cell parameters and space group, but no atomic positional coordinates were reported. Furthermore, although polymorphism is a very common phenomenon in APIs, no reports on the polymorphism or solvates of TH appear to have been published in the literature. In some cases, a lack of polymorphism in APIs may be an advantage, since no phase transformations, which could affect the performance of the drug, can occur during manufacturing, storage and administration [25,26]. However, the presence of different TH crystal habits may be of concern and needs to be controlled, since the crystal morphology plays an important role in relation to the technological procedures [27].

Concerning the determination of a new crystal form, structure elucidation based on single crystal analysis is preferred. Essential information, such as iso/anisotropic displacement parameters, disorder locations, atomic coordinates and geometric parameters, is obtained through this approach. Also, single crystal data yields detailed structural information which complements spectroscopic and thermoanalytical analysis and can be useful for quality control, understanding the polymorphism behavior, determining physicochemical correlations and characterizing the morphology.

The aim of this study was to determine the single crystal structure and study the solid properties and dissolution behavior of TH, through an analysis of the commercial raw material (THr) and crystallized samples with different crystalline habits (plate-like crystals [THp] and needle-like crystals [THn]).

2. Materials and methods

2.1. Materials

The TH raw material was obtained from Zhejiang East-Asia Pharmaceutical, batch DC-0107-09122001, and is referred to in this paper as THr. All other materials and solvents used were analytical reagent grade.

2.2. Methods

2.2.1. Obtainment of the crystal-habit-modified TH (THn)

A new crystalline habit of TH was obtained through the slow solvent evaporation technique. A saturated solution of TH in ethyl acetate was maintained at room temperature and protected from light. Under this condition a needle-like crystalline sample was observed, which was characterized through optical microscopy, as reported in Section 2.2.2.5.

2.2.2. Solid state characterization of TH

2.2.2.1. X-ray single crystal diffraction (XRSCD) and X-ray powder diffraction (XRPD). Single crystals of TH were grown from an ethanol:water (50:50 v/v) solution by slow evaporation of the solvent at 281 K. A colorless crystal with a plate-like habit (THp) and dimensions of 0.50 mm × 0.40 mm × 0.13 mm, suitable for XRSCD analysis, was obtained. The crystal was mounted on glass fiber and measurements were taken on a single crystal diffractometer (Enraf-Nonius CAD-4). The radiation used was graphite-monochromated Kα molybdenum radiation (0.71073 Å) and the temperature was set at 293 K. Unit cell dimensions were obtained via least-squares fits of the 2θ values of 25 high-order reflections. The structure was solved by direct methods and refined applying the full-matrix least-squares method using SIR97 [28] and SHELXL97 [29] software programs, respectively. The figure for the molecular structure was produced with the PLATON program [30].

All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at their idealized positions with distances of 0.93 Å for C—H_{Ar}, 0.97 Å for C—H_2 and 0.96 Å for C—H_3 groups. The U_{iso} values for the hydrogen atoms were fixed at 1.2 times (for aromatic compounds and methylene) and 1.5 times (for methyl) the U_{eq} of the carrier atom (C).

XRPD patterns were collected on a θ–θ X-ray diffractometer (Xpert Pro Multi-Purpose Diffractometer, PANalytical) with Kα copper radiation (λ = 1.5418 Å), operating at a voltage of 45 kV and current of 40 mA, equipped with a sample spinner and a Real Time

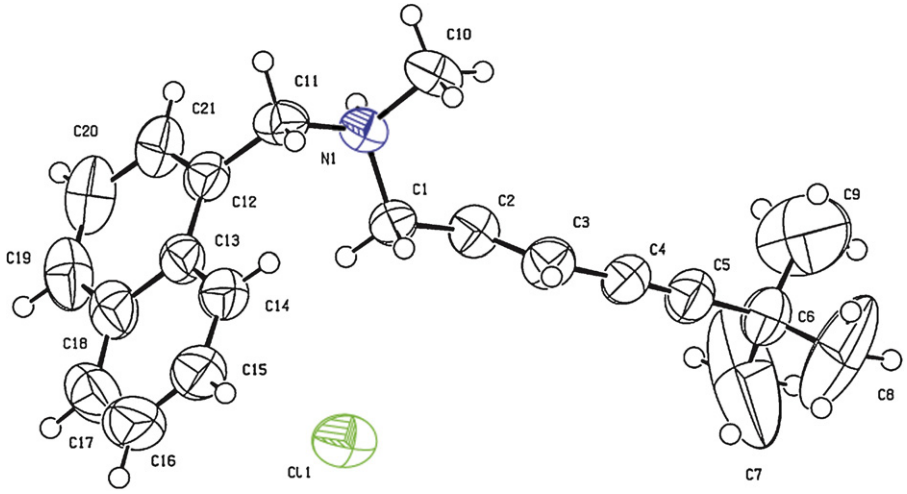

Fig. 2. ORTEP view of the asymmetric unit of TH showing atoms labeling and the 50% probability ellipsoids.