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The effect of pH on polymorph formation of the pharmaceutically active compound tianeptine

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ABSTRACT

The anti-depressant pharmaceutical tianeptine has been investigated to determine the dynamics of polymorph formation under various pH conditions. By varying the pH two crystalline polymorphs were isolated. The molecular and crystal structures have been determined to identify the two polymorphs. One polymorph is an amino carboxylic acid and the other polymorph is a zwitterion. In the solid state the tianeptine moieties are bonded through hydrogen bonds. The zwitterion was found to be less stable and transformed to the acid form. During this investigation an amorphous form was identified.

1. Introduction

Polymorphism is essentially a solid-state phenomenon. Two polymorphs are different forms of the same chemical compound which have distinctive properties is perhaps a very good description of polymorphs (Buerger, 1971). This description of polymorphism implies the possibility of a number of polymorphs. Polymorphs are essentially the same compound, their main differences manifest themselves in their physiochemical properties. The properties most often affected by polymorphism are of some importance in the pharmaceutical industry and include stability, solubility, bioavailability of pharmaceutically active substances, and density. A distinguishing feature of polymorphs is their structural difference which can be observed as a difference in the spatial arrangement of the atoms of the molecule or as a difference in packing arrangements of the molecules in the unit cell. The structural differences in turn, may, or may not affect all or some of the physiochemical properties of the compound in the solid state. Polymorphism has been extended to include zwitterions of acids containing amide groups able to accept protons (Brown and Ehrenberg, 1985).

Preparation of polymorphs include traditional methods such as crystallization from solutions and crystallization from melts (Hilfiker et al., 2006), as well as methods such as supercritical fluid crystallization (Kordikowski et al., 2001; Bouchard et al., 2007), capillary crystallization (Chyall et al., 2002; Hilden et al., 2003; Childs et al., 2004), non-photochemical laser-induced nucleation (Sun et al., 2006), crystallization with polymer heteronuclei (Price et al., 2005; Grzesiak and Matzger, 2007), and template-assisted crystallization (Mei and Wolf, 2004). A potentiometric method for the crystallization of polymorphic forms of active pharmaceutical ingredients (APIs) has also been described (Du-Cuny et al., 2007). This method illustrates the effect of changing pH on the crystallization of polymorphs of weak acidic and basic compounds.

The problems associated with polymorphism and the possible methods for isolating the desired polymorphs and their analysis have been reviewed (Llinàs and Goodman, 2008; Kitamura, 2009). Perhaps one of the more challenging properties of polymorphs is the difficulty of preparing the desired polymorph in a pure form. It has been suggested that the production of polymorphs in their pure form may be possible by applying thermodynamic and kinetic principles to control polymorph formation (Jiang et al., 2010). In many instances there is a search for suitable solvents, or mixture of solvents, in which the selected compound dissolves and one of the polymorphs will crystallize (Weissbuch et al., 2005; Hamad et al., 2006). The addition of other compounds to initialize, or enhance formation of one, and only one, polymorph have been reported (Lou

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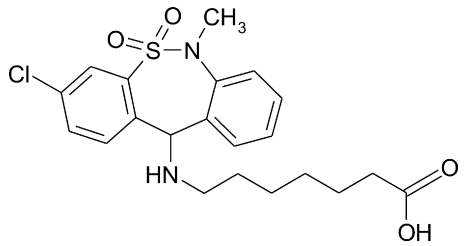

Fig. 1. Molecular structure of tianeptine.

et al., 2009; Li et al., 2011). Monte Carlo crystal growth simulation to identify possible sites retarding or enhancing growth is a theoretical approach for the design and selection of specific additives (Deij et al., 2007).

The API tianeptine (7-[(3-chloro-6,11-dihydro-6-methyldibenzo[c,f][1,2]thiazepin-11-y)lamino]-heptanoic acid S,S-dioxide, Fig. 1), is an effective antidepressant. It is reported to be a safe therapeutic agent that shows almost no side effects.

Reviews of the pharmacology of tianeptine have been presented (Preskorn, 2004; Preskorn and Ross, 2004). The tianeptine molecule is chiral and while the racemate is used in therapy the (+) enantiomer is less active than the (−) enantiomer. Two forms of tianeptine, arbitrarily labeled I and II, in the patent application, have been reported (Sansone, 2008). Because polymorph II is the stable form while I is metastable, the stable form is herein labeled A and the metastable B.

Guzman et al. (2010) report on the preparation and properties of tianeptine hemisulfate monohydrate which can take several forms such as hydrates, solvates, possible sulfate ions to tianeptine ion stoichiometries, polymorphs, cocrystals as well as amorphous forms.

The tianeptine molecule has a 3-chlorodibenzothiazepine linked to aminoheptanoic acid and may form a zwitterion polymorph. This study was undertaken to investigate the possible effect of pH variation on the dynamics of zwitterionic and neutral polymorph formation and the use of pH titration as a method to obtain pure polymorphs. As part of this study the crystal and molecular structures of racemic mixtures of the A and B forms of tianeptine were determined by single crystal diffractometry.

2. Experimental

2.1. Materials

Tianeptine acid and the sodium salt of tianeptine were supplied by the Stock Company Grindeks. All reagents were procured from a commercial source and used as received. The solutions of sodium hydroxide and hydrochloric acid used to adjust the pH of the solutions were standardizes to 0.5000 M and 0.5470 M respectively.

2.2. Preparation of tianeptine forms at selected pH values

Fourteen samples of the sodium salt of tianeptine (0.40 g) were each dissolved in 20 mL of ethanol (96%). The pH of each solution was measured using an Adrona AM1605 pH meter. The solutions were titrated with hydrochloric acid (0.5470 M) to the following pH values: 6.96, 6.79, 6.59, 6.57, 6.53, 6.07, 5.80, 5.66, 5.50, 5.39, 5.36, 5.28, 5.16 and 5.01. These fourteen pH-adjusted solutions were allowed to crystallize at ambient temperature. PXRD was used to characterize the resulting crystals.

Another series of fourteen samples of the sodium salt of tianeptine (0.20 g) were each dissolved in 50 mL of water. The pH of each solution was measured with an Adrona AM1605 pH meter. Titration with hydrochloric acid (0.5470 M) to the following pH values: 4.00, 4.60, 4.81, 5.01, 5.08, 5.21, 5.42, 5.59, 5.79, 6.02, 6.18, 6.42, 6.62 and 6.82 was performed. In all cases some precipitate formed. The fourteen pH-adjusted solutions were allowed to crystallize at ambient temperature and then filtrated. PXRD was used to characterize the resulting product.

2.3. Crystallization of tianeptine polymorphs in the presence of additives

Mixtures of equimolar amounts (0.17 mM) of tianeptine and the following additives: glutaric acid, suberic acid, nicotinamide, 4,4′-bipyridine, were dissolved in hot ethanol. The solutions were allowed to crystallize at ambient temperature. A mixture of equimolar amounts of tianeptine and mildronate dihydrate (3-(2,2,2-trimethylhydrazinium) propionate dihydrate), a zwitterion, was dissolved in hot 1:1 water/ethanol solution and left to crystallize at ambient temperature.

2.4. Single crystal preparation

Crystals suitable for single crystal structure analysis of the A polymorph were obtained the following method: 0.06 mM (0.025 g) of tianeptine acid were dissolved in 10 mL ethanol, permitted to crystallize at ambient temperature and colorless crystals were isolated.

To obtain crystals of the B polymorph an approximate 1:1 mixture of 0.073 g (0.17 mM) tianeptine acid and 0.03 g (0.16 mM) mildronate dihydrate was dissolved in 5 mL of a 1:1 water/ethanol solution. Colorless crystals suitable for diffraction study grew at ambient temperature.

2.5. Single crystal X-ray diffraction

X-ray diffraction data were measured using a Nonius Kappa CCD diffractometer (Bruker AXS GmbH, Germany) with Mo Kα radiation (0.71073 Å) at 173 K. All structures were solved by direct methods using SIR92 (Altomare et al., 1994) as implemented in the program package WinGX (Farrugia, 1999). Refinement was carried out by full-matrix least-squares method with the CRYSTALS (Betteridge et al., 2003) program. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located by difference Fourier method. During refinement hydrogen atoms were refined in the riding mode.

2.6. Powder X-ray diffraction (PXRD)

X-ray powder diffraction data were obtained using a Bruker AXS D8 Advance powder diffractometer (Bruker AXS GmbH, Germany) with Cu Kα radiation (λ = 1.5418 Å), 40 kV, 40 mA. Patterns were recorded at room temperature with a 0.02° step and a scan speed of 0.1 s/step.

2.7. Thermal analysis

Differential thermal analysis (DTA) was performed with Seiko Exstar6000 TG/DTA6300 (Seiko Instruments Inc., Japan) equipment. The samples (5–8 mg) were heated in open aluminum pans at a rate of 10 °C/min in air.

2.8. Fourier-transform infrared spectroscopy (FTIR)

FTIR spectra were obtained using an Avatar 330 FT-IR spectrometer (Thermo Nicolet, USA). Spectra were recorded having a 2 cm^{-1} resolution over the range of 400–4000 cm^{-1}. A sample of