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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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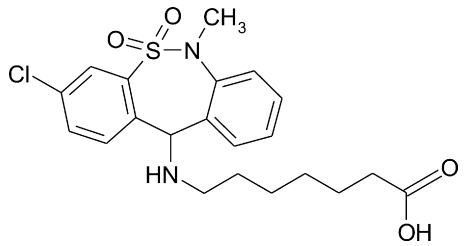

Fig. 1. Molecular structure of tianeptine.

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

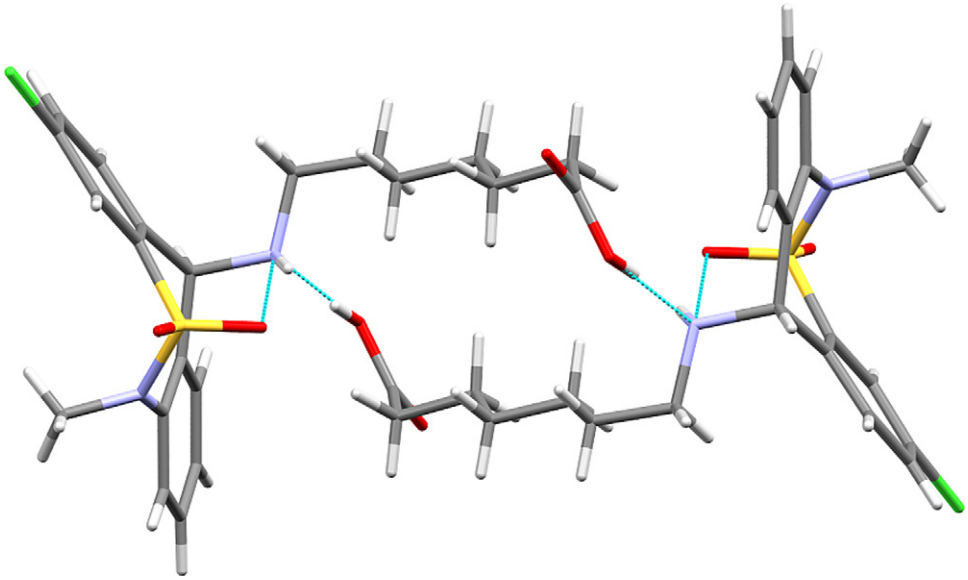

Fig. 2. Hydrogen bond formation in tianeptine form A.

each polymorph was ground with KBr and pressed into disc form to record the spectra.

2.9. Stability of the polymorphs A and B

To investigate the relative stability of A and B 1:1 mixture of A and B were ground at ambient temperature in ethanol to form a thick slurry. After evaporation the PXRD pattern was determined. This process of grinding and evaporation was repeated successively three times on the same sample, the PXRD patterns were recorded each time and examined to determine changes in composition.

3. Results and discussion

3.1. Crystal and molecular structure analysis

The crystallographic data for tianeptine forms A and B are presented in Table 1.

The crystal structure of the A polymorph has one molecule of tianeptine acid in the asymmetric unit (Supporting Material, Fig. S1). There are two acid moieties symmetrically located about the inversion center and are joined by hydrogen bonds between the acid —OH group and the chain nitrogen atom of the aminoheptanoic acid side chain attached to the 3-chlorodibenzothiazepine nucleus thus O—H···N (Fig. 2), resulting in a graph set $R_2^2(20)$ assembly. The observed hydrogen bonds are presented in Table 2.

Table 1
Crystallographic data for tianeptine form A and form B.

	A	B
Chemical formula	$C_{21}H_{25}ClN_2O_4S$	$C_{21}H_{25}ClN_2O_4S$
Formula weight	436.96	436.96
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2_1/c$
a (Å)	9.284(1)	9.3200(3)
b (Å)	10.869(1)	20.0547(6)
c (Å)	11.385(1)	22.6698(9)
α (°)	97.496(1)	90
β (°)	108.99(1)	93.372(1)
γ (°)	102.34(1)	90
V (Å^3)	1036.1(2)	4229.9(3)
Z	2	8
D_c (g cm^{-3})	1.401	1.372
R_1 [$I > 3\sigma(I)$]	0.0425	0.0575
wR_2	0.1112	0.1159

The crystal structure of the B polymorph has two zwitterions in the asymmetric unit (Supporting Material, Fig. S2). The two moieties are held together by two hydrogen bonds. The bonds are formed by a hydrogen atom of the quaternary nitrogen atom (NH_2^+) and an oxygen atom of the carboxylic groups (COO^-) of the aminoheptanoic acid side chain of each moiety resulting in a graph set $R_2^2(20)$ assembly of the two tianeptine zwitterions. These assemblies are further connected through hydrogen bonds formed by the second carboxylic oxygen and the second hydrogen of the quaternary nitrogen atom and these hydrogen bonds result in parallel chains —N—H···O—C—O···H—N—H···O—C— (Fig. 3).

The result is a one-dimensional interconnecting pattern of $R_2^2(20)$ assemblies. Table 2 presents the observed hydrogen bonds. The hydrogen bond arrangement is such that the dimer is neutral as a result of the negatively charged carboxylic group forming a hydrogen bond to the positively charged quaternary nitrogen of each B polymorph moiety.

While both polymorph structures are essentially homosynthons, there are structural differences between the molecules of the two polymorphs. Apart from the difference in space group and cell dimensions, in the molecular structure of the A polymorph the methyl group of the seven-member ring points away from the amino acid side chain and the torsion angle defined by N15—C11—N8—C29 is 166.1(2)°. The SO_2 group of 3-chlorodibenzothiazepine is oriented toward the carboxylic acid group and conformation of the carbon chain results in a *syn* configuration between the 3-chlorodibenzothiazepine nucleus and carboxylic acid group. The distance between S5 and C22 is 7.729(3) Å. In both molecules of the B polymorph the methyl group is displaced toward the side chain and the torsion angles defined by N15—C11—N8—C29 and N44—C43—N49—C58 are −19.7(6)° and −21.6(7)° respectively. The SO_2 group is oriented away from the carboxylic acid group and in these molecules the CO_2 group is *anti* to the 3-chlorodibenzothiazepine nuclei. The distance between S5 and C22, and S37 and C51 are 11.389(7) Å and 11.412(6) Å respectively and do not differ significantly. The *syn* and *anti* configuration is probably the result of packing forces.

Table 2
Selected hydrogen bonding parameters for tianeptine form A and form B.

Form	D—H···A	d_{D-H} (Å)	$d_{H\cdots A}$ (Å)	$d_{D\cdots A}$ (Å)	∠D—H···A (°)	Symmetry code
A	O23—H231···N15	0.87	2.10	2.874(2)	148	$1-x, 1-y, -z$
B	N15—H151···O52	0.89	2.07	2.840(5)	144	
	N15—H152···O23	0.91	1.67	2.560(5)	169	$1-x, 1-y, 1-z$
	N44—H441···O24	0.89	2.07	2.841(5)	144	
	N44—H442···O53	0.89	1.70	2.577(6)	168	$2-x, 1-y, 1-z$

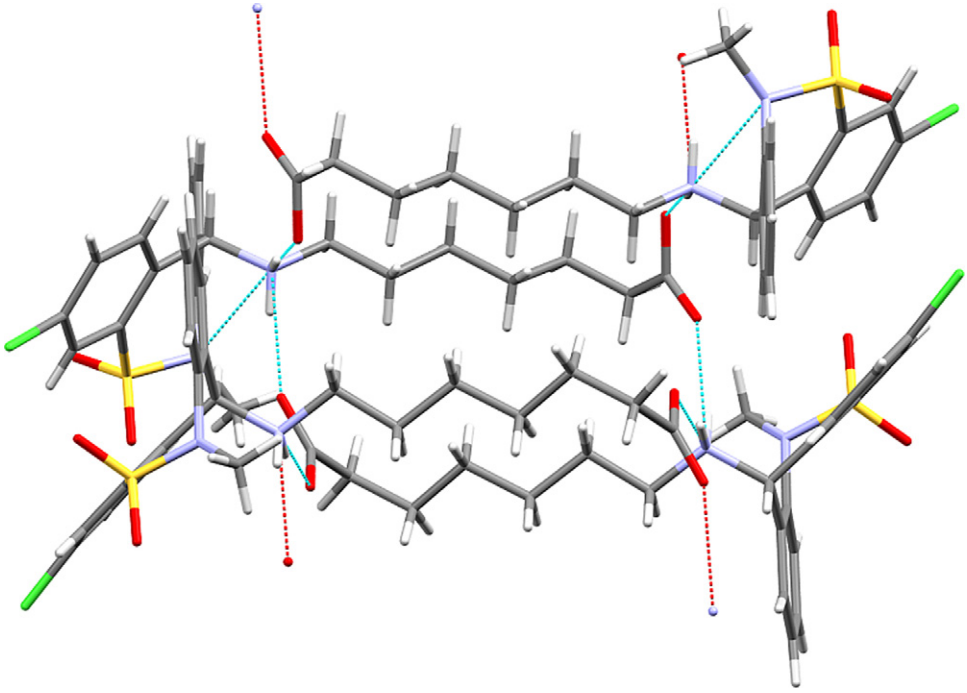

Fig. 3. Hydrogen bonding in the form B of tianeptine.

3.2. Characterization of tianeptine polymorphs in the solid state

The FTIR spectra of A and B are shown in Fig. 4.

The A polymorph shows strong absorption peaks at 3425, 3300, 1714, 925 and 767 cm^{-1}. For polymorph B absorption takes place at 3500, 3400 and 1637 cm^{-1}. From the FTIR absorption peaks it can be concluded that the A and B are not identical. For A the absorption at 1714 cm^{-1} corresponds to the C=O bond and absorption at 3425 and 925 cm^{-1} to the C—OH bond of the carboxylic acid group. The —NH— absorption is at 767 cm^{-1}. The absorption peaks for B are at 1637 cm^{-1} corresponding to the COO^- group and at 3500 and 3400 cm^{-1} corresponding to the quaternary $—NH_2{}^+—$ group.

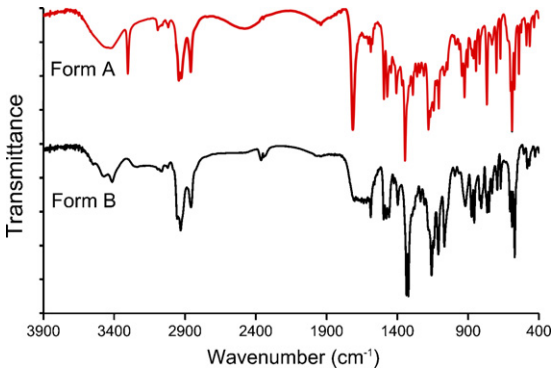

Fig. 4. FTIR spectra of tianeptine form A and form B.

Using DTA analysis the melting points of A and B were determined to be 148.4 and 140.5 °C respectively (Fig. 5).

The areas under the peaks of the endothermic curves of the DTA plot indicate that the heat of fusion for A is about 10% higher than for B. From these data it may be concluded that the relationship between the polymorphs is monotropic.

The PXRD patterns of tianeptine forms A and B are presented in Fig. 6 are different.

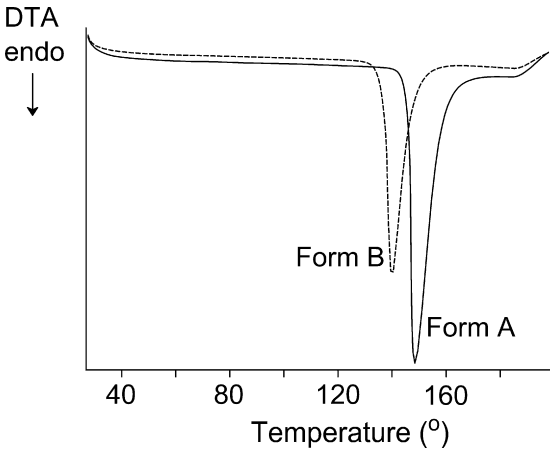

Fig. 5. DTA plots of tianeptine form A and form B.

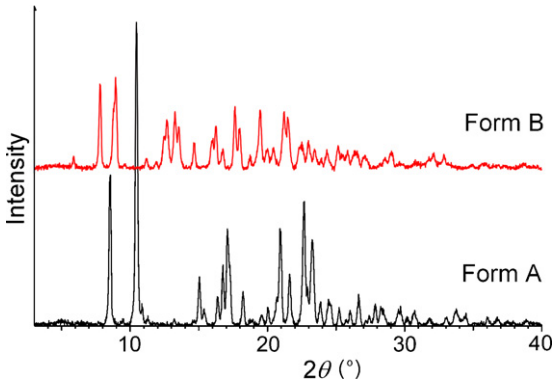

Fig. 6. PXRD patterns for tianeptine form A and form B.

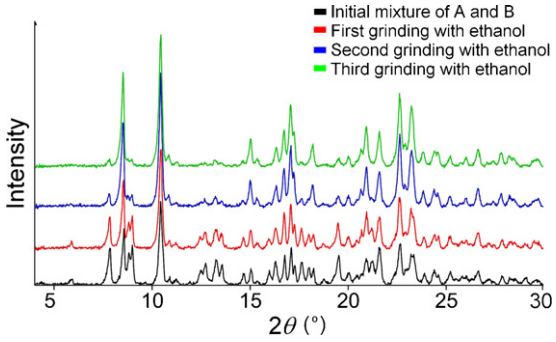

Fig. 7. Sequence of PXRD plots of tianeptine A and B 1:1 mixture.

The characteristic diffraction peaks for A are at 2θ values 8.50, 10.43, 15.01, 17.06, 20.94°, and for B at 2θ values 5.82, 7.56, 8.62, 8.96, 12.41, 12.66, 13.21, 13.49°.

The stability of the polymorphs was investigated by PXRD. The results obtained by repeated grinding of the 1:1 mixture are shown in Fig. 7.

The trend is for the B polymorph to undergo phase transition to the A polymorph indicating that A is more stable than B.

3.3. Tianeptine crystallization dynamics with changing pH

The pH adjusted samples of the sodium salt of tianeptine in ethanol yielded pure A, pure B, a mixture of A and B, and also a mixture of A and tianeptine hydrochloride (Table 3).

Table 3
Effect of pH on the product in 96% ethanol and in water.

pH	Resulting product from 96% ethanol	pH	Resulting product from water
6.96	B	6.82	A, B, C
6.79	B	6.62	A, B, C
6.59	A (2%), B	6.42	A, B, C
6.57	A (12%), B	6.18	A, B, C
6.53	A (20%), B	6.02	A, B, C
6.07	A (63%), B	5.79	Amorphous
5.80	A (76%), B	5.59	Amorphous
5.66	A (65%), B	5.42	Amorphous
5.50	A (87%), B	5.21	Amorphous
5.39	A	5.08	Amorphous
5.36	A	5.01	Amorphous
5.28	A	4.81	Amorphous
5.16	A	4.60	Amorphous
5.01	A (58%), tianeptine hydrochloride	4.00	Amorphous

The initial pH of the sodium salt ethanol solution is about 9.1. At pH 6.96 and above pH 6.79 the metastable polymorph B crystallized from the solution of the sodium salt of tianeptine. Between pH 6.59 and 5.50 the crystallization product was a mixture of both stable polymorph A and metastable polymorph B. From pH 5.39 to 5.16 the stable polymorph A crystallized. A mixture of A and the hydrochloride of tianeptine formed at a pH less than 5.16. The respective polymorphs and their mixtures were determined by PXRD analysis (Supporting Material, Fig. S3) of the crystal samples harvested at indicated pH values. The results show that with a decrease of pH the metastable polymorph B changes to the stable polymorph A. The crystallization results of the pH-adjusted ethanol solutions of tianeptine sodium salt show that there is a region between the pH value of 5.50 and 6.59 where A and B forms coexist in a state of equilibrium between the two polymorphs (Fig. 8).

This equilibrium is pH dependent and as the hydrogen ion concentration increases the equilibrium shifts to the left and the stable acid form A of tianeptine predominates. The equilibrium shifts to the right as the hydrogen ion concentration decreases and form B predominates.

Crystallization of the pH-adjusted water solution of the tianeptine sodium salt yielded a mixture a crystalline product when the pH of the solution was above 6.02 (Table 3). Utilizing PXRD the crystals were determined to be an equilibrium mixture the stable A polymorph as well as the zwitterion B, and C, with A predominating (Supporting Material, Fig. S4). An amorphous precipitated was observed in water solutions after addition of hydrochloric acid when the pH was below 5.79 (Table 3). The PXRD pattern of the

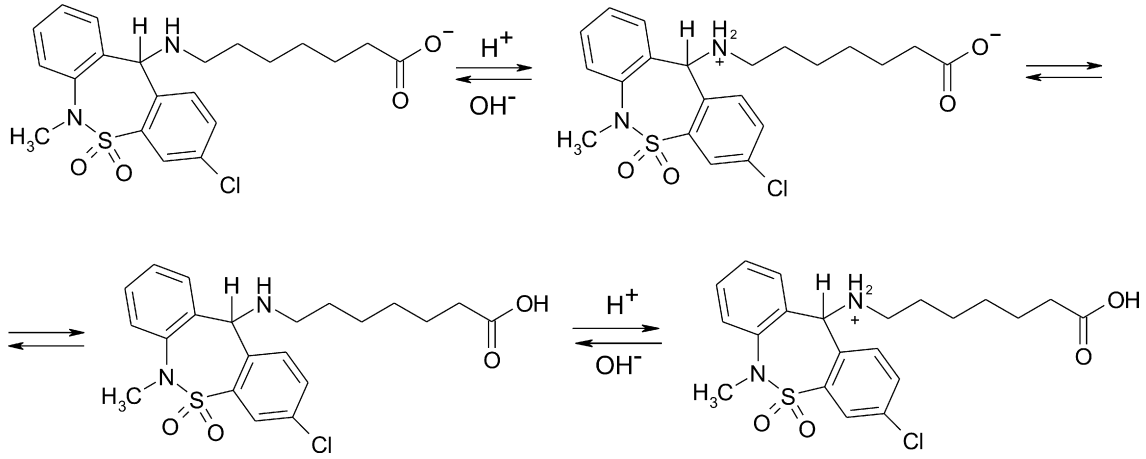

Fig. 8. Dynamic equilibrium of tianeptine polymorphs on changing the pH.

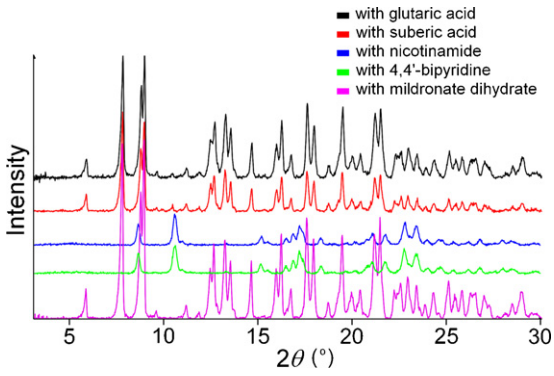

Fig. 9. PXRD patterns of tianeptine in the presence of additives.

amorphous form is featureless (Supporting Material, Fig. S4). The formation of a supersaturated solution of the acid form as the pH decreases probably promotes the formation of an amorphous form (Petit and Coquerel, 2006) however repetition of the experiment did not duplicate the results exactly.

3.4. Effect of the presence of additives on crystallization of tianeptine polymorphs

Crystallization of tianeptine employing equimolar amounts of glutaric or suberic acid resulted in the formation of polymorph B with a small addition of A. Crystallization of tianeptine in the presence of nicotinamide or 4,4′-bipyridine resulted in the formation of pure polymorph A. The pure form of B was obtained by crystallizing a solution that contained equimolar amounts of tianeptine and mildronate dihydrate. Crystallization of the stable form A is apparently enhanced by additives having a basic character, but the pure metastable B form, itself a zwitterion, crystallizes when the additive is a zwitterion (Kemme et al., 1983). The results suggest that additives having similar acid/base characteristics as the polymorph tend to block development of its crystals. If there is the possibility that the additive forms a zwitterion the growth of the acid polymorph A may be retarded by maintaining a relatively high pH of the solution. In this report it may be noted that only the metastable form B forms at a pH above 6.79 (Fig. 9).

4. Conclusions

Three polymorphs of tianeptine have been isolated. The crystal and molecular structures have been determined and confirm the existence of a stable carboxylic acid polymorph A and a metastable zwitterion B. An amorphous form has been obtained as a result of the pH changes in water solution of tianeptine sodium salt. By pH titration it has been established that A predominates below pH 5.39 but B above pH 6.59. A mixture of A and B, as determined by PXRD, is formed between these two pH limits. The use of additives to block or enhance the formation of a single polymorph indicate that, in this instance, an organic acid will enhance the formation of the zwitterion polymorph/acid polymorph mixture, but the presence of an organic base promotes the formation of the acid polymorph. Addition of a zwitterion did however result in crystals of the zwitterion polymorph. In solution, mixing A and B in equimolar ratios the metastable B transforms to the stable A polymorph. Although melting points of zwitterions are usually higher than those of the specific amino acid, in this instance a lower melting point is observed for the zwitterion notwithstanding the fact that there are more hydrogen bonds in this moiety. The volume occupied by each tianeptine molecule in A and B is respectively 518 $Å^3$ and 528 $Å^3$. This suggests that the hydrogen bonds in B are relatively weak because each nitrogen atom must form multiple hydrogen bonds to adjoining oxygen atoms.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2012.04.061.

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