PHARMACEUTICS, PREFORMULATION AND DRUG DELIVERY

Conformational Polymorphism of Tolbutamide: A Structural, Spectroscopic, and Thermodynamic Characterization of Burger's Forms I–IV

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ABSTRACT: Crystal polymorphism of the anti-diabetic drug Tolbutamide (TB) has been studied using various analytical techniques. TB crystallizes in four polymorphic forms (Forms **I–IV**), which differ in their mode of packing and in molecular conformation but with similar hydrogen bonding synthon (urea tape motif). All the structures were solved from single crystal X-ray data, except for Form **IV**, which was solved using conventional powder X-ray diffraction (PXRD) data. The conformational differences in the TB molecule arise primarily from torsional variations in the alkyl tail which result in two types of conformers (U and chair). The packing differences are mainly due to the orientation of adjacent molecules in the hydrogen bonding networks. Based on the DSC data, thermodynamic stability relationships of polymorphic pairs were evaluated and graphically visualized in a schematic energy-temperature diagram. Form **II** is found to be the thermodynamically stable polymorph from absolute zero to ~353 K and beyond which Form $\mathbf{I^H}$ is the stable polymorph. The anisotropic lattice contraction of TB polymorphs which resulted in severe variations in PXRD patterns at ambient and low temperature was highlighted. The present work also highlights and resolves several discrepancies in the published data on the structural and thermodynamic features of TB polymorphs. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:2975–2990, 2010

Keywords: Tolbutamide; polymorphism; crystal structure; stability; X-ray powder diffractometry; thermal analysis; anisotropic lattice contraction; energy-temperature diagram; density rule; lattice energy

INTRODUCTION

Sulfonylurea compounds are considered as an important class of therapeutical agents in medicinal chemistry for their hypoglycemic activity.[1] Tolbutamide (1-butyl-3-(4-methylphenylsulfonyl) urea, TB) is a first generation oral anti-diabetic drug that belongs to this class. It is used in the treatment of noninsulin-dependent (type II) diabetes as an adjunct to diet control. It controls the blood glucose levels by stimulating the pancreas for secretion of insulin. TB tablets are marketed under the brand name Orinase®. The chemical structure of TB (Fig. 1) shows that apart from the rigid benzene ring, it has seven bonds that can rotate freely along the alkyl chain. Due to this flexibility, one can expect this molecule to crystallize into different polymorphic structures.

Polymorphism, the existence of more than one crystalline form of a compound, has received particular attention in the drug development,[2,3] because of its ability to alter the properties of the drugs, such as stability, manufacturability, solubility and bioavail-

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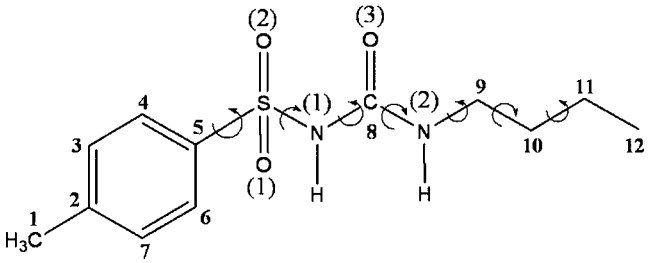

Figure 1. Chemical diagram of Tolbutamide (TB) with several rotational degrees of freedom (τ = torsional angle).

ability, etc.[4] Hence, characterization of all possible polymorphs and identifying the desired form to design a reliable process for its consistent production is critical for a successful drug development.[5–7] But, even after a thorough search, new polymorphs can suddenly appear or previously known polymorphs can disappear at any stage of the process development.[8–11] This inability to control the appearance of polymorphs clearly demonstrates the lack of understanding in this phenomenon. Conformational polymorphism arises when different conformations of a molecule pack into the same and/or different packing motifs.[12] It is often observed among active pharmaceutical ingredients which are molecular units with several flexible moieties. Polymorphism is more prevalent when the molecule has binding sites for solvent molecules in the crystal lattice leading to pseudopolymorphs.[13]

The first study on polymorphism of TB was reported in the extensive study carried out by Kuhnert-Brandstätter and Wunsch[14] on polymorphism and drugs using hot-stage microscopy. The existence of three polymorphic forms with melting points of 127, 117, and 106°C were reported. Subsequently, the system was studied by Simmons et al.[15] who reported two polymorphic forms which were prepared by crystallization experiments and named them as Forms **A** and **B**. Later, Burger further investigated the polymorphism of this drug and was able to prepare four polymorphic forms (Forms **I–IV**).[16] He claimed that Forms **I** and **III** were identical with Simmon's Forms **A** and **B**. The stability order was estimated to be Form **I** > Form **III** > Form **II** > Form **IV** with Form **I** being the most stable form at ambient conditions. Later, Rowe and Anderson[17] further examined the stability order of Forms **I** and **III** and observed that Form **I** readily transforms to Form **III** in solution at ambient conditions. Hence, they claimed that Form **I** is less stable than Form **III**.

In Cambridge Structural Database (CSD), two crystal structures of TB, reference codes ZZZPUS01[18] and ZZZPUS02,[19] are indexed and both correspond to Form **I**. Form **I** crystallizes in the orthorhombic, $Pna2_1$ space group ($Z = 4$; $a = 20.23$ Å, $b = 7.83$ Å, $c = 9.09$ Å). The unit cell data for Form **III** has been reported but without atomic coordinates.[20] Form **III** crystallizes in the monoclinic, $P2_1$ space group ($Z = 2$; $a = 8.11$ Å, $b = 8.96$ Å, $c = 10.19$ Å, $\beta = 101°$). More recently, Kimura et al.[21] further characterized Burger's Forms **II** and **IV** using various physical methods. The unit cell data of Form **II** was determined and deposited in CSD (refcode: ZZZPUS03) without atomic coordinates. This form crystallizes in the monoclinic, $P2_1/n$ space group ($Z = 4$; $a = 11.81$ Å, $b = 9.06$ Å, $c = 13.98$ Å, $\beta = 104.5°$).

From the previous studies, it is evident that TB can crystallize in at least four polymorphic forms which have been well characterized by various techniques. However, there is some confusion about the stability order of TB polymorphs at ambient conditions. Moreover, the structural origin of polymorphism in TB is not known and this is accessible only by elucidation of the internal arrangement of TB molecule in the crystal structures of the various polymorphs. Except for Form **I**, the crystal structures of other polymorphic forms (Forms **II–IV**) have not been reported to date. We also note that since the unit cell data of Forms **II** and **III** were already reported, it can be assumed that the crystal structures have been determined but not reported in the literature. In the case of Form **II**, the comparison of calculated X-ray powder pattern from its crystal structure with the experimental powder pattern was reported.[21]

With this background, the objectives of the present work are to understand the structural origin of polymorphism in TB and also to clarify the stability order of TB polymorphs at ambient conditions. With these objectives in mind, we report in this article the preparation and full structural characterization of TB polymorphs (Forms **I–IV**). The structures of Forms **I–III** were determined by single crystal X-ray diffraction, whereas the structure of Form **IV** was solved from the conventional powder X-ray diffraction (PXRD) data. Furthermore, a schematic energy-temperature diagram of TB polymorphs was constructed to elucidate their thermodynamic relationships and stability order.

While this manuscript was in preparation, Hasegawa et al.[22] reported a detailed analysis on the thermal behavior of Form **I** and showed that this form undergoes a reversible structural transformation to a new crystal form upon heating beyond 38°C. The newly transformed phase has been named as Form $\mathbf{I^H}$ and the phase below 38°C as Form $\mathbf{I^L}$. We adopt this naming convention for our discussion in this work.

EXPERIMENTAL SECTION

Materials

Tolbutamide is obtained from Sigma-Aldrich (St.Louis, Missouri, USA) with 99.0% purity and

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