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Crystal forms of tolbutamide from acetonitrile and 1-octanol: effect of solvent, humidity and compression pressure

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Abstract

The possibility of obtaining tolbutamide polymorphs was investigated using the solvents acetonitrile and 1-octanol. Tolbutamide is an oral hypoglycemic agent that exists in four polymorphic forms. Characterization of the various polymorphs was carried out by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), infrared spectroscopy (FTIR), optical microscopy and dissolution studies. Form A, crystallized from acetonitrile, resembled the form I polymorph, while form O, crystallized from 1-octanol, resembled the form III polymorph. Tablets of both form A and form O were produced at compression pressures of 2500 lbs and 5000 lbs using cornstarch and talc and were exposed to 40%, 75% and 95% RH conditions. DSC and PXRD studies did not show any significant drug-excipient interaction. Moreover, the change in the crystalline state of either form upon exposure to humidity was not evident. Dissolution studies showed a significantly lower drug release rate from form O tablets compressed at 5000 lbs pressure and exposed to 95% RH. Pressure and humidity had no significant effect on the dissolution profiles on the form A tablets. It was concluded that form A was the robust choice for further formulation development.
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1. Introduction

The existence of a pharmaceutical solid as a polymorph, pseudo-polymorph or a solvate, have been the focus of continuous research because of their influence on the physicochemical properties of the drug (Giron, 2001). Many pharmaceutical solids exhibit "polymorphism", which may be defined as the ability of the same substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (Haleblian and McCrone, 1969; Haleblian, 1975; Brittain, 1999). Polymorphic changes can be induced by heat, stress, or solvent mediated processes (Byrn, 1982). Different polymorphs of the same substance can have different physical properties such as melting points, chemical

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reactivities, dissolution rates and bioavailability (Byrn, 1982; Brittain, 1999), due to differences in molecular packing. Thus, the knowledge of polymorphism is of importance in pharmaceutics since it can impact the dissolution rate, stability and the bioavailability of the formulation (Byrn, 1982).

The solvent plays an important role in the formation of polymorphs, as well as in polymorphic transitions. For example, in desolvation reactions, the product separates into a new crystal form, and the process usually involves (i) molecular loosening, (ii) breaking of host-solvent bonds, (iii) solid solution formation, and (iv) separation of another polymorph as a product phase (Byrn, 1982). Polymorphs can also be obtained by crystallization from a single solvent. Commonly used crystallization methods involve controlled temperature changes such as slow cooling of a hot saturated solution (for compounds more soluble at higher temperatures) or slow warming (for compounds less soluble at higher temperatures). Crystallizing solvents having varying polarities are preferred since molecules in such solutions tend to form different types of hydrogen-bonded aggregates (Byrn et al., 1994). Some solvents favor the crystallization of a particular form because they selectively adsorb to specific faces of the crystal. Hence, they either inhibit their nucleation (cluster formation), or retard their post-nucleation growth. Some of the commonly used crystallizing solvents are water, methanol, propanol, ethanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane, etc (Brittain, 1999). For example, sulfur crystallizes as orthorhombic crystals (α) from a carbon disulfide solution and as monoclinic crystals (β) from the melt (Byrn, 1982).

Stability of compounds exhibiting polymorphism is one of the primary concerns in the pharmaceutical area. Drug degradation in the solid and the semi-solid states is usually affected by water content, and the polymorphs having different affinity for water often exhibit different chemical reactivities. Moisture catalyzes chemical degradation either by (i) participating in drug degradation as a reactant, or (ii) by adsorbing onto the drug surface and forming a moisture-sorbed layer in which the drug is dissolved and degraded (Yoshioka and Stella, 2000). Other physico-chemical properties of pharmaceutical products that are affected by the presence of water, include flow, compaction and dissolution (Adeyeye et al., 1995).

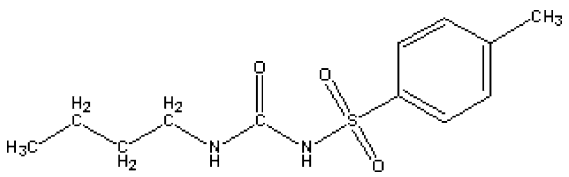

Fig. 1. Chemical structure of tolbutamide.

Compression pressure is an important parameter that needs to be monitored while investigating drug and excipients in tablet dosage forms. Several properties of tablets are influenced by compression pressure, namely (i) density and porosity, (ii) hardness and tensile strength, (iii) disintegration, and (iv) dissolution properties (Lieberman and Lachman, 1982). Compression pressures may also alter the crystal form of the drug leading to a polymorphic transformation (Brittain, 1999), which may also affect the tablet properties. For example, piroxicam showed phase transformation during compression when the needle like α-phase was converted to the cubic β-phase upon compression (Ghan and Lalla, 1992).

Tolbutamide (Fig. 1) (Chu et al., 1977) belongs to the aryl sulfonylurea group of compounds. Four polymorphic forms (I, II, III and IV) have been reported and characterized earlier (Simmons et al., 1972; Burger, 1975; Leary et al. 1981; Kimura et al., 1999), and these studies cite the use of benzene, hexane and ethanol as the crystallizing solvents for obtaining polymorphs. There are conflicting reports regarding the stability data of form I and III (Rowe and Anderson, 1984; Kimura et al., 1999). We investigated the possibility of crystallization of tolbutamide from two solvents acetonitrile and 1-octanol, and have compared them with the results in the literature. The effect of other factors such as compression pressure and humidity on crystalline properties has also been reported. In all cases, the dissolution profile of the drug has been investigated to note the effect of these factors on drug release from tablets.

2. Materials and methods

2.1. Materials

Tolbutamide (Sigma–Aldrich Co.), acetonitrile (Mallinckrodt Baker Inc.), 1-octanol (Fisher Scientific), cornstarch U.S.P. and talc U.S.P., sodium hy-

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