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Structural characteristics and crystal polymorphism of three local anaesthetic bases Crystal polymorphism of local anaesthetic drugs: Part VII

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Abstract

Benzocaine (BZC), butambene (BTN) and isobutambene (BTI) are basic local anaesthetic agents of the ester type, preferentially used for surgery and dental procedures. The compounds, official in the USP (BZC and BTN) and Ph. Eur. (BZC), were each found to exist in two polymorphic crystal forms and their solid state characteristics have been determined by thermomicroscopy, differential scanning calorimetry (DSC), FTIR-, FT-Raman-spectroscopy as well as X-ray powder diffractometry. This work further emphasizes the comparison of solid state characteristics of three compounds with closely related structural features on molecular level, leading to opportunities for the investigation of structure-property relationships. Mod. I^0 is the particular thermodynamically stable form at room temperature in all of the three systems. This form is present in commercial products and can be crystallized from solvents at room conditions. Mod. II can be obtained by annealing the supercooled melt or fast cooling of a saturated solution, respectively. The endothermic transformation of mod. II to mod. I^0 upon heating confirms that mod. I^0 is thermodynamically stable at ambient conditions (heat of transition rule) whereas mod. II is enantiotropically related to mod. I^0, i.e. is metastable at temperatures above the transition temperature. The metastable forms show different kinetic stabilities at room temperature.

Keywords: Local anaesthetics; Crystal forms; Crystal polymorphism; Thermal analysis; Hot-stage microscopy; Solid state properties

1. Introduction

Local anaesthetics (LA) of a general formula lip–CO–hydr (lip: lipophilic end, mostly phenyl ring; CO: negatively charged linkage, commonly ester or amide; hydr: hydrophilic group, tertiary or secondary amine) are representatives of a drug class well known for the formation of polymorphs and solvates (Giron et al., 1997; Borka and Haleblian, 1990). The hydrophilic group is responsible for the receptor binding whereas the lipophilic and the linking group

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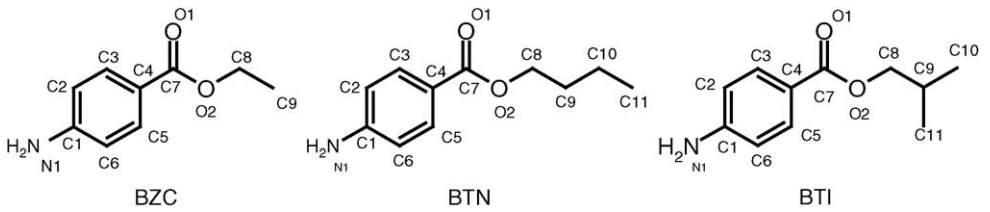

Fig. 1. Molecular structure of three local anaesthetic bases benzocaine (BZC), butambene (BTN), isobutambene (BTI) with atomic numbers.

affect the duration of action (Goodman and Gilman, 1998).

The present paper deals with the solid state characterization and phenomena of crystal polymorphism of three local anaesthetic basic compounds (Fig. 1), which cause reversible local loss of feeling before and during surgery, dental procedures (including dental surgery) or labor and delivery. They generally are used in topical compositions and methods for treating pain (Williams and Zhang, 2003). Benzocaine (BZC) and isobutambene (BTI) moreover are used in sunscreen lotions as UV-absorbing active compounds with a Sunscreen Index (SI) at a medium level of 9.6 (BZC), 9.2 (BTI), 8 (BTN) determined at an optical density of 3.080 Å in a concentration of 1% (Boyle et al., 2002). BZC is official in the European (Ph. Eur.) and the US Pharmacopoeia (USP) and BTN only is official in the USP. BTI, mainly used in cosmetics, is not official in any pharmacopeia. The structural related methyl *p*-hydroxybenzoate was one of the earliest being recognized as organic polymorphic compound showing six polymorphs (Lindpaintner, 1939; Kofler and Kofler, 1954; Kuhnert-Brandstätter, 1971) and the crystal structure of the stable form (monoclinic) was solved with crystals grown from organic solution (Zhengdong et al., 1997). Thus, we expected the structural relatives BTN and BTI to be polymorphic, too.

The existence of polymorphic crystal forms of BTN and BTI has not been mentioned in any of the previous analytical studies dealing with the solid state properties of these compounds. The stable crystal form of BTN was determined to be monoclinic (Watanabe, 2002). BZC was found to be dimorphic (Gruno et al., 1993) and the crystal structure of the stable form was solved (Baptista, 1968; Sinha and Pattabhi, 1987) as orthorhombic ($P2_12_12_1$) and revised (Lynch and McClenaghan, 2002) with crystals grown from an ethanolic solution being also monoclinic ($P2_1/c$). They all agree that the compound comprises a flat molecule arranged, head to tail, in linear ribbon arrays via a N–H···O=C association as found in some other local anaesthetics.

In the present study, we describe the formation, the physical properties and similarities of polymorphic behaviour of the structural related BZC, BTN and BTI by thermal analytical methods, vibrational spectroscopy, powder X-ray diffraction and water-vapor sorption analysis evaluating their relative thermodynamic and kinetic stabilities. Although the other analytical methods indicate a strong relationship between the three compounds, X-ray studies show different crystal systems.

2. Materials and methods

2.1. Materials

BZC: four samples of benzocaine ("uk aus H_2O/ether 10/77", "Dr. E. Ritsert's Anaesthesin AMNG", "Anästhesin Benzocain INN", "Benzocaine B.P. Herba") were available for this study. BTN/BTI: "Butamben EC No. 202-317-1 Lot 99H2514" and "Cycloform Curta & Co. Berlin-Britz 941249" were used. All solvents used in this study were of p.a. ("pro analysis") quality.

2.2. Methods

2.2.1. Hot-stage microscopy

The thermal behaviour of the solid state forms was observed using a Olympus BH-2 polarizing microscope (Olympus Optical Co. Ltd.) equipped with a Kofler hot-stage (Reichert, Vienna, A) and linked with a digital camera (Olympus DP50, Olympus Optical Co. Ltd.) using AnalySIS® Image Processing software.