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The Polymorphs of Oxybuprocaine Hydrochloride

A. Schmidt[1]. U. J. Griesser[1], T. Brehmer[2], A. Burger[1]
[1] Institut fur Pharmazie, Abt. Pharmakognosie, Universität Innsbruck, Innrain 52, A-6020 Innsbruck
[2] Institut fur Mineralogie und Kristallographie, Universität Wien, Althanstr. 14, A-1090 Wien

Oxybuprocaine hydrochloride (OBPHC) is a local anesthetic drug developed in the eighties and mainly used in eyedrop formulations *(e.g.* Benoxinat®) for the diagnosis of eye-diseases. OBPHC was found to exist in three polymorphic forms which have been characterized by thermomicroscopy, differential scanning calorimetry (DSC), pycnometry, FTIR- and FT-Raman-spectroscopy as well as X-ray powder- and single-crystal X-ray diffractometry. The relative thermodynamic stability of the forms was determined and is represented in a semi-schematic energy/temperature diagram[1].

Mod. II is the thermodynamic stable form at room temperature, present in commercial products and crystallizes from an ether/ethanol-mixture (1:1). Mod. I can be obtained by crystallization from methanol, acetone and other solvents. Mod. II exhibits an endothermic phase transition ($\Delta_{trs}H_{II-I}$: 4.0 kJ-mol^{-1}) at about 135°C into the metastable mod. I (melting point 160°C, $\Delta_{fus}H_I$: 36.2 kJ mol^{-1}). According to the heat of transition rule[1] the two modifications are thus enantiotropically related. Mod. I is kinetically stable in the solid state, *i.e.* the back transformation to mod. II is only achievable by a solvent mediated transformation process below the thermodynamic transition temperature (T_{trs}: 90 ± 10°C). Moreover the density- and IR-rule[1] are not fulfilled. The density of mod. I is 1.0 % higher than that of mod. II and the first absorption band in the infrared spectrum (NH-vibrations) of mod. I (3464 cm^{-1}) is lower than that of mod. II (3469 cm^{-1}). Cooling mod. II. below -30°C leads to the low temperature form (mod. HO which is structurally related to mod. II. The transformation (($\Delta_{trs}H_{II-III}$: 0.4 kJ-mol^{-1}) is reversible and a enantiotropic relationship between mod. in and the two other forms can be concluded.

OBCHC is a classic example of conformational polymorphism. Mod. n (space group $C_{2/c}$) shows only one conformer in the asymmetric unit, whereas in mod. I ($P2_{I/n}$) and III ($P2_{1/a}$) two conformations are present. This explains the high packing efficiency of mod. I compared to the thermodynamically stable mod. II. Because of the high kinetic stability the metastable mod. I is usable for solid drug formulations.

1 A. Burger, R. Ramberger. Mikrochim. Acta II (1979) 259-271