Crystal Polymorphism of Local Anaesthetic Drugs: A Summary

A.C. Schmidt, U.J. Griesser

Institute of Pharmacy, Department of Pharmaceutical Technology, University of Innsbruck, Innrain 52, A-6020 Innsbruck, Austria

This report is the résumé of a comprehensive investigation of the solid state properties and on the polymorphism of a great number of local anaesthetic drugs (LA´s) with the goal to explore the relationship between crystal polymorphism and structural features of drug molecules.

23 local anaesthetics with common structural features have been characterized by thermomicroscopy, differential scanning calorimetry (DSC), pycnometry, FTIR-, FT-Raman- and solid state NMR-spectroscopy as well as X-ray diffraction methods (single crystal, powder). Based on these data, the relative thermodynamic stabilities of different crystal forms in every polymorphic system were evaluated in semi-schematic energy/temperature diagrams[1].

LA´s of the p-amino benzoic acid structural type (PAB) show classical conformational polymorphism. The longer the alkyl chain in the para-position to the acid function, the more polymorphs were found. The p-oxy-substituted compounds (POB) form substantially less forms, which is likely due to a reduced conformational flexibility. The water-soluble salts (mostly hydrochlorides) of the local anaesthetics show distinctly more cases of polymorphism than the free bases. The hydrochloride salts form between two and four polymorphs in average. The thermodynamic transition temperatures of the enantiotropic modifications can be found in the temperature range between 90 and 120°C with enthalpies of transition between 3 and 4 kJ mol^{-1}. Only those PAB´s which crystallize as hydrates from water, show unusually high enthalpies of transition (~17 kJ mol^{-1}). The compounds with a hydroxyl-substituent in C3- or C4-position of the phenyl ring are thermally labile. These compounds frequently show polymorphism and also non-stoichiometric hydrates, i.e. isomorphic desolvates[2] (dehydrates).

This study is a first step to recognize relationships between the structure and solid state properties within this limited group of active substances with common structural elements. The results show clearly that there are common relationships but in order to understand the phenomenological behaviour in more detail, more structural information must be collected and analyzed by computational methods.

[1] Burger A., Ramberger R.: On the Polymorphism of Pharmaceuticals and other Molecular Crystals. I. Mikrochim. Acta II (1979) 259-271

[2] Stephenson G.A., Groleau E.G., Kleemann R.L., Xu W., Rigsbee D.R.: Formation of Isomorphic Desolvates: Creating a Molecular Vacuum. J. Pharm. Sci. 87/5 (1998) 536-542.