

Characterization of solvates and crystal polymorphs of (R/S)- Bupivacaine hydrochloride

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Bupivacaine hydrochloride (BPVCN-HCl) is a classic local anaesthetic drug (amide type) which is used for local anaesthesia including infiltration, nerve block, epidural and intrathecal anaesthesia. The water soluble hydrochloride is specified in the European and United States pharmacopoeia. The existence of a monohydrate (commercial form), which transforms to an anhydrous form on heating was reported by Giron et al. [1] who also indicated the potential existence of solvates from ethanol, isopropanol and ethylacetate. Within a systematic study of a series of structurally similar compounds we performed a more comprehensive polymorphism screening program of this local anaesthetic, applying a variety of analytical methods such as hot stage microscopy, differential scanning calorimetry, thermal gravimetric analysis (TGA), FTIR-spectroscopy, moisture sorption analysis and powder- as well as single crystal X-ray diffraction.

The monohydrate of BPVCN-HCl is highly stable in dry atmosphere (over desiccants, 25 °C) but desolvates at temperatures above 60 °C. Thermal dehydration of the hydrate, lyophilization or crystallization from solvents such as acetonitrile or acetone results in mod. A (T_{fus} : ca. 257 °C under decomposition). During crystallization experiments we discovered two new polymorphs, namely mod. B (crystallized from chloroform) and mod. C (crystallized from ethylacetate), which was confirmed by powder X-ray diffraction, IR- and Raman-spectroscopy. These forms are stable (ambient storage conditions) for at least 6 months.

Furthermore four solvates were obtained and characterized. The hemi-ethanol solvate, which crystal structure is already known [2] was reproduced and its properties were analyzed. Crystallization from other low alcohols (methanol-, 1-propanol and 2-propanol) yielded in solvated forms as well. From the weight-loss (TGA) it is clear that the methanol-solvate of BPVCN-HCl is a mono-solvate whereas the other three solvates are hemi-solvates. Upon heating the solvents show incongruent melting to the anhydrous form A, form C or a mixture of the two forms. Suitable single crystals of the four solvates were obtained and their crystal structure was determined. The solvates are isostructural showing chains of BPVCN molecules, which are mainly linked through the chlorine anions via strong (N-H...Cl⁻, N⁺-H...Cl⁻) and weak (C-H...Cl⁻, C-H...O) hydrogen bonds. The close packing of these chains results in tunnel like voids (along *a*-axis) which are filled with solvent molecules. The solvent molecules are highly disordered and form only weak interactions with the host molecules. The ethanol and 2-propanol hemi-solvate show the highest thermal stability (desolvation > 140 °C, TGA), followed by the 1-propanol hemi-solvate (>100 °C) and the methanol mono-solvate which completely desolvates below 110 °C. This demonstrates clearly that an optimal space filling of the structural voids, i.e. a maximum in interactions between the solvent and the host is one of the most crucial parameter for the stability of such kind of solvates.

References

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- [2] H. J. Bruins Slot: Structures of the Local Anaesthetics Ropivacaine and Bupivacaine: Structure Determination and Molecular-Modelling Study. Acta Cryst., B46, 1990, 842-850.