Solid State Properties and Stability of Crystal Forms of Pentamidine Isethionate

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Pentamidine isethionate is a member of aromatic diamidines which is successfully used in the treatment and prophylaxis of protozoal infections, especially for pneumocystis carinii pneumonia in the case of non-treatability with cotrimoxazol or AIDS infection. The compound (Ph.Eur.) shows interesting solid state properties and is reported to form at least six crystal polymorphs [1], a trihydrate [2,3] and a dihydrate [4], but so far no systematic solvent crystallizations have been reported. In order to close knowledge gaps in the solid state behaviour of this drug compound, crystallizations from various solvents and further experiments such as moisture sorption/desorption studies and thermal analysis (hot stage microscopy, thermogravimetry, differential scanning calorimetry) have been performed. One of the goals of this study was the production of a highly crystalline Form A. Though this is the thermodynamically stable form at 20°C the known production procedures result in a partially disordered product. The solvent screening revealed several so far unknown solvates, which were characterized by thermal analysis and powder X-ray diffraction.

All six polymorphs (Form A to F) could be verified and further characterized by hot stage microscopy and DSC. Additionally an annealing method turned out the be a suitable way for the production of highly crystalline form A. Moisture sorption/desorption experiments showed that one water molecule in the trihydrate is weakly bound and is released between 50 and 10% RH in a non-stoichiometric way without significant changes of the crystal structure. Below 10% the two remaining water molecules are released in a distinct step indicating a clear phase transition to a polymorph (Form B). From this result we doubt the existence of an individual dihydrate structure as reported [4], which likely represents only a partially desolvated trihydrate. The sorption isotherms of the three polymorphic forms, which can be produced in larger amounts (form A, B, C), show a transformation to the trihydrate at and above relative humidities (RH) of 50% (form A and the high-temperature form C) respectively at 40% RH (metastable form B).

The solvent screening resulted in a series of highly unstable aliphatic alcohol-solvates ($C_1 - C_4$). From the powder pattern it can be assumed that these solvates are isostructural to the trihydrate. They transform easily to the hydrate during harvesting due to environmental moisture and in the presence of traces of water also in the mother liquor. Additionally, a monosolvate from pyridine was found, which is stable at room conditions and desolvates thermally not below 100 °C.

References

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