

The Physicochemical Properties of Emetine Dihydrochloride

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Emetine is a natural alkaloid widely used as emetic agent for children. The hydrochloride (ETDC) is official in the European Pharmacopoeia (Ph.Eur) as penta- and heptahydrate whereas the USP XXIII just specifies a water content of 15 to 19 % (*i.e* 17.6 to 23,5 % referred to the dry material).

Our investigations of the solid state properties applying crystallization experiments, thermal analysis, ^{13}C solid-state NMR studies, X-ray powder diffractometry (XRPD) and water sorption/desorption studies finally showed that ETDC can exist in at least 4 crystal forms. All forms are associated with water and show a more or less continuous course of the water vapor sorption isotherm, with a small hysteresis between the sorption and desorption curve. Thus we can classify the forms as non-stoichiometric hydrates.

Form HxA crystallizes from ethanol and HxB from water. Both forms were found in commercial product. Their water ratio may range from almost zero (in dry air) to five (HxA) or seven (HxB) mol water per mol ETDC at 80% relative humidity (25°C, see figure). This explains why the Ph.Eur. states monographs for a penta- and a heptahydrate respectively. However, the most stable hydrate form is HxC, which can be obtained by precipitation from water/acetone or via solvent mediated transformation of other forms in different solvents. The water content of HxC is more or less constant between 40 and 90% relative humidity, close to 5 mol/mol water. XRPD and the CPMAS spectra show that the removal of the water affects

the structure of the forms in different ways. The crystal lattice of HxA and HxB shrinks distinctly upon dehydration and the dehydrated solids are partially (HxA) or highly (HxB) disordered. The desolvation of HxC results in more distinct structural changes but the desolvated hydrate shows high order which is also indicated by the highest melting point (247°C) and highest entropy of fusion ($90 \text{ J mol}^{-1} \text{ K}^{-1}$). The metastable form HxD crystallizes from methanol and transforms to HxC on exposure to high relative humidity.

In conclusion the study emphasizes the importance of comprehensive solid state characterizations of drug substance in order to guarantee meaningful and correct specifications in pharmacopoeias.

