Crystal forms of Thiamine hydrochloride (Vitamin B1): New analytical data of a compound with an intriguing solid state history

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The industrial production of thiamine (Vitamine B1) started in 1937 and today the world production is estimated at more than 4000 t per year.[1] The most common salts, also official in the pharmacopoeias, are the hydrochloride and the nitrate. The better soluble hydrochloride (TMNCL) is generally specified as a fairly reactive, hygroscopic substance with a low chemical stability. Thus it is often replaced by the mononitrate salt in formulations, which is described as a non hygroscopic, less reactive but also much less soluble and definitely less acceptable from a toxicological point of view. Therefore, the hydrochloride is exclusively used for high dosage forms of TMNCL.

TMNCL can exist in several crystal forms.[2,3] Pharmacopoeias just specify a water content below 5% but do not dictate a specific crystal form. Commercially available batches always consist of the so called monohydrate, which is a metastable hydrate. The water content of this hydrate varies with the relative humidity conditions, ranging from 0 to almost 0.9 mol water per mol TMNCl. The hydrate is kinetically stable at relative humidities below about 60% but transforms to the hemihydrate at higher humidities or when suspended in aqueous solvents. This transformation also occurs during wet granulation or the storage of the dry granulated monohydrate.[4] The monohydrate always crystallizes directly from aqueous solvents (kinetic form) or alcohols, whereas the hemihydrate is formed indirectly by solution mediated transformation of the monohydrate in aqueous solutions. In contrast to the monohydrate the water in the hemihydrate is tightly bound and cannot be removed by thermal treatment without chemical decomposition of TMNCL. Its high stability is also obvious from the fact that McCrone[5] and originally also Watanabe and Nakamachi[6] regarded this hydrate as anhydrous form. The consolidation and bulk properties of the hemihydrate and the monohydrate are similar[4] and therefore the hemihydrate is clearly the more attractive form for the production of solid state formulations.

Crystallization from methanol may also result in a highly unstable methanol solvate. A second monohydrate[7] with a more constant water the commercially available hydrate content was obtained by freeze drying. The dehydration of this hydrate results in a new anhydrous form. The characterization of the different crystal forms was performed by thermal analysis, X-ray powder and single-crystal diffraction, Raman- and IR-spectroscopy as well as moisture sorption-desorption studies.

From the results of the present and previous studies it can be clearly drawn that many of the bad solid state properties of TMNCl stated in the literature are mainly based on the selection of the wrong crystal form. In using the thermodynamically stable hemihydrate, which, however, is not commercially available, most of the known solid state problems of TMNCL can be minimized. TMNCL, which was introduced to the market long before pharmaceutical manufacturers and regulatories became aware of the importance of polymorphism and pseudopolymorphism for the drug development, is an excellent example of possible consequences derived from lacking studies of the solid state properties of a drug substance.

References

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