

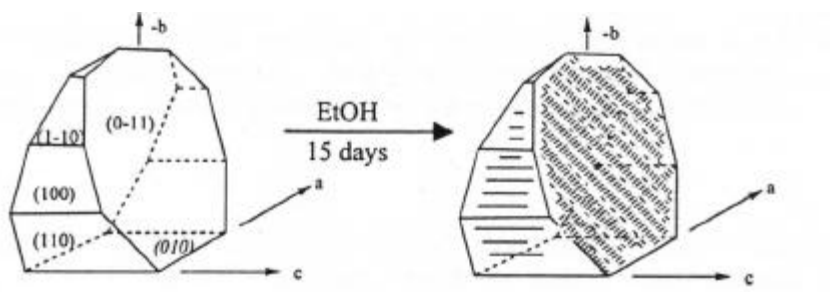
Dehydration and Crystallisation Behaviour of α -Lactose Monohydrate: New Unexpected Results.

Stephanie Garnier, Samuel Petit, Gerard Coquerel.

Unité de Croissance Cristalline et de Modelisation Moleculaire (UC^2M^2) Sciences et Méthodes Séparatives (SMS), UPRES EA 2659, IRCOF, Université de Rouen, 76821 Mont Saint-Aignan Cedex - France. E-mail: Samuel.Petit@univ-rouen.fr

In our communication presented last year¹, it has been suggested that the research of new polymorphs of a pharmaceutical compound could be made more exhaustive by using as starting material a solvate. Indeed, the choice of suitable desolvation conditions can in some cases lead to different crystal packings, differing from each other by the existence or not of structural filiations with the hydrated mother variety². As a result, different behaviours of dehydrated solids regarding crystallisation and physical properties can be expected.

The present communication deals with an attempt to apply this methodology to a famous excipient, α -lactose, in order to elucidate the mechanism(s) of solid-solid transitions and to reach an improved control on the suitable conditions for the preparation of a desired solid-state variety. According to Figura & Epple³, two anhydrous forms can be successively prepared from the monohydrate, a hygroscopic form (a_H) and a stable form (a_S). The a_H form exhibits a crystal packing similar to that of the monohydrate, so that its hygroscopicity results from the fact that ambient moisture is sufficient for rebuilding the H-bond network of the monohydrate. This mechanism is discussed on a structural basis, and confirmed by the observation of single crystals dehydrated in ethanol.



By contrast, the a_S form consists of a different (and unknown) crystal packing, so we aimed at determining its crystal structure from X-ray diffraction on a single crystal. When trying to prepare single crystals for this variety, we obtained new unexpected solvates in solvents such as N-methylpyrrolidinone and DMSO.

Furthermore, our attempts to apply the methodology proposed by Ulrich *et al.*⁴ in methanol and acetone produced a surprising result: although the a_S anhydrous form can be easily obtained as a powder in these solvents, using single crystals of the monohydrate led to single crystals (whiskers-like) of anhydrous β -lactose. Since mutarotation is not supposed to occur (α -lactose is almost insoluble in acetone and methanol), these results are discussed in terms of local amounts of water in the suspension sufficient to allow the nucleation of β -lactose crystals.

1. C. Habare, S. Petit, G. Coquerel, *Desolvation of solvates : possible application for the research of new polymorphic forms*, PhandTA 4, 1999, Karlsruhe, (abst. Book, KC5)
2. S. Petit, G. Coquerel, *Chem. Materials*, 1996, 8 (9), pp. 2247-2258
3. L.O. Figura, M. Epple, *J. Thermal Analysis*, 1995, 44, pp.45-53
4. S. Nordhoff, J. Ulrich, *J. Thermal Analysis and Calorimetry*, 1999, 57, pp. 181-192