Formation of New Crystalline Phases by means of Solvent Exchange and Growth of Whisker-like Crystals

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Understanding the desolvation and/or the solid state transitions of solvated pharmaceutical compounds is an important issue during the development of new drugs because of the potential consequences, mainly in terms of stability and storage[1-3]. In the frame of our continuous investigations devoted to the dehydration or desolvation mechanisms of molecular crystals[4], and in view to identify new solvated or polymorphic forms[5], we have recently investigated the behavior of several steroids (mainly dexamethasone acetate – Acedex hereafter – and cortisone acetate – Aceco) in several organic solvents. In the case of Acedex, a DMSO solvate has been identified and its crystal structure was determined.

In order to investigate the desolvation mechanism of this phase, we have applied the methodology recently published by Nordhoff and Ulrich[6], consisting of the immersion of single crystals in a solvent in which the compound is almost non soluble. This methodology has been mainly designed to prepare samples with high specific surface areas, but can also induce the formation of new crystalline packings, which can be of interest due to their physical and biological properties, in particular their solubility, bioavailability, granularity, thermal stability, etc. As a result of: (i) the quasi-insolubility of the solute in the added solvent, (ii) the miscibility of the two solvents and (iii) the high local supersaturation in the vicinity of the solid particles, the new phase precipitates as "whisker-like" crystals, with a dendritic growth mechanism[6]. This phenomenon was previously observed and described by E. Laine et al.[7] and Evans[8].

When single crystals of the Acedex-DMSO solvate are immersed in water, a new sesquihydrated form appears. The nucleation and growth mechanisms can be discussed in connection with structural data, and compared with results obtained with other steroids. The mechanism describing both the desolvation step and the formation of the whiskers seems to be consistent with a destructive-reconstructive transformation.

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