HYDRATION / DEHYDRATION TRANSFORMATION MECHANISM OF PHARMACEUTICAL CRYSTALS REVEALED BY SDPD METHOD

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Hydration / dehydration phenomena (pseudo-polymorphic phase transformation) during manufacturing or storage are critical for the pharmaceutical crystals because their physicochemical properties such as stability, solubility, and bioavailability largely change depending on the crystal structures. However, after dehydration, single crystal integrity tends to degrade resulting in powdery crystal. We have succeeded to reveal solid-state structural rearrangements using ab initio Structure Determination from Powder X-ray Diffraction data (SDPD) technique [1-9]. Interestingly, a group of compounds shows "isomorphic desolation" in which the XRD pattern does not change significantly even after dehydration and the initial structure is almost preserved. In order to reveal the mechanism of "isomorphic desolation", such pseudo-polymorphic transformation has been investigated by SDPD technique.

Antibiotic drug Erythromycin A dihydrate released the water molecules at dry condition to form anhydrous phase (I) through “isomorphic desolvation” process. Also, this phase showed thermal phase transition to another anhydrous phase (II) around 433K. From the DVS measurement, stoichiometric hydration was observed for the phase (I) to form dihydrate phase even at low humidity condition (R.H. 5%). However, the hydration of the phase (II) did not give the dihydrate phase and was variable non-stoichiometric type. Crystal structure analysis by the SDPD technique revealed that the structure of phase (I) is isomorphic with the dihydrate phase and has channel type void spaces in the hydrophilic region that correspond to crystalline water position in the structure of the dihydrate phase (Fig.1). This void explains the “isomorphic desolvation” and fast hydration even at low R.H condition. On the other hand, the anhydrous phase (II) have completely different crystal structure with isolated voids around hydrophobic region, which contributes to non-stoichiometric hydration as another “isomorphic (de)hydration”.

Also in the other “isomorphic dehydration” crystals such as Cefalexin, Cefachlor, and Azithromycin, the SDPD technique successfully elucidated their characteristic crystal structures.

**Figure 1**: Final PXRD fitting of Anhydrate (I) phase, and crystal packing drawing with void spaces.