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Keywords: powder diffraction, synchrotron radiation, protein crystallography

MS.10.4

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Pseudo-polymorphic transition of pharmaceutical crystals revealed by SDPD method

Hidehiro Uekusa, Masahide Aoki, Kotaro Fujii, *Department of Chemistry and Materials Science, Tokyo Institute of Technology, Tokyo, (Japan).* E-mail: uekusa@cms.titech.ac.jp

Many pharmaceutical crystals show pseudo-polymorphic transition via hydration / dehydration processes depending on their storage environment or mechanical treatment. Sometimes, even after dehydration, the XRD pattern does not change significantly showing "isomorphic desolvation" which attracted much interest. Also, as their physicochemical properties such as color, stability, and solubility largely differ depending on the crystal structures, the structural investigation of the transition is important especially to utilize the pharmaceutical polymorphic crystals as API. However, after the transition, single crystal integrity tends to degrade and powdery crystals are formed. In such case, *ab initio* Structure Determination from Powder X-ray Diffraction data (SDPD) is efficient technique. We have succeeded to reveal several solid-state structure rearrangement phenomena so far by using the technique [1-7].

Herein, some examples of the pseudo-polymorphic transitions relating "isomorphic desolvation" are presented, which have been investigated by SDPD technique.

Cephalexin (cephem antibiotic) has five hydrated forms and their reversible transformations are induced by the change of relative humidity. Three pseudo-polymorphs (anhydrate, monohydrate, and dihydrate) were successfully analyzed by SDPD technique. As the structure has three independent API molecules, the number of parameters was adjusted during the direct space calculations. Water molecules of hydration were located from the residual map, cavity volume, and geometrical considerations. The hydrate phases show water tunnel structure between L-shaped building blocks that were formed by three independent cephalexin molecules connected by hydrogen bonds. In the hydration process, the blocks slide each other to increase the tunnel volume from 0 to 280 Å^3 (see figure), which is accompanied by elongation of the *a*-axis length by 17%. Such "sliding block" mechanism enables the large structural change with retention of crystallinity.

Erythromycin is used as a macrolide antibiotic drug in the dihydrate form. It released the water molecules at 355K or at dry condition to form anhydrate phase that has analyzed by SDPD technique. The structure (isomorphic desolvate) has void tunnel regions that were occupied by water molecules in the dihydrate phase. Thus, it should be transformed to more stable anhydrate structure.

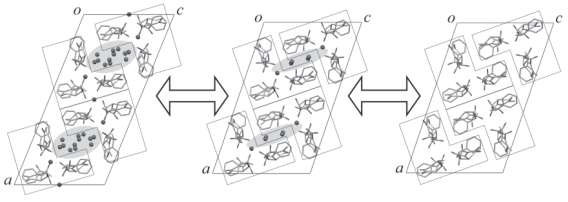

Fig. Cephalexin dihydrate, monohydrate, and anhydrate

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Keywords: polymorphism, pharmaceutical, hydration

MS.10.5

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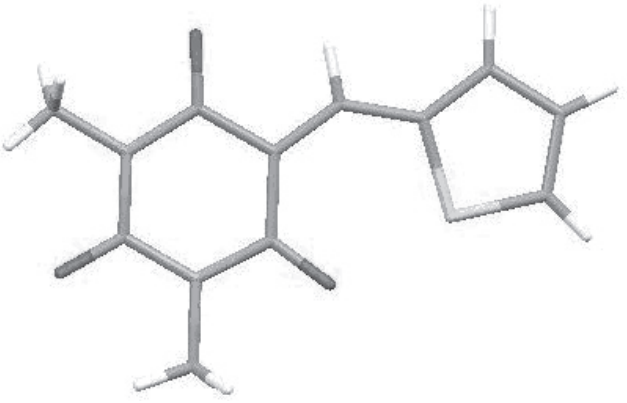
Structure Determination of Barbiturate Derivative Using X-Ray Powder Diffraction

Aisha Mohamed Moustafa, Ibrahim Farag and El-Sayed Mohamed Shalby, *Solid State Department, Physics Division, National Research Centre, Dokki, Giza (Egypt).* E-mail: aishamous@yahoo.com

The barbiturate derivative namely 1,3-dimethyl-5[(2-thienyl)methylene]-2,4,6-pyrimidinetrione ($C_{11}H_{10}N_2O_3S$) has numerous biological activities as anti-inflammatory, anticonvulsant and antibacterial. The molecular structure of this compound has been determined by the method of simulated annealing as implemented in Dash program from high resolution laboratory X-ray powder diffraction data collected at ambient conditions. It has been found that the compound crystallize in the monoclinic space group $P2_1/c$ with lattice parameters a=7.2384Å, b=13.2319 Å, c=13.8221 Å, β =123.74° and unit cell volume=110.89 Å^3. The crystal structure was refined using Rietveld refinement method on a data collected at 1.5 Å resolution yielded R-Bragg values of 7.91% and R_{wp} value of 6.4%. The molecules are stacked in parallel layers and are stabilized by hydrogen bonds.



Keywords: structure_determination, x-ray_diffraction, antibacterial

MS.11.1

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Accurate mass, models and resolution for high-throughput structural analyses

John A. Tainer,[a,b] Robert P. Rambo,[a] Greg L. Hura,[a] Michal Hammel,[a] [a]*Lawrence Berkeley National Laboratory, Berkeley, CA, (USA).* [b]*Department of Molecular Biology & The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, (USA).* E-mail: jatainer@lbl.gov

Efficiently characterizing biologically relevant conformations of macromolecules and their complexes is a critical challenge for