P.25.10.2
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The study on the Stability of a Drug. Can a Product have Life?
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A product of a pharmaceutical company was received to make a study on the possible polymorph forms that this product could present. The first study was the characterization by XRPD, DTA, TG, IR spectroscopy and Raman scattering. The supplied product was crystallized and the crystal structure by single-crystal X-ray diffraction was determined. 567 different preparations in different conditions were made which were analyzed by XRPD, TG and DTA. These preparations were classified in three different clusters according to the XRPD patterns and melt/decomposition temperatures of the product. 58.3% of these preparations showed the supplied form, 25% in the second group and in the third 16.7%

At same time different bags, prepared in different years, were analyzed, being observed better the same variations in the patterns and in the melt/decomposition temperature that had been observed with the 567 preparations. The variations could also be ordered according to the time lapsed from their preparation.

The variations in the melt/decomposition temperature, enthalpy and entropy indicated that the product evolved with the time toward less stable states. The observation of the aging of the supplied product. The recovery of the aged phases by re-crystallization makes conclude that the product is not stable. The TG analyses show that the aged product doesn't have a losses of mass before to the melt temperature and the Rietveld analyses of all XRPD patterns show an increase of cell volume less than 15 $Å^3$, then the aging doesn't take place for the adsorption of other products: The width of the pattern peaks doesn't grow in the aged samples indicating that a lost of crystallinity doesn't take place.

Keywords: pharmaceutical crystallography, stability, polymorphs

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Ab-initio Structure Determination of two Kinds of Forma for Adrenal Cortical Hormone, Predonisolone
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Predonisolone is a very well known adrenal cortical hormone. It has been used as medicine almost for 40 years. Predonisolone has two different crystal forms and both of them are used as drug substances. At that time when Pledonisolone was approved, it was not thought that detailed crystal structure or polymorphism is so critical for medical use. But recently it has been recognized that crystal structure or polymorphism is very important for effectiveness and patents as drugs.

It is very important to know crystal structures from powder X-ray diffraction patterns because drug substances themselves are powder state in the production process. In this study, we show ab initio structure determination of two different crystal forms of Pledonisolone.

X-ray powder data are collected at BL02B2, SPring-8 in order to have better resolution. A program for ab-initio structure determination is developed based on genetic algorithm. It is found that one of polymorphism is monoclinic and the other is orthorhombic. After determining crystal structure, both of structures are refined by Rietveld method. R factor based on Bragg integrated intensities reached 4.78% for monoclinic form and 5.06% for orthorhombic form, respectively. These small factors guarantee that both of crystal forms of Predonisolone are determined successfully. There are two and four molecules in a unit cell for monoclinic and orthorhombic crystals, which are very consistent with cell volume.

Keywords: predonisolone, ab-initio structure determination, genetic algorythm

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Crystal Structure of MCoA-ACPT from *Thermus thermophilus* HB8
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As a part of Protein 3000 project in Japan, Joint research group of PCprot has solved the crystal structure of malonyl CoA-acyl carrier protein transacylase (MCoA-ACPT) from *Thermus thermophilus* HB8 by the collaboration with RIKEN. The structure has been solved by the molecular replace method (Molrep) using molecular structure of MCoA-ACPT from Escherichia coli. There is 42 % homology in the amino acid sequences in each other. This is the first structure determination of MCoA-ACPT from thermophilic organisms. Crystals were obtained with using full-automatic protein crystallization and observation robotics system named TERA in RIKEN Harima Institute. Data set was collected by the CCD detector at the Pharma-ceutical Industry Beamline (BL32B2) in SPring-8. Data set was processed by the software HKL2000 and 2.2Å data set was obtained.

In the crystal structure MCoA-ACPT from TTHB8 makes dimer that is relatively tight, though MCoA-ACPT from TTHB8 is thought to work as monomer in the solution. By the way, MCoA-ACPT exists in the bacterial body but not in the human body. Therefore it is very possible that this structure would give the light to the structure based drug design for antibiotics.

Keywords: protein 3000 project in Japan, malonyl CoA-acyl carrier protein transacylase, *Thermus thermophilus* HB8

P.25.10.5
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Pharmaceutical Application of Synchrotron X-ray Powder Diffraction at SPring-8
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We have performed the *ab-initio* crystal structure determination of phamaceutical compounds from powder data collected by an Imaging Plate system of large Debye-Scherrer camera at BL19B2. Use of synchrotron radiation has the important advantage of using variable wavelength for data collection with a highly pararell beam.

As a standard sample, cimetidine ($C_{10}H_{16}N_6S$) and trehalose dihydrate (C_{12} H_{22} O_{11} $2H_2O$) are used, and their crystal structures are significant-

ly solved by the method of Simulated Annealing (*DASH* and *Powder Solve*) and also by the direct method (*EXPO2004*). After Rietveld refinement, refinement parameters of trehalose dehydrate data is *Rp*=2.27, *Rwp* = 3.4 [1]

Using Imaging Plate system rapid data collection of 2- 5 minute exposure is sufficient for structure determination and continuous data collection at different temperature is easily occupied.

We have also been planning to determine in-situ structure determination in transition of trehalose dehydrate at high temperature and under humidity control [2].

These results suggest that the powder diffraction system at BL19B2 is useful for pharmaceutical solids including polymorph and its phase transition.

[1] Altomare A., et al., *J Appl. Cryst.*, 2004, **37**, 1025-1028. **[2]** Kishi A., Toraya H., *The Rigaku Journal*, 2004, **21**, 25-30.

Keywords: powder diffraction in industry, pharmaceutical structure determination, synchrotron radiation applications