MS20 O1

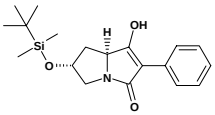
Modulated structures in pharmaceutical crystallography -a bitter pill to swallow? Trixie Wagner[a], Andreas Schönleber[b], Karl Baumann[c], [a]*Novartis Institutes for BioMedical Research, Basel, Switzerland.* [b]*Laboratory for Crystallography, University of Bayreuth, Germany.* [c]*Novartis Institutes for BioMedical Research, Vienna, Austria.* E-mail: trixie.wagner@novartis.com

Keywords: modulated structures, pharmaceutical crystallography, teaching

Together with quasicrystals and composite crystals modulated structures constitute the category of aperiodic crystals. Their diffraction pattern is characterized by the existence of additional reflections, the so-called satellite reflections, and for an integer indexing (3+*d*) indices are required. As a consequence of this loss of 3-dimensional periodicity, the concept of superspace was developed in which the atoms are treated as *d*-dimensional atomic domains [1]. The aperiodic structure in real space is then interpreted as a cut through this (3+*d*) dimensional superspace description.

Up to now only few modulated structures have been described which consist of biologically active or interesting compounds [2]. Looking at the number of examples from our organic service lab in the past four years one can expect, however, that the need to handle this type of structures properly will be increasing - especially in a pharmaceutical environment where the non-ambiguous, correct and complete description of a crystal structure can be essential for patenting as well as for quality-control purposes.

In this context we will present the crystal structure of the tetrahydro-pyrrolizinone $C_{19}H_{27}NO_3Si$, an intermediate for potential inhibitors of the LFA1/ICAM1 interaction, as an illustrative example for handling and describing the modulated structure of a typical pharmaceutical compound.



$C_{19}H_{27}NO_3Si$ shows a monoclinic basic cell and satellite reflections in the (**a*c***) plane. The structure can be described in the (3+1)-dimensional superspace group $P2_1(\alpha 0 \gamma)0$. The modulation wave vector is **q** = (0.142 0 0.382).

Having established a working knowledge of the concept and terminology of superspace descriptions of modulated structures we will discuss several aspects of the indexing, data processing, and scaling procedure for this particular compound, including e.g. the selection of the **q**-vector or the validity of a (classical 3-dimensional) superstructure approach.

Various possibilities of structure solution (including the only recently extended charge-flipping algorithm [3]) will be commented on. Furthermore, a subsequent possible transition from a conventional refinement of the average structure with SHELXL into superspace refinement with JANA2006 [4] will be explained. Finally, additional quality control features offered in JANA2006, such as overlays of electron density and atomic modulation functions are described.

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MS20 O2

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Keywords: Grinding, pharmaceuticals, phase transformations

About 80% of the drugs are formulated in the solid state which can be crystalline or amorphous (glassy). The molecular nature of these solids - either active substances or excipients – gives them specific properties: low melting point, low molecular and crystalline symmetry, easy vitrification (difficulty of recrystallization)….. and also a great sensitivity to the external disturbances. The industrial formulation processes impose strong constraints which involve dynamic aspects in addition to temperature or pressure variations. These specific perturbations are, for example, the frequency of the shocks during grinding or the rate of desolvatation during atomizations (spray drying) or freeze-drying. The dynamic aspects are also clearly important during extrusions. These materials which are driven by dynamic stresses often undergo modifications of their physical state. One can observe amorphizations or on the contrary recrystallizations. In other circumstances, one can observe phase transformations between polymorphic crystalline varieties; transformations which can generate either metastable phases or more stable phases. All these modifications which affect properties such as solubility, can have a strong impact on the bioavailability. In addition, the physical stability of these compounds becomes dubious and can involve modification of chemical stability and reactivity. The identification of the relevant physical parameters that it is advisable to control during the driving processes is a requirement for the industrial formulation. It is also a challenge in condensed matter physics. The wealth of situations provided by the pharmaceutical science offers new possibilities to progress in the understanding of this type of non equilibrium phase transformations. In this presentation, we will consider the transformations induced by grinding and dehydration. Exemples will be taken among excipients (lactose, trehalose, sorbitol, mannitol…) and active substances like indomethacine. The structural and microstructural evolutions will be described. We will show how it is possible to identify the driving parameters of the non equilibrium phase transformations. Time permitting we will present possibilities offered by mechanical alloying of molecular compounds.

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MS20 O3

Crystal Engineering of Pharmaceutical Solids Involving Antitubercular Drugs Victor Ch. Kravtsov, *Institute of Applied Physics of Academy of Sciences of Moldova, Chişinău, Moldova.*
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Keywords: crystal engineering, co-crystals, antitubercular drugs

Pharmaceutical co-crystallization is reliable method to amend physical and technical properties of drugs such as solubility, dissolution rate, stability hygroscopisity, and compressibility without alternating their pharmacological behavior [1]. This methodology is not routine still and understanding of the factors, which control co-crystallization, represents the challenge to modern crystal engineering. Carboxylic acid-pyridine synthon is a reliable tool in design a number of co-crystals with dicarboxylic acids [2]. We have utilized this approach as recurring strategy in supramolecular synthesis of solid-state compositions of pharmaceutical phases with relative to isonicatineamide antitubercular drugs. Isonicotinic acid hydrazide (INH) is used as a first-line treatment for tuberculosis, in combination with other drugs for the treatment of active disease and also used for prevention of tuberculosis in people who have been exposed to active disease. Crystallizations of INH with dicarboxylic acids resulted in 2:1 co-crystals of with malonic, succinic and adipic acids, co-crystals 1:1 with glutaric acid and 1:1 organic salts with oxalic and D-tartaric acids. In co-crystals adipic, succinic and malonic acids invariably form acid – pyridine O-H···N hydrogen bond synthons with two neighboring INH molecules, glutaric acid forms different acid-pyridine and acid-hydrazide syntons. In the structure of malonic acid : INH co-crystal strong O-H···N bonds demonstrate the case of partial proton transfer. Acid-pyridine synthon has not been found in the structure of INH : D-Tartaric acid, but bifurcated N-H···O/N-H···N bonds unite protonated on basic nitrogen INH in the chains. We have extended this approach on another anti-tubercular drugs with relative molecular structure and utilize different co-crystal formers for fine-tuning the properties of new compositional matter. Two anti-tubercular drugs, 2-Ethyl- and 2-Propyl-4-thiocarbamoylpyridine were employed as a target molecules in two parallel series of co-crystallizations with homologous of alkanedicarboxylic acids (COOH-$(CH_2)_n$-COOH, n=0-7) and 18-membered crown ethers as a co-crystals formers. Co-crystals having 2:1 drug:co-crystal former stoichiometry have been obtained only with adipic and suberic acids (n-4, 6), 18-crown-6 and isomer B of DCH-18-crown-6. In the co-crystals, the dicarboxilic acid invariably interacts with both nitrogen atoms of drug molecules via O-H…N and N-H…O hydrogen bonds, resulting in the similar H-bonds pattern regardless of S-shape or linear conformation of dicarboxilic acid. Only the amino group of the drug participates in H-bonding with the crown ether, whereas the best acceptor of the drug (i.e. aromatic N) doesn't form any strong H-bond. Co-crystallization of 2-Ethyl-4-thiocarbamoylpyridine with D-Tartaric acid ulted in monohydrate with 1:1:1 drug : acid : H2O stoichiometry and no acid-pyridine synthon has been found in the structure.Two conformational polymorphs have been found for Propyl-4-thiocarbamoylpyridine in its pure form. Co-crystallization with crown ethers and dicarboxilic acids allowed separate different conformers.This study was supported by MRDA–CRDF award: MRDA-008 : BGP-III, MOC2-3063-CS-03.

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MS20 O4

Applications of X-Ray Diffraction in the Pharmaceutical Industry Andreas Fischer, [a]*Grünenthal Research Centre Aachen, Germany.*
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Keywords: Pharmaceutical Crystallography, Industrial Applications, Solid State Properties

With increasing interest in the physico-chemical properties of solid pharmaceutical active compounds and their galenical formulation, the X-ray diffraction technique has become a fundamental technology in the pharmaceutical industry.
Pharmaceutical industry is an interesting employer for crystallographically skilled scientists. Nowadays solid state characterization covers the whole development of a drug substance from early research up to submission and even beyond approval of the finished drug product.
Selected chapters of X-ray diffraction applications within the journey through pharmaceutical development are presented.
1. Which compound is the right one for development (early pre clinical research)?
2. First comprehensive characterization of the development candidate (early clinical research).
3. Supportive quality control within upscaling and optimization of the drug substance.
4. Galenic formulation investigations.
5. Setting up the production scale processes according to International Conference on Harmonisation (ICH) quality guideline concerning specifications settings for new drug substances (Q6A requirements [1]).
6. Patent support during development and life cycle of the product.
Whereever possible, real-life examples are provided.

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, Step 4 version, 1999; www.ich.org.