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

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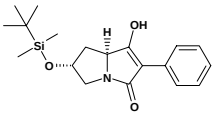
Together with quasicrystals and composite crystals modulated structures constitute the category of aperiodic crystals. Their diffraction pattern is characterized by the existence of additional reflections, the so-called satellite reflections, and for an integer indexing (3+*d*) indices are required. 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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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.

[1] Solid State Communications 132 (2004) 693-696
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