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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.

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