MS9-P3 Investigating nanocrystalline drugs embedded in a polymeric matrix by Debye Function Analysis

Carlotta Giacobbe[1], Dritan Hasa[2], Dario Voinovich[2], Antonio Cervellino[3], Norberto Masciocchi[4], Antonietta Guagliardi[5]

1. European Synchrotron Radiation Facility CS 40220 - 38043 Grenoble Cedex 9, France
2. Department of Pharmaceutical Sciences, University of Trieste, P. le Europa 1, I-34127 Trieste, Italy
3. Paul Scherrer Institut, 5232 Villigen PSI, Switzerland
4. Dipartimento di Scienza e Alta Tecnologia, Università dell'Insubria, I-22100 Como, Italy
5. Istituto di Cristallografia, CNR, I-22100 Como, Italy

email: giacobbe@esrf.fr

The release rate of a solid drug is directly related to particle size; smaller crystals have, in fact, an enhanced ability to reach their physiological target[1]. To this goal, the use of mechanical energy, inducing size/morphological modifications, represents a straightforward, green, and innovative approach. The process takes the name of *mechano-chemical activation*, and has recently been introduced as an efficient pharmaceutical processing technique.[2] The release rate of a solid drug is directly related to particle size; smaller crystals have, in fact, an enhanced ability to reach their physiological target[1]. To this goal, the use of mechanical energy, inducing size/morphological modifications, represents a straightforward, green, and innovative approach. The process takes the name of *mechanochemical activation*, and has recently been introduced as an efficient pharmaceutical processing technique.[2] In our work, coground mixtures of Vinpocetine (VIN) ($C_{22}H_{26}N_2O_2$), a poorly soluble drug used for the treatment of cognitive disorders and related symptoms[3], and Cross-Linked Polyvinylpyrrolidone $(C_6H_9NO)n$ (PVP-CL), have been investigated at variable milling time and 1:4 and 1:7 VIN:PVP weight ratios. The Debye Function Analysis (DFA) of several mixtures is applied for the first time to extract information about structure, size and size distribution, morphology and amorphization of drug nanoparticles. To this aim, we used high resolution data collected at the Material Science beamline MS-X04SA of the Swiss Light Source, and the DEBUSSY suite of programs[4] modeling the total (Bragg and diffuse) sample scattering. Quantitative results on the diverse microstructure modifications controlled by the milling time and the drug-to-polymer ratio will be presented. They show a clear trend between time, size distribution and weight ratio. Moreover, investigations on the biopharmaceutical performance of the most activated systems are in progress to be correlated to the previous results. Significantly, while other methods are commonly used to characterize nanocrystalline drugs, especially in terms of size and morphology (TEM, HRTEM – at the expenses of sample deterioration), the DFA method here discussed offers a novel, exhaustive (and statistically sound) characterization tool[5,6].

Keywords: drugs, debye function analysis, particle size

MS9-P4 Understanding packing interactions and physicochemical properties of novel multicomponent crystal forms of azelaic acid-based anti-inflamatory drugs combining X-ray and NMR

M. Teresa Duarte[1], Inês C.B. Martins[1], Mariana Sardo[2], Luís Mafra[2]

1. Centro de Quimica Estrutural, Instituto Superior Tecnico, Universidade de Lisboa, Av. Rovisco Pais 1, 1049-001 Lisboa, Portugal,
2. CICECO, Universidade de Aveiro, 3010-193 Aveiro, Portugal

email: teresa.duarte@tecnico.ulisboa.pt

In this work we are presenting complementary studies of X-ray single crystal and powder diffraction as well as SSMNR crystallography in the understanding of packing interactions in multicomponent crystal forms. This approach presents a new insight into the understanding of the new physicochemical properties of this new pharmaceutical entities. Our aim is to optimize crystal engineering methods for the structural elucidation of pharmaceutics, following an X-ray and NMR Crystallography approach where NMR techniques sensitive to crystal packing arrangement are used in tandem with diffraction and computer modeling Structure-activity relationship and solid-state analysis, in particular X-ray diffraction and solid-state NMR spectroscopy, are particularly relevant in pharmaceutical industry where the majority of active pharmaceutical ingredients (APIs) occur as solids. [1, 2] Multicomponent crystal forms of APIs (co-crystals, molecular salts, solvates, hydrates and salts) have been extensively studied over the last years. [2, 3] These new forms proved to be an efficient method of improving physicochemical properties of drugs without changing the biological activity, resulting in the improvement of important characteristics such as solubility, dissolution rate, stability under variable RH conditions and bioavailability. [2] Azelaic acid (AA) is an antibacterial product used to treat acne and other skin disorders. This API exhibit low solubility and its performance would benefit from a solubility enhancement. [4] We developed new crystalline solid forms structural, chemical and thermal characterizations will be presented.

Acknowledgments The authors acknowledge funding of the projects POCI/QUI/58791/2004, PEst-OE/QUI/UI0100/2013, **PTDC/CTM-BPC/122447/2010, RECI/QEQ-QIN/0189/2012** and post-doc grant SFRH/BPD/78854/2011 by Fundação para a Ciência e a Tecnologia

References [1] André, V.; Piedade, M. F. M.; Duarte, M. T., *CrystEngComm* **2012,** 14, 5005-5014. [2] Braga, D.; Maini, L.; Sanctis, G.; Rubini, K.; Grepioni, F.; Chierotti, M. R.; Gobetto, R., *Chem.Eur.J.* **2003,** 9, 5538. [3] Martins, I.; Martins, M.; Fernandes, A.; André, V.; Duarte, M. T., *CrystEngComm* **2013,** 15, 8173. [4] Hebert, R. F., Therapeutically improved salts of azelaic acid. U.S. Patent 6,734,210. May 11, **2004**.

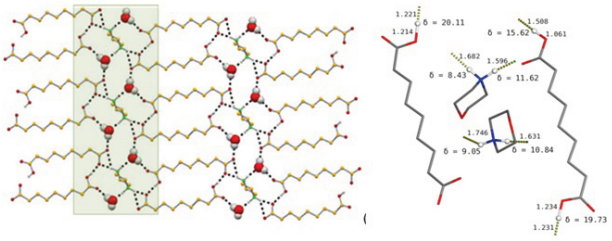

Figure 1. Crystal packing od Azelaic acid:piperazine cocrystal from SCXRD; molecular salt of Azelaic acid: morpholine from SSNMR crystallography

Keywords: Pharmaceutical cocrystals; X-ray Crystallography ; NMR Crystallography; Physicochemical properties

MS9-P5 Envisaging ZMOFs towards improved drug delivery and release

Vania Andre[1], M. Teresa Duarte[1]

1. Centro de Química Estrutural, Instituto Superior Técnico, Universidade de Lisboa, Av Rovisco Pais, 1049-001 Lisbon, Portugal

email: vaniandre@ist.utl.pt

The continuous quest for efficient and cost-effective novel alternatives to improve drugs' performance assumes a key role in pharmaceutical industry. One of the topics that has received great attention in this quest is the development of systems that facilitate the controlled delivery and release of drugs. Over the past 7 years, the application of metal organic frameworks (MOFs) for controlled delivery of drug molecules has emerged. These supramolecular chemistry-based structures display several properties that transform them into promising drug carriers: remarkable high surface areas and large pore sizes for drug encapsulation; intrinsic biodegradability; versatile functionality for post-synthesis grafting of drug molecules; scalability to the nanoregime. [1,2]

Among MOFS, zeolite-like metal-organic frameworks (ZMOFs) and zeolitic imidazolate frameworks (ZIFs), MOFs with zeolitic architectures, exhibit particularly interesting properties that make them powerful platforms for drug delivery and/or controlled release of drug molecules. ZIFs are comprised of tetrahedral transition metal ions connected by imidazolate units arranged in topologies with large cages and small apertures, while in ZMOFs the scope of ligands connected to the metal ions is not limited to imidazolate compounds. ZIFs exhibit high thermal and chemical stability, overcoming two of the main issues when considering the use of MOFs in biomedical applications. [3,4]

We have been exploring this type of materials for controlled drug delivery and release of psychoactive drugs and several promising results have been already obtained.

References:

1. Allendorf MD, Stavila V: **Crystal engineering, structure-function relationships, and the future of metal-organic frameworks.** *CrystEngComm* (2015) **17**(2):229-246.

2. Horcajada P, Gref R, Baati T, Allan PK, Maurin G, Couvreur P, Ferey G, Morris RE, Serre C: **Metal-organic frameworks in biomedicine.** *Chemical Reviews* (2012) **112**(2):1232-1268.

3. Eddaoudi M, Sava DF, Eubank JF, Adil K, Guillerm V: **Zeolite-like metal-organic frameworks (zmofs): Design, synthesis, and properties.** *Chemical Society reviews* (2015) **44**(1):228-249.

4. Guillerm V, Kim D, Eubank JF, Luebke R, Liu X, Adil K, Lah MS, Eddaoudl M: **A supermolecular building approach for the design and construction of metal-organic frameworks.** *Chemical Society Reviews* (2014) **43**(16):6141-6172.