MS20 P07

Non-steroidal antiinflammatory drugs interaction with biological membrane Michal Markiewicz[a,b], Marta Pasenkiewicz-Gierula[b], Pawel Serda[c], Tadeusz Librowski[d], Szczepan Mogilski[d], Henryk Marona[e], Sergio Funari[f], Stanislaw Hodorowicz[a], [a]*Department of Crystal Chemistry and Crystal Physics, Jagiellonian University, Cracow, Poland,* [b] *Faculty of Biochemistry, Biophysics and Biotechnology, JU,* [c]*Regional Laboratory, JU,* [d]*Department of Pharmacodynamics, Medical College, JU,* [e] *Department of Chemical Technology of Drugs, MC, JU,* [f]*Max-Planck Institute for Colloids and Interfaces, c/o HASYLAB DESY, Hamburg, Germany.*
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Keywords: non-steroidal antiinflammatory drugs, molecular dynamics simulations, small and wide-angle diffraction

Non-steroidal antiinflammatory drugs (NSAID) belong to the most commonly used remedies. However, NSAID administration is often associated with several adverse effects, the most frequent being gastrointestinal complications, such as gastric ulcers and bleedings. The NSAID action relies on the cyclooxygenase (COX) inhibition, which leads to the prostaglandin synthesis suppression. The lack of prostaglandin's cytoprotective effect on gastric mucosa was previously thought to be fully responsible for their gastrointestinal toxicity. After the discovery of two subtypes of COX: COX1 and COX2, the former is considered physiologically active and responsible for the "gastroprotective" effect, while the latter is active during pathological processes. Unfortunately, gastrotoxicity of selective COX-2 inhibitors and non-toxic COX-1 selective inhibitors were also observed and suggested that there is additional mechanism of NSAID gastrotoxicity. Recently, that mechanism has been linked to direct NSAID's interactions with the gastric phospholipids [1]. These interactions may disturb the gastric mucosa hydrophobicity, which can result in lowered resistance of the gastric mucosa to luminal acid [2].
In this project, the influence of commonly used NSAIDs – aspirin, ketoprofen and piroxicam – with diverse gastrotoxicity and newly synthestized xanthone derivatives on the lipid bilayer structure and dynamics using both experimental and computer simulation approach was studied. The effects of NSAID with different toxicity on the bilayer thickness, lipid surface area, electron density profiles and other physical properties of the membrane were determined from molecular dynamics simulation giving opportunity to correlate the gastrointestinal side-effects with NSAID-membrane interactions at the atomic level. The multilamellar vesicles of POPC-cholesterol containing investigated NSAIDs were prepared and measured at different hydrations using SAXD and WAXD methods. The results of the measurements showed about 0.6nm diversity in the repeat periods *d* of the lamellar phase at 1:30 lipid-water molar ratio between aspirin and ketoprofen vesicles.

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MS20 P08

Negative Thermal Expansion in several solvated crystals form of an organic compound. J. Montejo-Bernardo & S. García-Granda, *Department of Physical and Analytical Chemistry, University of Oviedo. Asturias, Spain.* E-mail: jmmb@fq.uniovi.es

Keywords: Negative Thermal Expansion, X-ray analysis, TGA/DSC

The semi-synthetic compound azithromycin is mainly known by its high antibacterial capacity against both Gram-positive and Gram-negative bacteria. Recently, we have discovered a new and interesting property of (at least) some of its solvated crystalline forms. These crystals show Negative Thermal Expansion (NTE) in a wide range of temperatures, even above room temperature. This behavior is not usual for small organic compounds and, in the examples (only seven) found in the literature, except in one, the remaining studies were conducted at temperatures below room temperature.
In this work, we present the results of the thermal study by X-ray single crystal diffraction, X-ray powder diffraction, ThermoGravimetry (TG) and Differential Scanning Calorimetry of the crystalline solvated forms azithromycin + $2H_2O$; azithromycin + H_2O + ½ EtOH (or *i*-PrOH), and azithromycin + ½ H_2O + ½ EtOH (or *i*-PrOH). The DiHydrate form shows uniaxial NTE, while both MonoHydrate and SemiHydrate forms show biaxial NTE. As a consequence of this behavior, the increasing in unit cell volume is very small in all the cases (< 1%). Even, for the MH crystals it seems to decrease slightly within a specific range of temperature. Moreover, attending to thermogravimetric data, we can confirm that the shortening of the axes is not due to the loss of solvent molecules
This results demonstrate the great potential and versatility of these crystal forms of azithromycin in the field of soft chemical materials.

MS20 P09

Tricyclic systems as potential bio-scaffolds: testing their relative flexibility Paola Paoli, [a] Maria Altamura,[b] Paolo Dapporto,[a] Antonio Guidi,[b] Nicholas J. S. Harmat,[b] Loïc Jierry,[b] Patrizia Rossi,[a] *Department of Energy Engineering, University of Florence, Italy.* [b]*Chemistry Department, Menarini Ricerche S.p.A., Florence, Italy.*
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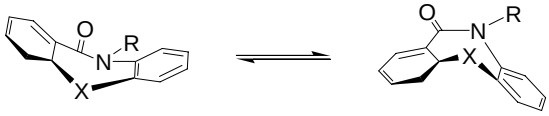
Keywords: ab-initio calculations, atropisomers, energy barriers

Tricyclic systems are amongst the most important scaffolds in medicinal chemistry and their possible inner chirality has been recognized for a long time. [1] 5-Ethyl-5,6-dihydro-11H-dibenzo[b,e]-6-one and the corresponding thiolactam are published examples of this



phenomenon.[2] We have considered these compounds on a scale of flexibility, at the rigid side of which, two kinetically stable atropisomers could appear. As a part of

our ongoing work [3] directed to manage together the diversity and flexibility within a pool of ligand candidates for bioassays, [4] we present here the results of a study concerning the replacement of CH_2 group (X in figure) in Irurre compounds, [2] with oxygen, sulfur, or with a SO_2 group. The structural properties of the resulting molecules were studied in the solid state, by single crystal X-ray diffraction, and calculated in the gas phase, by ab-initio methods. In each case the energy barrier to be overcome for the enantiomers interconversion as well as the transition state have been determined. The resulting scale of flexibility has been correlated with the chemical and structural features of the diverse library members.

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MS20 P10

Quantification of pharmaceuticals in solid dosage forms Hana Petrickova[a] [a]*Zentiva a.s., R&D Analytical department, U kabelovny 130, 10237 Prague 10 – Dolni Mecholupy, Czech Republic.*
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Keywords: quantitative XRPD, pharmaceuticals, phase identification

XRPD is nowadays a routine widespread tool for characterisation pharmaceutical solids. The qualitative phase analysis is essential for development either API itself or the final solid dosage form and a lot of applications were introduced ranging polymorphic screenings, pre-formulation, formulation, stability testing or crystallography [1]. On the other hand importance of quantitative phase analysis (QPA) of polycrystalline mixtures comes into ever-increasing attention. After identification comes, of course, question: “How much?”. Crutial for the analysis is to decide which of the quantitative information is expected, concrete number, limit test or simple positive/ negative evidence.
Examples of different approaches of QPA will be presented using the FullPat [2], the Rietveld [3] and the single peak method. Influence of the sample (amorphous/crystalline, with/ without knowledge of 3D crystal structure, crystal size and shape) will be discussed on two examples: crystalline three component mixture and almost amorphous tableting mixture.

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MS20 P11

Structural investigation of new insulin derivative at room temperature Biserka Prugovečki[a], Stjepan Prugovečki,[b] Detlef Beckers,[b] Dubravka Matković-Čalogović;[a] [a]*Department of Chemistry, University of Zagreb, Croatia.* [b]*Panalytical B.V., Almelo, The Netherlands.* E-mail: biserka@chem.pmf.hr

Keywords: insulin, protein crystallography, powder diffraction

Insulin is a hormone protein that regulates carbohydrate metabolism and it also takes part in the metabolism of fat and proteins. It is used medically in patients with Type 1 diabetes mellitus. Occasionally some patients with Type 2 diabetes mellitus also require insulin.
Owing to its crucial metabolic role and its pharmaceutical importance many structural studies on chemically and genetically modified insulins have been done.
We will present the results of our investigation on human bromo-derivative of insulin. Both single crystal and powder diffraction data were collected on laboratory instruments at room temperature. The investigated insulin derivative belongs to the $T_3R_3^f$ rhombohedral form [1] with cell parameters a = 80.96 Å and c = 37.30 Å. The unit cell parameter c at room temperature is two times smaller in comparison to the one at 100 K [2]. Coordination of zinc ions and conformation of insulin molecule will be discussed.

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MS20 P12

Structure solution and metastable zone width experiments of a tri-substituted aromatic compound. . Andrew O’Neill, Chick C. Wilson, WestCHEM, *Department of Chemistry*, *University of Glasgow*, Glasgow G12 8QQ, Alastair J. Florence, *Department of Pharmaceutical Sciences*, *University of Strathclyde*, 27 Taylor Street, Glasgow G4 0NR.

Keywords: polymorphism, crystal nucleation, metastable zone

Polymorphism in molecular crystals is the ability of a substance to exist in different crystal packing arrangements [1]. Understanding the phenomenon of polymorphism has become an increasingly important challenge, particularly in the pharmaceutical industry, where there would be considerable advantages were it possible to be able to identify which compounds will be likely to display different polymorphic forms from a knowledge of molecular structure alone. We are part of the UK Research Councils' Basic Technology CPOSS project (Control and Prediction of the Organic Solid State), which has been set up to tackle this problem.
Whilst accurate thermodynamic models are available to predict polymorphism, they do not currently accommodate kinetic factors such as nucleation and crystal growth resulting in an inclination to overestimate the tendency to polymorphism [2]. Nucleation is the initial process leading to the growth of crystals. Due to rapid onset, nucleation studies have proven to be a highly challenging area to study experimentally. However, an understanding of the process is essential as increasing numbers of important materials are found to exhibit polymorphism, even when grown under seemingly identical conditions.
This poster will describe the experimental approach to study model systems, the identification and structure solution of suitable systems and establishment of conditions that are suitable for subsequent examination by scattering techniques.
Methyl 2,5-dibromobenzoate ($C_8H_6O_2$ Br_2), a tri-substituted aromatic compound, with a previously unsolved crystal structure, has been selected for the investigations. The choice of this material is governed by