

It is indicative that the equimolar mechanic mixture of enantiomers (*R+S*) undergoes a solid phase transformation into (*R,S*)-racemic modification I ($P2_1/c$). The transformation being extended in temperature starts at 90°C and finishes close to the melting point (118°C).

The work is granted by RFBR (10-05-00891, 10-02-01303).

[1] M. Kuhnert-Brandstatter, L. Friedl, *Microchimica Acta* **1977**, *II*, 507-516.

[2] H. Kaemmerer, S.N. Lorenz, A. Black, Seidel-Morgenstern *Crystal Growth & Design* **2009**, *9*, 4, 1851-1852.

Keywords: polymorphism, chirality, racemic

MS53.P27

Acta Cryst. (2011) **A67**, C569

Physical Form Screening of Olanzapine and Amoxapine

Rajni Miglani, Gary Miller, Iain Oswald, Alastair J. Florence, *Strathclyde Institute of Biomedical Sciences, University of Strathclyde, Glasgow, G4 0RE (United Kingdom)*. E-mail: rajni@strath.ac.uk

The pharmaceutical field is frequently confronted with the phenomenon of multiple solid forms (polymorphs, solvates, salts and co-crystals) of the same chemical entity. Sometimes the properties of two solid forms of a drug are quite similar but can, and often do, vary substantially with potentially significant impact on pharmacokinetics, ease of manufacturing and stability of drug in dosage form and bioavailability. Hence, it becomes critical to have in depth knowledge of solid forms of a candidate molecule, so that the appropriate solid form can be taken forward as a clinical candidate.

Experimental screening is often used to explore all possible physical forms and has been implemented at a variety of different scales and throughputs [1]. Whilst fully automated parallel crystallisation capabilities are available in our laboratory, these require 10s of grams of material for a comprehensive solution crystallisation search [2]. However, we have established a method of high throughput crystallisation (HTC) for physical form screening of compounds using quartz 96/48 multi well plate formats with an automated system for collecting high quality Raman spectra (Thermo DXR system). This methodology has various advantages including reduced material requirements, fast data collection, no separate sample preparation, and analysis of sample in suspension. Multi-well plate approaches are complementary to the larger scale automated methods as in high throughput screening. It has various advantages in the context of solid form screening when only small amounts of compound are available. The analytical technique utilized in this methodology, Raman spectroscopy has emerged as an efficient analysis tool to differentiate between various solid forms like (polymorphs, solvates or amorphous) [3]. High throughput crystallisations of two marketed drugs, olanzapine and amoxapine were carried out on 96/48 multi well plates under various conditions i.e. solvents, antisolvents, concentrations, different counter ions. Raman spectra were collected automatically using array software. Various chemometric tools were used to classify the samples and to identify novel forms. In one example of olanzapine, 96 crystallizations utilizing 144 mg of olanzapine and ~20 ml of 48 solvents yielded 21 novel forms. The results of high throughput crystallisation were used as guide to scale up experiments to fully characterize the 30 novel physical forms.

[1] A.J. Florence, H.G. Brittain, *Informa Healthcare*, New York **2009**, 2 139-184. [2] A.J. Florence, A. Johnston, P. Fernandes et al. *J. Appl. Cryst.* **2006**, *39*, 922-924. [3] S.L. Morissette, O. Almarsson, L.M. Peterson, *Adv. Drug Deliv. Rev.* **2004**, *56*, 275-300.

Keywords: solid state, physical form screening, high throughput crystallisation, raman spectroscopy

MS53.P28

Acta Cryst. (2011) **A67**, C569

New insight into the desmotropy of irbesartan

Kurt Schenk-Job,^a Michel Bonin,^a Philippe Ochsenbein,^b Jérôme Kieffer,^b Mohamed El-Hajji,^b Marie-Hélène Lemée-Cailleau,^c Sax Mason,^c ^a*LCr-IPSB-FSB-EPFL, Le Cubotron, Dorigny, Lausanne, (Switzerland)*. ^b*Analytical Science Departement, Sanofi-Aventis, Montpellier, (France)*. ^c*The diffraction Group (DIF) Institut Laue-Langevin, Grenoble, (France)*. E-mail: Kurt.Schenk@EPFL.CH

Polymorphism, the ability of a compound to exist in more than one modification, is a widespread phenomenon of extreme importance in pharmaceutical development. Irbesartan, an anti-hypertensive agent (angiotensin II antagonist), crystallizes in two distinct solid state modifications because of a tautomerism, first established in solution by M. El-Hajji and J.-P. Bezdard (1998). This special case of polymorphism is termed desmotropy and occurs within a tetrazole ring in which the unique hydrogen may be either on an α - (adjacent) or β -nitrogen (opposite) with respect to carbon. Even if the two desmotropes exhibit different sizes and morphologies, crystals of form A (trigonal, thin needles) and B (triclinic, large prisms) could be grown concomitantly from ethanol/water. Form A, analysed by synchrotron diffraction (ESRF Grenoble) at room temperature (RT), builds up sixfold helix-chains through non covalent N-HN hydrogen bonds (HB), and recent laboratory X-ray data showed that the channels in the molecular packing may contain non-stoichiometric water. The structure of form B consists of head-to-tail dimers also linked by N-HN HB.[1] Irbesartan has been studied by solid state NMR at RT and at 253K:[2] the authors easily distinguished the two modifications by ¹³C CP/MAS. They also carried out ¹⁵N CP/MAS studies and concluded that, in contrast to form A in which the 6 expected signals of the 6 molecular nitrogens are found at RT, only two sharp peaks appeared in the spectrum of form B at the same temperature (with a broad resonance region) and the 6 expected signal were only recovered at 253K for this modification. The NMR data of form B, together with the results of a ¹⁵N CP/MAS dipolar dephasing experiment and of a 2D EXSY spectrum, allowed the authors to claim that form B undergoes, at RT, an exchange process consisting of simultaneous proton hopping (i.e. jumps from one β -nitrogen to the other) and internal rotation of the tetrazole ring. We present new RT and 125K diffraction data on Form B, using either X-rays or neutrons. X-ray data show that the triply disordered butyl-chain established at RT [1] perfectly locks in at 125K, Neutron diffraction data (ILL Grenoble), show that the hydrogen is perfectly localized on the nitrogen opposite the tetrazole-carbon such as to establish a HB with its neighbouring imidazole. This is corroborated by X-ray difference-maps also supporting a single tetrazole-protonation at RT. Atomic vibrational amplitudes can under no circumstances account for a 180° rotation of the tetrazole around the phenyl-tetrazole bond at RT.

Consequently, we do not believe Bauer and al.'s model for form B; we merely sustain that the unexpected ¹⁵N resonances at RT are attributed to the vicinity of the tetrazole ring and the disordered butyl-chain, which was indeed revealed by diffraction methods.

[1] Z. Böcskei, K. Simon, R. Rao[†], A. Caron, C.A. Rodger, M. Bauer, *Acta Cryst.*, **1998**, C54, 808-810. [2] M. Bauer, R. Harris, R. Rao, D. Apperley, C.J. Rodger, *Chem. Soc. Perking Trans. II*, **1998**, 475-481.

Keywords: desmotropy, polymorphism, NMR

MS53.P29

Acta Cryst. (2011) **A67**, C569-C570

A new pharmaceutical co-crystal: (S)-naproxen-isonocotinamide
Consuelo Yuste-Vivas,^a Manuela Ramos Silva,^a Ricardo A. E.