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Robotic Adventures in Crystallisation Space
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An automated parallel crystallisation screen has been applied to the systematic recrystallisation of the thiazide diuretic hydrochlorothiazide. The work is carried out as part of the collaborative project "Control and Prediction of the Organic Solid-State" funded under the auspices of the UK Research Councils Basic Technology Programme. The screening approach provides accurate control of key crystallisation parameters, namely: solvent identity; temperature; agitation and rate of evaporation. Polycrystalline samples are characterised using a multi-sample X-ray powder diffractometer equipped with foil transmission geometry, CuKα1 radiation and a linear PSD [1]. The instrument is highly effective where there is a requirement to analyse 20 – 30 recrystallised samples per day, with an emphasis on obtaining the high-quality data that are important in pattern recognition (using e.g. PolySNAP [2]) and imperative in indexing. The results of multivariate analysis of the solvent properties and physical forms produced in the screen is presented along with the crystal structures of the novel forms with a view to identifying the factors underlying the formation of polymorphs and solvates of hydrochlorothiazide.

[1] Florence A.J., Baumgartner B., Weston C., Shankland N., Kennedy A.R., Shankland K., David W.I.F., *Int. J. Pharm.*, 2003, **92**, 1930. [2] Barr G., Dong W., Gilmore C., *J. Appl. Cryst.*, 2004, **37**, 658-664.
Keywords: parallel crystallisation, polymorph screening, powder X-ray diffraction

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Crystal Structure of a Polymorph of Carnidazole from Synchrotron X-ray Powder Diffraction
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The crystal structure of a polymorphic form of carnidazole, a nitroheterocyclic compound active against both anaerobic protozoa and bacteria, has been determined using synchrotron powder diffraction. The simulated annealing approach, as implemented in the program FOX [1], was used to obtain the initial model. The model was refined with the Rietveld refinement program Fullprof [2]. This monoclinic polymorph crystallizes in $P2_1/n$ space group with a = 13.907(3), b = 8.091(2), c = 10.643(2), β = 110.831(5), Z = 4. The imidazole ring is planar. The molecules are held in the crystal forming two infinite zig-zag chains along [010] *via* hydrogen bonds of the type N-H…N. A structural comparison with the previously reported polymorph and the monohydrate forms of this drug is presented.

[1] Favre-Nicolin V., Cerny R., *J. Appl. Cryst.*, 2002, **35**, 734. [2] Rodriguez-Carvajal J., 2001, *FullProf, version 1.9c*, LLB, CEA/Saclay, France.
Keywords: carnidazole, powder diffraction, polymorphism

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High-throughput Polymorph Screen of Cimetidine and Clarification of its Nomenclature
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Polymorphism evaluation as a part of preformulation studies of a candidate drug is a critical step in the drug development process. The progress of high-throughput experimentation in recent years has led to a significant reduction of the amount of time and the quantity of the active pharmaceutical ingredient needed to perform these studies. In order to investigate the effectiveness and efficiency of a rational high-throughput polymorph screen (HTPS) the compound cimetidine was used as a case study for the formation of its polymorphic forms under different crystallization conditions.

The characterization of the various forms that occurred after crystallization was realized by means of X-ray powder diffraction experiments, differential scanning calorimetry and thermogravimetric analysis. As it turned out the HTPS was an effective means for obtaining all of the commonly reported solid-state forms of cimetidine (A, B, C, D, M1) and led to the formation of a new solid form (F). An analysis of the results will be given and the influence of the various crystallization conditions on the formation of the various solid forms will be discussed.

In order to assess the obtained results a literature investigation was carried out revealing a large confusion with respect to the nomenclature of the various cimetidine forms. A general and unifying nomenclature is proposed and compared with the older literature.
Keywords: high-throughput polymorph screen, rational design, cimetidine

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***In situ* X-ray Diffraction, DSC and Raman Spectroscopy Thermal Investigation of Chlorpropamide**
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Thermal analysis techniques, especially DSC, provide very useful information to identify and characterize APIs. What is more, DSC is widely accepted as a thermo-analytical tool for the study of phase transitions in different type of compounds. Unfortunately, this method does not reveal the identity of the transforming phases and their identification is often difficult without the aid of techniques that give information regarding structures and reactions. In this respect, X-ray diffraction and Raman spectroscopy are reliable techniques for phase identification. Thus, these methods are considered complementary to each other and the development of the instruments combining some of these techniques is a very powerful methodology with can have many applications for the characterization of pharmaceutical solids. For all these reasons, the aim of the present work is to apply Simultaneous WAXD-DSC, using Synchrotron Radiation, and temperature dependent Raman spectroscopy measurements to the study of the model drug chlorpropamide, which presents several polymorphs and phase transitions.
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Keywords: active pharmaceutical ingredients, *ab-inito* calculations, polymorphism

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Quantification of (Pseudo)Polymorphic Mixtures Using Full Pattern Analysis of X-ray Powder Diffraction Data
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The solid-state structure of drug substances influences their bioavailability, chemical stability, formulation properties etc. For that reason, analytical methods for identification and quantification of polymorphs, solvates, and amorphous forms are required. The analysis of X-ray powder diffraction data using a full-pattern analysis is a quantitative method that is both robust and precise. The ratio of

predefined reference patterns is fitted to the measured pattern using a least squares calculation. Because the full diffraction pattern is used for quantification this method is less sensitive to peak overlap. The method can be used to differentiate between crystalline forms and to estimate the crystallinity of a sample that is mainly amorphous. We present the application of a full-pattern quantitative method for the analysis of Saquinavir free base.

Saquinavir is a protease inhibitor that prevents the proliferation of the human immunodeficiency virus (HIV). The worldwide first HIV protease drug contains crystalline Saquinavir mesylate (INVIRASE). Later amorphous Saquinavir free base was developed in order to improve bioavailability (FORTOVASE). Using X-ray powder diffraction the (pseudo)polymorphic forms of Saquinavir free base are distinguishable. To assure optimum performance of the active pharmaceutical ingredient analytical methods have been developed to prove the content of crystalline components.

Keywords: pharmaceuticals, polymorphism, quantification

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Effect on Additive Structure on Crystal Nucleation: Sulfathiazole

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Crystal nucleation events are notoriously susceptible to influence by extraneous molecular specie. Researchers Blagden, Davey *et al* have shown that in the presence of small quantities of the *N*-acetyl precursor to sulfathiazole selective nucleation of the metastable polymorph sulfathiazole can be achieved [1]. It was proposed that the difference in the hydrogen bonding at the sulfathiazole aniline moiety which particularly distinguishes form I from the other three polymorphs. In form I, only one of the aniline hydrogens is utilised while in forms II, III and IV both are used. It was proposed that the *N*-acetyl derivative is capable of entering the interwoven hydrogen bonded chain network without disrupting the structure, while incorporation into crystal nuclei of forms II, III and IV prevents further development of the hydrogen bonding network of these forms.

A feature of the above hypothesis worth further examination is the toleration of the replacement of an amine proton with the considerably more sterically demanding acetyl group. We have investigated the effect of various sulfathiazole *N*-substituents, in particular the effect of groups which are less (e.g. *N*-formyl,) or more (e.g. *N*-pivaloyl,) sterically demanding than N-acetyl. Additives of 'polymeric' design with the potential for increased efficacy have also been investigated, where design of the additives is based on consideration of the crystal structures of the polymorphs under study.

[1] Blagden N., Davey. J., Rowe R., Roberts R., *Int. J. Pharm.*, 1998 **172**, 169-177.

Keywords: polymorphism, crystallization, crystal nucleation

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Polymorphism Dependent Crystalline Photochromism of Salicylideneanilines

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Some salicylideneanilines show crystalline-state photochromism. The reversible color change from yellow to red upon irradiation by UV light is the result of the photo-isomerization from the enol to the *trans*-keto form, which is explained as an intra-molecular proton transfer followed by a crank-shaft-motion type conformational change. The red-colored crystal fades to yellow by a thermal process.

The salicylideneaniline derivative *N*-3,5-di-tert-butylsalicylidene-3-carboxyaniline has three polymorphs: the α phase (pale yellow needle), the β phase (yellow plate), and the γ phase (orange block). Only the α and β forms are photochromic, whereas the γ form is thermochromic. X-ray crystal structure analyses of these three forms revealed the significant differences in dihedral angles in these molecules. The large dihedral angle in the α and β forms makes the enol conformation (yellow) unstable, which explains why the yellow to red photochromic reaction occurs easily.

In order to investigate the large difference in the lifetime of the red *trans*-keto conformation in the α (17min.) and β forms (780min.), the crystal structure of the irradiated (red-colored) crystal was analyzed. Newly established inter-molecular hydrogen bonds were observed in this red-colored β form but not in the red-colored α form. This result indicates that the inter-molecular hydrogen bond is stabilizing the red *trans*-keto conformation and preventing it from converting to the yellow enol conformation.

Keywords: polymorphism, photochromism, hydrogen bonding

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The Nature of the HB. 1. HB Empirical Rules from Crystal Structure Correlations

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HB is a D•–•H---:A three-centre-four-electron proton-shared interaction characterized by an extreme variability of HB properties (energy, geometry, shape of the proton-transfer pathway, electrostatic/ covalent nature) even for a same D…A couple of donor and acceptor atoms. Not surprisingly, its complete rationalization has turned out to be a formidable problem. This communication shows that the partial results obtained by systematic CSD screening over the years can now be unified to give a coherent interpretation of all factors determining HB strength in any molecular system. It is shown that all HBs can be reduced to only six specific molecular patterns, the six Chemical Leitmotifs (CL), out of which *four* have the curious property of turning *weak, long and proton-out-centred HBs of electrostatic nature* into *strong, short and proton-centred ones classifiable as 3-center-4-electron covalent bonds*, and *the last two* are deputed to form the moderately strong σ-cooperative …O-H…O-H…O-H… bonds typical of water or the almost infinite variety of weak HBs.

CLs are interpreted in terms of differences of proton affinities (PA) or acid-base dissociation constants (pK_a) of the HB donor and acceptor group, showing that all HB phenomenology can be reduced to a more basic "PA/pK_a Equalization Principle" stating that the HB properties are completely determined by the differences of these quantities (PA or pK_a) and that the strongest possible HB can only be associated with the conditions ΔPA or ΔpK_a = 0.

Keywords: hydrogen bond, PA/pKa equalization, chemical leitmotifs

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The Nature of the HB. 2. Predicting HB Strength by the pKa Slide Rule

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All HBs between neutral molecules are to be considered acid-base equilibria, R-D-H---:A-R ⇔ R-D$^-$---H-A$^+$-R, and their strength is determined by the difference ΔpK_a = pK_{AH}(R-D-H) – pK_{BH}(R-A-H$^+$), the HB becoming the stronger the smaller ΔpK_a is. In fact, the limit ΔpK_a = 0 corresponds to the condition by which the proton is equally shared by the two groups so that the HB is transformed from a weak electrostatic interaction into a strong proton-centred 3-centre-4-electron R-D$^{1/2-}$---H---$^{1/2+}$A-R covalent bond. The *a priori* appraisal of ΔpK_a is therefore a promising method for predicting HB strengths among organic compounds provided the pK_a values of the interacting molecules are known. This communication presents for the first time detailed lists of pK_{AH} and pK_{BH} values covering most classes of organic compounds and arranges them in an unique chart, called the *pK_a slide rule*, that makes it possible to predict the approximate strength of the HBs formed by any couple of organic HB donors and acceptors by simple inspection. Previsions obtained through the *pK_a slide rule* are compared with the results of diffraction experiments through an extensive search of all reasonably accurate R-O-H---:NR$_3$ ⇔ R-O$^-$---H-N$^+$R$_3$ HBs present in the CSD and subdivided in