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**

**P.08.11.4**

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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 (p$K_a$) of the HB donor and acceptor group, showing that all HB phenomenology can be reduced to a more basic "PA/p$K_a$ Equalization Principle" stating that the HB properties are completely determined by the differences of these quantities (PA or p$K_a$) and that the strongest possible HB can only be associated with the conditions ΔPA or Δp$K_a$ = 0.

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

**P.08.13.2**

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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 Δp$K_a$ = p$K_{AH}$(R-D-H) – p$K_{BH}$(R-A-H$^+$), the HB becoming the stronger the smaller Δp$K_a$ is. In fact, the limit Δp$K_a$ = 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 Δp$K_a$ is therefore a promising method for predicting HB strengths among organic compounds provided the p$K_a$ values of the interacting molecules are known. This communication presents for the first time detailed lists of p$K_{AH}$ and p$K_{BH}$ values covering most classes of organic compounds and arranges them in an unique chart, called the *p$K_a$ 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 *p$K_a$ 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