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Low-temperature polymorphic transitions in chlorpropamide and tolbutamide

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Structure solution of molecular crystals at low temperatures does not necessarily mean, that it is the same as at ambient temperature, even if there are no visible changes in the crystal colour, shape, transparency and integrity on temperature variation. This can be illustrated at the examples of two recently discovered low-temperature polymorphic transitions in the antidiabetic drugs with related molecular structures, chlorpropamide, $C_{10}H_{13}ClN_2O_3S$, [1], and tolbutamide, $C_{12}H_{18}N_2O_3S$, [2]. These transitions are reversible and leave the crystals intact. Solving crystal structure at low temperature only, one cannot make a correct conclusion on the crystal structure under the crystallization conditions.

The polymorphic transitions are very interesting, since they are accompanied by a peculiar conformational ordering on cooling, resulting in an increase in *Z'*. In other words, several conformers not related by any symmetry operations are distributed regularly in the crystal structures of the low-temperature forms, in contrast to high-temperature phases, which have only one conformer per unit cell. An increase in *Z'* is accompanied by changes in either the elementary translations, or the crystal system. Thus, at temperatures below 260 K β-chlorpropamide transforms from the orthorhombic into the monoclinic polymorph, and this transition is accompanied by non-merohedral twinning; below 150 K one of the cell parameters doubles. In tolbutamide III below 150 K one of the cell parameters triples. All the transitions were studied by single-crystal and powder variable-temperature X-ray diffraction. The crystal structures of the high-temperature and low-temperature polymorphs were solved and refined at multiple temperatures. The changes in the translational symmetry was shown to be related to the regular changes in the conformations of the alkyl tails in some of the molecules, regularly distributed in the structure. All the low-temperature transitions were observed on cooling the polymorphs, which are metastable already at ambient conditions. At the same time, the stable forms of these compounds, which correspond to the commercially available samples, do not undergo any phase transitions on cooling.

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[1] T.N.Drebushchak, V.A. Drebushchak, E.V. Boldyreva, *Acta Cryst.* **2011**, *B67*, 163-176. [2] T.N.Drebushchak, N.A. Pankrushina, E.V. Boldyreva, *Doklady Phys. Chem.* **2011,** *437*, 61-64.

Keywords: phase transitions in solids, drug polymorphism, low-temperature structure

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Detection, by X Ray Diffraction, of new bisphosphonate polymorphs of alendronate and risedronate treated hydroxyapatite

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Introduction: We studied the physicochemical characteristics of the processes taking place on the surface of the bone of osteoporotic people treated with bisphosphonates.

In vitro essays were performed in osteoporetic human bones and in synthetic hydroxyapatite (Ha).

Alendronate and risedronate were used to treat bone samples and synthetic Ha. Both drugs are used almost exclusively in anti-resorptives therapies for bone diseases, and in post-operative treatments for cancer ablation (breast, prostate, etc.)

Methods: The nano hydroxyapatite was synthesized by the sol/gel method. The material obtained was analyzed by x-ray diffraction and Scherrer's equation to determine its crystallinity. The X-ray diffraction (diffractometer and radiation synchrotron) pattern of synthetic hydroxyapatite was compared with healthy human bone obtaining an excellent correspondence. The lattice parameters were determined by the Rietveld method. Scanning Electron Microscopy was used to obtain the Ca/P ratio and transmission electron microscopy to study the microstructure.

In Vitro treatment simulating the natural conditions in which the drugs interact with the patient's bones and synthetic hydroxyapatite (temperature and medium) was performed using alendronate and alendronate/risedronate respectively.

Results: None of the analysis methods used was able to match a known polymorph to that found on the surface of the bone. They were able to ascertain that its composition was the same, in all cases, to that of the known polymorph.

Conclusions: We observed a formation of new polymorphs in the treated surfaces; they have been characterized but not identified as any of those in the literature.

[1]- Kathryn L. Kavanagh, Kunde Guo, James E. Dunford, Xiaoqiu Wu, Stefan Knapp, Frank H. Ebetino, Michael J. Rogers, R. Graham G. Russell, and Udo Oppermann. **2005** The molecular mechanism of nitrogen-containing bisphosphonates as anti osteoporosis drugs. PNAS (Proceedings of the National Academy of Science of the United States of America) Canada. [2]- Ebetino, 1996 . Russell, 2007. Bisphosphonates mode of action and pharmacology. Pediatrics, 119 Suppl / 22007, S150-162. [3]- Delguste C., Lepaje O. M., Amory H., Doucet M. **2007** Pharmacologie clinique des bis phosphonates : revue de littérature axée sur le tiludronate chez le cheval. Ann. Méd. Vét., 151 269-280. [4]- James E. Dunford, Aaron A. Kwaasi, Michael J. Rogers, Bobby L. Barnett, Frank H. Ebetino, R. Graham G. Russell, Udo Oppermann, and Kathryn L. Kavanagh, **2008** Structure–Activity Relationships Among the Nitrogen Containing Bisphosphonates in Clinical use and Other Analogues: Time-Dependent Inhibition of Human Farnesyl Pyrophosphate Synthase J. Med. Chem., *51,* 2187:2195.

Keywords: alendronate, risedronate, polymorphs

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Novel polymorphs of curcumin

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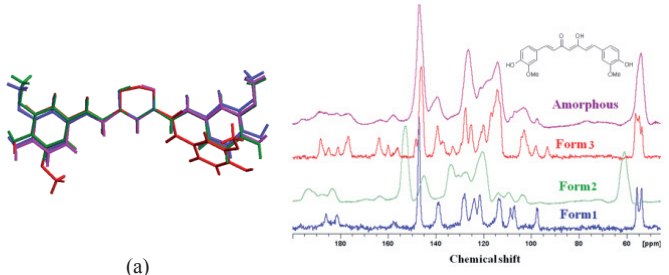
Curcumin, a hydrophobic phenol (chemical name diferuloylmethane), is principal curcuminoid of the popular Indian spice turmeric, possesses diverse pharmacological effects including anti-inflammatory, antioxidant, antimalarial and anticancer activities.[1] It has negligible solubility (8.7μg/ml) in water, at acidic or neutral pH and also

low bioavailability due to poor absorption. Curcumin decomposes upto 90% in pH 7.4 buffer solution within 30 minutes. Polymorphs and cocrystals were screened to improve stability and bioavailability of curcumin. The crystal structure of Stable form 1 (Z'=1) of Curcumin is reported in literature.[2] Single crystals of a new polymorph (form 2) were crystallized in the orthorhombic space group $Pca2_1$ (Z = 8, Z' = 2) upon attempted cocrystallization of curcumin with 4-hydroxypyridine in EtOH at room temperature. The same form 2 was obtained from DMSO at room temperature and also from a saturated solution of curcumin in EtOH. A third polymorph of Curcumin (form 3) was obtained with 4,6-dihydroxy-5-nitropyrimidine as the coformer, now in space group *Pbca* (Z = 8, Z'=1). Torsional flexibility[3] (Fig. 1a) along the seven carbon chain connecting two phenyl rings and also in phenolic –OH group orientation suggests conformational polymorphs of Curcumin. In the crystal structures, all the forms have similar O–H···O hydrogen bond between phenolic-OH and carbonyl group but differ in the C–H···O interaction. Curcumin amorphous form was also obtained by cooling of the melt phase. All the four forms are well characterized by IR, Raman and ss-NMR spectroscopy (Fig. 1b), DSC, HSM, XRPD and single crystal X-ray diffraction.[4] Metastable form 2 dissolves 3.1 times faster and is 1.8 times more soluble than commercial form 1 in 40% EtOH-water medium.



(a) (b)

Fig. 1 (a) Molecular overlay and (b) ss-NMR comparison of three polymorphs and one amorphous phase of Curcumin

[1] H. Hatcher, R. Planalp, J. Cho, F.M. Torti, S.V. Torti, *Cell. Mol. Life Sci.,* **2008**, *65,* 1631-1652. [2] S.P. Parimita, Y.V. Ramshankar, S. Suresh, T.N. Guru Row, *Acta Cryst.*, **2007**, *E63*, o860-o862. [3] A. Nangia, *Acc. Chem. Res.* **2008**, *41*, 595-604. [4] P. Sanphui, N.R. Goud, U.B.R. Khandavilli, S. Bhanoth. A. Nangia, *Chem. Commun.* **2011**, 10.1039/C1CC10204D.

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A Novel Ternary Complex Involving Two Antitubercular Drugs

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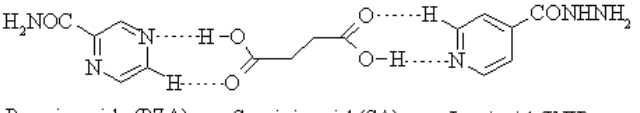
Pyrazinamide (PZA) and Isoniazid (INH) are the first-line antibacterial drugs used in monotherapy and also in combination to treat tuberculosis.[1] A fall in the bioavailability of Isoniazid and Rifampicin due to drug interactions in the fixed dose combination (FDC) drug formulation was reported in the literature.[1] Recently, the cocrystallization approach is under active research as a means of modulating the physicochemical properties of drugs in addition to its conferment of Intellectual Property Rights.[2] We report the usage of cocrystallization strategy for bringing combination drugs together in a crystal lattice through a GRAS (Generally Regarded As Safe) coformer. The pyridyl coformers were reported to form 2:1 binary cocrystals with homologous alkanedicarboxylic acids wherein the carboxylic acid groups on either side of the diacid hydrogen bond to each of the pyridyl moieties of two coformer molecules.[3] 2:1 binary cocrystals of INH with succinic acid and few other diacids were reported in literature[4,5] and we prepared a 2:1 cocrystal of PZA and succinic acid. We reasoned that PZA and INH can bind to the diacid groups of succinic acid on either side through acid–pyridine synthon to form a 1:1:1 ternary complex (Figure). As such, a 1:1:1 ternary complex of PZA and succinic acid and INH (PZA·SA·INH) was synthesized and characterized by x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), nuclear magnetic resonance (NMR) and Fourier transform infrared (FT–IR) spectroscopy. Whether this new supramolecular material is a cocrystal, eutectic or solid solution, is not fully established. The multicomponent adduct is found to be stable at ambient temperature and humidity and has superior intrinsic dissolution rate (IDR) than PZA and INH and their respective 2:1 binary cocrystals with succinic acid.



[1] H. Bhutani, S. Singh, K.C. Jindal, A.K. Charkraborti, *Journal of Pharmaceutical and Biomedical Analysis* **2005**, *39*, 892-899. [2] N. Bladgen, M. de Matas, P.T. Gavan, P. York, *Advanced Drug Delivery Reviews* **2010**, *59*, 617-630. [3] P. Vishweshwar, A. Nangia, V.M. Lynch, *Crystal Growth & Design* **2003**, *3*, 783-790. [4] Y. Simonov, V. Kravtsov, E. Ganin, T. Lis, *Acta Crystallogr.* **2006**, *A62*, s219. [5] A. Lemmerer, J. Bernstein, V. Kahlenberg, *CrystEngComm* **2010**, *12*, 2856-2864.

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Cocrystallization of GABA Adducts

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Pharmaceutical cocrystals are crystalline molecular complexes that contain therapeutically active molecules [1]. Polymorphs [2] and cocrystals, or other engineered multicomponent crystals [3] have been demonstrated to alter properties important to the bioavailability or processing of pharmaceutical solids. The structural elements (strong hydrogen bond donor, strong hydrogen bond acceptor, and nonpolar region) of γ-amino butyric acid, GABA, are typical of small drug molecules, and GABA is a major neurotransmitter inhibitor of the central nervous system. GABA and oxalic acid, OX, were cocrystallized as part of a study on formation of cocrystals of pharmaceutically interesting molecules via supramolecular bonding. 2:1 GABA/OX was prepared by both solution crystallization and solid-state grinding, and single crystal X-ray diffraction quality cocrystals were grown from ethanol solution by slow evaporation at room temperature. The single crystal X-ray structure of the resulting transparent colorless cocrystal shows it to be the oxalate salt of γ-amino butyric acid.

The supramolecular structure contains extensive O–H···O, N–H···O and C–H···O interactions leading to an elaborate three-dimensional hydrogen bonded network. The ammonium cation participates in three separate O···H–N–H···O motifs (half of the $R_4^2(8)$ synthon [3]), but the $R_4^2(8)$ synthon itself is not found. Notable features in the structure include an $S_3^3(10)$ string containing a serpentine carboxylic acid-