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The interest in co-crystals has increased in the last years within the pharmaceutical industry and also the solid-state community due to the possibility of obtaining solid materials with new properties [1]. Co-crystal crystallization strategies, supported by solvent- and solid-based techniques, have also received attention in the search and development of robust methodologies for the screening of co-crystals. This work explores the use of gels in a solvent-based approach to obtain co-crystals. The use of gels as a media permitting diffusive mass transport has been reported for the crystallization of small molecules [2] and proteins [3]. However, most of the gels used for this purpose can only be prepared from aqueous solutions thereby limiting their use to compounds that have been synthesized in aqueous media. Therefore, it is of the utmost importance to find gels that can be prepared from organic solvents and to test their suitability to growth (co-)crystals [4].

A series of co-crystals obtained using model molecules (APIs) and selected co-crystals formers (mainly GRAS carboxylic acids) and grown in water- and/or organic solvent-compatible gels will be presented.

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Structure of Mildronate, its Pharmaceutical Salts and Cocrystals

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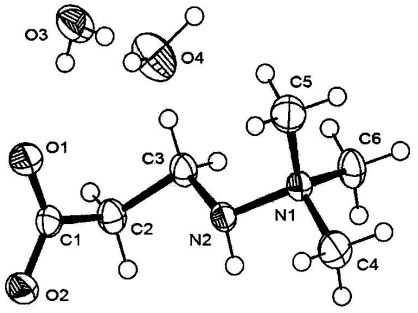
Mildronate is a trade mark of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate (meldonium dihydrate) which is an antiischemic and stress protective drug in treating various cardio-vascular diseases and other pathologies involving tissue ischemia [1]. The only shortcoming of the mildronate is its hygroscopicity. It liquefies into syrup after 24 h maintenance at 100% air humidity [2]. Mildronate (in the figure) in crystal adopts zwitterionic, or betaine, form and its hygroscopicity is related to the presence of water channels of 5-7 Å in diameter along **a** axis of the structure.

Search for non-hygroscopic crystalline forms, methods of preparation and physico-chemical properties of meldonium salts were described in [2]. In this work we present crystal structures of meldonium addition salts with phosphoric (in stochiometric ratio 1:1), sulphuric (2:1), boric (1:1), oxalic (1:1) and (2:1), fumaric (2:1) acids and saccharin (1:1). In case of meldonium saccharinate (1:1) two polymorphic forms have been detected. Dependent on the counterion we observed pure salt structures or mixed salt and cocrystal structures. For example in meldonium oxalate (2:1) crystal structure one meldonium molecule has betaine structure while the second one is protonated. In meldonium borate (1:1) structure in the asymmetric unit there are four pairs of meldonium and boric acid molecules. Three meldonium molecules have betaine form and only one is protonated thus forming mixed salt and cocrystal structure. Other structures exhibit pure addition salts.

Meldonium molecule shows considerable conformational flexibility. The values of C1-C2-C3-N2 torsion angle cluster around 72.0° (5 hits) and 177.7° (9 hits) while angle C2-C3-N2-N1 assumes values in the range of 160.1° - 179.9°.

Hygroscopicity test as described in [2] revealed significant water absorption only for meldonium sulphate (2:1). Inspection of its crystal packing showed two structural features which can contribute to water absorbtion. The first is the formation of channels along **a** axis containing sulphuric acid residues and the second is the fact that one oxygen atom of SO_4 residue is not involved in hydrogen bonding and thus is able to interfere with air humidity.



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Aging driven decomposition in Zolpidem hemihydrate

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Zolpidem is a non benzodiazepine hypnotic drug which effects are similar to those of benzodiazepines by promoting the presence of a particular inhibitory neurotransmitter (gamma-aminobutyric acid, GABA), through the binding to GABA receptors in a similar way and at the same location as benzodiazepines bind. Its usual commercial presentation is in the form of an hemi-tartrate, hydrate, of which several polymorphs are known, the most common of which are usually referred to in the literature as Form A and an alternative Form E. Stable crystallographic forms of different derivatives have also been described in the literature, among them a full tartrate, the free base, a saccharinate, etc. For one of the commercial Forms the crystal structure had been very briefly described, but with no numerical data available as to sustain the description either for checking or comparison purposes. This was the state of the art until recently, when a detailed structural analysis using powder methods reported Form E and two decomposition products [1], identified as the anhydrous 1:1 full tartrate and the free base. The products were derived from a "thermally driven" decomposition process and at the same time that the paper provided valuable structural information on crystalline derivatives of Zolpidem, it threw light onto a very important aspect of Zolpidem hemitartrate thermal decomposition because Form E suffers on heating the same decomposition process as Form A.

While this paper came to light we were engaged in a rather similar project, the structural study of the products generated in an "aging driven" decomposition process of Form A, which ended up to be complementary to the already mentioned "thermally driven" one.

In this work the "aging driven" decomposition of Zolpiden hemitartrate hemihydrate (Form A) was followed by XRPD, and the crystal and molecular structures of the decomposition products studied by single crystal methods. The process is very similar to the "thermally driven" one

described for Form E, resulting in a two-phase system: the neutral free base (common to both decomposition processes) and, in the present case, a novel Zolpidem tartrate monohydrate, unique to the "aging driven" decomposition. Our R.T. single crystal analysis gives for the free base comparable results as the H.T. XRPD ones already reported: orthorhombic, Pcba, a= 9.6360 (10)Å, b= 18.2690 (5)Å, c= 18.4980 (11)Å, V= 3256.4 (4)Å^3. The unreported Zolpiden tartrate monohydrate, instead, crystallizes in monoclinic $P2_1$, which for comparison purposes we treated in the non-standard setting $P112_1$ with a= 20.7582 (9)Å, b=15.2331 (5)Å; c= 7.2420 (2)Å, γ= 90.826 (2)°, V= 2289.73 (14) Å^3. The structure presents two complete moieties in the asymmetric unit (z=4, z'=2). The different phases obtained in both decompositions are readily explained considering the diverse genesis of both processes.

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Keywords: polymorphism

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Exploring phases of a physiologically-active nitronyl nitroxide free radical

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Nitronyl nitroxides are free radicals that are interesting both in biology and magnetism [1], [2], [3]. Their crystal structures have been largely studied: over 300 are reported. The study of different phases (polymorphs, salts, co-crystals) is relevant because properties strongly depend on crystal structure; therefore, about 13% of the structures quoted above are polymorph. In one remarkable case, 10 polymorphs have been found for a single compound [4].

Derivatives of 2-phenyl-4,4,5,5-tetramethyimidazoline-1-oxyl 3-oxide (PTIO) react with ·NO to form the corresponding iminonitroxides (PTIs) and $\cdot NO_2$. Under inflammatory conditions, ·NO is produced in much greater amount than normally, undergoing transformations which cause tissue damage, therefore the ·NO scavenger behaviour of nitronyl nitroxides is interesting to be used as potential therapeutic agents [1], [2].

2-(4-Carboxyphenyl)-4,4,5,5-tetramethyimidazoline-1-oxyl-3-oxide (cPTIO) is a compound similar to PTIO studied by some of us [5]. It has been shown that cPTIO exerts beneficial actions on systemic inflammatory response.

Some crystal phases of cPTIO have been described including co-crystals and salts [6], [7]. In the context of a study on cPTIO crystal phases, it is presented here the new crystal structure of the cPTIO perchlorate whose free radical nature has been stated by means of EPR. Suitable single crystals of cPTIO perchlorate (intense orange colour) have been studied using X-ray diffraction. Crystals are monoclinic ($P2_1/n$, Z=4) having the following unit-cell parameters: a=7.815(2), 20.736(4), 10.478(2) Å, β =91.83(3)º.

The comparison with cPTIO crystal structure [8] shows that N-O bond lengths are shorter (1.22 *vs.*1.30 Å) being the rest of bond distances very similar. The imidazoline ring is plane whereas in cPTIO adopts a half-chair conformation. The crystal packing is also different, in cPTIO, molecules are linked by COOH···O-N(nitroxide) H-bonding and form infinite zigzag chains whereas in the present structure, organic ion is surrounded by perchlorate groups and no chains are formed.

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MS53.P26

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X-ray powder diffraction study of malic acid

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The system of two malic acid enantiomers (components of the system) is typical example of a binary chiral system. It forms limited solid solutions as well as racemic modification at the equimolar composition [1]. Racemic malic acid is able to crystallize in different polymorphic modifications that complicates investigations of the system.

The molecule of malic acid $C_4H_6O_5$ (HOOC–CH_2–HCOH–COOH) has one chiral centre. Accordingly this compound can exist in the forms of two enantiomers *R* (+) and *S* (–). The database ICDD (Intern. Centre for Diffraction Data) contains characteristics of malic acid for its (–)-enantiomer ($P2_1$) and two monoclinic polymorph modifications of (*R,S*)-racemate ($P2_1/c$ и *Cc*). Referring to [2], (*R,S*)-malic acid grown from acetone solution is the stable modification, while that grown from water solution is the metastable modification. Unfortunately, these authors [2] did not indicate crystallochemical data (crystal system, space group, indices *hkl*, elementary cell parameters, etc.) for the phases of malic acid they synthesized.

We studied the polymorphic variety and structural deformations of racemic malic acid by means of X-ray and thermo-X-ray powder diffraction methods.

Initial samples of the enantiomers and racemate belong to the space groups $P2_1$ and $P2_1/c$ respectively. Besides, samples of malic acid obtained at different conditions were investigated at room temperature. Samples of the racemate (*R,S*), enantiomers (*R* and *S*), and mechanic mixture of the enantiomers (*R*+*S*) were grown from water, ethanol, and acetone solutions. Samples of the racemate (*R,S*) and equimolar mixture of enantiomers (*R*+*S*) were obtained after washing initial samples in heptane. Samples of crystallized melts of the racemate (*R,S*) and equimolar mixture of enantiomers (*R*+*S*) were obtained.

We found that (*R,S*)-malic acid could crystallize at least in three (probably in four) polymorph modifications: I ($P2_1/c$), II (*Cc*), III and supposedly IV (the space groups of III and IV ones were not identified for the present). Besides, X-ray characteristics (interplanar distances, *hkl* indices, parameters of monoclinic elementary cells, etc.) of two known (ICDD et al.) polymorphic modifications of racemic (*R,S*)-malic acid (I and II) were defined. Thermal phase transformations of *R*-enantiomer ($P2_1$), (*R,S*)-racemic modification I ($P2_1/c$), and equimolar mechanic mixture of malic acid (*R*+*S*) enantiomers were investigated at heating (the range was 50–140ºC, the temperature step was 2–10ºC). It was revealed that *R*-enantiomer and racemic modification I undergo only structural (thermal) deformations at heating: all the linear parameters *a*, *b*, and *c* (Å) and volume (Å^3) increase monotonously but angular parameter β decreases.