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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.

[1] N. Blagden, D.J. Berry, A. Parkin, H. Javed, A. Ibrahim, P.T. Gavan, L.L. De Matos, C.C. Seaton, *New J. Chem.*, **2008**, 32, 1659. [2] H.K. Hensch, *Crystal Growth in Gels and Liesegang Rings*, Cambridge University Press, Cambridge **1988**. [3] J.M. Garcia-Ruiz, *J. Crystal Growth*, **2001**, 232, 165. [4] D. Choquesillo-Lazarte, J.M. García Ruiz, *J. Appl. Cryst.* **2011**, 44, 172-176.

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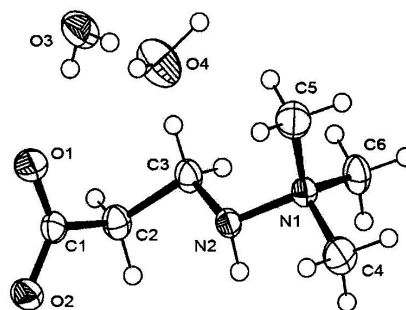
Structure of Mildronate, its Pharmaceutical Salts and Cocrystals
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Mildronate is a trade mark of 3-(2,2,2-trimethylhydrazinium) propionate dihydrate (meldonium dihydrate) which is an antiischemic and stress protective drug in treating various cardio-vascular 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 stoichiometric 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 absorption. 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 SO₄ residue is not involved in hydrogen bonding and thus is able to interfere with air humidity.



[1] R.S.Karpov et al, *Kardiologiya*, **2000**, 6, 69-74. [2] I.Kalvins, A.Birman, US patent 7223797 B2., **2007**.

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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 Zolpidem 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