COCRYSTALLIZATION SCREENING FOR "DRUG-DRUG" TYPE OF COCRYSTALS

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Cocrystallization became well known bottom-up approach starting from intermolecular interactions among, either selected neutral, ionic or zwitterionic molecules to design and control the properties of the multicomponent crystals. [1] In the scope of interest for drug design and formulation, the main advantage for designing Pharmaceutical Cocrystals (PCCs) is, through their modulating properties, to improve the performance of the native Active Pharmaceutical Ingredients (APIs) such are: biopharmaceutical profile (solubility and dissolution rate), thermodynamical stability (phase transition of polymorphs, solvate/ hydrate formation, decomposition) or bulk powder processability (flowability, compressibility, particle size and shape control). [2,3] Many debates regarding semantic and classification in cocrystals (CCs) based on accomplishments in research of supramolecular chemistry, highlighted the complex reality of *multi-component systems*, and the wide scope associated between salts and cocrystals in *the salt-cocrystal continuum.* [4]

N,*N*-dimethylbiguanide is used as oral antidiabetic drug, well known as Metformin (MET). It directlyimproves insulin action and is the only approved hypoglycemic drug of the biguanide class.
Because of the biguanide π-conjugated system, MET can exist in three resonance-stabilized forms, *i.e.* as neutral molecule (MET), monoprotonated ($METH^+$) or diprotonated ($METH^{2+}$) cation, with dissociation constants in water typical of biguanides (pK_{a1}12.40 and pK_{a2} 2.96).
A search of the MET fragment in the structural literature, both in the CCDC database and in patents, shows that in crystals it exists as $METH^+$ or $METH^{2+}$ but never in its neutral form MET.

We have undertaken a systematic study of the crystal chemistry of MET with the aim of understanding its properties in the solid state and finding relationships with its biopharmaceutical profile. We have obtained 29 PCCs of quality suitable for crystal structure determination by single crystal X-ray diffraction with the CFs listed below.
Inorganic acids: nitric, phosphoric and carbonic acid; Organic NH-type acids: saccharine and acesulfame; Organic OH-type acids: squaric and picric acid; Monocarboxylic acids: fumaric, acetic, trifluoroacetic, trichloroacetic, dichloroacetic, monochloroacetic, glycolic, salicylic, dichlofenac; Dicarboxylic acids: oxalic, malonic, maleic, fumaric, succinic, adipic.

In the poster are presented structures analyses for "*drug-drug*" type of PCCs where both API and CF exhibit pharmacological effect: MET/ Dichloroacetic acid 1:1 and 1:2 molar ratio, MET/ Diclofenac 1:1, MET/ Glycolic 1:1 acid and MET/ Salicylic acid 1:1 molar ratio.

Literature:
[1] Braga D., Crystal Engineering, *Chem Comm*, 2003, 2751-2754,
[2] Good J. D., et al. N *Cryst Growth Des.*, 2009, 9 (5), pp 2252–2264
[3] Cheney ML, et al. .,*J.PharmSci*. 2011Jun;100(6):2172-81
[4] Childs, S.L., Stahly, G.P., Park, A., 2007. *Mol. Pharm*. 4, 323–338