Pharmaceutical cocrystals of the biguanide drug Metformin

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Increased publications and released patents relating to multicomponent crystals of pharmaceutical relevance caused the Food & Drug Administration (USA FDA) to issue the draft guideline for regulatory classification of Pharmaceutical Cocrystals (PCC) of active pharmaceutical ingredients (APIs) as solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds, generally in a stoichiometric ratio [1,2].
The main advantage of PCCs is to improve the performances of the native APIs by modulating their properties, such as: 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).

N,*N*-dimethylbiguanide is used as oral antidiabetic drug, well known as Metformin (MET). It directly improves insulin action and is the only approved hypoglycemic drug of the biguanide class. It is the drug of first choice for oral therapy of the type 2 diabetes, marketed as hydrochloride, embonat (pamoate) and *p*-chlorophenoxy acetate salt.
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:
Metformin = L; [HL]/[L][H] pK_{a1}(N−H^+) ~ 12.40; [H_2L]/[HL][H] pK_{a2}(N−H^+) = 2.96 (NIST database)
The high basicity of pK_{a1} and the difference between the pK_a values qualify MET as organosuperbase and determine the stability of its monoprotonated form $METH^+$ within a wide range of pH.
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 prepared series of PCCs of MET in combination with a variety of organic or inorganic acids as Coformers (CFs) in different experimental conditions of formulation (stoichiometric ratio) and processing (solvent, temperature, crystallization technique). We have obtained 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: acetic, trifluoroacetic, trichloroacetic, glycolic, salicylic, dichlofenac; Dicarboxylic acids: oxalic, malonic, maleic, fumaric, succinic, adipic.
We have so far determined 26 crystal structures, 22 containing the $METH^+$ and 4 the $METH^{2+}$ form. In all structures the C-N bond distances of MET are fully delocalized and the fragment is never found to be planar. The crystal packing analysis reveals that MET and CF molecules are linked by extended H-bond networks that, though different, show a number of conserved patterns (dimers, ribbons, rings, sheets, *etc*). Results of the crystal structure analysis for representative PCCs will be shown in the poster.

[1] http//www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
[2] Aitipamula, S., *et al., Cryst. Growth Des.* **2012**, *12*, 2147−2152