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PHARMACEUTICAL COCRYSTALS OF THE BIGUANIDE DRUG METFORMIN

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Introduction

Biguanide functional group is found in compounds in relation of the following drug classes: oral antidiabetics for the treatment the type-2 diabetes, antimalarics, antiseptics and anticancer [1]. *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;

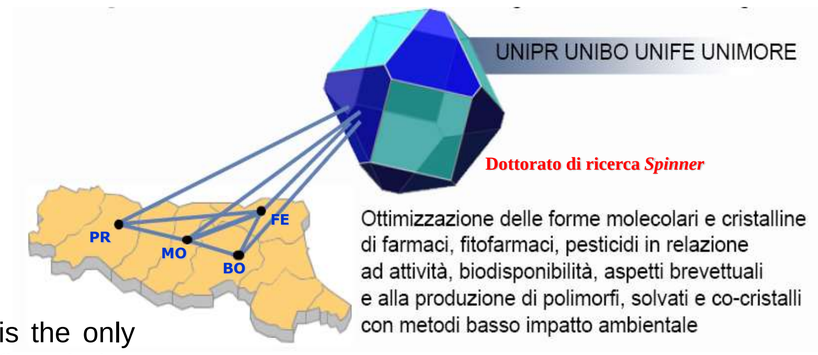
[H_2L]/[HL][H] pK_{a2}(N−H$^+$)= 2.96 (NIST database)

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 [2].

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.

Pharmaceutical Cocrystals (PCC) as solids are crystalline single phase materials composed of two or more different molecular and/or ionic compounds, one of which is a drug molecule (DM) and the other is known as conformer (CF), generally in a stoichiometric ratio [3].

PCC represent multicomponent complexes where the Charge Transfer (CT) or Electron Donor-Acceptor (EDA) Interactions between DM and CF may determine the crystal packing motifs that alter the drug's physicochemical properties (*e.g.* solubility, melting point etc.) which directly affect its biopharmaceutical profile (e.g. drug dissolution, absorption) and processability of its solid phase (*e.g.* hygroscopicity, compressibility) [4].



Compounds Studied

DM	CF	*pKa (CF)*	*M/M (molar ratio)*
Metformin free base pKa1: 12.4 pKa2: 2.96	Formic acid	pKa: 3.75	1/1
	Acetic Acid	pKa: 4.762	1/1
	Trichloroacetic acid	pKa: 0.77	1/1; 1/2
	Trifluoroacetic acid	pKa: 0.23	1/1
	Glycolic acid	pKa: 3.83	1/1
	Salicylic Acid	pKa$_1$: 2.97 pKa$_2$: 13.7	1/1
	Maleic Acid	pKa$_1$: 1.93 pKa$_2$: 6.28	1/1
	Fumaric Acid	pKa$_1$: 3.02 pKa$_2$: 4.48	1/1
	Malonic Acid	pKa$_1$: 2.84 pKa$_2$: 5.69	1/1
	Succinic Acid	pKa$_1$: 4.2 pKa$_2$: 5.63	1/1
	Picric Acid	pKa: 0.35	1/1; 1/2
	Saccharin	pKa: 1.31	1/1
MetforminHCl	Saccharin Na	pKa: 1.31	1/2

Source: NIST Database

Sample Preparation

Fourteen (14) PCC were prepared using metformin free base and acidic compounds for monocarboxylic acids (fumaric acid, acetic acid and its halogenated derivatives, glycolic acid and acetyl-salicylic acid), dicarboxylic acids (maleic, fumaric, malonic, and succinic acid), saccharin and picric acid, as well as one (1) polymorphic form of PCC metformin/saccharin prepared from metformin·HCl and saccharine·Na.

Methods

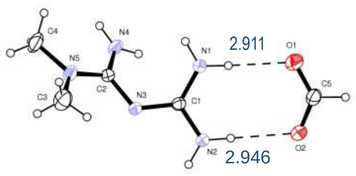
Single crystals of PCC were obtained by slow evaporation of the solvent:
Solvent for cocrystallization with organic acids:
Mixture of n-pentanol and methanol (50/50 v/v%) .

Characterization of PCC

PCC absolute structure determination was performed by Single Crystal X-Ray Diffraction Analysis confirming the PCC structure to be a New Chemical Entity (NEC) not so far deposited in the Cambridge Structure Database CCDC.

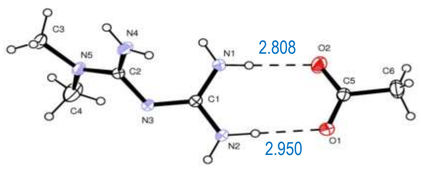
Crystal Structures

Metformin formate 1/1 *MM*
Prepared from Metformin free base/ formic acid 1/1 M/M



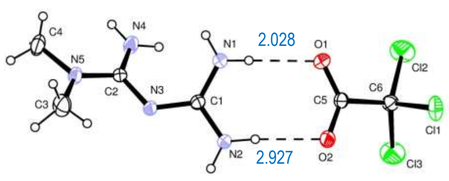
P 2$_1$/n

Metformin acetate 1/1 *MM*
Prepared from Metformin free base/Acetic acid 1/1 M/M



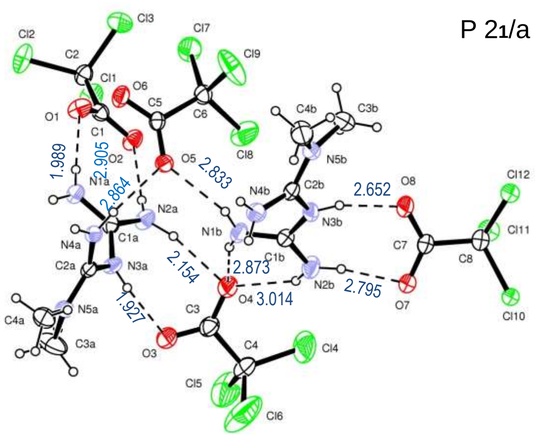
P 2$_1$/n

Metformin trichloroacetate 1/1 *MM*
Prepared from Metformin free base/ Trichloroacetic acid1/1 M/M



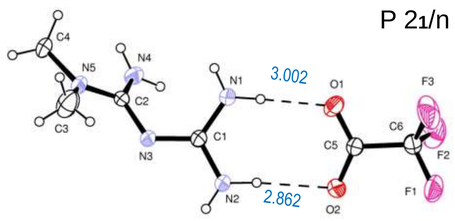
P 2$_1$/n

Metformin trichloroacetate 1/2 *MM*
Prepared from Metformin free base/ Trichloroacetic acid1/2 M/M



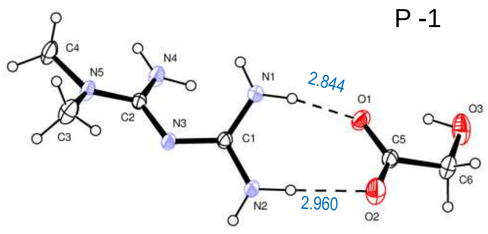
P 2$_1$/a

Metformin trifluoroacetate 1/1 *MM*
Prepared from Metformin free base / Trifluoroacetic acid1/1 M/M



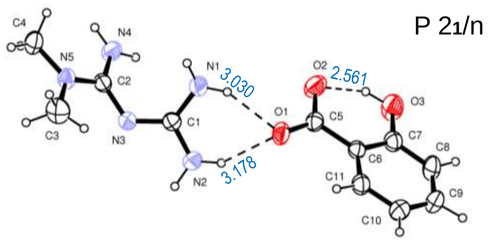
P 2$_1$/n

Metformin glycolate 1/1 *MM*
Prepared from Metformin free base / Glycolic acid1/1 M/M



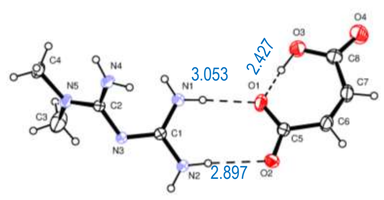
P -1

Metformin salicylate 1/1 *MM*
Prepared from Metformin free base/ Acetylsalicylic Acid1/1 M/M



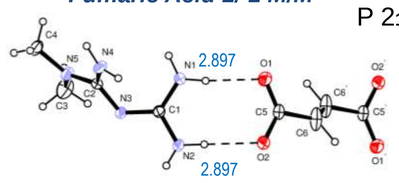
P 2$_1$/n

Metformin maleate 1/1 *M/M*
Prepared from Metformin free base / Maleic acid 1/1 M/M



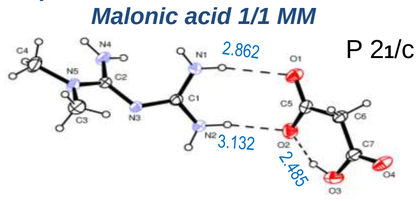
P 2$_1$/n

Metformin fumarate 1/ 0.5 *M/M*
Prepared from Metformin free base / Fumaric Acid 1/ 1 M/M



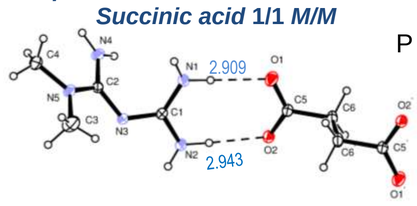
P 2$_1$/n

Metformin malonate 1/1 1/1 *M/M*
Prepared from Metformin free base / Malonic acid 1/1 MM



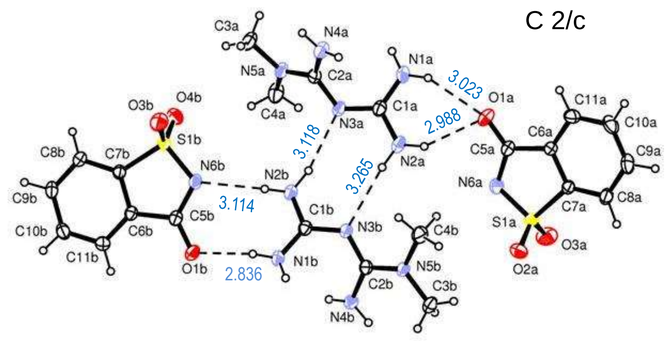
P 2$_1$/c

Metformin succinate 1/0.5 *MM*
Prepared from Metformin free base / Succinic acid 1/1 M/M



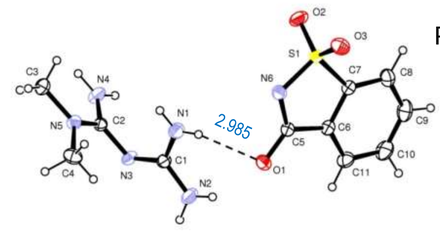
P 2$_1$/n

Metformin / Saccharinate 2/2 *MM*
Prepared from Metformin·HCl & Saccharin·Na



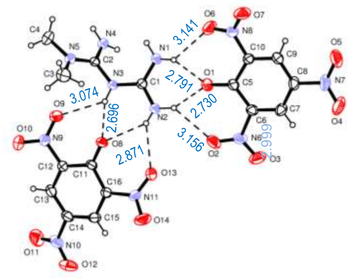
C 2/c

Metformin / Saccharinate 1/1 *MM*
Prepared from Metformin free base & Saccharine



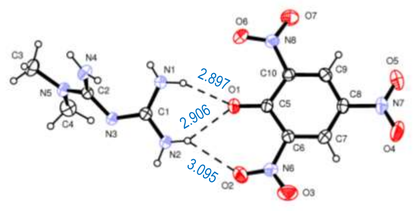
P 2$_1$ 2$_1$ 2$_1$

Metformin picrate 1/2 *MM*
Prepared from Metformin free base / Picric acid 1/2 MM



P -1

Metformin picrate 1/1 *MM*
Prepared from Metformin free base / Picric acid 1/1 MM



P 2$_1$/c

Further Work

Possible correlations between ΔpKa values of metformin and CFs are presently under investigation. The systematic analysis of the molecular geometries and crystal packing, as well studying of the thermodynamic properties are expected to establish Structure-Properties Relationships for each of the aforementioned PCC with metformin.

1st European Crystallography School, Pavia (Italy), August-September 2014

References

[1] Saczewski, F. & Balewski, Ł. *Expert Opin. Ther. Patents* (**2013**) 23**(**8)
[2] Prugnard, E .and Noel, M. Physicochemical properties and analytical methods of determination of biguanides. In Oral Antidiabetics, Kuhlmann J. and Puls W. (eds). Springer: Berlin, **1996;** pp. 287-304
[3] Dunitz, J. D. *CrystEngComm* **2003**, *5*, 506
[4] Bertolasi, V.; Gilli, P.; Gilli, G., *Cryst. Growth Des.* **2012**, *12*, 4758−4770