PHARMACEUTICAL COCRYSTALS OF BIGUANIDE DRUGS: METFORMIN CASE STUDY

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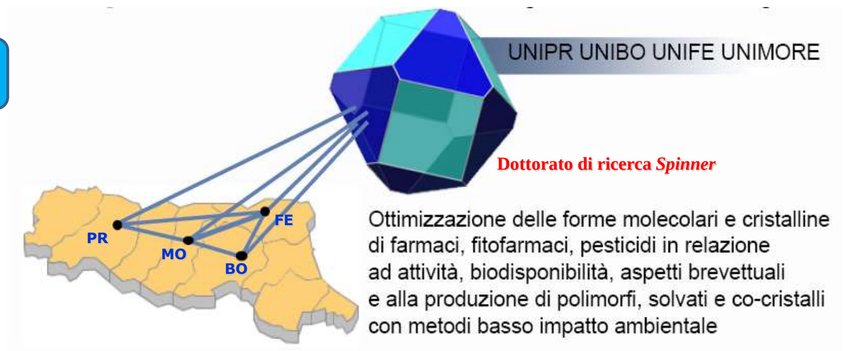
Introduction

Biguanide functional group is found in compounds in relation to the following drug classes:[1]

- Oral antidiabetics for the treatment the type-2 diabetes: Metformin (Metformin·HCl in Glucophage™, Brystol-Mayer Sqibb) , Buformin (Buformin·HCl in Silubin™, Grünenthal), Phenformin (Phenformin·HCl in DBI™, Ciba-Geigy),
- Antimalarics: Proguanil (Proguanil·HCl in Paludrine™ by AstraZeneca),
- Antiseptics: Chlorhexidine (Hibitane™, ICI),
- Drugs in pipelines: anticancer (e.g pyrimidinebiguanides, mono- and di-substituted biguanides), spasmolythic (1-substituted phenyl biguanides) and antimicrobial treatments (1,5-disupstituted biguanides; 3,4-dichlorobenzyl derivatives; polyhexamethylene biguanide, and polymeric biguanides).

Metformin as a biguanide derivative is a diacidic strong base (pKa_1 12.4 and pKa_2 2.96). The only comercial salt in which metformin exists as Activ Pharmaceutical Ingrediant (API) is hydrochloride crystalline form. In the metformin structure the four amino groups are almost equivalent and the positive charge is distributed among them with consequent formation of stabilized monocation and dication after first and second protonation, respectivaly. [2]

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]. One promising approach for designing PCC is to make use of the molecular recognition properties of the functional groups and their allocations in entire structures of the molecules which, depending on the polarity and atom's electronegativity, are linked one to another by H-bonds [4]. Hence, 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).



Compounds Studied

DM	CF	*pKa (CF)*	*M/M (molar ratio)*
Metformin free base pKa1: 12.4 pKa2: 2.96	Nitric Acid	pKa: -1.3	1/1
	Phosphoric Acid	pKa_1 : 2.1 pKa_2 : 7.2 pKa_3: 12.3	1/1
	Acetic Acid	pKa: 4.762	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
	Oxalic Acid	pKa_1 : 1.25 pKa_2 : 4.26	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

Twelve (12) PCC were prepared using metformin free base and acidic compounds for monocarboxylic acids (acetic acid and acetyl-salicylic acid), dicarboxylic acids (maleic, fumaric, oxalic, malonic, and succinic acid), inorganic acids (nitric and phosphoric acids), saccharin and picric acid, as well as one (1) polymorphic form of PCC metformin/saccharin prepared from metformin·HCl and saccharine·Na.

Methods

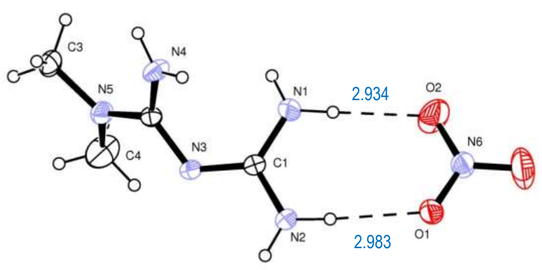
Single crystals of PCC were obtained by slow evaporation of the solvent:
Solvent for cocrystallization with organic acids: n-pentanol.
Solvent for cocrystallization with inorganic acid: methanol.

Characterization of PCC

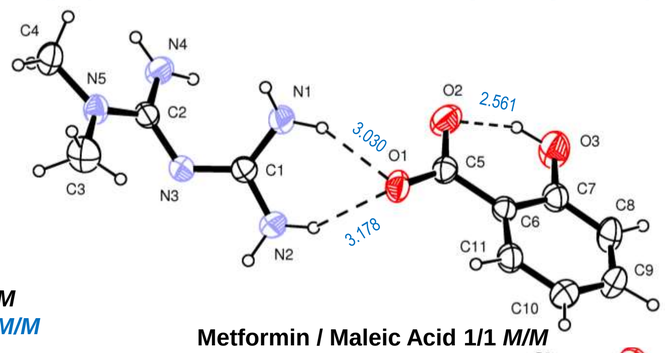
PCC absolute structure determination was performed by Single Crystal X-Ray Diffraction Analysis confirming the PCC structure to be a New Chemical Entity (NEC) not so far deposited in the Cambridge Structure Database CCDC.

Crystal Structures

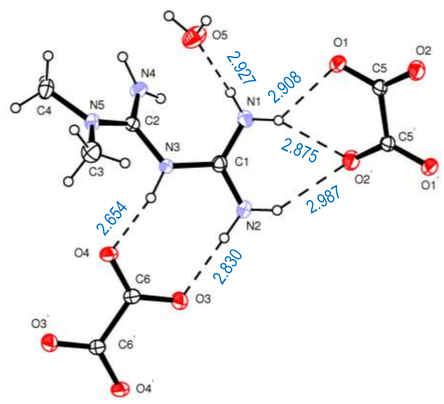
Metformin / Nitrate 1/1 *MM*
Prepared from Metformin/Nitric Acid 1/1 MM



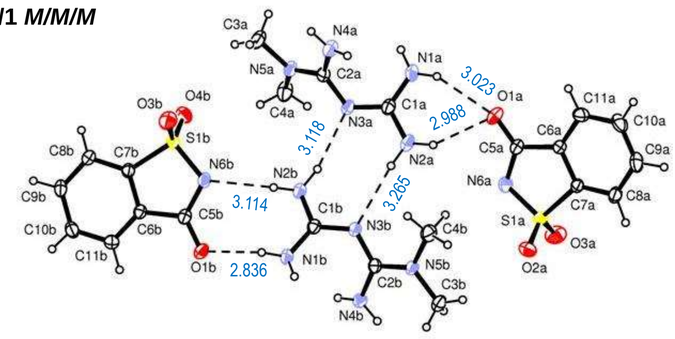
Metformin / Salicylic Acid 1/1 *MM*
(prepared from neutral Metformin/Acetyl Salicylic Acid)



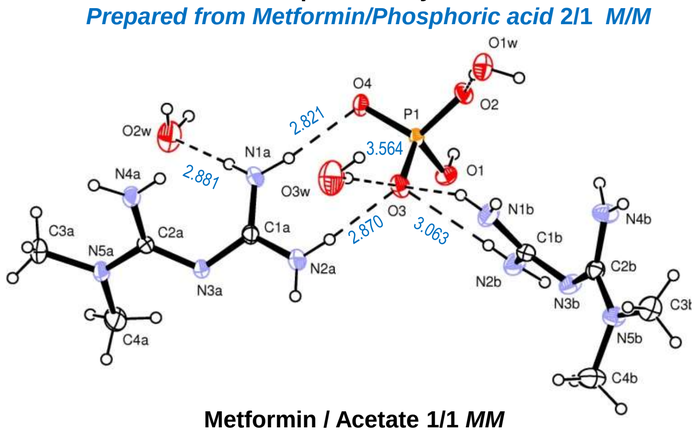
Metformin / Oxalic Acid Hydrate 1/2/1 *M/M/M*



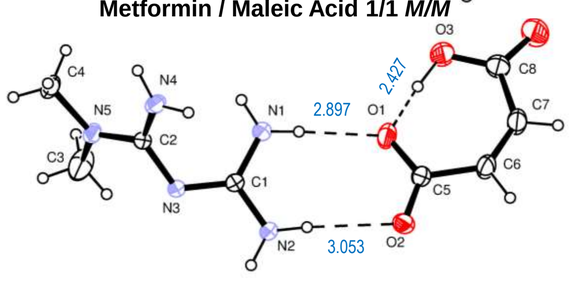
Metformin / Saccharin 2/2 *MM*
Prepared from Metformin·HCl/Saccharin·Na



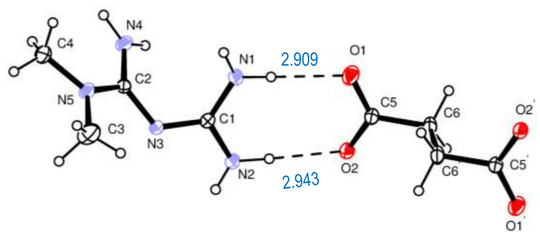
Metformin / Phosphate/ Dihydrate 2/1/2 *MM/M*
Prepared from Metformin/Phosphoric acid 2/1 M/M



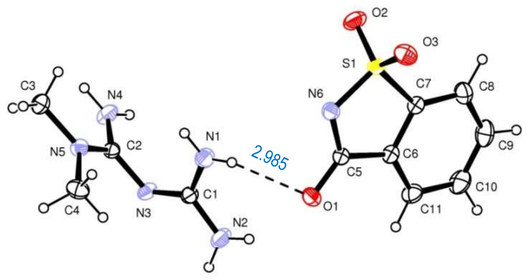
Metformin / Maleic Acid 1/1 *M/M*



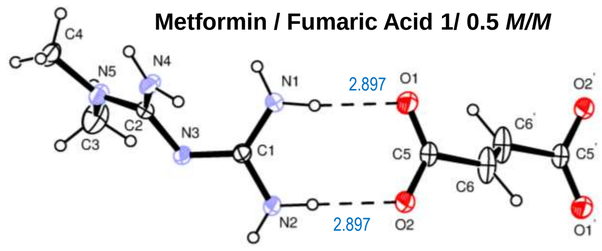
Metformin / Succinic Acid 1/0.5 *MM*



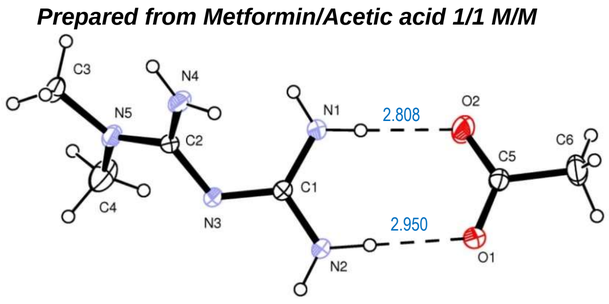
Metformin / Saccharin 1/1 *MM*
Prepared from neutral forms of Metformin/Saccharine



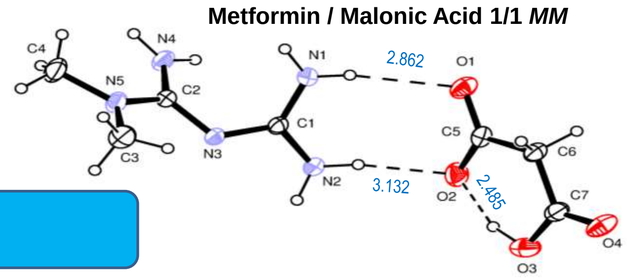
Metformin / Fumaric Acid 1/ 0.5 *M/M*



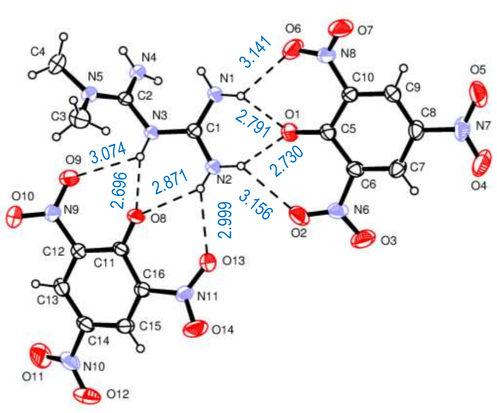
Metformin / Acetate 1/1 *MM*
Prepared from Metformin/Acetic acid 1/1 M/M



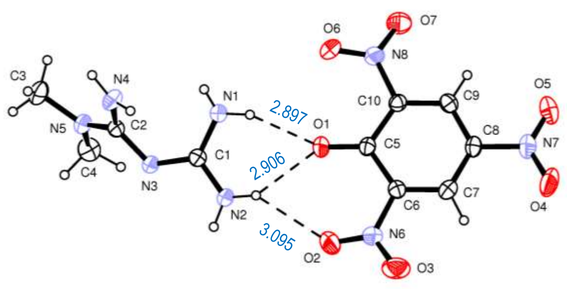
Metformin / Malonic Acid 1/1 *MM*



Metformin / Picric Acid 1/2 *MM*



Metformin / Picric Acid 1/1 *MM*



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.

La XIII Giornata della Chimica dell'Emilia Romagna, Bologna, il 18 Dicembre 2013

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