COST Action CA16205, COST Association
European Network on Understanding Gastrointestinal Absorption-related Processes

Preliminary study on screening the intermolecular interactions of organic cation drugs from BSC Class III case study Metformin

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Introduction

Among the orally administered drugs, about 40% share the properties of organic cations (protonated bases) or neutral bases at physiological pH, which indicates one important point for studying their transport mechanisms [1]. Antineoplastic platinum compounds [2,3], the histamine H_2 receptor antagonist cimetidine [4], the antiviral drugs (acyclovir, gancyclovir, lamivudine and zalcitabine) [5-7], the antidiabetic drug metformin [8,9], and the antiarrhythmic drug quinidine [10], are the identified to be transported by the organic cation transporters OCT1, OCT2 and OCT3 (membrane transporters) [2]. The case study of drug model (DM) metformin (MET), that according to Biopharmaceutical Classification System (BCS) belongs to the class III drugs (high solubility, low permeability) [11], emphasizes the importance of non-covalent interactions of this dication drug with range of ligands selected from the GRAS (Generally Recognized as Safe by FDA for food additives list) [12].
MET (*N,N*-dimethylbiguanide) is the only approved hypoglycemic drug of the biguanide class used in oral therapy of type 2 diabetes, marketed as hydrochloride, embonat (pamoate) and *p*-chlorophenoxy acetate salt [13]. Because of the biguanide *π*-conjugated system, MET in solution 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:

Compounds Studied

Molecular salts of metformin

Drug-Drug type of molecular crystals

Dichloroacetic acid and Dichloroacetate (DCA):
Introduced as novel class of oral ant diabetic drug that reduce blood glucose and lipids without stimulating insulin secretion. Recent studies reveled its anticancer effect []
MET-DCA 1: 1 & 1:2 exhibited enhanced *in vitro* anti-leukemic activity [13]

Acetic acid: Ameliorate the insulin secretion [14]

Diclofenac: Widely used anti-inflammatory drugs in pain-killer therapy.

Metformin = L;

[HL]/[L][H] pK_{a1}(N−H$^+$)~12.40;

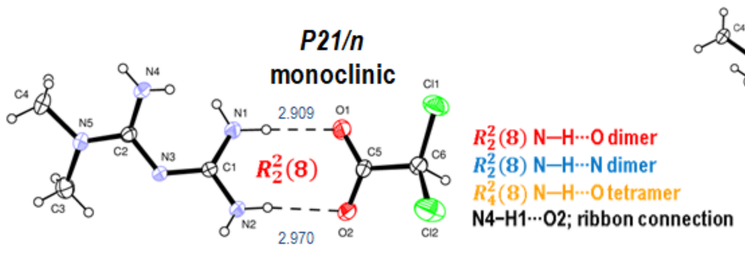
[H_2L]/[HL][H] pK_{a2}(N−H$^+$)= 2.96 (NIST database)

Crystal Structures

MET – Dichloroacetate 1:1

Metforminium monocation/ monoprotonated

P21/n
monoclinic



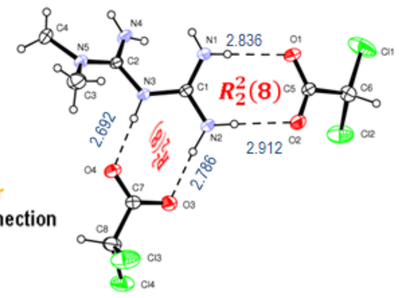
$R_2^2(8)$ N—H···O dimer
$R_2^2(8)$ N—H···N dimer
$R_4^4(8)$ N—H···O tetramer
N4–H1···O2; ribbon connection

Charge-assisted H- bodnding motifs

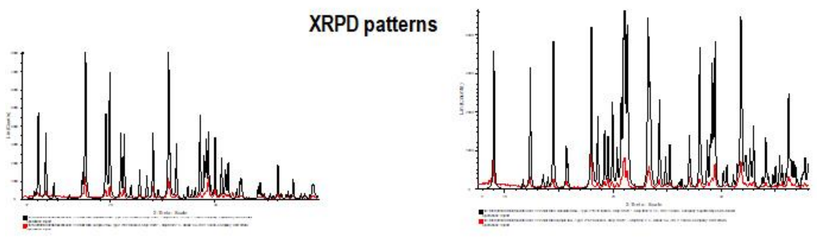
MET – Dichloroacetate 1:2

Metforminium dication/ diprotonated

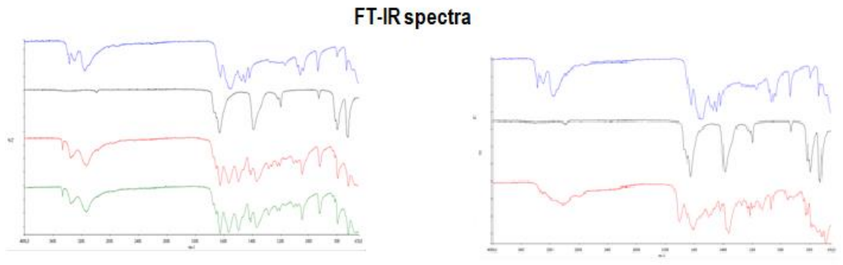
P-1
triclinic



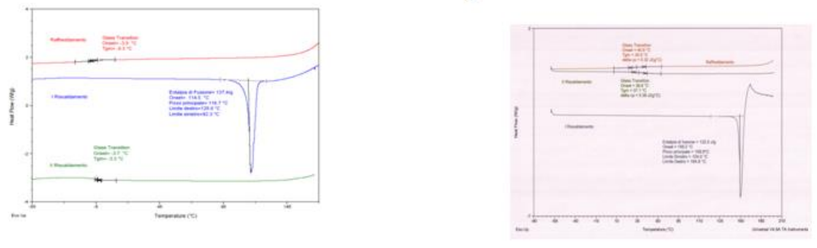
XRPD patterns



FT-IR spectra



DSC Thermograms

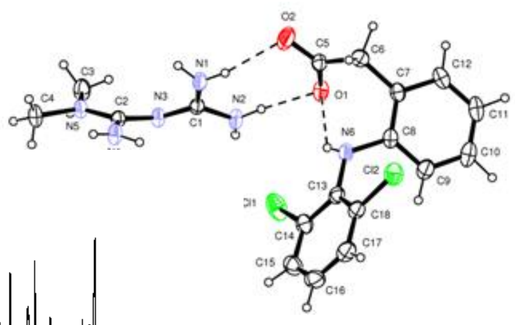


Characterization of PCC

Structure determination was performed by Single Crystal X-Ray Diffraction Analysis confirming the structure 1 and structure 2 to be molecular salt forms of New Chemical Entity (NEC) not so far deposited in the Cambridge Structure Database CCDC.

MET diclofenac 1 : 1

Metforminium monocation/ monoprotonated



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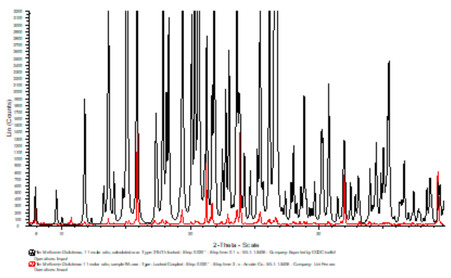
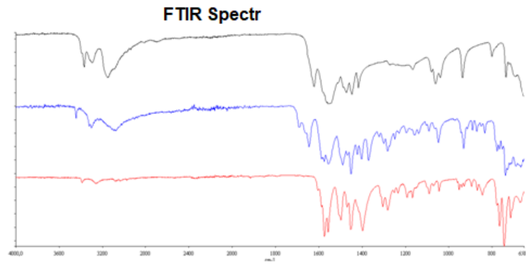
PXRD patten



FTIR Spectr



Work in Progress

Testing Dissolution patterns of MET molecular salts, and flow- cytometry testing

References

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