# COCRYSTALLIZATION SCREENING FOR "DRUG-DRUG" TYPE OF COCRYSTALS

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## Introduction

"Drug-drug" cocrystals (CC) are part of pharmaceutical cocrystals (PCC) wherein two costitutive components (drug and coformer) represent Active Pharmaceutical Ingredients (APIs) cocrystallized in stoichiometric ration into crystalline single phase. "Drug-drug" represent multicomponent complexes where the Charge Transfer (CT) or Electron Donor-Acceptor (EDA) Interactions between two APIs molecules may determine their crystal packing motifs that in first line exert dual or complementry pharmacological effect and 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) [1-4].

"Drug-drug" CCs offer opportunities for formulations fixed-doses drug delivery systems including one API substance in form of "drug-drug" CC as New Chemical Entity (NCE)to obtain dual effect in therapy.

First Drug model (DM) Metformin (MET), *N,N*-dimethylbiguanide is the only approved hypoglycemic drug of the biguanide classis used as oral type 2 diabetes, marketed as hydrochloride, embonat (pamoate) and *p*-chlorophenoxy acetate salt [5].

Because of the biguanide $\pi$-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:

**Metformin = L; [HL]/[L][H] p$K_{a1}$(N−H$^+$)~12.40;**
**[$H_2$L]/[HL][H] p$K_{a2}$(N−H$^+$)= 2.96** (NIST database)

The high basicity of p$K_{a1}$ and the difference between the p$K_a$ values qualify MET as organosuperbase and determine the stability of its monoprotonated form $METH^+$ within a wide range of pH [2].

Drug models used as CFs are:

Dichloroacetic acid Dichloroacetate (DCA) was introduced as novel class of oral ant diabetic drug that reduce blood glucose and lipids without stimulating insulin secretion. Recent study reveled its anticancer effect [6].

Diclofenac and salicylic acid are widely used anti-inflammatory drugs in pain-killer therapy.

Glycolic acid is drug applied for acne treatment in dermatology, as well it is a strong enhancer for drug transdermal delivery [7].

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## Compounds Studied

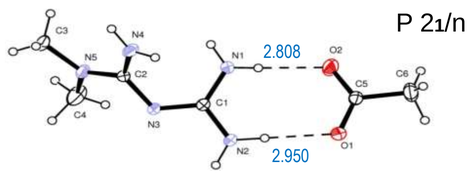
| DM I | DM II (CF) | pKa (CF) | Molar ratio | Slow-rate solvent evaporation (SRSE) | "drug-drug" CCs |
|---|---|---|---|---|---|
| Metformin neutralized (MET) pKa1 : 12.4 pKa2 : 2.96 | Acetic acid | 4.75 | 1:1 | methanol, SRSE | MET acetate 1:1 |
| | Dichloracetic acid | 1.1 | 1:1 & 1:2 | methanol /n-pentanol 50/50 *V/V* % | MET dichloroacetate 1:1 & 1:2 |
| | Diclofenac | 3.99 | 1:1 | methanol /n-pentanol 50/50 *V/V* % | MET Diclofenac 1:1 |
| | Glycolic acid | 3.83 | 1:1 | methanol /n-pentanol 50/50 *V/V* % | MET glycolate 1:1 |
| Metformin·HCl | Dichloroacetate Sodium (DCAA·Na) | 1.1 | 1:1 | Kneaded in n-pentanol, filtrated, clear solution | MET dichloroacetate 1:1 |
| | Diclofenac Sodium | 3.99 | 1:1 | Kneaded in ethanol: sediment re-suspended in n-pentanol, filtrated, clear solution | MET diclofenac 1:1 |

## Characterization of PCC

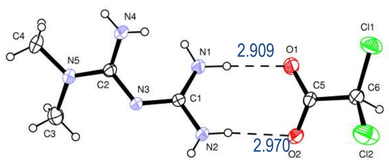
Crystal structure were determined by single X-ray diffraction analyses. For quality control of the prepared large scaled batches, X-Ray powder diffraction (XRPD) and FT-IR Spectroscopy were applied. Thermodynamic properties were tested on Different Scanning Calorimetry (DSC)

## Crystal Structures

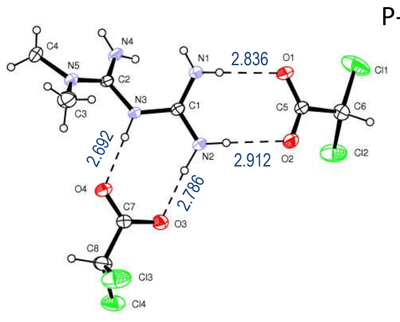
**Metformin acetate 1: 1** P 2$_1$/n



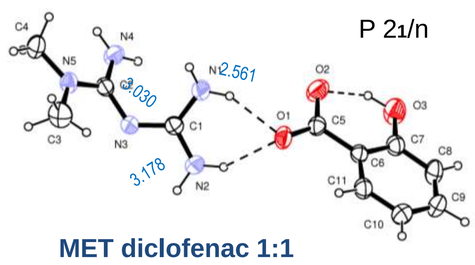

**MET dichloroacetate 1:1** P21/n



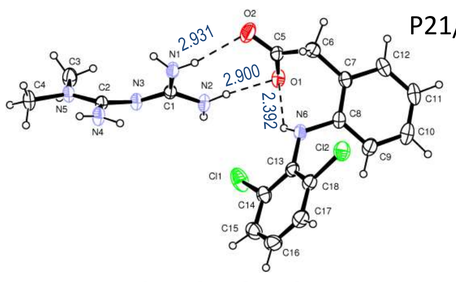

**MET dichloroacetate 1:2** P-1



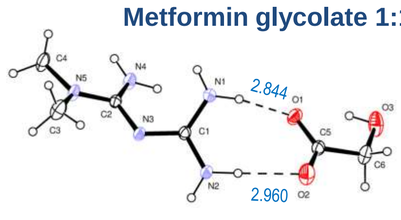

**Metformin salicylate 1:1 *MM*** P 2$_1$/n



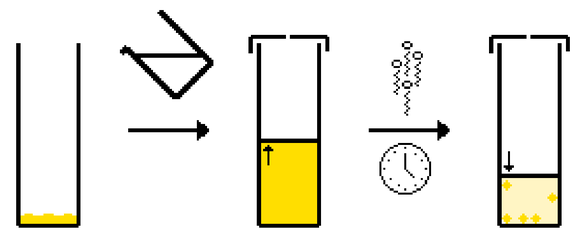

**MET diclofenac 1:1** P21/c




**Metformin glycolate 1:1** P-1

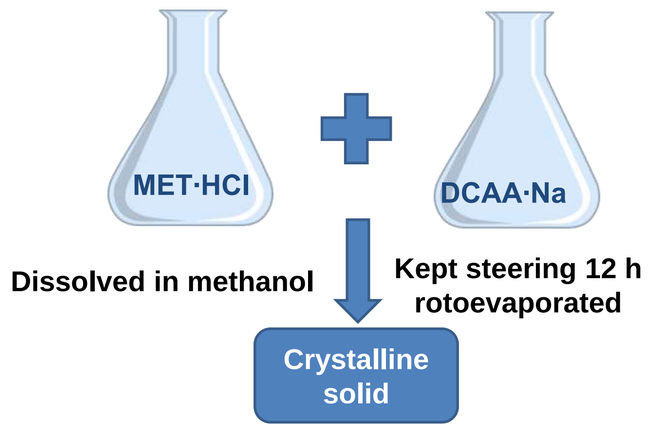



## CC screening (small scale)



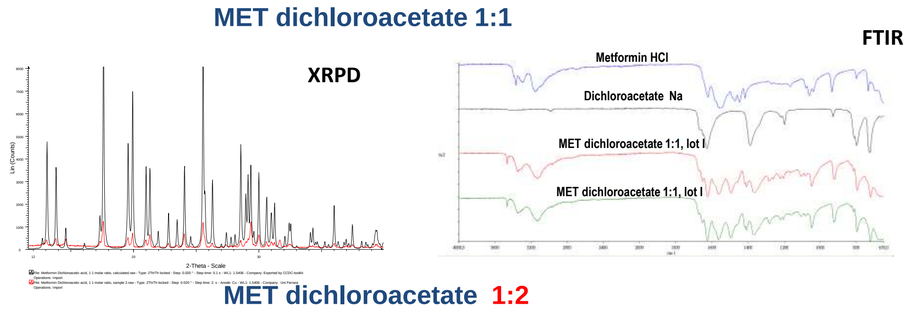
Single crystals with quality for structure determination were obtained by slow controlled rate of solvent evaporation techniques.

## Method of preparation (Large scale )

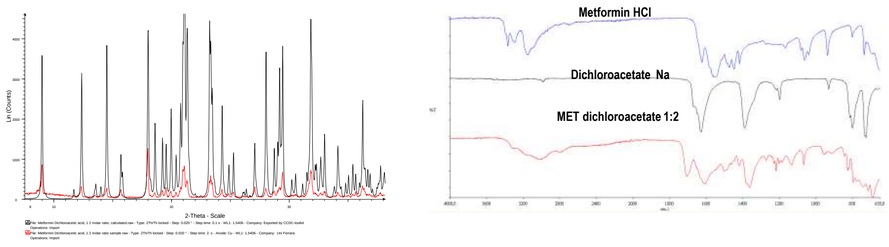



The same method was applied for preparation of MET Dichloroacetic acid 1:2; MET:Diclofenac 1:1; and MET glycolate

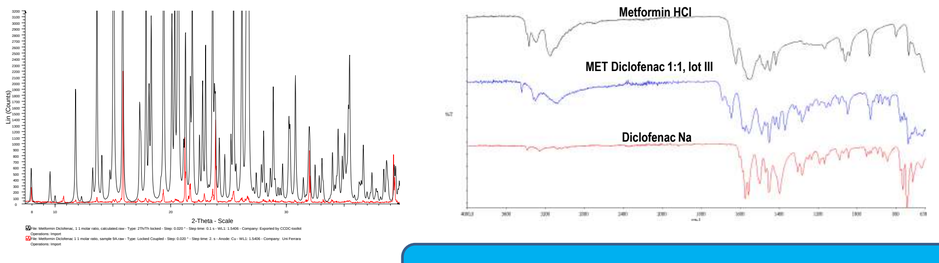
**MET dichloroacetate 1:1**




**MET dichloroacetate 1:2**




**MET diclofenac 1:1**




## Further Work

Measurements for equilibrium solubility and dissolution profiles are upcoming in order entire solid state profile to "drug-drug" CCs to be resolved.

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## References

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