# The role of cocrystallization screening for the assessment of structure-activity relationship in drug development

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The selection of the crystalline phases in a form of molecular cocrystals has become scientific challenge at the early stage of drug development of pharmaceutical formulations and in the late stage of synthesis and isolation of Active Pharmaceutical Ingredients (APIs) in desirable defined crystalline forms. Optimal crystal form of API interactively interrelates and impacts its aqueous solubility and dissolution rate that are benchmark for drug delivery and absorption determining the extent of its bioavailability and pharmacokinetics profile. Hence, determining the crystal structure and revealing the crystal packing forces and geometry of the API impact upon its physicochemical properties what it is a threshold for controlling the performance of the API. The range of crystal forms in which molecular cocrystals of APIs may exist are advantageous comparing to its polymorphs, salts, solvates and hydrates due to the vast number of potential coformers which extend the limited counterions for salt formation implying the existence of more complex intermolecular interactions based on different H-bonding patterns with API that lead to conformational changes and flexibility for crystal packing in process of cocrystallization.

Cocrystallization became well known bottom-up approach starting from intermolecular interactions among, either selected neutral, ionic or zwitterionic molecules to design and control the properties of the multicomponent crystals. [1] In the scope of interest for drug design and formulation, the main advantage for designing Pharmaceutical Cocrystals (PCCs) is, through their modulating properties, to improve the performance of the native APIs such are: 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). [2,3] Many debates regarding semantic and classification in cocrystals (CCs) based on accomplishments in research of supramolecular chemistry, highlighted the complex reality of *multi-component systems*, and the wide scope associated between salts and cocrystals in *the salt-cocrystal continuum.* [4]

Cocrystallization screening reveals protocol was undertaken in order to grown single crystalline phases of PCCs composed of drug models selected from biguanides class of drugs and coformers that belong to dufferent pharmacotherapy and functional group classes, respectively.

Biguanide drugs are well known and wide used oral antidiabetic drugs for oral therapy of diabetes type-2 that directly improve insulin action. Recent studies point out that biguanides in combination with targeted inhibitors in order to obtain synergy in reduction cell viability and inhibited tumor growth in the mutated neuroblastoma rat sarcoma oncogene (NRAS) protein from melanoma cells [5]. Hence, it is expected that combination of biguanides which affect activation of the AMP-activated protein kinases (AMPK) and the regulation of energy metabolism with outcome to cell's energy sparing, in combination with other anti-cancer drug-models influence directly blocking cell's signaling and hindering the resistance.
The published research for both pro-cancer and anti-cancer effects of biguanides on cancer cells indicate to existence the association of the antidiabetic therapy and reduced risk of cancer in diabetic patient.

Because of the biguanide $\pi$-conjugated system, the drug models with this structure can exist in three resonance-stabilized forms, *i.e.* as neutral molecule (BIG), monoprotonated ($BIG^+$) or diprotonated ($BIG^{2+}$) cation, with dissociation constants in water in range from $pK_{a1} \approx 12.00$ to $pK_{a2} \approx 2.00$).

A search of the biguanide fragments in the structural literature, both in the CCDC (Cambridge Crystallography Database Center) database and in patents, shows that in crystals it exists as monoprotonated ($BIG^+$) or deprotonated ($BIG^{2+}$) but never in its neutral form BIG.

We have undertaken a systematic study of the crystal chemistry of biguanide drugs with the aim of understanding its properties in the solid state and finding relationships with its biopharmaceutical profile. We have obtained 29 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: fumaric, acetic, trifluoroacetic, trichloroacetic, dichloroacetic, monochloroacetic, glycolic, salicylic, dichlofenac; Dicarboxylic acids: oxalic, malonic, maleic, fumaric, succinic, adipic.

In the poster are presented structures analyses for "*drug-drug*" type of PCCs where both API and CF exhibit pharmacological effect. This approach of designing "*drug-drug*" type of PCC aligned to the strategy for drug repositioning, the idea for use of a drug for treating diseases other than the drug-specified. This concept was prompted in 2012 through the Discovering New Uses for Existing Molecules program, initiated by US's National Institute of Health (NIH).

The case study underline the crystal growth and the method of preparation for "drug-drug" type of PCCs wherein two different APIs cocrystallized in single crystal cell, and that represent new paradigm for approaching in development of "fixed-doses" or "combo" pharmaceutical formulations. Preliminary results of the Structure-Activity Relationship study on the cocrystals composed of biguanide drug-models with dichloroacetic acid indicate dual and complementary anti-cancer activities of the two selected drug models for cocrystallization.

Literature:

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