CIRCE
Crystal Engineering

# Virtual Cocrystal Screening

## Introduction

Active Pharmaceutical Ingredients (APIs) are those bioactive molecules used in the medical diagnosis, cure, treatment, or prevention of diseases. They are normally used in solid form. The solid states of molecules are grouped in amorphous and crystalline forms. A crystalline solid is one in which there is a regular repeating pattern in the structure, whereas an amorphous solid is one which does not have long-range order. Although APIs can be part of a medicine in amorphous forms, the major part of medicines contain APIs in crystalline forms like salts or polymorphs.

Because the API solid form affects its physicochemical properties such as solubility, dissolution rate, hygroscopicity, physical and chemical stability, and mechanical properties, the research focused on finding polymorphs of new or existing drugs concentrates many economics and time consuming efforts. If a new polymorph undergoes improved physicochemical and pharmaceutical properties, it can be patented as a new drug (1). Another way to find new drugs is to get different salts from the same API. Accordingly to the Food and Drug administration (FDA) (2), a salt is any of numerous compounds that result from replacement of part or all of the acidic hydrogens of an acid by a basic radical giving place to an ionic or electrovalent crystalline compound. From the current regulatory scheme, different salt forms from the same active moiety are considered different active ingredients.

Recently, the interest for another kind of solids, the cocrystals, is originating a conflict about their regulatory scheme. Cocrystal's definition is still a bit controversial; the FDA has affirmed twice (2, 3) that cocrystals are solids that are crystalline materials composed of two or more molecules in the same crystal lattice where the cocrystal's components are in a neutral state and interact via non-ionic forces. They also affirmed that an API that has been processed with a cocrystallizing excipient to generate an “API-excipient” cocrystal should be treated as a drug product intermediate. This mens that a cocrystal formed with an existing API would not be a new drug substance but rather an alternative formulation. In contrast, a new salt form is considered a different drug substance. More recently, in the Technology Forum titled “The Evolving Role of Solid State Chemistry in Pharmaceutical Science” held in India, (February, 2012), important members of the scientific community accorded to resolve that a cocrystal have to be treated as a new drug. These conclusions were published in April 2012 in Crystal Growth & Design (4). Some pharmaceutical companies have expressed their conformity with these scientist's affirmations.

Cocrystals formed by an API and a coformer are known to enable changes in their physicochemical properties that might improve the overall stability and efficacy of a dosage form, change the melting point, improve the stability to hydration and increase the plasma bioavailability (5-10). Therefore, pharmaceutical cocrystals represent an opportunity to diversify the number of crystal forms of a given API and, in turn, fine-tune or even customize its physicochemical properties without the need for chemical (covalent) modification (11). Cocrystals formed by two different APIs have been recently described increasing even more their pharmaceutical potential (12).

Regardless of how it will end the polemic between the FDA and academia, the improved properties that cocrystallization provides, make cocrystals an attractive target for the pharmaceutical industry.

The screening methods for cocrystals are very similar to those for polymorphs and salts. The typical screening for polymorphs and salts consists in using different solvents at different crystallisation conditions. Other co-crystallization screening methods are grinding, cocrystallization at the interface between two immiscible solvents, mixed fusion method, solvent drop grinding, slurrying, the use of experimentally determined phase diagrams and sublimation (10, 13, 14).

Since there are, in principle, thousands of coformer candidates to cocrystallize a particular API, a comprehensive experimental screening can be very expensive in terms of time and resources. Thus, it becomes clear that reducing the number of candidates to those with high probability of cocrystallization is a real need. And in this sense, virtual cocrystal screening methods able to predict for a specific API what coformers are the most suitable candidates for cocrystallization, have been investigated recently.

## Our approach

Professor Chris Hunter (from the Department of Chemistry at the University of Sheffield) and his co-workers have developed a software with this commitment. This work, recently published in the Royal Society of Chemistry's flagship journal *Chemical Science* (14), resulted in the development of a software capable to predict, with high fidelity, what combinations of APIs and coformers are likely to form cocrystals.

This approach has an advantage that allows accelerating the computational process: the knowledge of the crystal structure is not required and, indeed, provides a simple strategy for predicting the pairwise interactions that will occur in the solid state.

The approach is based on the principle that the hierarchical organization of functional group's interactions determines the structure of a crystalline solid. It means that the strongest H-bond is formed between the best H-bond donor and the best H-bond acceptor, the next best H-bond donor interacts with the next best H-bond acceptor, and so on. Assuming that a solid optimizes all possible interactions, all H-bond donors would be free to interact with all H-bond acceptors. The total interaction site pairing energy of the solid is estimated as the sum over all contacts.

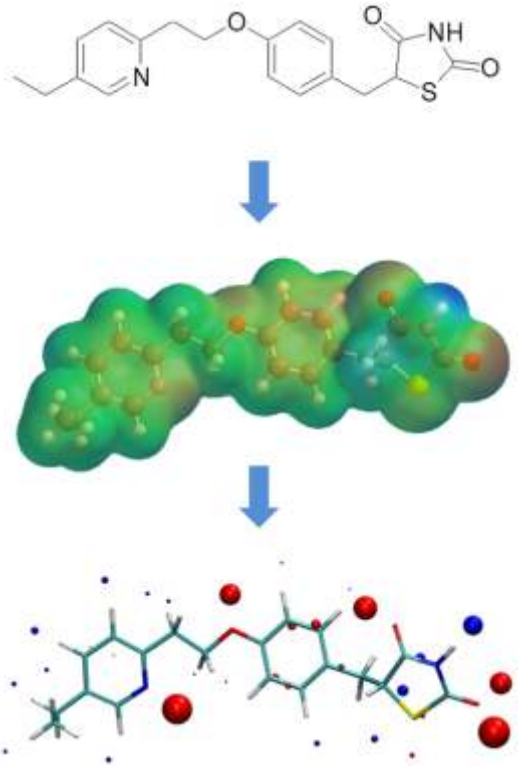


Figure 1. The computational methodology determines for the API and each potential coformer the H-bond interaction sites from the Molecular Electrostatic Potential Surface at the DTF level of calculation.

Our approach assumes that cocrystals only have attractive electrostatic interactions and that the difference between the interaction site pairing energies of the cocrystal and the two pure forms provides a measure of the

probability of forming a cocrystal based on the formation of more favourable intermolecular interactions. This is reflected by the following mathematical equation: $\Delta E = Ecc - nE1 - mE2$; where *E1* is the interaction site pairing energy of the pure form of component 1, *E2* is the interaction site pairing energy of the pure form of component 2 and *Ecc* is the interaction site pairing energy of the cocrystal of stoichiometry 1n2m. Thus, the higher is the $\Delta E$ value, the greater is the likelihood of forming a cocrystal. The approach allows a fast assessment of molecular libraries (i.e. GRAS, EAFUS).

## Validation

The virtual cocrystal screening methodology was tested in two different ways. Some reported studies on experimental cocrystal screening were chosen from the literature as the first stage validation. The theoretical probability of cocrystallization was determined for those API/coformer cocrystals described in the literature and they correlated very well with the experimental data. These studies included well known, from a solid state point of view, compounds such as caffeine or carbamazepine.

After checking the good performance of the computational methodology with literature data, a real blind test has been conducted with four APIs. Less than 1% of those coformers from the GRAS list with the highest probability of cocrystallization were tested under standard experimental screening conditions and new cocrystals for three out of four APIs were isolated.

Thus, different tests have been used to validate the utility of the method, and the results provide a calibration between the value of $\Delta E$ and the probability of cocrystal formation.

This new approach therefore appears to be a very useful computational tool for improving the efficiency of cocrystal screens by limiting the number of candidate coformers to be studied experimentally to only those compounds that show promise by virtue an array of functional groups that are complementary to the API of interest.

## Conclusions

Although it is believed that the number of polymorphs mainly depends on dedicated study time (15), the finding of new polymorphs susceptible to be patented is every year harder. Given this situation, cocrystallization represents a highly probable opportunity to change physicochemical properties in order to improve pharmacokinetic features of current drugs. However, the huge number of coformers makes the experimental screening long and complicated.

The new technology presented herein was developed in the Department of Chemistry of the University of Sheffield by Professor Christopher A. Hunter, Fellow of the Royal Society, and his collaborators. The access to this prediction software represents for those companies that want to be leaders in cocrystal developing and in drug discovery in general, a chance to be more competitive and an advantage respect their competitors.

# Bibliography

**(1)** U.S. Department of Health and Human Services - Food and Drug Administration - Center for Drug Evaluation and Research (CDER). ANDAs: Pharmaceutical Solid Polymorphism. July 2007.

**(2)** U.S. Department of Health and Human Services - Food and Drug Administration - Center for Drug Evaluation and Research (CDER). Regulatory Classification of Pharmaceutical Cocrystals. April 2013.

**(3)** U.S. Department of Health and Human Services - Food and Drug Administration - Center for Drug Evaluation and Research (CDER). Regulatory Classification of Pharmaceutical CoCrystals. December 2011.

**(4)** Aitipamula S. et al. Crystal Growth & Design. 2012 (12), 2147–2152.

**(5)** Almarsson O. and Zaworotko MJ. Chemical Communications. 2004, 1889–1896.

**(6)** Banerjee R. et al. Crystal Growth & Design. 2005 (5), 2299–2309.

**(7)** Trask AV. et al. International Journal of Pharmaceutics. 2006 (320), 114–123.

**(8)** McNamara DP. et al. Pharmaceutical Research. 2006 (23), 1888–1897.

**(9)** Vishweshwar P. et al. Journal of Pharmaceutical Sciences. 2006 (95), 499–516.

**(10)** Blagden N. et al. New Journal of Chemistry. 2008 (32), 1659–1672.

**(11)** Cheney ML. et al. Crystal Growth & Design. 2010 (10), 10.

**(12)** Blagden N. et al. Advanced Drug Delivery Reviews 2007 (59), 617–630.

**(13)** Eddleston MD. et al. CrystEngComm. 2013 (15), 175–181.

**(14)** Musumeci M. et al. Chemical Science. 2011 (2), 883–890.

**(15)** McCrone WC. Physics and Chemistry of the Organic Solid State. 1965 (2), 725–767.

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