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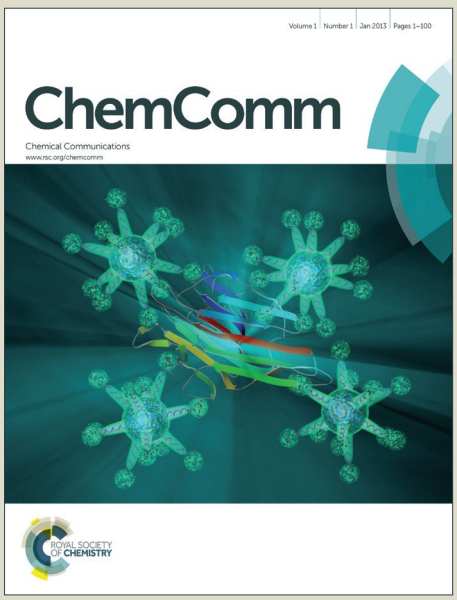

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Pharmaceutical Cocrystals: Along the Path to Improved Medicines

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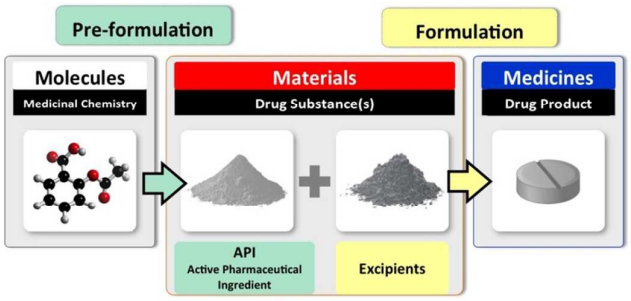
Cocrystals, a long known but understudied class of crystalline solids, have attracted interest from crystal engineers and pharmaceutical scientists in the past decade and are now an integral part of the preformulation stage of drug development. This is largely because cocrystals that contain a drug molecule, pharmaceutical cocrystals, can modify physicochemical properties without the need for covalent modification of the drug molecule. This review presents a brief history of cocrystals before addressing recent advances in design, discovery and development of pharmaceutical cocrystals that have occurred since an earlier review published in 2004[1]. We address four aspects of cocrystals: nomenclature; design using hydrogen-bonded supramolecular synthons; methods of discovery and synthesis; development of pharmaceutical cocrystals as drug products. Cocrystals can be classified into molecular cocrystals (MCCs) that contain only neutral components (coformers) and ionic cocrystals (ICCs), which are comprised of at least one ionic coformer that is a salt. That cocrystals, especially ICCs, offer much greater diversity in terms of composition and properties than single component crystal forms and are amenable to design makes them of continuing interest. Seven recent case studies that illustrate how pharmaceutical cocrystals can improve physicochemical properties and clinical performance of drug substances, including a recently approved drug product based upon an ICC, are presented.

Introduction

An awakening has occurred in the first part of the 21st century to the potential of crystal engineering and materials science to optimise performance of drug products. The phrase "Molecules, Materials, Medicines", which has been the banner of conferences since 2007,[2] succinctly reflects the idea that drugs are formed from a convergence of synthetic chemistry, materials science and engineering coupled with pharmacological and clinical evaluation. Drug discovery and development can therefore be regarded as being comprised of three distinct stages that might be termed "molecules, materials and medicines", respectively[2] (Scheme 1).

The "molecules" stage includes medicinal chemistry for the discovery of new chemical entities along with biological and pharmacological screening for activity. The "materials" or pre-formulation stage addresses the discovery of a drug substance, normally a solid, suitable for use as a material in a drug product. The "medicines" or formulation stage combines this drug substance (also known as the active pharmaceutical ingredient, API) with inactive ingredients, excipients, to afford a drug product. The materials stage came to the fore in the 1990's after regulatory bodies issued guidance that in effect mandated characterisation of the solid forms of a drug substance.[3] Intellectual property issues, highlighted by litigations involving ranitidine hydrochloride, Zantac®,[4] which at the time was the world's best-selling drug product, further emphasized the importance of pre-formulation research. This was compounded by performance problems caused by a previously undiscovered polymorph of ritonavir, in a capsule formulation marketed under the trade name Norvir®. The reduced solubility of this polymorph resulted in market withdrawal and subsequent reformulation.[5]



Scheme 1. The three stages of early drug discovery and development: Identify a molecule that is biologically active; create a material suitable for use in a drug product; formulate the material into a medicine with excipients.

The motivation to create new solid forms of drug molecules is therefore a consequence of how important drug substances are to the performance of orally administered drug products, the heart of which is almost always a crystalline solid.[6] It should be noted that amorphous solids have also been selected for use in drug products, but the need to meet specifications in terms of thermodynamic stability, purity and processing means that crystalline drug substance are generally preferred.[7] That the physicochemical properties of a crystal

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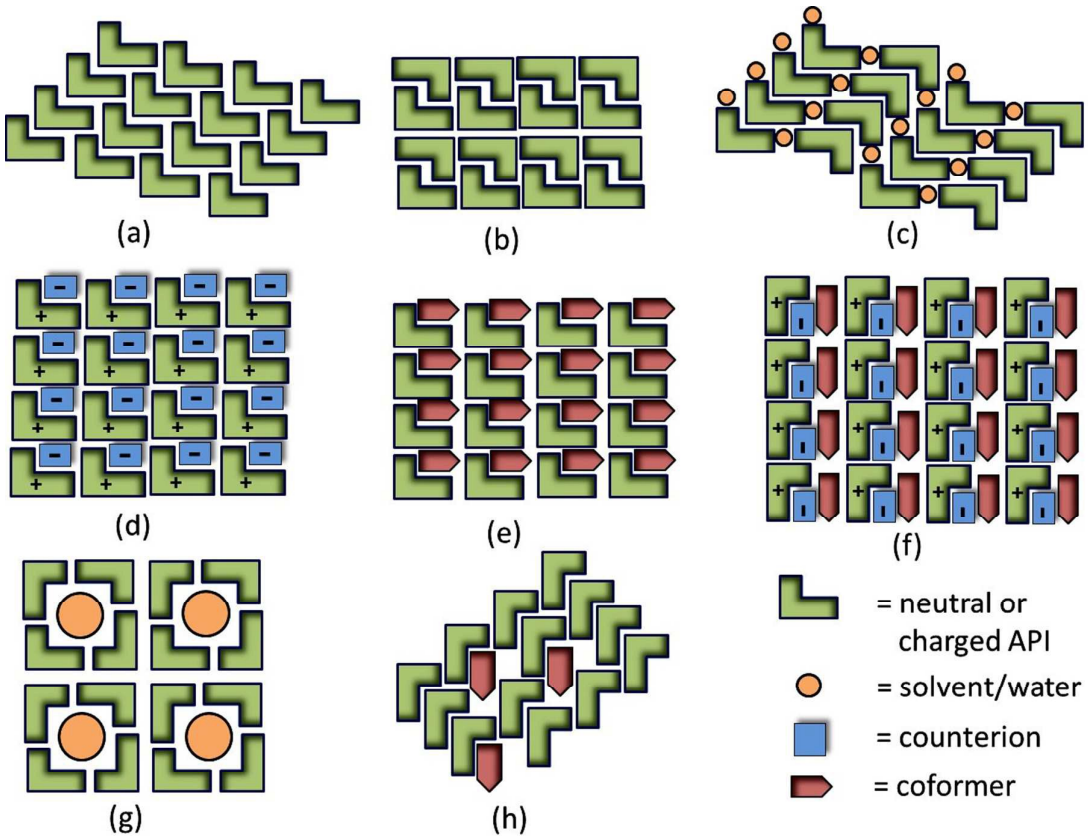


Scheme 2. Possible crystalline forms for an API: (a) & (b) polymorphs; (c) solvate/hydrate; (d) salt; (e) molecular cocrystal; (f) ionic cocrystal; (g) non-stoichiometric inclusion compounds including channel hydrates, solvates; (h) solid solutions (mixed crystals).

form are inherently dependent upon the composition and the crystal packing of the molecules/ions means that exerting control over composition and crystal packing could in turn lead to control over properties. It is in this context that crystal engineering[8] research on pharmaceutical cocrystals started in earnest with the main goals of improving the stability and/or the solubility of drug substances.[1, 9] Crystal forms of drug molecules, as would be expected, are a microcosm of molecular solids in general. In particular, they can be either single-component or multi-component. Single-component crystals provide limited opportunity to modulate the physicochemical properties of a compound since they are limited to polymorphs, which tend to exhibit only subtle changes in physicochemical properties.[10] Indeed, the solubility difference between two polymorphs is typically less than two-fold. Multi-component crystals, however, are a different story. They can be stoichiometric or non-stoichiometric and encompass hydrates, solvates, salts, solid solutions (mixed crystals), inclusion compounds and cocrystals (Scheme 2). However, the development of multi-component crystalline drug substances presents additional challenges vs. single component variants. For example, physical stability can be an issue for solvates, hydrates or inclusion compounds.[11] Hydrates, which have been termed a "nemesis to crystal engineering",[12] are of particular relevance, thanks to the ubiquity of water vapour. However, that they can exhibit variable stoichiometry and low thermal stability, often works against their use in drug products.[13] Nevertheless, hydrates have been selected and developed for use in marketed drug products.[14] A solvate might also suffer from poor stability to elevated temperature or humidity, making it an unlikely candidate for a drug product.[15] Salts are a well-established approach to generate novel solid forms with improved physicochemical properties.[16] The primary drawback of salts is

that they are limited to API's that contain ionisable moieties. Crystalline solid solutions (mixed crystals) could enable a continuum of physical properties because of their variable stoichiometry, but they are not generally amenable to design and preparation of reproducible phases is nontrivial.[17] In principle, cocrystals do not suffer from the limitations of the other classes of multi-component crystalline solid mentioned above. Further, that they can be designed using crystal engineering approaches means that suitable coformers can be rationally selected from libraries of hundreds or even thousands of potential cocrystal formers. Herein we address the evolution of pharmaceutical cocrystals since 2004.

History and Nomenclature

Although cocrystals are long known, there was little consensus concerning the scope of the term cocrystal until a recent perspective authored by 46 scientists in the field.[18] According to the perspective '*Cocrystals are solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts*.' If at least one of the coformers is an API and the other is pharmaceutically acceptable, then it is recognized as a pharmaceutical cocrystal.[1]

The notion of classifying cocrystals based upon the type of coformers dates back to 1922 and Paul Pfeiffer[19]. In 2009, Stahly reported examples of cocrystals containing inorganic components.[20] Our research group has also classified cocrystals as "molecular" or "ionic" depending on the nature of the coformers. Molecular cocrystals (MCCs) contain two or more different neutral coformers in a stoichiometric ratio and are typically, but not always exclusively,[21] sustained by hydrogen bonds or halogen bonds. Most reported pharmaceutical cocrystals fall into this category. The term 'ionic cocrystal' was coined by Braga's research group in 2010.[22] Ionic cocrystals (ICCs) are typically sustained by charge assisted hydrogen bonds and/or coordination bonds (if metal cations are present). Thus, some ICCs could also be classified as coordination polymers. Large families of ICCs include acid salts[23] (cocrystals containing a carboxylate salt and carboxylic acid) and conjugate acid-base cocrystals (cocrystals containing an ion and its neutral counterpart[24])

Ionic Cocrystals (ICCs)

ICC's can be traced back to at least 1783 when Romè de l'Ise observed a habit change in NaCl when crystallised from aqueous urea.[25] Bunn (1933)[26] and Seifert (1937)[27] subsequently attributed this habit modification to the adsorption of urea on certain crystal faces of NaCl. Bunn also noted that "*There is one complication; in the aqueous system there is a compound NaCl.CO(NH_2)$_2$.H_2O, the structure of which is not known*". In 1950, Kleber et al.[28] detailed the morphology and optics of this compound before Palm and MacGillavry isolated colourless, transparent crystals from slow evaporation of an equimolar solution of sodium chloride and urea.[29] Single-crystal X-ray crystallographic analysis revealed that the compound in question is a 1:1:1 ICC of NaCl, urea and water (Figure 1). A related family of ICCs is comprised of sodium and calcium salts and sugars, a noteworthy example being NaCl and glucose, first reported by F.V. Kobell in 1843.[30]

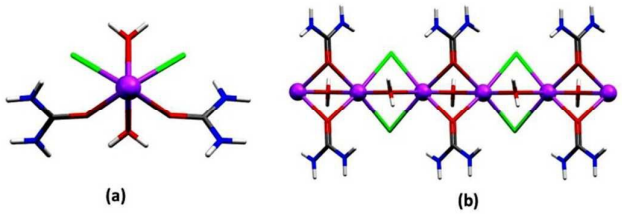


Figure 1. (a) Sodium cation coordination environment and (b) 1D chain observed in hydrated sodium chloride urea ICC.

ICCs based upon carboxylic acids and carboxylate salts were first reported in 1853 by Gerhardt, who studied the compound formed from cooling an alcohol solution containing stoichiometric amounts of potassium hydrogen benzoate and benzoic acid.[31] The composition of this ICC was confirmed in 1954.[32] In a subsequent review by Speakman, this family of ICCs was classified as '*acid salts*'[23] and he noted that '*in some cases an acid salt is more easily made than the neutral salt; it may crystallize preferentially when one is trying to prepare the neutral salt'*.[23] Speakman explored acid salts extensively through X-ray and neutron diffraction studies and suggested that they could be further classified into two types depending upon the nature of the carboxylate ion. In type A, the proton is shared between carboxylates (Figure 2a) whereas in type B the proton is associated with only one oxygen atom, i.e. it is a carboxylic acid (Figure 2b). The systematic study of Speakman salts ultimately afforded an understanding of the structural features of short, strong hydrogen bonds.

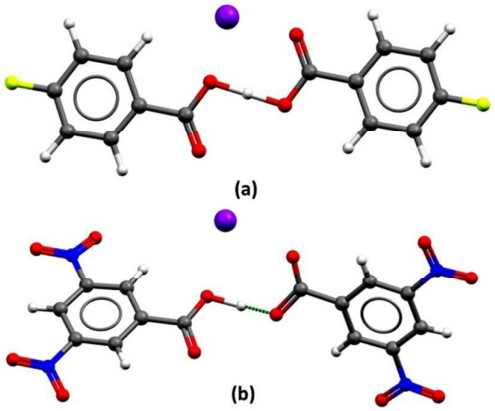


Figure 2. Examples of Speakman type A and type B acid salts: (a) potassium hydrogen bis(4-flourobenzoate) and (b) potassium hydrogen bis(3,5 dinitrobenzoate).

Improved solubility of ICCs was also addressed in early literature: phenylquinoline carboxylic acid with pyrazolones, '*molecular compounds*';[33] streptomycin acid salts with alkaline earth metal halides, '*complex salts*';[34] theophylline with sodium salts such as sodium acetate, sodium salicylate and

sodium glycinate.[35] Clinical trials conducted upon theophylline-sodium glycinate involved >300 patients over 18 months and indicated that the ICC produced a typical theophylline response. Pharmacodynamics studies in a rat model revealed that the LD_{50} of theophylline and the ICC are 200 mg/kg and 350 mg/kg, respectively, suggesting decreased toxicity for the ICC. Hoffmann-La Roche Inc. subsequently reported the ICC of theophylline (Tp) and magnesium (Mg) salicylate (S) with the formula $Tp_2MgS_2.5H_2O$.[36] This ICC was crystallized using magnesium salicylate (0.5–2.0 mol) and theophylline (1.0 mol).

Another ICC that demonstrated improved performance involved a tetracycline, a class of broad spectrum polyketide antibiotics that tend to exhibit low solubility. Reverin, a derivative of tetracycline, was found to exhibit increased solubility vs. tetracycline but also increased toxicity.[37] Two ICCs or '*additional complexes*', tetracycline-sodium methylene salicylate and chlorotetracycline-sodium methylene salicylate, were administered as distilled water solutions to albino mice. The ICC was found to be less toxic (LD50: 375 mg/kg) vs. Reverin (225 mg/kg).

A patent filed by George and Ernest in 1971, claimed 56 ICCs formed by 3-isothiazolones and metal halides as '*metal salt complexes*' and reported improved thermal stability vs. the corresponding isothiazoles.[38] For instance, 5-chloro-2-methyl-3-isothiazole and its hydrochloride salt undergo 30% and 58% decomposition, respectively, at 50 °C whereas the $CaCl_2$ ICC was found to be thermally stable.

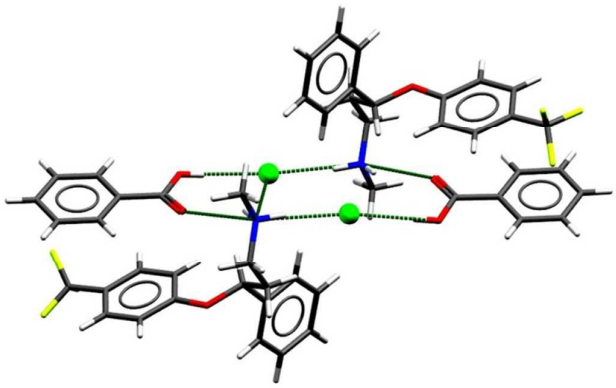


Figure 3. The discrete assembly that is sustained by charge assisted hydrogen bond interactions in fluoxetine hydrochloride-benzoic acid.

ICCs based upon organic cation halides were studied by Childs et al. who invented fluoxetine hydrochloride ICCs with a series of carboxylic acid coformers.[39] The ICC of fluoxetine hydrochloride with benzoic acid is shown in Figure 3. Modulation of dissolution rate with respect to fluoxetine hydrochloride was reported for this family of ICCs. Saxagliptin hydrochloride, Onglyza®, exists as a monohydrate that converts to a chemically unstable dihydrate during a coating process. To overcome this problem, Enantia synthesized and patented novel ICCs of saxagliptin hydrochloride.[40]

Molecular Cocrystals, (MCCs)

The MCC of quinone and hydroquinone, quinhydrone, was reported in 1844 by Wöhler.[41] The composition was not confirmed by single-crystal X-ray analysis until the 1960's when it was revealed to be a 1:1 MCC sustained by a C=O···H-O supramolecular heterosynthon[42] (Figure 4). An early example of an MCC with pharmaceutical utility was patented by Von Heyden et al., who claimed compositions of barbiturates with 4-oxy-5-nitropyridine, 2-ethoxy-5-acetaminopyridine, N-methyl-α-pyridine and α-aminopyridine.[43]

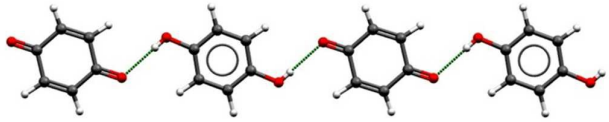


Figure 4. Illustration of the 1D chain sustained by O-H···O hydrogen bonds in hydroquinone-quinone, quinhydrone.

Nomenclature of MCCs was inconsistent in the early literature: '*molecular organic compounds*' was used by Buehler and Heap to describe MCCs of 1,2-dinitrotoluene, 2,4-dinitrobenzene and 2,4-dinitrophenol with amino derivatives of naphthalene, benzidine and aniline;[44] '*organic molecular compounds*' was used by Anderson in 1937.[45] Use of MCCs (termed '*complex*'[46]) to improve the performance of a drug substance was exemplified by digoxin and hydroquinones. Digoxin is indicated for the treatment of mild to moderate heart failure but its dissolution rate and bioavailability are low. Higuchi and Ikeda found that the solubility of digoxin increases in the presence of hydroquinone.[46] Bochner et al.[47] later conducted clinical trials in humans that compared MCCs of digoxin with commercially available tablets of digoxin. These studies revealed that peak serum digoxin concentrations for the MCC were achieved faster than commercial digoxin tablets. Even as early as 1974, the potential use of MCCs to improve the clinical performance of low solubility drugs was envisioned by the authors who stated that '*the principle of complexing a drug with substances such as hydroquinone to enhance the dissolution might be applied to other medication whose absorption is erratic following poor in vivo dissolution.*'

Ambiguity concerning whether a compound should be classified as a salt or a cocrystal is a topical subject[48] but was also discussed as far back as the 1930's. Two MCCs from 1934, were initially considered to be salts formed between urea and oxalic acid (in 1:1 & 1:2 stoichiometry).[49] Subsequent analysis by Harkema et al. revealed that they are addition compounds, i.e. MCCs, (CSD refcodes: UROXAL[50] and UROXAM[51]).

Another term that has been used to describe MCCs is '*hydrogen bond complex*'. Hoogsteen prepared such MCCs to provide evidence for the existence of purine-pyrimidine base pairs in DNA. The MCC between 9-methyladenine and 1-methylthymine[52] exhibits what is now known as a Hoogsteen base pair. The crystal structure is sustained by 2-point hydrogen bonds (N-H···O and N-H···N) as shown in Figure 5. It was later determined by Margaret Etter that this Hoogsteen base pair is persistent even in the presence of a third competing coformer by solid-state grinding.[53]

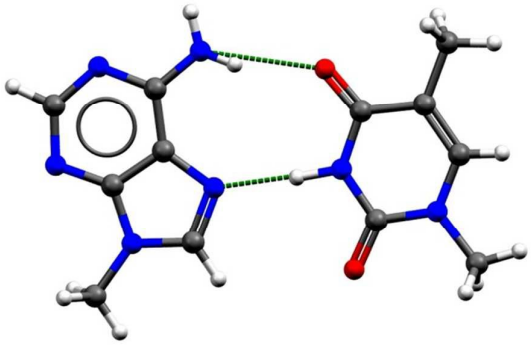


Figure 5. The Hoogsteen base pair observed in the MCC of 9-methyl adenine and 1-methyl thymine is sustained by N-H···O and N-H···N hydrogen bonds.

The term cocrystal was not popularized until the 1990's, due in large part to Etter, who extensively studied hydrogen bonds as design elements for the preparation of multi-component crystals. Her research contributions to the field of cocrystal design include concepts that are still used today for determining the propensity for hydrogen bond interactions.[54] Nevertheless, despite increasing use of the term cocrystal in the crystal engineering field, some researchers have coined different terms. For example, Pekker et al. reported '*heteromolecular crystals*' of fullerene and cubane in 2005.[55]

In summary, ICCs have been known as *acid salts, molecular compound, complex salt, additional complexes, metal salt complexes and adduct*. MCCs have been termed *molecular organic compounds, organic molecular compounds, addition compounds, mixed crystals, complexes, hydrogen bonded complexes and heteromolecular crystals*.

Design of Pharmaceutical Cocrystals

The design and synthesis of new cocrystals may appear to be established given that thousands of cocrystals have been synthesized. However, the complexity of most drug molecules requires an understanding of intermolecular interactions in a competitive hydrogen bond environment, i.e. crystal engineering. In this section, we address how crystal engineering has been applied to cocrystal design.

Crystal Engineering - Supramolecular Chemistry in the Solid State

The term crystal engineering can be traced back to 1955 and Pepinsky.[8] His ideas were subsequently implemented by Schmidt's group to control organic solid-state photochemical reactions.[56] Crystal engineering further evolved in the 1980's largely thanks to Desiraju.[57] Today, crystal engineering has evolved to encompass a broad range of chemical species ranging from drug molecules (especially in the context of cocrystals) to transition metal clusters or cations (especially in the context of coordination networks[58]). A unifying theme that cuts across chemical types is that crystal structures are treated as if they are sustained by a series of repeating supramolecular interactions. The first step in a crystal engineering experiment is therefore to understand the interactions that sustain and direct crystal packing. Etter developed a set of empirical rules to determine the propensity for hydrogen bonding given various donor/acceptor combinations. Etter's rules included the following: the best proton donor will hydrogen bond to the best proton acceptor; six membered ring intramolecular hydrogen bonds are favourable.[59] Etter's rules are applicable to cocrystals and are particularly useful when there are multiple functional groups capable of hydrogen bonding. Etter also pioneered the use of graph set theory to describe hydrogen bonded motifs in crystals.[60] However, this type of analysis has been superseded by supramolecular synthons, which are functional group specific.[61]

Cocrystals and Supramolecular Synthons

There are two main types of supramolecular synthons: supramolecular homosynthons between the same complementary functional groups (e.g. carboxylic acid dimers); supramolecular heterosynthons between different but complementary functional groups (Figure 6).[62] Supramolecular heterosynthons are of particular relevance to cocrystal design since, if the functional groups of a supramolecular heterosynthon are in different coformers, they can be the driving force for cocrystal formation. Carboxylic acid-amide,[63] carboxylic acid-aromatic nitrogen,[64] alcohol-aromatic nitrogen,[65] and alcohol-amine[66] supramolecular synthons have all been widely studied in this context.

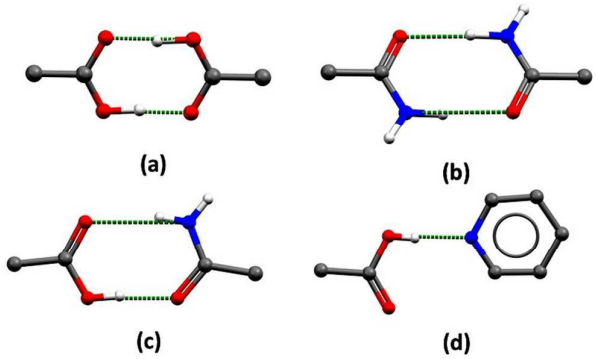


Figure 6. Supramolecular homosynthons (a) carboxylic acid homosynthon exist as dimer (b) amide homosynthon exist as dimer; supramolecular heterosynthons (c) carboxylic acid-amide heterosynthon (d) carboxylic acid-pyridine heterosynthon.

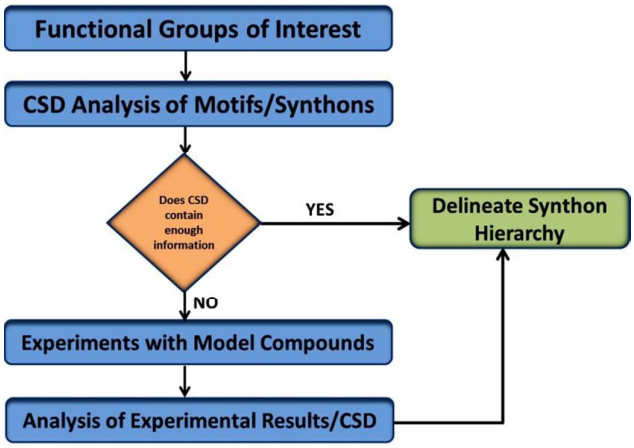
During 2003-2004 four pharmaceutical cocrystal papers were published by three groups emphasizing the key role that crystal engineering can play in cocrystal design. Indeed, the first two words in each of these papers were "crystal engineering".[63f, 67, 62, 39] Indeed, it was these four articles that spurred the development and publication of the precursor[1] to this review. In a sense, these papers could be called the beginning of the modern era of cocrystals. Drug molecules typically contain multiple hydrogen bond donor and acceptor groups and so they are ideally suited to the formation of cocrystals. This creates a challenge to crystal engineers since understanding the hierarchy of these functional groups in the presence of other functional groups is key to controlling not just the stoichiometry of cocrystals, but also their existence.

Addressing this matter is not usually as simple as it may sound. For example, carboxylic acids would be considered to be better hydrogen bond donors than phenols based upon pK_a. However, this is not necessarily the case as we[68] and Aakeröy[69] have reported. Further, although the CSD contains > 700,000 entries and continues to grow rapidly, this does not mean that the CSD provides statistically valid hit lists to address even relatively simple permutations of donors and acceptors. Therefore, systematic supramolecular synthon hierarchy studies remain an important aspect of crystal engineering and cocrystal design. Molecular surface electrostatic potentials and density functional theory calculations (DFT) are also useful tools to support cocrystal design. Another approach to predict cocrystal formation, initially reported by Galek et al.[70] utilized the CSD to generate a statistical analysis of hydrogen bond propensity between drug molecule and coformer.

Hierarchy of Supramolecular Synthons

Several research groups have published studies that delineate donor/acceptor hierarchies involving one or more of the following moieties: carboxylic acids, carboxylates, amides, aromatic nitrogens, alcohols, phenols, cyano groups, cyanooximes. One of our studies addressed the hierarchy of supramolecular synthons between carboxylic acids and aromatic nitrogens in the presence of phenols.[71] Interestingly, both carboxylic acid-aromatic nitrogen and phenol-aromatic nitrogen supramolecular heterosynthons were encountered. This observation suggests that carboxylic acid and phenol groups are competitive with respect to forming supramolecular heterosynthons with aromatic nitrogen atoms. Aakeröy and co-workers also examined hydrogen bond hierarchy between carboxylic acids, phenols and basic nitrogen atoms.[69] Two nitrogen atoms with different basicity were exploited to assess interactions. Electrostatic surface potential calculations indicated that phenolic -OH moieties would be preferred to carboxylic acid moieties. Indeed, carboxylic acids consistently formed supramolecular heterosynthons with the second best basic nitrogen.

In another of our hierarchy studies we used ICCs as a vehicle to examine the propensity for chloride anions to interact with carboxylic acids vs. phenols.[68] Crystal structures and DFT/lattice energy calculations suggest that phenol to chloride anion interactions persist over carboxylic acid to chloride anion interactions. Supramolecular synthon hierarchy of alcohols vs. aromatic nitrogen atoms in the presence of a cyano moiety[72], hydrogen bonds between carboxylates and weakly acidic hydroxyl moieties in cocrystals of zwitterions[73] and phenols to the most basic acceptor in the presence of cyanooxime have also been addressed.[74] The above hierarchy studies are consistent with Etter's "best hydrogen bond donor to best acceptor" guideline. These studies have collectively provided insight into donor/acceptor hierarchy and it is likely that they can be generally applied to cocrystal design. However, many drug molecules fall outside the realm of current studies and the information archived in the Cambridge Structural Database, CSD,[75] requiring that new hierarchy studies to be conducted. A flowchart that details a general process for delineation of supramolecular synthon hierarchy is presented in Scheme 3.



Scheme 3. A general approach to delineate synthon hierarchy among various functional groups, copyright

Advances in Pharmaceutical Cocrystal Development Since 2004

The surge of interest in pharmaceutical cocrystals within the past decade has been driven by their potential utility as alternative drug substances with improved physicochemical properties. However, developing a drug substance into a drug product is not a trivial task. In general, the development of a pharmaceutical cocrystal as the active ingredient in a drug product can be separated into eight stages (Scheme 4).

Stage 1: Design + Coformer selection

Selection of a library of complementary coformers for a particular drug molecule is a critical aspect of cocrystal design and screening. A suitable coformer in the context of pharmaceutical cocrystals must be inherently safe enough for use in a drug product. The Priority-based Assessment of Food Additives (PAFA) database contains chemical and toxicological information for ca. 2,000 substances, including those with the Generally Recognized As Safe (GRAS) designation,[76] which can be directly added to food. Including an additional 1,000 substances that are considered safe food additives, there are ca. 3,000 compounds that constitute the Everything Added to Food in the United States (EAFUS) database. The selection of a library of coformers (typically 40-50) that are likely to form cocrystals for a given API based upon supramolecular compatibility is the first step in discovery of a pharmaceutical cocrystal. Other approaches that have been used for library development include the following: Fabian's method[77] (based upon shape and polarity of coformer with respect to API);

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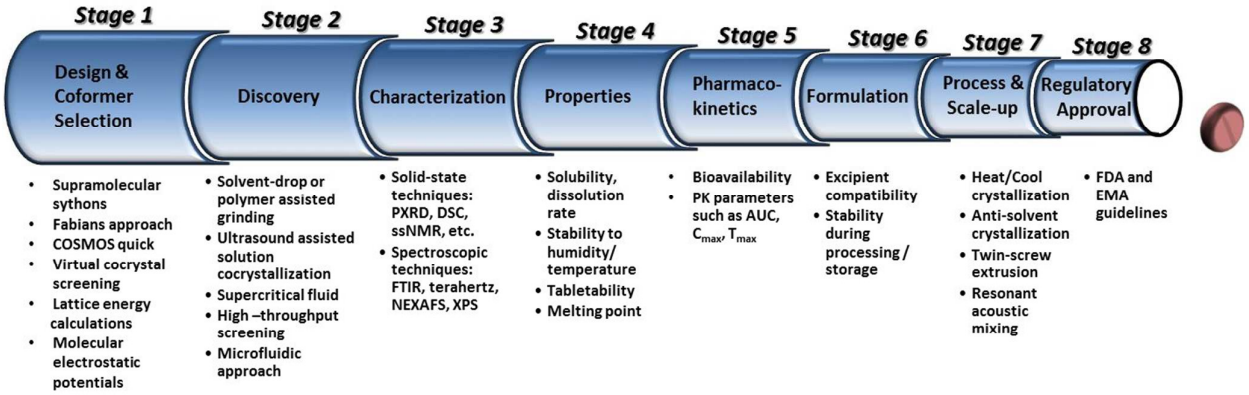


Scheme 4. Illustration of various states and advances at each stage along the drug development pathway of pharmaceutical cocrystals

lattice energy calculations;[78] virtual cocrystal screening (based upon molecular electrostatic potential surfaces (MEPS));[79] the conductor-like screening model for real solvents (COSMO-RS).[80] Each approach has its merits and could be used independently or coupled with others.

Stage 2: Discovery

Once a library of coformers has been selected, then the next stage is discovery. Traditional methods used to discover cocrystals include slow solvent evaporation, slurry mediated transformation and mechanical grinding (both neat and solvent-drop or liquid assisted).[81] More recently, polymer assisted grinding has been reported as an alternative to liquid assisted grinding to improve the rate of formation of cocrystals.[82] Other methods that are known to facilitate the formation of cocrystals include ultrasound assisted solution cocrystallization,[83] high-throughput screening,[84] microfluidic approach[85] and supercritical fluid technologies.[86] Thermal and microscopic methods have been also utilized for identification of new cocrystals. Berry et al.[87] demonstrated the use of hot stage microscopy to identify cocrystal phases of nicotinamide with seven API's. Computational approaches have advanced to the stage where stable cocrystals can be predicted in advance of being prepared experimentally. However, this does not mean that they can be easily obtained through traditional methods. Alternative techniques such as heteronuclear seeding have proven successful at the generation of such an elusive MCC, that of caffeine-benzoic acid.[88] In short, comprehensive screening including multiple techniques should be conducted to enable the discovery of new cocrystals. It is perhaps appropriate to paraphrase McCrone's statement concerning polymorphism[89] and assert that the number of cocrystals that will ultimately be discovered will only be proportional to the amount of time and money devoted to researching them.

Stage 3: Characterization

The primary techniques used to characterize novel cocrystals are those used generally for crystal forms including powder X-ray diffraction (PXRD), single-crystal X-ray diffraction (SCXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), infrared and Raman spectroscopies and solid-state nuclear magnetic resonance (ssNMR). SCXRD confirms composition but single crystals are not necessarily always available from the discovery stage. In such situations, structure solution from microcrystalline powder samples or advanced spectroscopic techniques has been demonstrated to be effective for cocrystals. For example, Lapidus et al.[90] determined crystal structures of 10 cocrystals from high-resolution synchrotron X-ray powder diffraction. Spectroscopic methods have also been applied to identify the cocrystal phase during the discovery. Desiraju identified MCCs sustained by amide dimers from diagnostic N-H···O bands in their IR spectra.[91] Raman spectroscopy has also been used to study cocrystals, including their formation during high-throughput slurry screening and to distinguish between a cocrystal and a physical mixture in formulated tablets.[92] Vogt et al.[93] demonstrated that ssNMR can be effective for the characterization of cocrystals by diagnosing hydrogen bonding and local conformational changes by ^{1}H-^{1}H, ^{1}H-^{13}C and ^{19}F-^{13}C coupling. Maruyoshi et al.[94] identified COOH···N_{arom} and CH_{arom}···O=C interactions in indomethacin-nicotinamide by using 2D ^{1}H double quantum and ^{14}N-^{1}H and ^{1}H-^{13}C heteronuclear magic angle spinning**.** Terahertz time-domain-spectroscopy has also been used to distinguish between chiral and racemic MCCs of malic acid and tartaric acid with

theophylline.[95] Near-edge X-ray absorption fine structure (NEXAFS) and X-ray photoelectron spectroscopy (XPS) were applied to differentiate between a salt and a cocrystal.[96]

Stage 4: Properties

A major motivation for the development of new solid forms of drug molecules is to improve those physicochemical properties that are of critical relevance to their performance as drug substances. These include aqueous solubility/dissolution rate and physical stability. Currently, there are >100 studies of cocrystals that have demonstrated improved solubility and/or dissolution rates and this subject.[9] Improved physical stability, chemical stability and manufacturability *via* cocrystallization have also been addressed. Anhydrous caffeine and theophylline readily convert to their respective hydrated forms. Jones' research group[97] prepared MCCs of caffeine and theophylline with oxalic acid and they were found to exhibit superior physical stability vs. the anhydrous crystal forms when exposed to accelerated stability tests (40 °C/75% RH). Vitamin D_3 cocrystals have also been studied in the context of chemical stability.[98] Vitamin D_3 is widely used in the food and nutraceutical industries but is chemically unstable because it is susceptible to topochemical reaction. MCCs of vitamin D_3 with cholesterol and cholestanol sustained by O-H···O-H supramolecular synthons were subjected to accelerated stability testing for 6 months. The assay value of vitamin D_3 decreased to 4.4% under these conditions whereas the MCCs afforded 97.6% and 96.6% assay values, respectively.

MCCs containing paracetamol and oxalic acid, theophylline, naphthalene and phenazine were pressed into tablets and subjected to mechanical stress. The MCCs were found to exhibit greater tensile strength than paracetamol.[99] The formulation of drug substances generally requires that the melting point is high enough to avoid plastic deformation. In a recent patent application from UCB Pharma an ICC of (2S)-2-2[(4S)-4-(2,2-difluorovinyl)-2-oxopyrrolidinyl]butanamide with $MgCl_2$ and H_2O (2:1:4 stoichiometry) was claimed with a melting point ca. 50 °C higher than that of the pure API.[100]

Stage 5: Pharmacokinetics

A recent review by Shan et al.[101] addressed the effect of cocrystallization upon API pharmacokinetics (PK). 64 cocrystals representing 21 API's afforded 76 PK studies. 80% of the APIs are classified class II (low solubility, high permeability) according to the Biopharmaceutics Classification System (BCS).[102] This is unsurprising given that improving solubility has motivated the study of pharmaceutical cocrystals. Analysis of the PK results suggests that solubility enhancements generally result in increases in area under the curve (AUC). The impact of cocrystals upon AUC can be significant, ranging from ca. 10.2-fold decrease to ca. 28.4-fold increase. C_{max} changes ranging from a 4-fold decrease to a 44-fold increase have been observed. Most cocrystals, however, were found to exhibit less significant changes in AUC and C_{max}.

Variations in PK after dosing different drug substances can affect the safety, efficacy and clinical performance of a drug product. Further, if the application for the API is fast onset of pain relief, then the ability to manipulate specific PK parameters becomes critical. For instance, to develop an API for acute pain relief, the time required to reach the effective concentration must be short. Weyna et al.[103] illustrated how meloxicam, an NSAID indicated for rheumatoid arthritis and postoperative pain, is impacted by cocrystallization. Meloxicam is a BCS class II API with a 4-5 hour T_{max}. MCCs of meloxicam were synthesized and PK studies in rats revealed an earlier onset of action, suggesting that a T_{max} of < 30 min is possible for some of the studied MCCs.

Stage 6: Formulation

Before a cocrystal can be introduced into a drug product it is necessary to formulate the cocrystal. That cocrystals are typically sustained by hydrogen bonds means that their stability in the presence of excipients which also contain hydrogen bonding groups becomes a risk. Remenar et al.[104] and Alhalaweh et al.[105] highlighted the use of excipients to alter the rate of dissolution and capture the maximum potential of celecoxib-nicotinamide and indomethacin-saccharin MCCs, respectively. Huang and Rodriguez-Hornedo[106] manipulated the micellar solubilisation and stability of cocrystal components in solution. Abourahma et al.[107] studied the robustness of theophylline *p*-hydroxybenzoic acid in the presence of additives during solvent-drop grinding experiments. Their results indicate that the cocrystal is robust in the presence of additives that contain carboxylic acid, amide and phenol functional groups but not in the presence of acetamide. Arora et al.[108] recently demonstrated that the carbamazepine-nicotinamide MCC can be formed in a formulated tablet, a phase change attributed to release of lattice water from an excipient (dibasic calcium phosphate dihydrate).

A pharmaceutical cocrystal sustained by halogen bonds was recently reported by Baldrighi et al.[109] The commonly used preservative 3-iodo-2-propynyl-N-butylcarbamate exhibits unfavourable manufacturing properties, including a low melting point and a tendency of particles to stick and clump together. Four cocrystals were prepared and SCXRD experiments revealed that three of the cocrystals are sustained by halogen bonds involving pyridyl moieties. The fourth cocrystal is an ICC of $CaCl_2$. Melting points were observed to increase in a manner that correlates with the coformer. The clumping tendency of 3-iodo-2-propynyl-N-butylcarbamate was improved, especially in the case of the ICC.

Given that formulation of cocrystals is a necessary stage in drug development, it is likely that studies addressing formulation issues will increase in frequency.

Stage 7: Process and Scale-up

The traditional solution methods (solvent evaporation/slurry) used for cocrystal discovery can present challenges for large-scale manufacturing since we are dealing with at least a ternary phase diagram (TPD). Indeed, cocrystallization from

solution could even be viewed as counterintuitive since this is the preferred approach to purify single component molecular compounds, in general, and APIs, in particular. However, if a cocrystal is thermodynamically favoured vs. single component crystals and the TPD is well delineated, then solution crystallisation is suitable to process cocrystals. For example, by understanding the TPD, Sheikh et al.[110] prepared carbamazepine-nicotinamide with >90% yield in a 1 L vessel.

It is also possible that cocrystallization can address problems associated with purification of APIs. A kinase inhibitor in development at Sanofi forms unstable solvates. Approaches such as chromatography, adsorption of impurities and multiple crystallizations afforded the API but with only ca. 90% purity. A purity of 99.1% was achieved using a process that involved cocrystallization of the API with benzoic acid. The process was successfully transferred to plant scale, affording a 10 kg batch size.[111] Myerson's research group has also used cocrystallization for purification of an API. By complexing an impurity in amoxicillin/amino acid solutions they improved the purity of amoxicillin trihydrate.[112] Cocrystallization has also been used to separate stereoisomers. Khan et al.[113] demonstrated selective separation of quinidine from its stereoisomer by forming MCCs with methylparaben. The authors attribute the separation to methylparaben serving as a *molecular hook* which sustains O-H···N supramolecular heterosynthons with only one isomer of quinidine as shown in Figure 7.

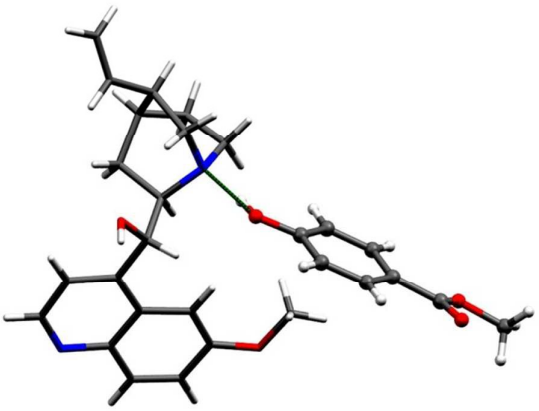


Figure 7. Illustration of O-H···N intermolecular hydrogen bond as seen in quinidine-methylparaben MCC.

In a study by Hickey et al.[114] the authors reported cocrystal scale-up in 30-gram scale by cooling from alcoholic solution The challenge for solution crystallization is the likely incongruent solubilities of molecular components. Thus, the less soluble compound in solution tends to supersaturate and crystallize first. Rodriguez-Hornedo and her research group addressed this issue through reaction crystallization by focusing upon the kinetics of cocrystallization and analysis of stability domains of cocrystals in solution.[115, 106]

A commonly used and eco-friendly method to prepare cocrystals at lab-scale is solid-state grinding (mechanochemistry). The main challenges with this method are high mechanical stress and the difficulty in achieving a homogeneous mix for larger scale processes. Alternatives to grinding include twin-screw extrusion (AMG517-sorbic acid[116]) and resonant acoustic mixing (carbamazepine-nicotinamide[117]). Resonant acoustic mixing can enable preparation of volumes greater than 200 L and requires the addition of only small amounts of solvent during mixing. Synthesis of such quantities does, however, often require slurrying to obtain the desired cocrystal in high purity. Other methods used for cocrystal synthesis include super critical fluid technology[86], spray drying[118] and a continuous oscillatory baffled crystallizer.[119] Such cocrystallization methods facilitated by process analytical technology tools (PAT) are growing and could enable development of large-scale manufacturing of cocrystals.

Stage 8: Regulatory approval

The ultimate step in developing a new drug is achieving regulatory approval. However, it should be noted that intellectual property protection will have supported an investment decision at some point during development. Within the past decade there have been numerous composition of matter patents granted for cocrystals on the premise that their cocrystals satisfy the three primary criteria for issuing a patent: 1) novelty (cocrystal is a new composition of matter), 2) non-obviousness/inventiveness (the physicochemical properties and pharmacokinetic properties are difficult to predict with any degree of certainty) and utility (the drug substance has pharmacological activity and/or improved performance vs. the corresponding single component drug substance). The pharmaceutical cocrystal patent landscape has been reviewed by Almarsson, Peterson and Zaworotko.[120]

In 2011 the FDA released draft guidance for industry on the subject of pharmaceutical cocrystals. Within that guidance, a cocrystal was considered to be a dissociable "API-excipient" molecular complex, a drug product intermediate, and not a new API. This distinction is important because an intermediate in a drug development process is treated very differently than a different API. To gain product approval, the FDA also required the applicant to address two matters:

- The API and excipient must completely dissociate prior to reaching the pharmacologically active site.
- The API and excipient are in neutral states and do not interact by ionic bonds. Use of the ΔpK_a rule was suggested as a way to satisfy the second criterion.

In response to the FDA guidance, a perspective article was published in 2012.[18] To summarize, the authors opined that cocrystals should not be treated any differently than salts as the difference between a cocrystal and salt depends only upon the position of a proton that can be temperature dependent.[121] Pharmaceutical companies responded directly to the FDA with consensus that cocrystals should be treated as salts. That there are marketed drug substances that are considered by many to be cocrystals lends support to this argument. Caffeine citrate,[122] sodium valproate-valproic acid

in Depakote®[123] and escitalopram oxalate with oxalic acid[124] are three such examples. The ICC of escitalopram oxalate oxalic acid is shown in Figure 8.

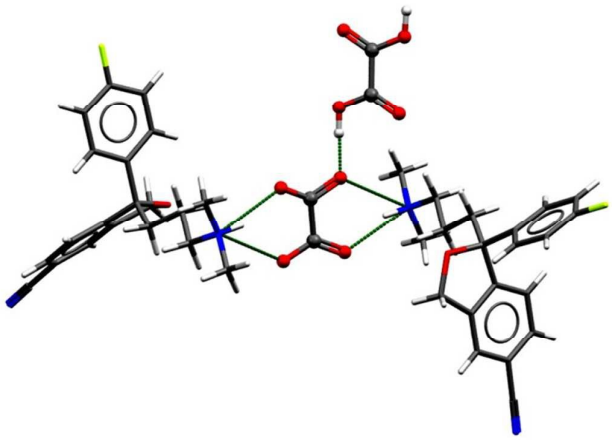


Figure 8. Observation of dioxalate anion and oxalic acid in the same crystal structure sustained by O-H···O interactions in the marketed drug; Escitalopram oxalate-oxalic acid ICC. A water molecule is removed for clarity.

The path to commercialization of a pharmaceutical cocrystal in the United States remains unclear with respect to regulatory approval. Interestingly, the European Medicines Agency (EMA), which reviews and approves products in Europe, published a reflection paper summarizing their position on the subject of pharmaceutical cocrystals.[125] Currently, the EMA considers cocrystals to be homogeneous crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ion pairing. Other salient matters raised by the EMA reflection paper on cocrystals include:

- Cocrystals are considered eligible for generic drug product applications in the same way as salts, solvates and amorphous solids would be.
- Cocrystals are not considered as New Active Substances (NAS) unless they demonstrate different safety and efficacy profiles.
- Cocrystals and salts share many conceptual similarities and therefore also similar principles for documentation should be applied.

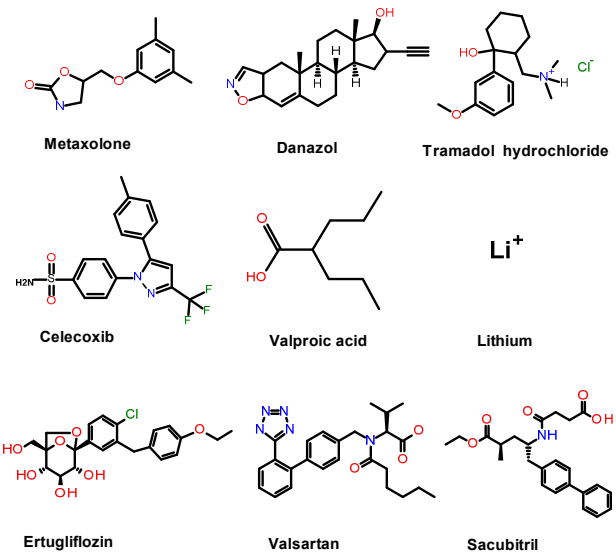
Despite the very different positions taken by the FDA and EMA with respect to pharmaceutical cocrystals, that there are position documents from both agencies provides guidance to industry and attests to the growing interest in the use of pharmaceutical cocrystals in drug products.

Pharmaceutical Cocrystal Case Studies

Seven case studies that address different issues in drug development are presented herein. The relevant drug molecules are illustrated in Scheme 5.

Improved bioavailability: Metaxalone

Metaxalone is the API in Skelaxin®, which is indicated for the relief of discomfort associated with musculoskeletal pain.[126] Nuformix has identified MCCs of metaxalone with superior properties that are currently in clinical trials. Metaxalone is a BCS class II drug[127] and its oral bioavailability is greatly influenced by food. Attempts have previously been made to develop alternative crystalline or amorphous forms of metaxalone;[128] however, MCCs of metaxalone show great promise with improved bioavailability in beagle dogs.[129] The oxazolidone moiety in metaxalone was exploited to form MCCs with adipic acid, fumaric acid, succinic acid, maleic acid and salicylic acid. A single dose PK study in beagle dogs was conducted to compare the fumaric and succinic acid MCCs with metaxalone. The greatest plasma concentration (C_{max}) was achieved after dosing the metaxalone fumaric acid MCC (3635 ng/ml). However the time to achieve maximum plasma concentration was the fastest for pure metaxalone. The area under the curve (AUC) for the metaxalone fumaric acid MCC and succinic acid MCCs were 5202 ng.h/ml and 4135 ng.h/ml, respectively, both greater than that of metaxalone.



Scheme 5. Molecular structures of APIs in the seven selected case studies.

Formulation: Danazol

The behaviour of a cocrystal during formulation is largely unknown in the public domain. However, a recent publication by Childs et al.[130] provide insight into a danazol cocrystal formulation. The cocrystallization and formulation of danazol, a synthetic steroid approved for endometriosis[131] was addressed. With its low aqueous solubility (0.0067 mg/mL)[132] limiting its bioavailability, danazol is a BCS class II compound. Danazol is also non-ionisable, making cocrystallization a logical approach for improving solubility and PK performance. A MCC with vanillin was prepared that was sustained by O-H···O and O-H···N interactions (Figure 9). The MCC was subsequently evaluated with a variety of solubilizing agents and precipitation inhibitors to determine their effect upon performance. Intrinsic dissolution studies were conducted

under non-sink conditions at 37 °C in fasted simulated intestinal fluid (FaSSIF) using compressed discs of pure MCC and danazol. During the first 15 minutes, the dissolution rate of the MCC was orders of magnitude greater than danazol although eventually the vanillin concentration was much greater than that of danazol, indicating crystallisation of danazol. In order to reduce or inhibit this effect, solubility studies were conducted using free flowing powder under sink and non-sink conditions. The sink condition powder dissolution study incorporated lactose to aid in the wetting and dispersion of the powder but the solubility advantage of the MCC appeared to be hampered due to transformation to danazol at the surface. The non-sink conditions included two different excipients, a solubilizer (D-α-tocopheryl polyethylene glycol succinate, TPGS) and a crystallization inhibitor (Klucel LF Pharma hydroxypropylcellulose, HPC). The use of TPGS and HPC enabled a 5.5-fold increase in supersaturation vs. that of danazol. Taking into consideration the 10-fold increase in solubility from the MCC and the increase enabled by excipients, the solubility of the formulated MCC is close to the anticipated requirement for a human to absorb the entire 20 mg/kg dose (based upon maximum absorbable dose calculation using a 250 mL volume, 270 minute intestinal transit time and absorption value of 0.05/min). The performance of the MCC vs. danazol was also addressed in Sprague-Dawley rats. A single oral dose (20 mg/kg danazol) of an aqueous suspension containing MCC or danazol plus lactose and PVP was administered and plasma concentrations were monitored. An additional arm of the study determined the effect of formulation (1% TPGS and 2% HPC) on the performance of the MCC and danazol. It was determined that danazol and the MCC perform best when formulated with TPGS and HPC vs. a suspension with lactose and PVP (10% bioavailability vs. 8% for danazol; 100% bioavailability vs. 13% for the MCC). Considering the *in vitro* and *in vivo* data collectively, a positive correlation between the increase in dissolution and increase in absorption of danazol was observed.

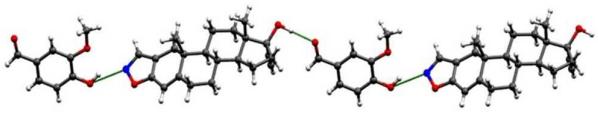


Figure 9. 1D hydrogen bonded chains observed in a danazol-vanillin MCC.

Improved efficacy: Tramadol hydrochloride with Celecoxib

Tramadol is a centrally acting synthetic opioid analgesic used to treat moderate to severe pain.[133] Tramadol has two chiral centres and in the marketed drug is a racemic mixture of the hydrochloride salt. The dosage of tramadol required to treat pain can be as low as 25 mg/day and is increased as needed, potentially building up to a dose of 100 mg every 4 to 6 hours. Unfortunately, such high doses of tramadol can cause severe side effects. Thus there is a need for a low dose formulation. Combination treatments with other COX inhibitors have shown greater efficacy (measured through reductions in pain scores) than with a tramadol paracetamol combination.[134] With a goal to develop an effective combination dosage form, Esteve reported an ICC of tramadol HCl with celecoxib.[135] Celecoxib is a COX-2 inhibitor selective non-steroidal anti-inflammatory drug (NSAID) used to treat osteoarthritis and acute pain.[136] Celecoxib is a BCS class II drug (7 ug/ml in water). Slow dissolution of celecoxib also contributes to its low bioavailability. Variations in the excipients used in the formulation of the ICC provided further enhancement in PK when compared to the marketed drug products Celebrex® and Adolonta® (celecoxib and tramadol HCl, respectively). Type A tablets consisted of Kollidon® VA 64, type B contained Soluplus® and type C contained Kollidon® VA 64 without Sepitrap® 80 & 4000. A single dose PK study involving tablets A, B, C and concomitant administration of celecoxib and tramadol HCl was conducted on beagle dogs. The PK profile revealed that, when compared to Adolonta®, the overall exposure ($AUC_{0-\infty}$) values were reduced for the formulations A, B and C by factors of 0.3, 0.4 and 0.9, respectively. However, similar T_{max} values were observed for all formulations, suggesting that the novel formulations could have a better safety profile vs. Adolonta®. For celecoxib, PK parameters were much more variable with respect to formulation with type C tablets providing the greatest AUC_{0-t} and shortest T_{max}, 37780 ng.h/mL and 2.3 hours, respectively. Celebrex® tablets had a much longer T_{max} (14.5 hours) and reached a maximum concentration of 1049 ng/ml. Therefore, the novel formulations of the ICC achieved higher plasma concentrations and greater exposure to celecoxib vs. Celebrex®. Thus, the ICC offers two key benefits not attainable when the components are administered separately: (1) the safety of tramadol is improved and (2) the bioavailability of celecoxib is increased.

Enhanced stability: Sodium valproate with valproic acid

Valproic acid is an anticonvulsant also used for the treatment of manic episodes associated with bipolar disorder.[137] Valproic acid (Depakene®) is a liquid at room temperature and is therefore difficult to develop as a solid dosage form. Various salts of valproic acids including the sodium, calcium and magnesium salts, were therefore prepared.[138] The use of calcium valproate has been discouraged due to adverse toxicological effects.[139] The magnesium and sodium salts of valproate were found to have similar pharmacological properties to that of valproic acid.[140] Sodium valproate is a solid at room temperature with a substantially high melting point (300 °C) but it is hygroscopic. An alternative solid form, sodium valproate with valproic acid in a 1:1 stoichiometric ratio (sodium valproate: valproic acid) was isolated by cooling an acetone solution of sodium valproate and valproic acid.[123] A stability test conducted at room temperature by exposing samples to 80% RH for 45 mins revealed that sodium valproate gained 17-24% weight whereas sodium divalproate exhibited no appreciable weight gain. Thus, due to its improved stability and comparable PK behaviour, sodium divalproate, marketed as Depakote®, is the leading marketed form of valproic acid. More recently, another solid form containing sodium valproate

was reported.[141] The asymmetric unit of the new form (Figure 10) consists of 3 sodium cations, 3 valproate anions, 1 valproic acid and a water molecule. Additional crystalline forms (characterized by PXRD and FTIR) for the three component ICCs of sodium valproate and valproic acid exist.[142]

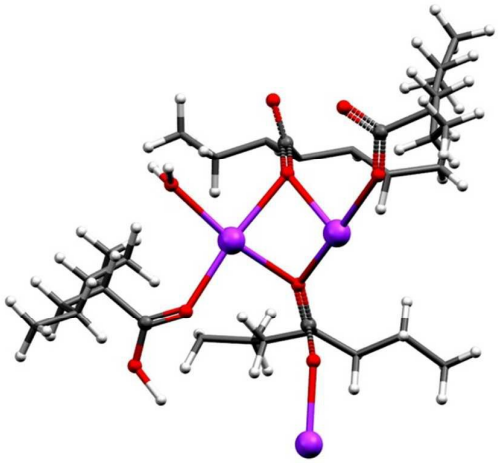


Figure 10. The asymmetric unit of the ICC containing three sodium cations, three valproate anions, one valproic acid and one water molecule. Hydrogen atoms of valproate near the carboxylate groups are removed for clarity.

Improved bioavailability and stability: lithium salts

Lithium salts have a long history in medication; in the mid-1800s lithium was used in the treatment of gout and rheumatic disorders.[143] The modern revival of lithium began in 1949 with Australian scientist John Cade, who demonstrated the clinical importance of lithium for mania.[144] To date, lithium is the only drug indicated for bipolar disorder that can also reduce suicidal tendencies.[145] Unfortunately, more widespread use of lithium is hindered by its low brain bioavailability and physical stability. To address these issues, the Braga research groups have synthesised novel ICCs of lithium.[146] Our research group has reported ICCs based upon lithium-carboxylate[147] and lithium-hydroxyl bonds.[148] Inorganic anions such as chloride, bromide and nitrate afforded ICCs with square grid, diamondoid and ABW topologies. Organic anions tend to exhibit square grid networks with lithium and carboxylates in 1:2 stoichiometric ratios. To determine if these ICCs improve the bioavailability of lithium, a rat PK study was commissioned.[149] Lithium salicylate-proline (LISPRO) was administered as a single oral dose to Sprague-Dawley rats and resulted in 39% and 56% plasma and brain relative bioavailability compared to lithium carbonate (Li_2CO_3). While the relative bioavailabilities were lower for LISPRO compared with the reference, the attenuated plasma and brain concentrations extended the lithium presence for 48 hours post dose. This low and steady concentration could be advantageous as the risk of toxicity associated with high serum levels of lithium is likely to be reduced. To address the poor physical stability of lithium salts an ICC of lithium chloride was prepared.[148] Lithium chloride was found to deliquesce at ca. 11% RH (at room temperature). The ICC of lithium chloride with glucose was found to improve the physical stability of lithium chloride, making it stable past 11% RH although it gained 4% by weight at 30% RH and the ICC is hygroscopic at higher RH. These studies further demonstrate the diversity of ICCs (changing anions and coformers systematically) and their ability to modulate relevant properties such as bioavailability and physical stability.

A pharmaceutical cocrystal in late-stage clinical development: Ertugliflozin pyroglutamic acid

The diabetes drug candidate ertugliflozin belongs to the class of SGLT-2 inhibitors, which promote excretion of glucose into urine and thus aid in the treatment of diabetes. Ertugliflozin reportedly[150] did not exist in a suitable crystal form for development until the cocrystal approach was employed to improve physicochemical properties. L-Pyroglutamic acid (also known as 5-oxo-proline) qualifies as a pharmaceutically acceptable choice given its occurrence in proteins.[16b] The crystal structure of ertugliflozin-L-pyroglutamic acid (1:1) was published in 2014 (Figure 11).[151] This MCC material is the basis of a drug product that is in late-stage (Phase 3) trials. The drug is subject to collaboration between Pfizer, the company that originally developed ertugliflozin, and Merck, which presumably reflects the value of the drug candidate.

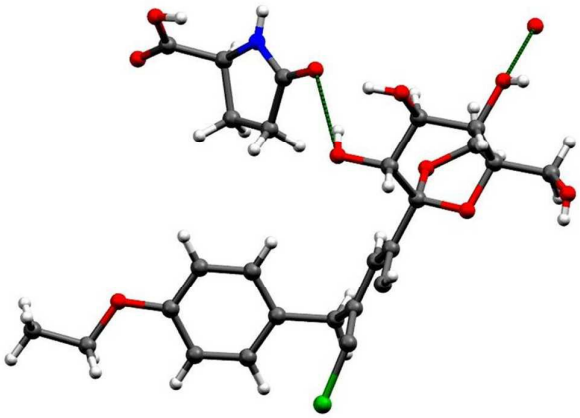


Figure 11. The structure of the MCC Ertugliflozin : L-pyroglutamic acid. The cif file was created from published fractional coordinates and unit cell parameters.[151a]

A pharmaceutical cocrystal approved by the FDA: Entresto™

Thus far there are a limited number of pharmaceutical cocrystals approved by the FDA as drug products. Earlier in 2015, Novartis gained approval for Entresto™ to treat chronic heart failure.[152] There are two ionised drug molecules in Entresto™, in which the drug substance is an ICC comprised of monosodium sacubitril, disodium valsartan and water (CSD Refcode: NAQLAU).[153] Indeed, there have been other examples of cocrystals reported in the literature where the two components are drug molecules or ions, i.e. drug-drug cocrystals.[154] Entresto™ has proven to be a treatment with a significant mortality benefit and has patient tolerance similar to enalapril. That there are demonstrated outcome metrics for this compound speaks to a significant database of clinical experience in patients with this cocrystal. Pending further

approvals from regulatory authorities, Entresto™ has a potential market value of several billion USD. This recent approval of a pharmaceutical cocrystal, occurring after the FDA guidance and EMA reflection paper, may spur increased interest from the pharmaceutical industry in cocrystals as materials for drug products.

Polymorphism in Cocrystals

The propensity for polymorphism in cocrystals has and continues to be a subject of interest and debate. That a cocrystal might be less promiscuous with respect to polymorphism and solvates/hydrates than its parent components can be traced back to a case study involving 550 crystallization experiments involving carbamazepine and saccharin.[114] In 2004, an article published by Almarsson and Zaworotko asserted that '*there may be opportunity to reduce the practical extent of polymorphism of drug compounds specifically by co-crystal formation although there may be exceptions*.'[1] In 2005, the Zaworotko research group further investigated the matter of polymorphism using MCCs derived from components known to be polymorphic (piracetam-gentisic acid and piracetam-*p*-hydroxybenzoic acid).[155] There was no evidence of polymorphism in these cocrystals but the authors concluded that '*the amount of data available concerning the extent of polymorphism in co-crystals remains minimal and that one will not be able to make definitive conclusions even if exhaustive high throughput screenings are conducted.'* In a recent review published by Aitipamula et al.[156] it was reported that only 114 polymorphic cocrystals were then known from amongst the thousands of cocrystals archived in the CSD. However, that these studies did not necessarily focus, if at all, upon polymorphism in cocrystals, means that such data cannot lead to general conclusions. An even more recent CSD analysis led the authors to conclude that '*cocrystals were found to be just as likely of being polymorphic as single component systems'.*[157] The latter is consistent with the position we took in a 2010 review article that presented case studies of polymorphism in cocrystals; *'there remains a dearth of systematic structure and property information on cocrystals. However, at this point there is no reason to believe that pharmaceutical cocrystals will be more or less promiscuous than single component APIs when it comes to crystal form diversity.'*[158] Whereas this is likely to remain the situation in general, it does not preclude the probability that highly promiscuous APIs will form specific cocrystals that are robust and parsimonious with respect to polymorphism.

Conclusions

After a decade of progress we return to reflect upon the question posed by Almarsson and Zaworotko in their review on pharmaceutical cocrystals: 'Do pharmaceutical co-crystals represent a new path to improved medicines?' It seems clear that significant progress has been made in all of stages of drug development (Scheme 4). In particular, pharmaceutical cocrystals can modulate important PK parameters such as T_{max}, C_{max} and AUC for APIs with poor solubility and they therefore offer an innovative approach to improve bioavailability. Pharmaceutical cocrystals can also be considered novel, non-obvious and of utility and as such they can be protected by composition of matter patents. Regulatory bodies have also recognized the potential of cocrystals by publishing guidelines for industry. In short, after 10 years of discovery and development of pharmaceutical cocrystals, many reported improvements in preclinical performance, regulatory attention and intellectual property protection, the answer is a qualified 'yes'. Further, ICCs have recently emerged and offer even greater diversity of composition to modulate physicochemical properties. This is because they are necessarily comprised of at least three components, meaning that two of them can be varied.

Challenges remain. Large-scale synthesis and stability in the presence of excipients are, as with any type of crystal form, unpredictable and must be addressed. Further, diversity is a double-edged sword, since the discovery of hundreds of cocrystals requires time for discovery, property evaluation and selection. Time is a precious and often limiting commodity in pharmaceutical development. It is presumed that, as more drug products based on and enabled by cocrystals are introduced, pharmaceutical cocrystals will gain widespread acceptance and secure an even firmer foothold in drug development.

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