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Review Article

Pharmaceutical Cocrystals: Regulatory and Strategic Aspects, Design and Development

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Abstract

Cocrystal is a concept of the supramolecular chemistry which is gaining the extensive interest of researchers from pharmaceutical and chemical sciences and of drug regulatory agencies. The prominent reason of which is its ability to modify physicochemical properties of active pharmaceutical ingredients. During the development of the pharmaceutical product, formulators have to optimize the physicochemical properties of active pharmaceutical ingredients. Pharmaceutical cocrystals can be employed to improve vital physicochemical characteristics of a drug, including solubility, dissolution, bioavailability and stability of pharmaceutical compounds while maintaining its therapeutic activity. It is advantageous being a green synthesis approach for production of pharmaceutical compounds. The formation polymorphic forms, solvates, hydrates and salts of cocrystals during the synthesis reported in the literature which can be a potential issue in the development of pharmaceutical cocrystals. The approaches like hydrogen bonding rules, solubility parameters, screening through the CSD database or thermodynamic characteristics can be utilized for the rational design of cocrystals and selection of coformers for synthesis multi-component cocrystals. Considering the significance of pharmaceutical cocrystals pharmaceutical regulatory authorities in the United States and Europe issued guidance documents which may be helpful for pharmaceutical product registration in these regions. In this article, we deal with the design, synthesis, strategic aspects and characteristics of cocrystals along perspectives on its regulatory and intellectual property considerations.

Introduction

During the last few years, a plethora of drug products has reached the market. The poorly water-soluble drug candidates are becoming more prevalent in the pharmaceutical industry (Lipinski, 2000).[1] Approximately 40% of the marketed immediate release oral products are categorized as practically insoluble (Takagi2006).[2] It was estimated that 70% and more new chemical entities (NCE) are being identified by combinatorial screening program are poorly water-soluble.[3]

The supramolecular chemistry was defined by Lehn JM, as "chemistry beyond the molecule" is the organization of entities that results from the association of two or more chemical species held together by non-covalent interactions.[4] The selective binding through molecular interactions was depicted by lock and key model of Emil Fischer.[5] The chemical systems under study are classified into two major categories organized self-assembly in the solid state as crystal engineering and molecular recognition in solution which is commonly referred to as supramolecular chemistry.[6]

The concept of crystal engineering in solid state chemistry was introduced by Pepinsky R, in 1955.[7] A work on photochemical reactions was reported by Schmidt (1971), provides learning for crystal engineering.[8] Desiraju G, defined crystal engineering as "the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties".[9] Pioneering work in prediction and interpretations of non-covalent bonding interaction using a Cambridge structural database (CSD) was carried out by Etter and Desiraju.[10,11]

Physicochemical properties of a drug govern solubility and dissolution profile which is indicative of drug bioavailability, which in turn can affect the biological activity of the drug. Solubility, dissolution, stability, micromeritics and mechanical characteristics of an active pharmaceutical ingredient (API) are common barriers in pharmaceutical drug development. The aqueous solubility of an API is a vital physicochemical parameter determining various aspects related to the formulation and delivery of a drug. During discovery and development stages the solubility data is required at various stages. It is used to characterize drug through structure-activity relationship, for assessment of

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absorption, distribution, metabolism and elimination constraints and to develop a formulation for early preclinical and clinical screening.[1] Formulation plays a major role in overcoming problems associated with drug delivery and it determines the biological availability of an API in terms the rate and extent of absorption from the gut.[3]

Physical modification often aims to enlarge the particle surface area, improve solubility and/or wetting of the powder and improving the stability of an API. The poorly water-soluble drugs can be formulated as amorphous forms, crystalline solid formulations, or by lipid formulations to improve their solubility. Crystal engineering through cocrystallization is a promising approach to address problems associated with the drug. Although definitions of cocrystals are available in the literature, it is still a topic of debate.[12,13] Broadly cocrystals can be defined as crystalline materials consist of two or more different components (or commonly called multi-component crystals). For the pharmaceutical cocrystals, one component is an API and other components are called as crystals former or conformers. Cocrystals have gained considerable interest in pharmaceutical research due to its ability to improve physicochemical characteristics of an API. Several papers have been published in the recent past which gives an overview of cocrystals[14-17] and some which show its clinical relevance.[18] Design strategies, synthesis procedures, cocrystal characteristics with an emphasis on its applications, regulatory, strategic and patentability considerations are discussed in this review. The process for cocrystal development is depicted in Figure 1.

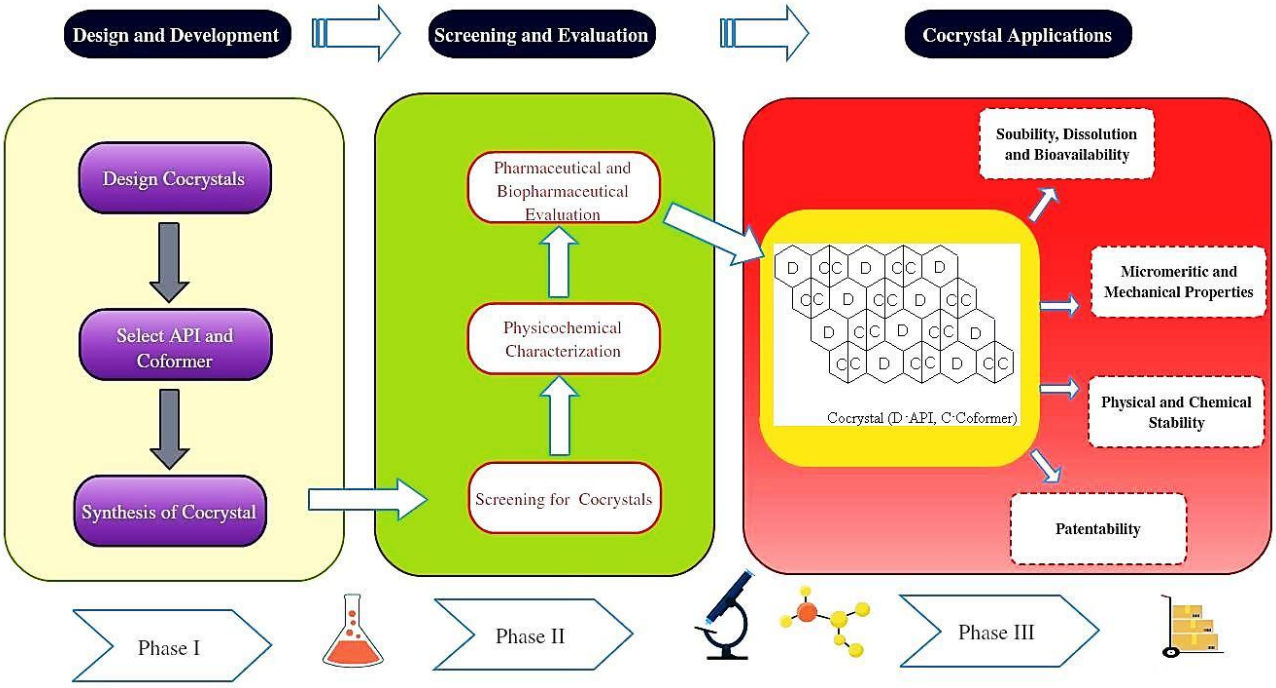

Figure 1. Process for cocrystal development, screening and applications

Regulatory and Strategic Aspects of Cocrystals

The formulation of cocrystals through crystal engineering has emerged as a promising approach in the formulation of poorly water soluble compounds. It has become a topic interest in the pharmaceutical industry, which can be traced from regulatory documents published by United States food and drug administration (USFDA) and European Medicine Agency (EMA).

USFDA defines cocrystals under 'Regulatory Classification of Pharmaceutical Co-Crystals' as, *Crystalline materials composed of two or more molecules within the same crystal lattice'*. The alteration of desired pharmaceutical properties viz. solid state properties, solution behavior, and dissolution, etc. is possible through crystal engineering of the drug with coformers without modifying the chemical structure of drug molecule. According to this guidance an API and excipients which are having Δpka (pKa (base) - pKa (acid)) ≥1 then there will be the formation of salts because there will be complete proton transfer which results in absolute ionization, which is an ionic reaction. If Δpka <1, then there will be negligible proton transfer and cocrystals are formed which is a result of the non-ionic interaction. Any of numerous compounds that result from partial or complete replacement of the acid hydrogen of an acid by a metal or a radical forming metal: an ionic or electrovalent crystalline compound are referred as salt. *Per se* the current regulatory scheme, different salt forms of the same API are considered as dissimilar active ingredients. Polymorphs are different crystalline forms of the same chemical substance. This may include hydration or solvation products (which is also known as pseudo-polymorphs) and amorphous forms. *Per se* the current regulatory scheme, unlike

polymorphic forms of the same compound is considered the same active moiety.[19]

The possible effects of adopting to this definition will be drug products with cocrystals will be considered as drug product intermediates, applications to FDA claiming to contain cocrystals will be required to prove the extent of proton transfer, the cocrystal must be revealed to dissociate in vivo prior it reaches active site (much ambiguous in case of topical formulations), the API cocrystal by definition seems to be physical mixture of API and excipients.[20] In FDA's view the cocrystal considered as a drug product intermediate that is expected to enhance pharmaceutical product performance, such as enhanced solubility and/or dissolution rate. It is less problematic to show dissociation of API and excipient before its pharmacological action. Brittain HG, has suggested that dilutions of cocrystal solutions can demonstrate a dissociation of cocrystal components[15] while recent study reported pH-dependent dissociation of cocrystal.[21] Another aspect that USFDA determines a cocrystal should be considered as a drug product intermediate and not as a new API. Consideration of cocrystals as drug product intermediate could lead variation in pharmaceutical as well as therapeutic properties which need to be analyzed case by case basis with different conformers. This aspect is may of great importance as it can open the door to the use of cocrystals without the need for the vast amount of clinical trials necessary as it considered as it drug product intermediate and not a drug. It may be as an opportunity to use cocrystals of APIs for new chemical entities and generic product development. If no clinical trials are required it may reduce the time taken by pharmaceutically improved cocrystals of the active chemical moiety with GRAS listed coformers to enter into the market, obliviously also cutting expenditure on pharmaceutical development.

Reflection paper released by the European Medicines agency has given subdivision of solid state materials based on the internal structure. It defined cocrystals as, homogeneous (single phase) crystalline structures made up of two or more components in a specific stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts).[22] Further, it discussed the regulatory implications of cocrystals understanding and other solid forms of API which may be of great value to the point of view to get a generic drug status for such forms as cocrystals are formed by non-covalent bonding. Cocrystals are not considered as a new drug if the applicant is able to demonstrate its safety and efficacy equivalent to parent API . An applicant can have the opportunity to claim for consideration of cocrystals with same approval or market authorization as given to an API. The applicability of good manufacturing practices (GMP) for active substances or finished pharmaceutical products where cocrystals are produced *in situ* during process shall be taken into consideration. It is possible to present a single active substance master file for cocrystals and API. Safety and quality of coformers must be ensured as for a given active substance there are so many possible coformers are available. It may be possible to form cocrystals of more than one therapeutic moiety in such cases proof showing on the careful rationalization of the dose ratio cocrystals components and its influence on the biopharmaceutical parameters and therapeutics effect shall be required. The regulatory status of Pharmaceutical cocrystals in the US and Europe is represented in Table 1.

Table 1. Regulatory status of Pharmaceutical cocrystals in US and Europe

Cocrystal Parameters	USFDA[19]	EMA[22]
Definition	Solids that are crystalline materials composed of two or more molecules in the same crystal lattice.	Homogenous (single phase) 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 ionic bonds (as with salts).
Regulatory status	Drug product intermediate (DPI), not regarded as a new API	New Active Substance status dependent upon demonstration of efficacy and/or safety
Sameness with parent API	Yes	Dependent upon demonstration of efficacy and/or safety
Coformers	Neutral guest compound (excipient)	Non-active components/Regeants (excipient)
Regulatory Consideration	Similar to Polymorph of same API	Similar to salts of same API
Chemical interactions	Nonionic	Nonionic
US-Drug master files (DMF)/EMA-Active substance master file (ASMF)	Not feasible being DPI	Can be filed
Applicable Good manufacturing practice (GMP) regulations/guide	cGMP for drug product	Part II of EU GMP Guide (active substances) and ICH Q7 and in rare cases Part I of EU GMP Guide (finished drug product)

Physical Forms of Solids Associated with Cocrystals

The chemical structure of an API in solution and its ability to interact with its targets determines its intrinsic activity. Depending upon a chemical nature and three-dimensional arrangement of the molecule, a compound can exist in single component systems known as the

amorphous state or in several different crystalline states, which are polymorphic forms of the parent chemical moiety. The crystalline, multi-component systems which include a complex with ion or molecules are salts, hydrates, solvates, or cocrystals.[23] The solid forms may exist in multiple crystalline forms as shown in Figure 2 and Figure 3. The identification of particular solid form is important with the view of the formulation of an optimal drug delivery system which will be associated desired biopharmaceutical parameters and it also decides its value as intellectual property.

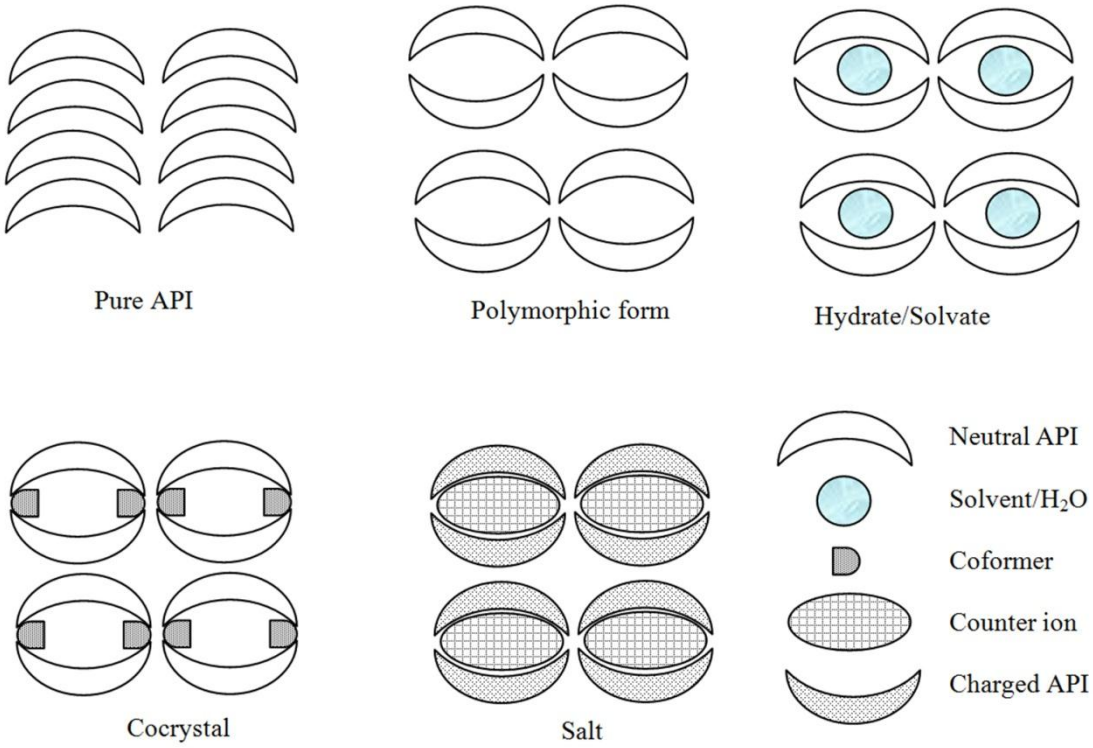

Figure 2. Schematics of salt, cocrystal and polymorphs

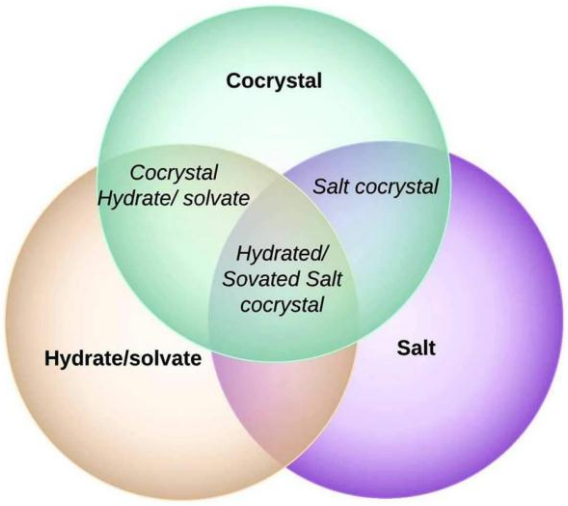

Figure 3. Multiple physical forms of solid with physical state continuum

Polymorphism and Cocrystals

Pharmaceutical polymorphic solids of the same chemical compound having a distinct internal solid-state structure and, have the ability of to crystallize as more than one distinct crystal species. Therefore, polymorphs possess different physical and chemical characteristics, including packing, thermodynamic, melting point, density, hardness, crystal shape, optical and electrical properties, spectroscopic properties, kinetic parameters, interfacial, and mechanical properties.[24,25] Polymorphs offer a unique opportunity to study the structure–property relationships of the same compound formed in different supramolecular environments. Investigating the polymorphic behavior of an API is a critical part of the drug development process.[26] Other crystal variations can be encountered where the crystal structure of the substance is defined by still other unit cells, where these unit cells vary in their elemental composition through the inclusion of one or more molecules of solvent which referred as solvatomorphism.[27] Polymorphism may result in differences in the physicochemical properties of the API and difference in these properties may result in a drug product variable bioequivalence, and hence in a product that is not considered as a therapeutically equivalent to the innovator product. This is because polymorphism can greatly influence pharmaceutical properties, such as solubility, bioavailability, stability, hygroscopicity, etc., and the economic significance of novel polymorphs as intellectual property. Therefore, in

the context of the ANDA review, careful attention should be given to the effect that polymorphism may have on a generic drug product equivalent as required by FDA with the innovator brand.[28]

During the search for and prevalence of Polymorphs and Cocrystals, about 90% of the screened compounds found to exist in multiple solid crystalline and noncrystalline forms. There were half of the compounds amongst screened compounds were polymorphic. The percentage of compounds that exist in multiple solid forms was the same for salts and non-salts (91%). Non-salts have been more frequently polymorphic than were salts (55% compared to 39%). Salts were found to exist as hydrates more frequently than did non-salts (48% compared to 30%). The tendency of forming cocrystal was found to be 61%.[29]

Polymorphism in cocrystals is being reported in the literature has significantly increased in the recent past. A detailed review of polymorphic cocrystals has been published by Aitipamula S, et al. which provides a classification of cocrystal polymorphs. Cocrystal polymorphs are classified as Synthon polymorphs, conformational polymorphs, packing polymorphs, tautomeric polymorphs, polymorphic cocrystal hydrates and solvates, ternary cocrystals polymorphs.[30] A summary of representative cocrystals polymorphs reported in the various literature is presented in Table 2. It was demonstrated by Aitipamula S, et al that generation of polymorphic forms of cocrystals is possible by the selection of solvents or mixture of solvents.[36] In an another study reported by same research group metastable polymorphs, EA-GA-II and III eventually convert to stable polymorphic form-I upon solid state grinding which enables the control of polymorphic form. EA-GA and Caffeine-GA cocrystals have relevance to the context of a combination of drugs.[37] The effect of milling experiments was demonstrated by Limwikrant, et al which suggests that polymorphic transformations could occur during processing of raw materials.[33] Stable polymorphic cocrystals of antitubercular drug Isoniazid (INH) tested as per ICH stability guidelines were reported by Swapna B.et al. Interestingly polymorphic cocrystals of INH with fumaric acid and hydroxyl benzoic acid had shown lower solubility and dissolution rate which is in contrast ability of cocrystals to enhance pharmaceutical characteristics of API.[43] Although polymorphic cocrystals of furosemide with nicotinamide and iso-nicotinamide improve solubility of API but their stability is in question as demonstrated through slurry experiment.[46] Interesting chiral and achiral polymorphic cocrystals of tryptamine with hydrocinnamic acid were reported by Koshima, et al.[52] In an attempt to search for stable cocrystals of hydrate-forming compounds, anhydrous caffeine–oxalic acid cocrystals form was reported to be thermodynamically stable in an aqueous environment. It confirmed that hydrate of caffeine can be converted to anhydrous form improving its physical stability.[55] The fact reported that cocrystals could be formed during the phase transition of the low-temperature stable polymorph of furosemide if coformer is available in close contact with the transforming component suggesting increased mass transfer rate can trigger cocrystal formation.[56]

In the summary polymorphic transformation of cocrystals has the ability to alter various pharmaceutical aspects related to an API, including but not limited to solubility, dissolution, bioavailability, and stability. It was also reported in the literature that processing parameters could lead to polymorphic transformations of cocrystals while some metastable polymorphic forms are converted to the stable form after storage. A careful and cautious selection of the specific form of cocrystals of API shall be required to maintain the quality of a pharmaceutical product within specified standards.

Salt-Cocrystal Continuum

A salt contains a single ionic compound, but multiple ions. Formation of salts of organic compounds involves the proton transfer from an acid to a base.[29] If any pair of molecules are ionized, and disordered solid form where the crystallography does not unambiguously locate the protons are called as salt.[57] It is generally accepted that reaction of an acid with a base will be expected to form a salt. Although as discussed above the USFDA guidance defined that API and excipients which are having $\Delta pka \geq 1$ then there will be the formation of salts and if $\Delta pka < 1$, then there will be cocrystals are formed. There are papers reporting the cases that which deviate from this definition in the guidance document.[58-61] At the same time, one shall consider the fact reported by Child SL, et al. that prediction power of cocrystal formation is poor when Δpka is 0 to 3. When the ΔpKa is negative, it correctly predicts the cocrystals formation. In this range, complexes between acids and bases can still form, although they can be salts or cocrystals or can contain shared protons or mixed ionization situation that cannot be assigned to any of these categories. In a study with theophylline complexes, sixteen salts, two cocrystals, and two mixed ionization states were observed, where the transition ΔpKa was ranging between 0 to 2.5.[60] Another case reported in literature for 5-fluorocytosine only salts were obtained with fumaric, maleic, and oxalic carboxylic acids, in water solutions, although the systems were exhibiting ΔpKa values of 0.23, 1.35, and 2.01, respectively.[61] Studies of crystal structures revealed that whether a proton is transferred from one component to another in a crystalline solid is dependent on the crystalline environment and cannot be predicted from ΔpKa values alone. Thus, it is reasonable to consider crystalline salts and cocrystals as species that exist at either end of a continuum of multicomponent crystal structures. At the salt end proton transfer is complete, and at the cocrystal end, proton transfer is absent. When a pair of ionizable components crystallizes, both the ΔpKa value and the crystalline environment, determine the extent of proton transfer and therefore the placement of the structure on the continuum.[27]

Table 2. Pharmaceutical Cocrystals and its Polymorphic forms

Sr. No.	API	Coformer	Polymorphs/hydrate	Stable Polymorph	Melting Point (ºC)	Phase Transition Temp.(ºC)	Ref.
1	Carbamazepine (CBZ)	Nicotinamide (NCT)	CBZ-NCT-I and II,	CBZ-NCT-I	158º	83–90º	Seefeldt, K. et al.[31]
		Nicotinamide	PN-CBZ-NCT and CBZ-NCT I	CBZ-NCT I	--	124-128º	William W. et al.[32]
		Saccharin (SAC)	CBZ-SAC I and II	CBZ-SAC I	173.8º	168º	William W. et al.[32]
		Malonic acid	Form A,B and C	Form A	192º	140-160º	Limwrilant W. et al.[33]
		Isonicotinamide (INA)	CBZ-INA I and II	CBZ-INA I	--	--	Horst J.H.T. et al.[34]
2	5-methoxy sulfadiazine (SMD)	Homosynthon	SMD-I and II	Isomeric forms	---	---	Caira, M. R.[35]
3	Ethenzamide (EA)	Gentisic acid (GNA)	EA-GNA-I,II,III	EA-GNA-I,	100.65º	98.5º	Aitipamula S., et al.[36]
		Ethylmalonic acid (EMA)	EA-EMA I and II	EA-EMA II	85.60º	77º	Aitipamula S., et al.[37]
		Saccharin	EA-SAC I and II	EA-SAC I	122.50º	--	Aitipamula S., et al.[38]
		3,5-Dinitro benzoic acid (DNBA)	EA-DNBA I and II, Solvates	EA-DNBA I	148.73º	--	Aitipamula S., et al.[39]
4	Caffeine	Gallic Acid (GA)	Caffeine–GA form I and II	*	--	--	Trask A.V, et al.[40]
		Trifluoroacetic Acid	Caffeine–TA I and II	Caffeine–TA I	--	--	Trask A.V, et al.[41]
5	Nalidixic acid	Pyrogallol	Hemihydrate	--	--	--	Gangavaram, S. et al.[42]
		Phloroglucinol	Hydrate	--	--	--	
6	Isoniazid (INH)	Vanillic acid (VLA)	INH-VLA 1,2 and 3	INH-VLA2	153.2º	142–144° (Form1)	Swapna, B. et al.[43]
		Ferulic acid (FRA)	INH-FRA 1,2 and 3	INH-FRA1	168.4º	--	
		Caffeic acid (CFA)	INH-CFA 1,2 and 3	INH-CFA2	153.1º	129º (Form-1)	
		Hydroxybenzoic acid (HBA)	INH-HBA I and II	INH-HBA II	123.0º	--	Aitipamula S.[44]
		Fumaric acid (FA)	INH-FA I and II	INH-FA I	169.4º	--	
7	Furosemide (FS)	Nicotinamide	FS-NCT forms I–V and hydrate [45] FS-NIC 1 and 2, [46]	FS-NCT-I > III > II > V > IV	154.9º (FS-NCT-I)	--	Ueto T. et al[45] Goud N.R. et al.[46]
		Isonicotinamide (INIC)	FUROS–INIC I and II	--	--	--	
8	Sulfacetamide (SACT)	Acetamide (ACT)	SACT–ACT I and II	SACT–ACT I	106.5º	79º	Goud N.R. et al.[47]
9	Sulfadimidine (SD)	4-Amino salicylic Acid (ASA)	SD:4-ASA I and II	SD: 4-ASA-I	175º	--	Grossjohan C.et al.[48]
10	Celecoxib	δ-valerolactam	Form –I, II and III	Form –I	106.0º	71.0º (Form-III)	Bolla G. et al.[49]
11	Temozolamide (TMZ)	4,4′-bipyridine-N,N′-dioxide(BPNO)	TMZ-BPNO I, II, and III	TMZ-BPNO I	--	--	Babu N.J. et al.[50]
12	Piroxicam	4-hydroxy benzoic acid	Form 1 and 2	Tautomeric forms	--	--	Childs S.L. et al.[51]
13	Tryptamine	Hydrocinnamic Acid	Chiral and achiral forms	Chiral form	--	--	Koshima H. et al.[52]
14	Chlorzoxazone	2,4-dihydroxybenzoic acid	Form 1 and 2	Form 2	177.4º	--	Child S.L. et al.[53]
15	p-Coumaric Acid	Nicotinamide	Form 1, 2 and 3	Form 1	154.0º	--	Bevill M.J. et al.[54]

*When **caffeine** and **GA** are ground together in the absence of solvent, cocrystal form I predominantly results. Similarly, the addition of four drops from a pipette of a nonpolar solvent, such as n-hexane, cyclohexane, or heptane also produces form I. Conversely, upon addition of four drops of a more polar solvent, including chloroform, dichloromethane, acetonitrile, and water, the grinding experiment results in predominantly form II.

In a study to synthesize the multicomponent solid forms involving pyridine included both salts and cocrystals, while 4-dimethylaminopyridine (DMAP) crystallized exclusively as a salt, in agreement with the differences in

the pKa values. During a crystallization of pyridine with carboxylic acids interestingly *cis-trans* isomers, maleic acid and fumaric acid resulted in same cocrystals solid form while DMAP formed a salt with these carboxylic acids. A similar case was demonstrated when terephthalic acid was used as coformer to form a multicomponent crystal with pyridine, resulted in cocrystal formation and with DAMP, a salt was formed.[57] In a study reporting cocrystals of fluoroquinolone salts, ciprofloxacin hydrochloride hydrate (CiHCl·1.34H2O) and 4-hydroxybenzoic acid (4-BHA) cocrystals lead to lower thermodynamic solubility and dissolution rate due to dense crystal packing. (S, S)-moxifloxacin hydrochloride hemihydrate (MoHCl·0.5H2O) formed cocrystals with 4-BHA but interestingly it improved solubility and dissolution as compared to parent salt which was contradictory to the behavior of CiHCl-4BHA cocrystals.[62] Hybrid salt-cocrystals solvate case was disclosed by Jacob A. et al. where the tertiary amine is protonated forming a charge-assisted hydrogen-bond ($N^{+}\cdots OH^{-}$) to the *p*-Coumaric acid (*p*-CA^{-}) anion and the quinoline nitrogen forms a hydrogen-bond (N···OH) to the neutral *p*-Coumaric acid molecule. The methanol molecules occupy voids as the system does not allow for the easy escape of the solvent molecules.[63]

It should be noted that as discussed above different salts of same compound are considered to be chemical moiety other than original compounds in regulatory aspect. It makes necessary to clarify for a multi-component crystal, component is either coformer which lead to cocrystals formation or complementary ion forming a salt. The experimental evidences produced here brings us to conclusion that USFDA's guidance document-'Regulatory Classification of Pharmaceutical Co-Crystals' is still topic of debate in the field.

Cocrystal Design and Coformer Selection

Hydrogen-Bonding Rules

One can design cocrystals based on empirical understanding hydrogen-bonds patterns can be determined using guidelines provided by Etter M.C[10] and Donohue J.[64] These rules are (a) all acidic hydrogen present in a molecule will be utilized in hydrogen bonding in the crystal structure of that compound, (b) all good acceptors will be used in hydrogen-bonding when there hydrogen-bond donors are available, (c) Preferentially hydrogen bonds are formed between the best hydrogen-bond donor and the best hydrogen-bond acceptor. The important systems which can form hydrogen bonds are N-H…N, N-H…C1, N-H…O, O-H…N, O-H…O, where dash indicates covalent and dots indicates non-covalent contacts with acceptor atom.[62]

Cambridge Structural Database (CSD)

The understanding intermolecular interaction is necessary for syntheses of supramolecular synthons. The study of hydrogen bond patterns in crystalline solids provide information about promising synthons that can be designed.[65] It is possible to determine the frequency of hydrogen-bond motifs and other interactions using CSD. CSD is the repository for small-molecule organic and metal-organic crystal structures developed in 1965 which is continuously updated after extensive validation and verification by experts. CSD provides a way for 'the systematic analysis of large numbers of related structures is a powerful research tool, capable of output results that could not be obtained by any other method'.[66] It is based predominantly on shape and polarity of cocrystal formers.[67] CSD provides the information common functional groups that engage in supramolecular synthon formation.[68] H-bond donor and acceptor counts showed no obvious statistical relationship. A potential drawback of the model is that it was trained on cocrystal observations in the CSD database, ignoring potential failures in realistic cocrystal screenings.[69]

Hansen Solubility Parameter (HSP)

Mohammad MA, et al reported the use of Hansen solubility parameter (HSP) for prediction of cocrystal formation.[70] The concept was originally proposed for predicting polymer solubility in paints by Hansen C.M. The basis of these so-called HSPs is that the total energy of vaporization of a liquid comprising of several individual component forces. These forces arise from (atomic) dispersion forces, (molecular) hydrogen bonding (electron exchange) and (molecular) permanent dipole–permanent dipole forces.[71] The difference in total solubility parameters (Δδt) of the API and conformer is calculated for the purpose of prediction of cocrystal formation. Δδt values less than $7MP^{0.5}$ indicates likely cocrystal may be formed and values greater than 10 $MP^{0.5}$ fewer chances of cocrystal formation. The result reported in the study indicates limited application of this approach in cocrystal prediction as only a few coformer formed cocrystals although $\Delta\delta_t$ was less than $7MP^{0.5}$.[68]

Cocrystal Design Based On Thermodynamic Characteristics

COSMO-RS (Conductor-like Screening Model for Real Solvents) is a universal theory to envisage the thermodynamic equilibrium properties of liquids, which was originally developed by Andreas Klamt.[72,73] The statistical physics of interacting molecular surface segments is the basis for COSMO-RS thermodynamics. The polar and H-bond interaction energies are quantified based on the surface screening charge densities, which result from a quantum chemical continuum solvation calculation. Because of its ability to treat mixtures at variable temperatures and to calculate accurate solvation energies using first principles, it has become very useful in the chemical engineering and in areas of physical and medicinal chemistry. It is possible to compute a virtually supercooled liquid mixture of the cocrystallization components and to compute the excess enthalpy (*H*ex) of stoichiometric *m*:*n* mixtures created out of the pure components A and B: by using following equation

$$H\text{ex} = (H\text{AB} - xm\ H\ pure,\ \text{A} - xn\ H\ pure,\ \text{B}) \text{ ------ } Eqn.1$$

*H*pure and *H*AB represent the molar enthalpies in the pure reference state and in the *m*:*n* mixture, with mole fractions *xm* = *m*/(*m* + *n*) and *xn*= *n*/(*m* + *n*). *H*ex contains all enthalpy contributions and is not limited to H-bonding interactions, although those may be separated from the overall enthalpy by utilizing COSMO*therm* software.[72] Virtual screening using COSMO-RS approach can be useful for hydrates and for coformer selection.[74,75]

Perlovich G.L. reported methodology for analysis thermodynamic functions for cocrystals formation. Prediction of cocrystal melting points by correlating it with conformer (CF) melting parameter and by using API melting parameters was attempted in the reported study, although good correlations were not obtained between the melting points and the descriptors. Thermodynamic functions of 79 cocrystals have been obtained through SciFinder and analyzed by the diagram method. Gibbs energy of cocrystal formation with the stoichiometric ratio (API)n(CF)m ΔG^{298}_{f} (CC), and was calculated by following equations-

$$\Delta G^{298}_{sub}(PM)=X_1 \Delta G^{298}_{sub}(API) + X_2 \Delta G^{298}_{sub}(CF)\text{----- Eqn.2}$$

where for (API)n(CF)m: X1 = n/(n + m) and X2 = m/(n + m). ΔG^{298}_{f} (PM), ΔG^{298}_{sub}(API) and ΔG^{298}_{sub}(CF) are the Gibbs energies of sublimation of the physical mixture, API, and CF, respectively.

$$\Delta G^{298}_{f}(PM)= \Delta G^{298}_{sub}(CC) - \Delta G^{298}_{sub}(PM)\text{------- Eqn.3}$$

and enthalpy(API)n(CF)m ΔH^{298}_{f} (CC) was calculated by using following equations-

$$\Delta H^{298}_{sub}(PM)=X_1 \Delta H^{298}_{sub}(API) + X_2 \Delta H^{298}_{sub}(CF)\text{------Eqn.4}$$

ΔH^{298}_{f} (PM), ΔH^{298}_{sub}(API) and ΔH^{298}_{sub}(CF) are the enthalpies of the physical mixture, API and CF, respectively.

$$\Delta H^{298}_{f}(PM)= \Delta H^{298}_{sub}(CC) - \Delta H^{298}_{sub}(PM)\text{ -------Eqn.5}$$

It was further reported that most of the cocrystals belong to the ΔG^{0}_{f}(CC) value interval between 5 and −10 kJ mol^{-1}, i.e. the region of thermodynamically stable cocrystals. This fact signifies that stabilization of the cocrystal crystal lattice compared to that of the physical mixture leads to ordering of molecules (entropy reduction).[76]

Cocrystal Synthesis

Cocrystals can be prepared by solid or liquid based methods. The only summary of cocrystals synthesis methods is presented below; interested readers may see review by Qiao N. et al[17] for details of various methods.

Solid-Based Methods

Solid-based methods include solid state grinding, melt extrusion, and melt crystallization. Solid state grinding or neat grinding is consists of mixing of API with coformers in a specific stoichiometric ratio and grinding them either manually or mechanically.[77] In hot melt extrusion (HME) stoichiometric blends of API and conformers are passed at controlled temperatures with determined residence time. Advantages of these methods are solvent-free process, continuous and scalable green techniques.[78]

Liquid-based methods

Liquid-based methods comprise of liquid assisted grinding (LAG), solvent evaporation, solution crystallization, slurry screening, reaction crystallization, cooling crystallization, spray drying, supercritical fluid assisted crystallization, planetary milling, and ultrasound assisted crystallization.[17]

Solution crystallization offers advantages of particle size and crystal habit control, as well as possible chemical purification and ability to prepare new cocrystal via solution growth.[38] It was demonstrated that use solvent mixtures is advantageous in increasing chances of cocrystal formation and further it also possible to thermodynamically suppress the solvate formation by a competing reaction in solution mediated cocrystallization trials.[79] Friscic T, et al. devised a parameter η, which is the ratio of solvent volume to sample weight. It can be utilized differentiate conditions that distinguish LAG from slurry sonication or slurrying additionally they reported that LAG would require lower amounts of solvent than Sonic Slurry experiments.[80]

Cocrystals Ability to Improve Physicochemical Characteristics of API

Alteration of Thermal Characteristics

The melting point of a substance is a fundamental physicochemical property, which is the temperature at which solid state substance is converted to a liquid state at atmospheric pressure. The melting point can be determined using a capillary method, Kofler bench or differential scanning calorimetry (DSC). DSC data also provide information about enthalpy.

The factors which affect this physical constant are the arrangement of molecules within the crystal lattice, molecular symmetry, intermolecular interactions, conformational degrees of freedom for a molecule, and composition, etc.[81,82] The melting point of cocrystal was either less than or greater than or between the melting points of components of cocrystal. It was demonstrated for carbamazepine cocrystals experimental solubility's shows poor correlation with ideal solubility values derived from enthalpy and melting temperature of crystals.[83] The relation between solubility curves and melting properties has been established by Nordström FL, et al. for predicting melting temperatures from solubility.[84]

Improvement in Micromeritics and Mechanical Properties

The micromeritics and mechanical properties of pharmaceuticals are of utmost importance in the pharmaceutical industry. The understanding of their flow properties is of critical significance in operations such as blending of raw materials, tablet compression, capsule

filling, transport, and in scale-up operations. Crystal engineering provides an opportunity for improvement of physical properties especially flow property of pharmaceutical powders.

The etravirine and nicotinamide co-crystal with better flow properties, showing better physical stability, was disclosed by Sansone M, et al.[85] It was demonstrated by Alhalaweh A, et al. that spray drying could produce cocrystal material with smaller surface energies as compared to milled theophylline cocrystal and ability to control particle physicochemical properties.[86] The mechanical properties of paracetamol were improved by cocrystallization with theophylline.[87] The improvement of physicochemical nature of ezetimibe was achieved by its cocrystallization with salicylic acid and benzoic acid.[88] It was demonstrated that Lamivudine: zidovudine cocrystal monohydrate improves flow properties as compared to component mixture.[89]

Enhancement of Solubility, Dissolution, and Bioavailability

The solubility improvement of drugs remains one of the trickiest challenges in formulation and development.[90] The drug dissolution is rate-limiting step in the absorption of a drug from the gastrointestinal tract. The poor aqueous solubility of drug potentially limits bioavailability of drug.[91] The greater understanding of a dissolution and absorption behavior of drugs with low aqueous solubility is necessary to effectively formulate them into bioavailable pharmaceutical drug products.

Several reports have shown that cocrystal is an emerging approach to address low drug solubility poor dissolution and bioavailability. Brittain HG, et al. developed intravenous water soluble cocrystal formulation of aspirin-theanine which has improved stability and bioactivity as compared previously available composition.[92] Buschman HH, et al. had identified drug-drug cocrystals of tramadol and paracetamol which improve pharmacokinetics and pharmacodynamics of components synergistically.[93] Bethune SJ, et al. had reported cocrystals of pterostilbene (neutraceutical antioxidant compound) with caffeine, carbamazepine, glutaric acid and piperazine as coformers showing improved solubility.[94] Zotepine HCl:Benzoic acid cocrystals were reported to amplify aqueous solubility and dissolution rates by several folds compared with a free base.[95] Solubility and bioavailability of quercetin were reported to improve by more than 10 folds by its cocrystallization with caffeine, caffeine: methanol, iso-nicotinamide, and theobromine as coformers.[96] It was demonstrated that solubility of sildenafil, 6-mercaptopurine and clotrimazole can be potentially increased by cocrystals and salt formation with mono and dicarboxylic acids and amides.[97-100] Bioavailability of 6-mercaptopurine was reported to remarkably enhanced by 168.7% as compared to the parent compound.[100] Prolonged mean resident time (MRT) of its parent compound Fluoxetine HCl forms cocrystals with benzoic acid as a co-former having low solubility and dissolution rate while its cocrystals succinic acid was with more solubility and dissolution rate showing contradictory behavior. The former cocrystal of Fluoxetine HCl with benzoic can be potentially used for slow release.[101] Recent studies with various pharmaceutical compounds with diverse chemical and pharmacological nature which includes myricetin (anticancer flavonol), itraconazole (antifungal), adefovir (antiviral), aceclofenac (nonsteroidal anti-inflammatory) and mirtazapine (antidepressant) reemphasize the solubility advantage of cocrystals exhibiting potential to improve bioavailability.[102-106]

Effect of pH and pKa on eutectic point or transition concentrations cocrystal was shown by Bethune SJ, et al.[107] It was demonstrated how cocrystal solubility of nonionizable API can be influenced by pH, pKa, and coformer concentration through mathematical prediction tools. This study was carried out for cocrystals carbamazepine with salicylic acid and p-aminobenzoic acid coformers, which can be exploited to study the behavior of other API's with acidic and basic nature. The unlike crystal forms of an API possess different solubility and permeability behavior which may alter the bioavailability. The correlation of crystal structure of cocrystals with solubility and permeability needs to be addressed with an exploration into aspects of the Biopharmaceutic Drug Classification system (BCS).[108,109] Cocrystals form of an API expected to enhance the solubility of the pharmaceutical compound as demonstrated in various reports cited above. If cocrystals enhance the solubility of pharmaceutical compounds then BCS class II and class IV compounds can be potentially converted to BCS class I and class III. Such studies addressing with the Biopharmaceutical class of cocrystals of pharmaceutical compounds may be helpful practically get bio-waivers from the FDA minimizing need of human involvement.

Impact on Physical Stability

The sorption of moisture can create a hydrated form or new polymorphic forms of drug which may potentially affect the quality of the drug. The hydrolysis of some drugs due to moisture is well documented in literature.[110,111] It can affect adversely on drug release from formulation, shelf life, handling and transportation of formulations.[26,112]

Cocrystals embodiments of tramadol and paracetamol possess the ability to reduce hygroscopicity of each other.[113] Cocrystal of c-glycoside derivative and l-proline were found to be optimally stable at various temperature conditions during ambient and accelerated stability studies with humidity stress.[114] Almarsson O. et al. disclosed that cocrystals prepared by solid and solution based methods either with or without heating have ability to decrease hygroscopicity of the parent compound.[115] The hygroscopic stability *S*-Oxiracetam was improved by cocrystallization with gallic acid. This enhanced stability was assigned to extended hydrogen-bonded network in cocrystal.[116]

The mechanism for moisture generated cocrystals was established by Jayashankar A. et al which can be advantageously utilized formulation development and predict stability conditions. Amount and rate of water uptake by cocrystal components decides the supersaturation which has its effect on the nucleation and growth rate of cocrystal.[117] Although reports for *in situ* formation of cocrystals during pharmaceutical processing, manufacturing and storage are available,[118-120] likelihood of phase separation and polymorphic transformations in cocrystals during storage shall be the challenge to the researchers working in crystal engineering.

Impact on Chemical Stability

Cocrystallization causes a change in the molecular arrangement in crystal lattice which may modify the chemical stability of the compound. The solubility of niclosamide was improved by theophylline cocrystals but at the expense of reduced stability.[121] The reported stability studies of mefloquine hydrochloride shows no significant differences in stability during storage at intermediate ICH stability conditions.[122] It was reported that propiconazole: oxalic acid cocrystal forms stable cocrystal polymorphic forms during stability studies.[123]

A study by Jayasankar A, et al. which revealed reactant solution composition and identification isothermal invariant points (cocrystal pHmax) are crucial for the stability of cocrystals.[124] The effectiveness of a surfactant to stabilize cocrystals is related to the differential solubilization of cocrystal components (Ks) which also applicable to other processes involving differential affinities of components such as complexation, adsorption, etc.[125] It was reported that solution stability of carbamazepine-cinnamic Acid cocrystal depends upon solubility of coformers while further shown that carbamazepine-nicotinamide cocrystal was unstable in water, addition of ethanol could improve stability.[126,127] These understandings can serve as a guide for the selection of coformers and surfactants to control its solubility and transformation during manufacturing, storage, and evaluation.

Cocrystal Patentability and Evergreening Motivation

Evergreening is an aspect of patents that leads to a patent life cycle management of drug or drug product. It can be done in an artful manner by protecting a large number of inventive aspects over basic invention, by avoiding imminent double patent rejection and extending patent term of the same drug product.[128] Innovators can erect 'picket fences' or families of dozens of patents around single drug molecule evergreening innovator domain retaining market monopoly.[129] Cocrystals are gaining interest in pharmaceutical field as it provides an opportunity for new and useful physical property modifications in API, which is demonstrated through recent research literature.[130,131]

As cocrystals are novel crystal form of an API, they possess particular practical regulatory advantages which have the sound scientific base. It provides a lucrative way for patent portfolio management through provisions under Drug Price Competition and Patent Term Restoration Act 1984 and by multiple patent filing.[132] The unique combination of API and a coformer and unique chemical bonding with stoichiometry distinguishing them from the simple physical mixture satisfying novelty requirements for cocrystals.[133] The relative paucity of patents with the keyword search for "pharmaceutically acceptable cocrystal" could suggest that the field is laden with opportunities for novel cocrystal inventions. The challenges in cocrystal prediction suggest obligation of trial and error experimentation rendering them non-obvious from a general patentability perspective.[134] The focus in both European inventive step approach and American obviousness analysis is ultimately the differences in claimed invention and the prior art. Often the prior art has been an API itself or salt or crystalline form of an API. The bonding combination of an API and conformer can provide a platform for the establishment of inventive step or non-obviousness.[133]

Latest Patents issued for cocrystal agomelatine and metaxalone with carboxylic acids shows improved dissolution characteristics and bioavailability of the pure drug.[135] A co-crystalline form of meloxicam with coformers which includes GRAS listed chemicals and others approved API's has shown to improve the bioavailability of pure meloxicam.[136] These patents further underline the impact of cocrystals as intellectual property and can serve as motivation for research on cocrystallization.

The improvements in micromeritics properties, solubility, dissolution rate, bioavailability and stability of API as discussed earlier offer effective pieces of evidence for utility and industrial application of cocrystals.

Conclusion

The importance of crystal engineering through cocrystallization in pharmaceutical field can be understood by looking at regulatory cocrystal considerations and CSD database growth. On the one hand, cocrystals are unexpectedly formed during processing[118-120] while on the other researchers will require the cautious selection of cocrystal design approach as in some cases, cocrystals are not formed as per predictions which indicate challenges in formulating cocrystals.[137] Cocrystal's ability to flourish desired physicochemical and biopharmaceutical properties of API to the optimal extent open a new landscape to Cocrystals of multiple active ingredients can be formulated as fixed dose combinations for better therapeutic applications. It will stimulate investigation of old API's to see new benefits. There is a need to explore into an understanding of cocrystallization mechanism, in vivo behavior of cocrystal for better therapeutics and other unanswered questions like polymorphic transformation. It is an opportunity to capture for patenting new cocrystal forms of API.

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Ethical Issues
Not applicable.

Conflict of Interest
We declare that there are no potential competing interests related to this manuscript.

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