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Pharmaceutical Cocrystals: Bridging Crystal Engineering and Drug Delivery for Improved Bioavailability

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Abstract

Pharmaceutical cocrystals represent a versatile and effective platform for addressing solubility and formulation challenges in drug development. Pharmaceutical cocrystals are gaining their importance by researchers due to the possibility of altering the physical, chemical and mechanical properties of API without affecting its pharmacological activity. In spite of much work being done in this area, it is still more exploring area because of many newer applications like stability, permeability, taste masking, compressibility, bulk density etc. In this review, cocrystals classification is identified and its types are discussed. Cocrystals are held together by non-covalent interactions such as hydrogen bonding, π–π stacking, and van der Waals forces. The designs for cocrystals formation including Cambridge Structural Database are also discussed. This collection may provide a guidance in developing a new cocrystal which can have a good commercial value in the pharmaceutical industry.

Keywords

Cocrystals, Polymorphs, Solubility enhancement, CSD, Designs of Cocrystals, types of cocrystals.

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INTRODUCTION:

The development of effective oral solid dosage forms remains one of the most significant challenges in pharmaceutical research, primarily due to the unfavorable physicochemical properties of many active pharmaceutical ingredients (APIs)(1). These properties, including poor aqueous solubility, low stability, inadequate flowability, and poor compressibility, can adversely affect drug formulation, manufacturability, and in vivo performance(2). Among these factors, poor aqueous solubility is considered one of the most critical limitations, as it directly influences the dissolution rate of a drug, thereby impacting its oral bioavailability(3). This issue has become increasingly prevalent in modern drug discovery, where a large proportion of newly developed compounds exhibit low solubility characteristics and fall under poorly soluble categories defined by the Biopharmaceutics Classification System(4) In addition to intrinsic physicochemical limitations, the physiological environment of the gastrointestinal (GI) tract further complicates drug absorption. The GI tract exhibits a wide range of pH conditions, varying from highly acidic in the stomach to near-neutral or slightly alkaline in the intestine. These variations significantly influence the solubility and dissolution behavior of orally administered drugs, particularly those that are weakly acidic or basic in nature. Consequently, many drugs display pH-dependent solubility, leading to inconsistent dissolution profiles across different regions of the GI tract. This variability often results in

nonlinear and unpredictable absorption patterns, which can compromise therapeutic efficacy and safety(5,6)

In recent years, pharmaceutical cocrystals have gained recognition as a promising crystal engineering approach to address these challenges. A pharmaceutical cocrystal is a crystalline system composed of an API and one or more pharmaceutically acceptable coformers, combined in a well-defined stoichiometric ratio. The components are held together through non-covalent interactions, including hydrogen bonding. Van der Waals forces, and π-π stacking.

To overcome these limitations, several formulation strategies have been developed to enhance the solubility and bioavailability of poorly water-soluble drugs. These include particle size reduction, solid dispersions, complexation, salt formation, nanoparticles, self-emulsifying drug delivery systems (SEDDS), the use of co-solvents, nanosuspensions, emulsions, and cocrystal formation. Each of these techniques possesses its own advantages and limitations, and the selection of an appropriate approach depends on various factors such as the physicochemical properties of the API, the nature of excipients, the formulation method employed, and the intended dosage form. The challenges associated with poor solubility and pH-dependent behavior have driven the development of various formulation strategies aimed at enhancing drug solubility and bioavailability. These approaches include particle size reduction, solid dispersions, lipid-based formulations, salt formation, and inclusion complexation. However, each of these techniques has its own limitations, such as physical instability, scalability issues, or limited applicability depending on the drug's chemical nature. In recent years, pharmaceutical cocrystallization has emerged as a promising and versatile approach to address these limitations. Pharmaceutical cocrystals are crystalline materials composed of an API and a suitable coformer, typically bonded through non-covalent interactions such as hydrogen bonding. This approach enables the modification of key physicochemical properties, including solubility, dissolution rate, stability, and mechanical characteristics, without altering the pharmacological activity of the drug(7).

The present review aims to explore the role of pharmaceutical cocrystals in modern drug development. Specifically, the objectives are to develop a clear understanding of the concept, principles, and importance of pharmaceutical cocrystals and to examine the various methods employed for the preparation of pharmaceutical cocrystals. To review the characterization techniques commonly used for the identification and analysis of cocrystals and highlight the pharmaceutical relevance and regulatory considerations associated with cocrystal development.

DEFINITION OF COCRYSTAL:

A pharmaceutical cocrystal is a single phase crystalline solid composed of an API and a coformer arranged together in a definite stoichiometric ratio within the same crystal lattice through noncovalent interactions without forming a salt or solvate. These interactions, typically hydrogen bonds or other supramolecular forces, allow modification of the drugs physical properties while retaining its chemical structure and therapeutic activity(8).

GENERAL SCIENTIFIC DEFINITION:

Different groups have proposed definitions for cocrystal. A widely accepted scientific description was introduced during the 2012 Indo-US Bilateral meeting. Defining cocrystals as crystalline materials containing two or more molecular or ionic species in stoichiometric properties that are neither simple salts nor solvates(9).

The USFDA later described crystals as multi component solids containing two or more molecules within the same crystal lattice(10).

SALTS:

Salts are ionic compounds produced when an acid reacts with a base, leading to the transfer of a proton (H+) from the acid to the base. This proton transfer generates a positively charged cation and a negatively charged anion, which then arranged themselves in a stable crystal lattice. Unlike cocrystals, which involve neutral molecules linked mostly through non-covalent interactions, salts are held together by strong ionic forces, giving them characteristics physical properties such as higher melting points and enhanced to solubility in polar solvent(10).

COFORMER:

A coformer is a neutral molecule or in some cases an ionic species that combines with an active pharmaceutical ingredient (API) or another compound to form a cocrystal. It appears in a defined stoichiometric ratio and interacts with the API through non-covalent interactions, such as hydrogen bonding, halogen bonding π-π, stacking, or Vander Waals forces. Importantly, a coformer does not chemically modify the API instead, it stabilizes the crystals structure through intermolecular interactions(10).

HYDRATES:

A hydrate is a crystalline solid in which water molecules are incorporated into a crystal lattice in a fixed, stoichiometric ratio. These water molecules are typically held in place through hydrogen bonding or coordination interactions with the parent compound. The water is an integral part of the crystal structure and not merely surface moisture(10)

CLASSIFICATIONS & TYPES OF COCRYSTALS:

A cocrystal is a solid made by combining an active drug (API) with another safe molecule called a coformer. They bind together through weak bond (like hydrogen bonds) and form a new crystal structure that can improve the drugs properties such as solubility, stability, and bioavailability(11–13).

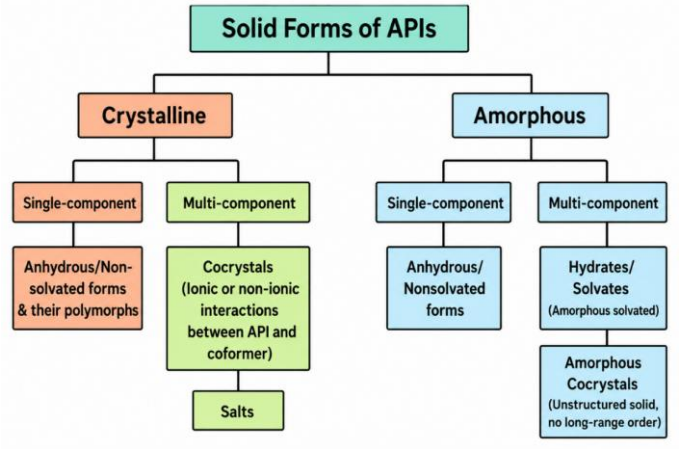

Figure 1: Classification of Solid Forms of API

The following classification has been proposed by the FDA: Cocrystals should be classified within the Agency 's current regulatory framework a dissociable API- Excipient molecular complexes(14,15).

Solid Forms of APIs Definition:

Solid forms of APIs are the different physical and chemical solid-state arrangements in which an active pharmaceutical ingredient exists, influencing solubility, stability, and bioavailability.

Crystalline Forms are solids in which API molecules are arranged in a highly ordered, repeating lattice structure.

Single-component Crystalline Forms contain only one chemical entity (the API).

Anhydrous / Non-solvated Forms: Crystalline API that does not contain solvent or water molecules in the crystal lattice. E.g. Anhydrous caffeine, Anhydrous paracetamol.

Polymorphs: Different crystalline forms of the same API, having the same chemical composition but different crystal structures(16,17). E.g. Ritonavir polymorphs, Carbamazepine polymorphs

Multi-component Crystalline Forms: Crystalline forms consisting of API with one or more additional components. Crystalline solids composed of an API and a neutral coformer bonded by non-ionic or ionic interactions. Eg. Carbamazepine–saccharin cocrystal Caffeine-oxalic acid cocrystal

Salts: Crystalline compounds formed when an API reacts with an acid or base, resulting in ionic bonding. E.g. Metformin hydrochloride Diclofenac sodium

Amorphous Forms: Amorphous forms are solids in which API molecules lack long-range molecular order and exist in a disordered arrangement.

AMORPHOUS FORM:

Single-component Amorphous Forms: Amorphous solids consisting of only the API, without solvent molecules. Anhydrous / Non- solvated Amorphous Forms. E. g. Amorphous indomethacin Amorphous nifedipine

Multi-component Amorphous Forms: Amorphous solids containing API plus other components.

Hydrates / Solvates are amorphous API containing water (hydrate) or solvent molecules (solvate). E.g. Amorphous lactose monohydrate Amorphous ethanol solvate

Amorphous Cocrystals: Amorphous mixtures of API and coformer with no defined crystal structure. E.g. Indomethacin–saccharin, amorphous cocrystals

TYPES OF COCRYSTALS:

Cocrystals are single crystalline materials containing two (or) more components, present into stoichiometric ratio and mainly solids at room temperature various types of cocrystals have been reported by the researchers based on the number of components present in the crystal structure(18,19).

Binary co-crystals:

Binary pharmaceutical cocrystals are single solid forms made of an API and a coformer, designed to improve drug properties without changing its pharmacological effect.

Using strategies like hydrogen-bonding and molecular synthons, suitable coformers can enhance solubility, stability, and dissolution. Studies, including indomethacin saccharin cocrystals, show that specific hydrogen-bond interactions help form stable structures and improve overall drug performance(20,21).

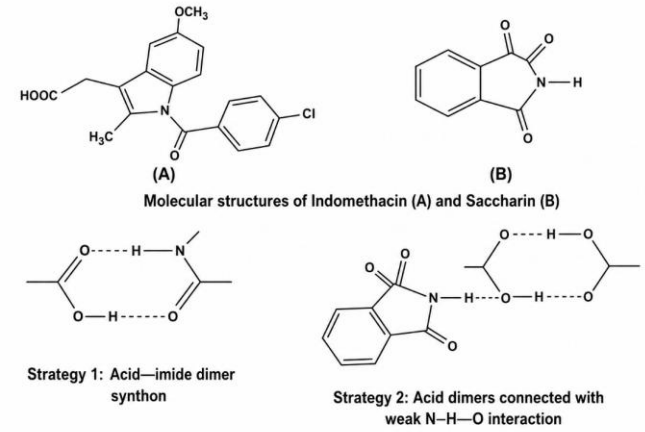

Figure 2: Molecular structures of indomethacin (A), saccharin (B) and strategies involved in the design.

Ternary cocrystal:

Ternary cocrystals are formed by three neutral solid compounds arranged in a single, well- defined crystal structure, usually guided by hydrogen-bond hierarchy. Several studies have successfully created ternary systems, such as those involving is nicotinamide or isoniazid with different acids, showing multiple strong and weak supramolecular interactions. Although challenging to design and isolate, ternary and quaternary cocrystals offer unique structural complexity and valuable potential in crystal engineering(22).

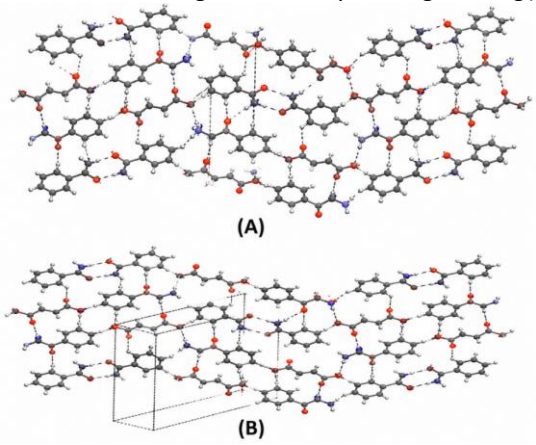

Figure 3(A). Molecular structures of 4-hydroxybenzoic acid and 2,3,5,6-tetramethylpyrazine and (B)supra-molecular homo- and heterosynthons present in the cocrystals.

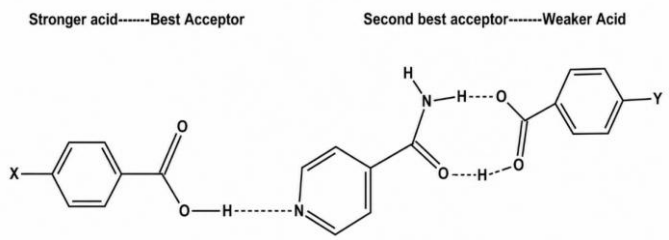

Figure 4. 2-dimensional sheet structure in the crystal structure of isoniazid-nicotinamide-fumaric acid.

Ionic cocrystal:

Ionic cocrystals (ICCs) are multicomponent crystals containing at least one salt and neutral molecules, allowing controlled modification of an API's solid-state properties(23). They often form through strong coordination and hydrogen bonds, as seen in lithium-based ICCs with amino acids, salicylates, or glucose. These structures can improve stability and solubility

and may enhance certain drug(24) and performance aspects, making ICCs a promising but still underexplored class of materials(25,26).

Polymorphic cocrystals:

Polymorphic cocrystals are crystal forms that share the same chemical composition but differ in lattice structure or molecular arrangement(27,28). Their discovery has increased with advances in experimental techniques, and they play an important role in improving pharmaceutical performance(29). Identifying and isolating new polymorphic cocrystals is challenging, as their formation depends.

Synthon polymorphs:

Synthon polymorphs arise when the same components from different primary hydrogen-bonding motifs(30). Their structures vary based on the type of homo- or heterosynthons involved. Studies on cocrystals of 4-hydroxybenzoic acid with tetra methylpyrazine or bipyridine showed that different hydrogen-bond arrangements could generate distinct crystal forms(31).

Molecules capable of multiple hydrogen-bond interactions are especially prone to forming synthon polymorphs(32).

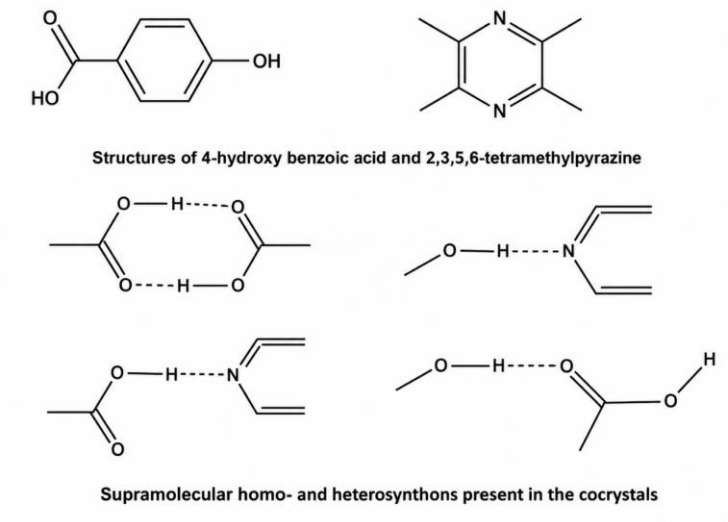

Figure 5: Molecular structures of 4-hydroxybenzoic acid and 2,3,5,6-tetramethylpyrazine and supra-molecular homo- and heterosynthons present in the cocrystals (33).

Tautomeric polymorphs:

Tautomeric polymorphs occur when different tautomer of a compound crystallize into distinct crystal forms due to the dynamic relocation of hydrogen atoms(33). Although rare in cocrystals, this phenomenon has been observed in systems like piroxicam-4- hydroxybenzoic acid, which exhibited multiple supramolecular synthons(34). Depending on the hydrogen-bonding patterns, some polymorphs existed as non-ionized tautomer, while others formed zwitter - ionic structures(35–38).

Packing polymorphism:

Packing polymorphism occurs when polymorphs differ mainly in their three-dimensional crystal packing rather than chemical composition or synthons. It is common in rigid and flexible molecule(39). Examples include cocrystal of benzoic acid bipyridine showed that different hydrogen-bond arrangements can generate distinct crystal forms observed in salicylic acid and picric acid systems, demonstrating how molecules can retain the same interactions yet adopt different overall crystal packing(40,41).

Conformational polymorphs:

Conformational polymorphs arise when molecules adopt different conformations within their crystal structures. Flexible molecules with low-energy conformers are more likely to show this behavior. For example, cocrystals of pimelic acid with 4,4'-bipyridine exhibited conformational polymorphism, where the main differences were in the molecular. conformations rather than overall packing(42). Similar conformational polymorphism has also been reported in cocrystals of ethanzamide with ethylmalonic acid, gentisic acid, and nicotinamide-pimelic acid(41,43).

Polymorphic cocrystals:

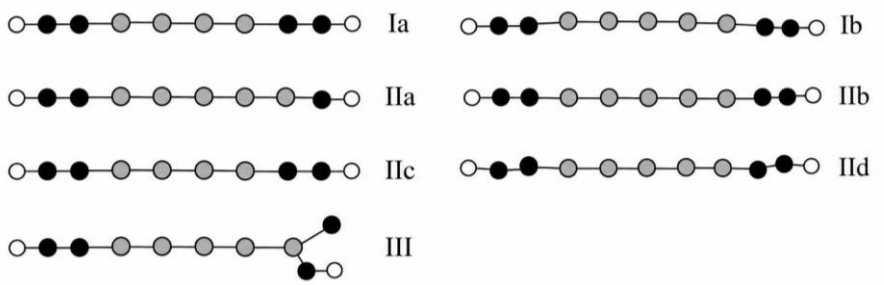

Figure 6: Conformations of the two, four and one independent pimelic acid molecule in the crystal-line forms I, II and III respectively (43).

Polymorphic cocrystal hydrates and solvates occur when the same cocrystal forms different crystal structures depending on the amount or arrangement of water or solvent molecules(44). Although rare, a few examples exist. For instance, the isoniazid- 4-hydroxybenzoic acid cocrystal shows two monohydrate polymorphs with distinct hydrogen-bonding patterns(45).

Similarly, polymorphic hydrate forms of 18-crown-6 with 3,5, dichloropicric acid have been reported, differing mainly in their molecular packing despite having similar overall structures(46)

DESIGNS USED IN COCRYSTALS

Pharmaceutical cocrystals are widely employed to improve key physicochemical properties of drug molecules, including solubility, dissolution rate, bioavailability, and stability, while maintaining their therapeutic activity(47). However, during the synthesis and development of cocrystals, the formation of different solid forms such as polymorphs, solvates, hydrates, and salts has been reported in the literature. The occurrence of these forms can pose significant challenges in the development of pharmaceutical cocrystals due to their potential impact on stability, performance, and reproducibility(48).

Approaches:

1. Hydrogen Bonding Rules
2. Hansen Solubility Parameters
3. Pka Rule
4. Cosmo- Rs (Conductor Like Screening Model For Real Solvents)

1. **HYDROGEN BONDING RULES:**

Hydrogen bonds are directional; that is why it plays a pivotal role in cocrystal design. Design of cocrystals depends on the interaction types, which are primarily noncovalent of multiple component systems within themselves(49).

SUPRAMOLECULAR SYNTHON APPROACHS:

Supramolecular synthon approach in chemistry, which is crucial for designing and preparing cocrystals. A "synthon" "term coined by core in organic chemistry, is defined as a structural unit assembled by intermolecular interactions, such as hydrogen bonding(50). These synthons act as non-covalent "adhesive forces" between molecules. They are categorized into 2 types, they are:

1.Homosynthons- (which are self- complementary)

2. Hetero synthon – (which have different functionalities)

Hydrogen bond patterns can be determined by using guidelines provided by Etter

M.C and Donohue J. These rules are all acidic hydrogen present in a molecule that will be utilized in hydrogen bonding in the crystal structure of that compound.

Good acceptors will be used in hydrogen – bonding. Preferentially, hydrogen bonds are formed between the best hydrogen – bond donor and best hydrogen - bond acceptor. The important systems which can form hydrogen bonds are N-H…. N, N-H……Cl, N-H……O , O-H……N, O-H……O, where (-) _ indicates covalent and (.) _ indicates non-covalent contact with acceptor atom.

CAMBRIDGE STRUCTURAL DATABASE (CSD):

It is possible to analyze the frequency and patterns of hydrogen-bonding motifs and other intermolecular interactions using the Cambridge Structural Database (CSD). The CSD is a comprehensive repository of small-molecule organic and metal–organic crystal structures, originally established in 1965 and continuously updated through rigorous validation and curation by experts. It enables systematic analysis of large datasets of related crystal structures, making it a powerful tool in crystal engineering and cocrystal design(51).

Such analyses are primarily based on the shape, size, and polarity of cocrystal formers, which influence their ability to participate in specific intermolecular interactions. The CSD provides valuable insights into

commonly occurring functional groups and their tendencies to form supramolecular synthons, thereby aiding in the rational design of cocrystals(52). The interactions that hold these synthons together in supramolecular structures include:

A. Ionic interactions or charge assisted intermolecular bonding.
B. Dipolar interactions.
C. Halogen bonding.
D. Close shell interactions.
E. Van der Waals interactions.
F. Pi -pi interactions or pi-stacking co-operations
G. Ion – Pi cooperation.
H. Cation -Pi interactions
I. Anion -π interaction
J. Hydrogen bonding in cocrystals

A. Ionic interactions or charge assisted intermolecular bonding:

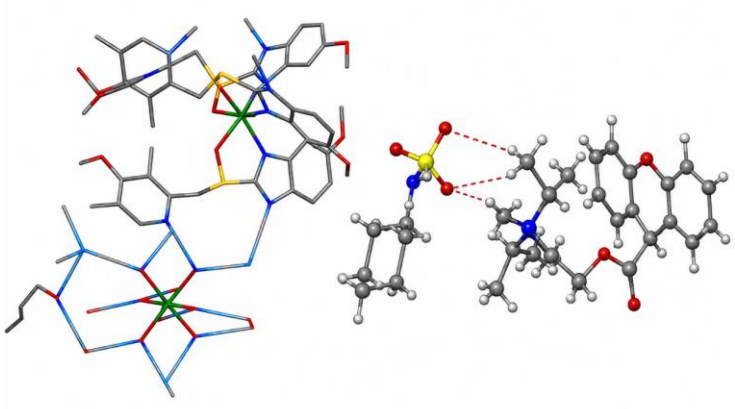

Figure 7: Multiple CHO interactions in salt of propantheline cyclamate, adopted from Re.

These intermolecular interactions are also commonly observed in salts and cocrystal salts. In solution, proton transfer is facilitated due to reduced steric hindrance, allowing protons to move readily from acidic moieties (e.g., carboxylic acids) to basic sites, resulting in salt formation(53).

The likelihood of proton transfer is often predicted using the ΔpKa rule, which considers the difference between the pKa values of the base and the acid. Generally, a larger ΔpKa favors salt formation, whereas a smaller difference tends to result in cocrystal formation. However, exceptions exist where other factors, such as concentration, play a determining role; for example, in the pyridine–formic acid system(54).

Salts typically exhibit strong charge-assisted hydrogen bonding due to the presence of ionic species. These charged entities interact readily with polar molecules such as water, making many salts hygroscopic in nature. Furthermore, larger organic cations and anions often possess significant hydration energies, which can lead to the formation of stoichiometric hydrates, such as trimethoprim sulfate trihydrate.

In addition to water (forming hydrates or aquo complexes), non-aqueous solvents can also participate in solvate formation. For instance, the magnesium salt of esomeprazole is known to form solvates with both water and organic solvents such as butanol.

B. Dipolar Interactions:

Dipolar interactions are generally weaker compared to conventional hydrogen bonding. Although such interactions can be observed in cocrystals, they are typically insufficient on their own to produce thermodynamically stable cocrystal structures(55). These interactions are most commonly associated with polar functional groups, particularly carbonyl moieties. Despite their relatively weak nature, dipolar interactions and their cooperative effects in polymorphs and cocrystals play a significant role in solid-state characterization techniques, especially solid-state NMR spectroscopy(56). This is because they provide valuable information about intermolecular distances and spatial arrangements within the crystal lattice(54).

C. Halogen bonding:

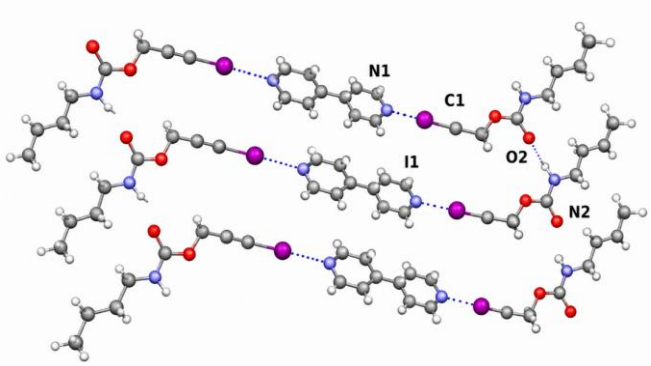

Figure 8: Cocrystal of 3-iodo-2-propynyl-N-butylcarbamate with 4,4'-bipyridine, a supramolecular-ribbons formed by orthogonal halogen and hydrogen bonding

Halogen bonding involves a directional interaction between atoms. The strength of the bond is dependent on the type of halogen atom present in the molecules. It plays a key role in the development of certain cocrystals(57). Interactions can be seen between the lone pair of an acceptor halogen (Cl, Br, I) and the lone pair of a donor situated on a heteroatom (N, O, S, P).

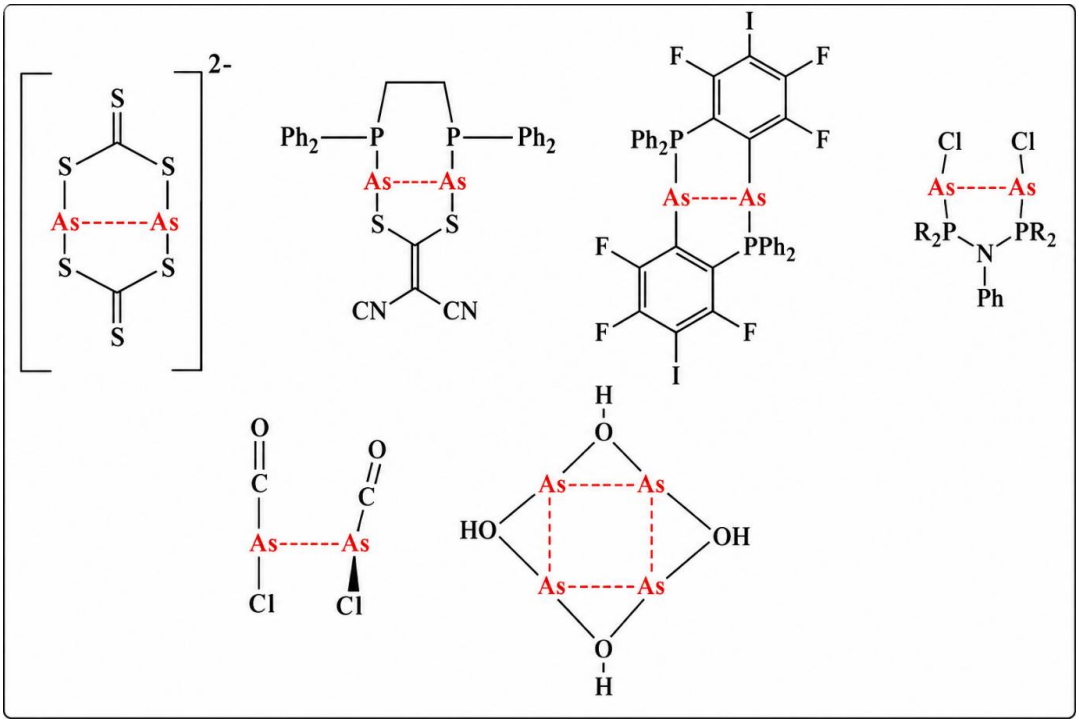

Figure 9: Closed shell interactions of Au-Au in its complexes.

Halogen bonding shows similarities to hydrogen bonding in terms of directionality and n to sigma donor-acceptor interactions(58,59). It causes a closed shell interaction, existing between heavier halogen such as iodine (electron deficient) and electron rich centers like the lone pair of pyridine molecules (acceptor)(60,61). Polyiodide anions are held together by halogen bonding. Halogen bonds are comparatively soft in nature than hydrogen bonds, hence their strength cannot be directly compared with H-bonding. cocrystal design offers a degree of predictability when both hydrogen and halogen bonds are present because they often result in orthogonal structures(62). Specific interactions, such as I….N and I…..S in diiodo tetra fluorobenzene and thiomorpholine cocrystals, demonstrate how different halogen bonds can lead to different cocrystal ratios and structures(63).

D. Closed shell interactions:

Closed-shell interactions (like aerophilic and argentophilic) are found in complexes with low-oxidation -state metal ions, particularly silver and

gold complexes. Nature of interactions: gold (1) is a (5d) system that experiences weak Vander Waals interactions, which are enhanced by relativistic effects and dispersion forces. Aurophilicity term: the term aurophilicity was introduced by Schmidbaur in 1981 to explain specific short distances absorbed between gold and atoms in solid state(64).

The concept expanded to include interactions between other metals where atoms are separated by less than the van der waals limit, including s2-d8 configurations. These interactions occur within molecules containing more than one gold atom, or indirectly via bridge groups (Au-B-Au). These Au-Au interactions are categorized into fully supported, semi-supported and unsupported frameworks based on connecting ligands(65).

Supported interactions involve intramolecular Au-Au contacts connected by molecular framework that provide structural support, mixed interactions, such as Au-Au and C-H...Au, enhance structural directionality and help form 2D and 3D architectures. Additionally, synergy with other interactions like hydrogen bonds and van der Waals interactions contribute significantly to structural arrangement and overall material stability(66).

E. Van der Waals interactions and molecular shapes:

Van der Waals interactions are a form of closed packing of molecules. These interactions help impact stability to a material through surface contacts between molecules. A key characteristic of van der Waals interactions in this context is the lack void spaces(67).

Solvent molecules can be incorporated into structures through "host – guest chemistry "to fill potential voids. Noncomplementary molecules are held firmly together to ensure all spaces are filled. Specific hydrates can be formed as a result of this void-filling process(68). Example, layers of tri mesic acid act as the guest, and water molecule act as the host to fill spaces in Un solvated form. Other molecules, like picric acid can replace water to form a ternary cocrystal (trimesic acid, picric acid, and water)(69). This distinct host-guest role helps explain complex structures such as the Z =12 structures and the unusual 5/6 stoichiometry in the fully ordered, stoichiometric structure.

F. Pi -pi interactions or pi-stacking cooperations:

Pi-pi and n-stacking interactions are forces that stabilizes molecules(70). Particularly those with aromatic rings, in face to face or edge to edge geometries within cocrystal. specific examples mentioned include the n-stacking observed in cocrystals of caffeine and benzoic acid and the interaction between electron – deficient hexa fluorobenzene and electron -rich bis (benzene) chromium(71). These interactions are also crucial for the formation and stability of inorganic cocrystals, such as a manganese complex involving 4,4-azobis (pyridine) ligands and non-coordinates guest molecules(72).

G. Ion -π- cooperations:

Ion pi -interactions involve the attraction between aromatic rings and cations, such as k+ or cs+, with a bond strength similar to hydrogen bonding. Anion -pi interactions also exist. Both interactions can be stabilise molecular salts of aromatic compounds, influencing process like crystallization. A notable example is the "calixarene cupped cesium "complex, where the cs+ ion sits within a calixarene anion with a cs……centroid distance of approximately 3.57 A(73).

H. Cation -π interactions:

Cation -π interactions are among the strongest non-covalent interaction and can be modulated by various factors. Common metal ion involved include Li+, K+, Na+, Mg2+ and Ca2+. making their combined strength comparable to hydrogen bonding. These interactions exhibit cooperativity with hydrogen bonds, further increasing overall strength. Ternary system can be prepared by two ways(74).1. If target compound combines with metal ion and is hold strongly by metal π interactions, and the complex and targets finally interacts with acceptor molecule forming ternary system held together with both hydrogen and metal pi-interactions. 2. The second way of preparing ternary system is, that target first make hydrogen bond with acceptor and finally in contact with metal ion(75).

I. Anion -π interaction

Anion -pi interactions are significant in the formation of supramolecular assemblies. In certain Mn complexes, the highly planar pi- electrons of ligands like 4,4-azobis (pyridine) facilitate these interactions with other conformers, adding stability to the resulting crystal structure(76) .

J. Hydrogen bonding in cocrystals:

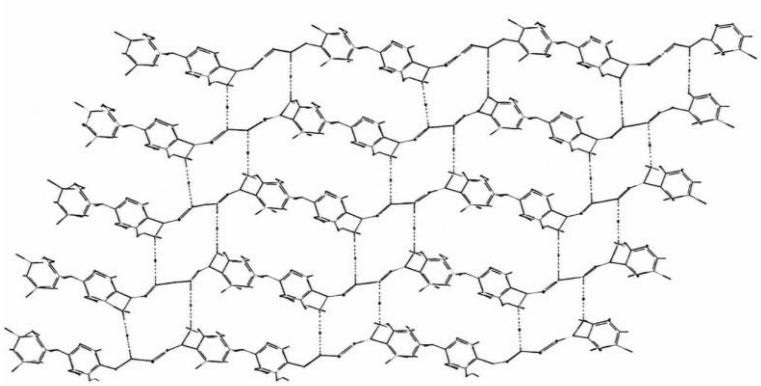

Figure 10: 2D structure of 6-bromobenzo[d]thiazol-2-amine cocrystal with fumaric acid, stabilized by secondary interaction-bonding

Hydrogen bonding is a primary non-covalent interaction responsible for cocrystal formation, leading to one, two- and three- dimensional crystal structures. This interaction occurs in numerous natural organic, and inorganic species through donor -acceptor interactions(77). Carboxylic acids are noted as bearing ideal sites for establishing these bonds. Hydrogen bonding is vital in medication and DNA binding due to its directional quality(78). Many cocrystal formed between weak acids and weak bases where the difference in pka is small, ensuring hydrogen bonding persists in solution and proton transfer does not occur(79). Which is particularly useful for enhancing the solubility of certain drugs.

Rules for hydrogen bonding:

These rules were proposed Etter and Donohue for structural prediction of molecular aggregates which are reproduced as under(80,81).

i. All acidic hydrogens will take part in hydrogen bonding present in a molecule.
ii. This bond will be formed between two species if a good donor and good acceptor sites exist. iii. No bond will form in the absence of anyone site.
iii. Donor and acceptor groups of molecules will favorably be linked to form hydrogen bonding.

Hydrogen bonding results fruitful crystallization thus affording supramolecular structures for molecules like 1,3,5- cyclohexane tri carboxylic acid, acid 1,3,5-benzene tricarboxylic acid (tri mesic acid) and other similar derivatives.

Effect of temperature on h-bonding:

Hydrogen bonding is a complex interaction influenced by temp and exhibiting both electrostatic and covalent characterization, as first proposed by Linus pouling. The strength and length of these bonds can be affected by factors such as charge transfer interaction, resonance assistance, and the specific atoms involved, with guanine -guanine pairs forming stronger bonds than cytosine – cytosine pairs due to higher charge on the oxygen atom.

Resonance assisted hydrogen bonds:

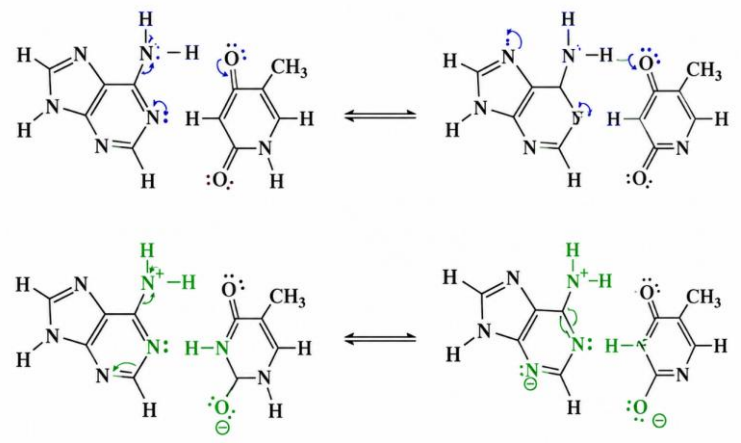

Figure 11: Resonance-assisted hydrogen bonding in adenine-thymine (AT) base pair.

Resonance assisted hydrogen bonding (RAHB) occurs when hydrogen bonds gain extra stability by cooperating with conjugated double bonds, causing bond contraction via charge delocalization. This phenomenon is observed in DNA base pairs, such as the adenine – thymine (AT) and cytosine -guanine (CG) pairs, studies confirm that the hydrogen bonds in these larger molecules are stronger than in their smaller analogues, with specific bond lengths and energies provided as evidence for the RAHB effect.

C-H...O and C-H…..π interactions :

The role of carbon- hydrogen bonds in forming supramolecular assemblies and crystal packing through C-H…O and C-H..π interactions. specific examples are given for 4,6-tris (4- methyl phenoxy) – 1,3,5 – triazine and dimeric 4-chlorocubane carboxylic acid, illustrating how these interactions, alongside traditional hydrogen bonding, influence molecular orientation and crystal structure. scheme 8 details hydrogen bond distances and energies for various complexes, while scheme a illustrates the different bonding patterns in 4- chlorocubane carboxylic acid.

2. HANSEN SOLUBILITY PARAMETERS:

The interaction between two solvent and solute molecular or ion is a key concept in solubility. The concept of solubility parameter (δ) was introduced by "Hildebrand and Scott" proposing that materials with similar δ values would be miscible. HSP model developed in 1967, the HSP model divides the total cohesive energy into individual components, dispersions and hydrogen bonding. HSP are recommended as a tool in the pre-formulation and formulation development of tablets(82).

Cocrystal prediction study investigated whether the miscibility of drug and its conformer components, as predicted by theoretical tools, could predict cocrystal formation. The concept of cohesive energy by means of no. is been used, and most common way is solubility parameters δ concept – δ is the square root of cohesion energy density (CED) of a material, as it was developed by Hildebrand et al. based on regular solution theory(83).

$$\Delta H = VT\left(\frac{\sqrt{EV1}}{Vm1} - \Delta EV2/Vm2\right)\emptyset - \emptyset 2 \quad \text{----------} \quad 1$$

ΔH = heat of mixing
VT = total volume
Δ EV = energy vaporization
Vm = molar volume

$$\delta = (CED) = \left(\frac{\Delta E}{V}\right) \quad \text{----------2}$$

Where,

V= molar volume

Hansen assumed that total cohesion energy is the sum of dispersion of ED, polar EP and hydrogen bond energy EH.

ET= ED+ EP+ EH----------3

And by dividing both sides of the equation by molar volume V , we will have the total Hansen solubility parameter or solubility parameter δT :

$$\delta T = \delta o + \delta p + \delta H$$

Where:

δ = total solubility parameter
δ = dispersion interactive (London) force
δ= permanent dipoles in interacting molecules, called dipole -dipole interactive forces.
δ= hydrogen bonding forces

Methods for estimating solubility parameter / group contribution method:

The partial solubility parameters describe the solubility of molecule to interact with another one of the some or different types through intermolecular forces(83). Fedors supposed group contribution to the molar volume of molecule and van krevelen/hoftyzer group contribution to molecular forces by combining both methods and partial solubility parameters solubility parameters can be calculated as follows:

$$\delta d = \frac{\sum i fdi}{\sum i vi} \quad \text{----------4}$$

$$\delta p = \frac{\sqrt{\sum i f2p1}}{} \quad \text{----------5}$$

$\sum ivi$

$$\delta h = \frac{\sqrt{\sum ifhi}}{\sum ivi} \quad \text{----------6}$$

Where,

i= structural group within the molecules
st Fd = group contributions to dispersion forces
Fp = group contribution to polar forces
Fh= group contribution to hydrogen bond energy
Vi = group contribution to molar volume

Table 1: Atomic and group contribution to the heat of vaporization

S.NO.	ATOM OR GROUP	ΔHi, cal / mol
1	CH3	1780
2	= CH2	1780
3	CH2	990
4	=CH	990
5	CH	-380
6	O	1630
7	OH	7250 4270
8	CHO	4700

MECHANISM OF SOLUBILITY ENHANCEMENT:

Solubility is determined by strength, crystal lattice and solvation of cocrystal components, solubility can be increased by lowering lattice energy or increasing solvent affinity. This is maintained by cocrystal formation. Examples of some API with improved solubility through co crystallization.

Table 2: List of examples of drugs with coformers whose solubility increased

Sl. No	DRUG	COFORMER	METHOD OF PREPARATION	SOLUBILITY		REF
				DRUG	CO-CRYSTAL	
01	Indomethacin	Saccharin	Supercritical fluid	2.5-4µg/ml	3.7mg/ml	(84)
02	Norfloxacin	Isonicotinamide	Solvent evaporation	0.21mg/ml	0.59mg/ml	(85)
03	Itraconazole	Succinic acid	Grinding	5µg/ml	18µg/ml	(86)
04	Tadalafill	Salicylic acid	Neat co grinding	0.41mg/ml	1.4mg/ml	(87)
05	Meloxicam	Aspirin	-	0.005mg/ml	0.22mg/ml	(88)
06	Miconazole	Succinic acid	Solvent evaporation	200µg/ml	600µg/ml	

3. ΔPKA RULE:

The pKa value is a widely used approximation for predicting the formation of multicomponent crystals such as salts and cocrystals. Generally, salt formation is favored when the difference in pKa between a base and an acid (ΔpKa) is greater than 3, indicating a high likelihood of proton transfer. In contrast, cocrystal formation is more likely when ΔpKa is less than 0, where proton transfer is minimal or absent. A near-linear relationship has been observed between ΔpKa and the probability of proton transfer in acid–base systems(89).

A comprehensive analysis by Miguel A. Cruz-Cabeza examined 6,465 crystalline complexes containing acid–base pairs and categorized them into three zones based on ΔpKa values. In Zone 1 (ΔpKa < −1), approximately 99% of the complexes were non-ionized, indicating cocrystal formation. In Zone 2 (−1 ≤ ΔpKa ≤ 4), a transition region was observed where both salts and cocrystals coexist, and the probability of ionization increases with increasing ΔpKa. In Zone 3 (ΔpKa > 4), salt formation predominates due to complete proton transfer.

The acid dissociation constant (pKa) also plays a critical role in drug absorption and solubility(90).

According to the Biopharmaceutics Classification System, Class II drugs (low solubility, high permeability) can be further subclassified based on pH-dependent solubility into:
Class IIa (weak acids)
Class IIb (weak bases)
Class IIc (neutral compounds)
Weakly acidic drugs with pKa ≤ 5 (e.g., Ketoprofen) exhibit higher solubility at the alkaline pH of the intestine and are categorized as Class IIa drugs. Overall, a ΔpKa greater than 2–3 typically indicates salt formation, whereas a ΔpKa less than 0 suggests cocrystal formation, making ΔpKa a valuable predictive tool in crystal engineering.

4. COSMO - RS (CONDUCTOR LIKE SCREENING MODEL FOR REAL SOLVENTS)

COSMO – RS is a universal theory to predict the thermodynamic equilibrium properties of liquids, which was originally developed by A. KLAMT COSMO – RS thermodynamic is based on the statistical physics of interacting molecular surface segments(91). The polar and hydrogen bond interaction energies are quantified based on the surface screening charge densities, which result from a quantum chemical continuum solvation calculation. Due to its ability to treat mixtures at variable temperature and to compare compute accurate solvation energies based on first principles, it has become very useful in chemical engineering and in wide areas of physical and medical chemistry(92). A complete computational modeling and prediction in of the crystallization process is currently out of the reach due to the complexity of the involved steps like nucleation and crystal growth. However, with COSMO-RS being a fluid phase thermodynamics, model it is possible to compute a virtually supercooled liquid mixture of the crystallization components and obtain the excess enthalpy of s-60chiometric min mixtures create out of the pure components A and B. In this approach, the excess enthalpy (H_{ex}) of a binary mixture is calculated as:

$$H_{ex} = H_{AB} - x_m H_A^{pure} - x_n H_B^{pure}$$

Where:
H_{AB} = molar enthalpy of the mixture
H_A^{pure}, H_B^{pure} = molar enthalpies of pure components
$x_m = m/m+n$, $xn = n/ m+n$ = mole fractions

The excess enthalpy H_{ex} includes all enthalpic contributions, not only hydrogen bonding, although COSMO-RS allows separation of specific interaction types though those may be separated from the overall enthalpy by COSMO-RS them software(93). It was found that the excess enthalpy hex is a superior descriptor to the pure liquids. In an extensive set of test calculations presented below we demonstrate that co formers miscibility as measured by hex corresponds nicely with an increased probability of forming cocrystals. Since it is reasonable to assume, that enthalpic preference of such super cooled liquid phase will also pertain in a mixed crystal, it is plausible to use the liquid phase excess enthalpy as a guide for cocrystal screening.

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Conflict of Interest
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Data Availability
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