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Crystal Engineering of Pharmaceutical Cocrystals: Emerging Strategies for Drug Solubility, Stability and Bioavailability Enhancement

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ABSTRACT

Pharmaceutical cocrystals have emerged as a promising crystal engineering strategy for improving the physicochemical and biopharmaceutical limitations of active pharmaceutical ingredients (APIs). In recent years, cocrystallization has gained significant attention in pharmaceutical research due to its ability to enhance solubility, dissolution rate, stability, permeability, bioavailability, and mechanical properties without altering the pharmacological activity of the drug molecule. This review comprehensively discusses the fundamental principles, classification, and preparation techniques of pharmaceutical cocrystals, including solvent evaporation, grinding, slurry conversion, hot melt extrusion, and supercritical fluid methods. The article further highlights the role of intermolecular interactions such as hydrogen bonding, π–π stacking, and van der Waals forces in cocrystal formation and stabilization. Various characterization techniques including Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), scanning electron microscopy (SEM), and nuclear magnetic resonance (NMR) are also summarized. Special emphasis is placed on the recent advancements of pharmaceutical cocrystals in improving therapeutic performance in oncology, antimicrobial therapy, and poorly water-soluble drugs. Additionally, regulatory perspectives, patent opportunities, industrial challenges, and future prospects associated with cocrystal-based formulations are critically analyzed. Overall, pharmaceutical cocrystals represent a versatile and innovative platform for modern drug development and offer substantial potential for enhancing drug efficacy, patient compliance, and formulation performance in advanced pharmaceutical applications.

KEYWORDS: Isoflavone, Cocrystal, Daidzein, Solvent Evaporation, Solubility Enhancement..

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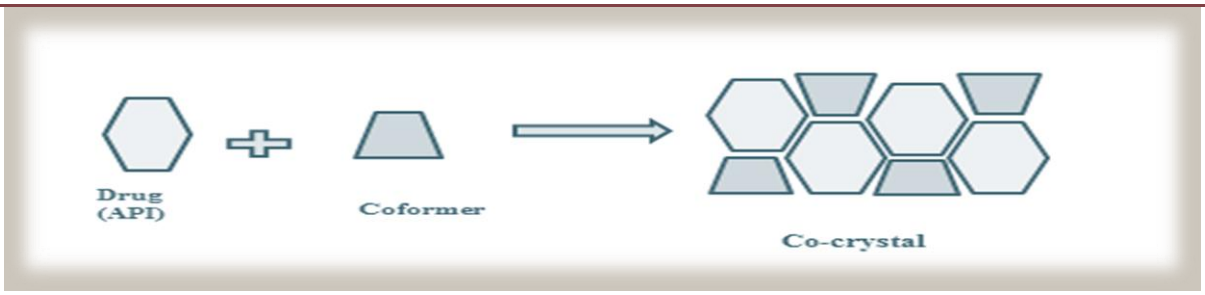
INTRODUCTION

Co-crystals are most dynamically homogenous structural crystalline multi component adduct, generated by a perfect definite selection of compounds in a stoichiometric ratio, with the establishment of reversible chemical interactions like hydrogen bonding, π-π, ionic bond or vander waals forces. Co-crystals had been defined in many different ways by named as addition compounds, organic molecular compounds, complexes, hetero molecular crystals.

The physiochemical and technical properties enhancement of pharmaceutical drug products had direct effect on the drug delivery, processing and efficacy of drug. The crystal structure of API directly affects the imperative factors of the substances. One scrutiny revealds that nearly 40% out of 90% of the new chemical entities (NCE) have limitation in solubility they cannot reach the action site in the body by normal conventional techniques. Nearly 80% of the drugs in solid dosage formed were observed via passive diffusion from gastrointestinal that are listed in worlds health organisation (WHO) were investigated to be insoluble and poorly water soluble as per the biopharmaceuticals classification system.[1]

One best approach of attaining the enhanced bioavailability of API was to prepare in salt forms although of ionisable groups which are responsible for the formation of respective salts. From all the facts it was necessary to generate a new solid-state formulation. A blaze of spark *Crystal Engineering* concept had shown a way to flash out all these drawbacks by the wide range of possibilities to design various crystalline solid-state formulations like, polymorphs and co-crystals etc.



A solid matter basically exists in two forms based on their structural arrangement, one is crystalline forms andanother is amorphous forms, these two are different in their properties. Again, crystalline substances are divided into two types, single crystal component and multi component crystalline substance. These multicomponent crystalline substances have more than one molecule assembled in different patterns resulting into variety of solid forms namely Hydrates, salts, solvates, polymorphs and co-crystal.

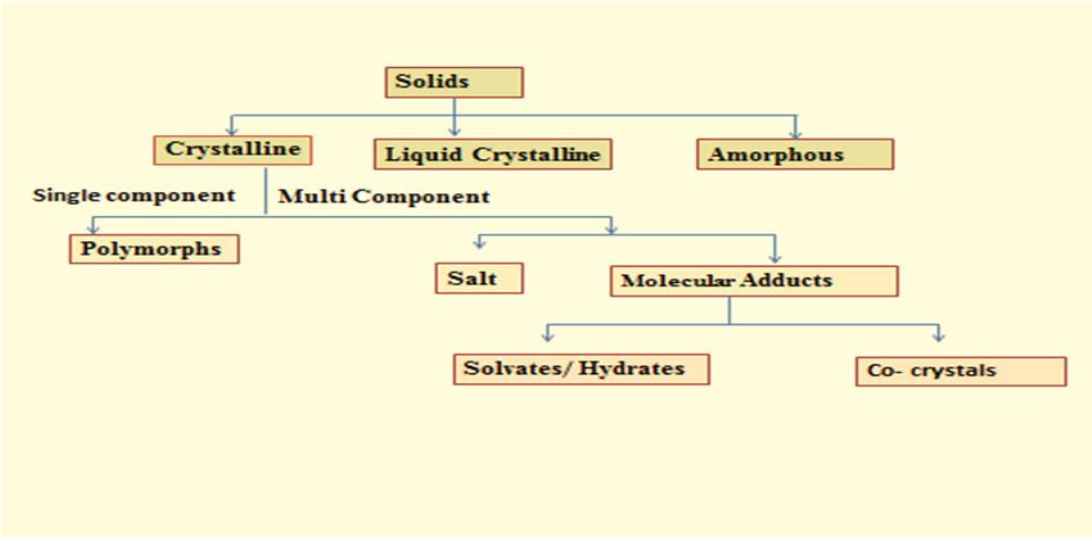


Fig :1 Type of solid form.

Difference between co-crystals, salt, solvates, and hydrates

The USFDA defined co-crystal, salt, and polymorphs in the suggested advice. Polymorphs are substances that can take on several crystalline forms, such as solvates or hydrates (pseudo polymorphs), as well as amorphous forms. Polymorphs display various physicochemical properties as a result of their diverse crystal lattice configurations. Salts are produced when a complete proton transfer occurs between two chemicals. It is possible to separate salts and co-crystals from one another by transferring a proton from an acid to a base. There is a complete proton transfer between pairs of bases and acids, but not when co-crystals are formed. Two components are held together by non-covalent interactions such as hydrogen bonds, van der Waal forces, and others. The pKa value can be used to forecast whether co-crystals will form or not. It is generally agreed upon those co-crystals will develop when the pKa value is less than 0 and salts will form when the pKa value is more than 3. Between pKa values of 0 and 3, this parameter cannot accurately predict the formation of co-crystals in solids, but as pKa rises, the likelihood of salt production increases. The co-crystals and solvates can be distinguished by the physical state of all the coformers. Solvates contain liquid at room temperature whereas co-crystals remain solid in the same conditioning the crystal lattice. In solvates when solvent molecules are water, it is termed as hydrates. Solvates and hydrates of API's are less important as they can change the physicochemical properties. Due to the solvent's presence in the crystal lattice, solvates have a different level of stability than unsolvated forms. Due to the solvent/water loss at high temperatures and slight humidity levels during storage, as well as the variable physiochemical characteristics between hydrated and dehydrated forms, solvates/hydrates are extremely unstable. The solvated versions of spironolactone increased the drug's rate of dissolution .Liquid-assisted grinding was used to create several polymorphic co-crystals and solvates.[2]

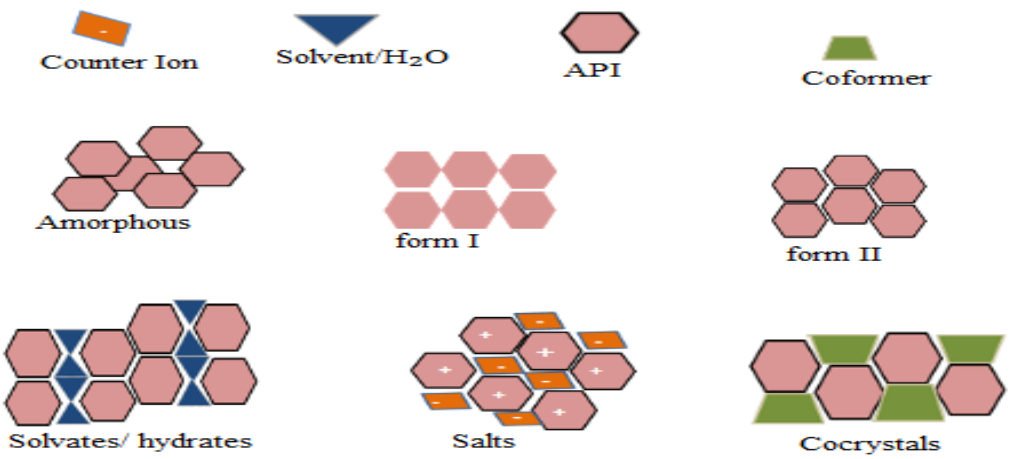


Fig 2: Difference between co-crystals, salt, solvates, and hydrates

SELECTION OF COFORMER

The compatibility of coformers with the drug must be thoroughly evaluated before proceeding with the development of pharmaceutical co-crystals, as this presents significant challenges that need to be addressed. Coformer screening serves as a method for identifying suitable coformers that can effectively be combined with the drug to form a co-crystal. The most promising candidate is then assessed for its physicochemical and pharmacological characteristics before being developed into an appropriate dosage form. Typically, coformers are chosen from substances listed as generally recognized as safe (GRAS) by the USFDA, ensuring that they do not interfere with the pharmacological effects of the active pharmaceutical ingredient (API).

Fig3: Selection of coformer

The choice of coformers presents a significant challenge in the development of pharmaceutical multicomponent crystals that are compatible with active pharmaceutical ingredients. Typically, the strategy for selecting coformers involves somewhat haphazard experimental methods, where a set number of candidates from compounds deemed safe according to the Generally Recognized as Safe (GRAS) list are utilized to create multicomponent crystals. For a substance to qualify as a coformer, it must be safe, non-toxic, and free from adverse effects.[3]

Most Popular Coformers Utilized in Cocrystal-Based Marketed Formulations.

S.no	Co-crystals	API	Co former	Uses	Status
1.	Suglat® (ipragliflozinL-proline) by Astellas pharma	Ipragliflozin	L-Prolin	Type 2 diabetes	Marketed
2.	Entresto™	Valsartan	Sacubitril	Chronic heart failure	Marketed
3.	Depakote® (valproate sodium cocrystal with valproic acid)	Valproic acid	Valproate sodium	Seizure disorder	Marketed
4.	Lexapro® (escitalopram oxalate)	Escitalopram	Oxalate	Depression and anxiety	Marketed

5.	Entresto® (sacubitrilvalsartan)	Valsartan	Sacubitril	symptomatic Chronic heart failure	Marketed
6.	Itraconazole (sporanoxR)	Itraconazole	succinic acid	Antifungal	Marketed
7.	(Prozac)fluoxetine hydrochloride	fluoxetine	succinic acid	Treatment of depression	Marketed
8.	TegretolR	carbamazepine	succinic acid	Anticonvulsant	Marketed
9.	Abilify	Aripiprazole	Fumaric acid	Schizophrenia	Marketed
10.	*Odomzo*	sonidegib	phosphoric acid	skin cancer	Marketed
11.	Lamivudine/zidovudine Teva	Lamivudine	Zidovudine	HIV infection	Marketed
12.	ESIX-10®	Escitalopram oxalate	Oxalic acid	Treat depression	marketed
13.	Beta-chlor®	Chloral hydrate	Betaine	Sedation	marketed
14.	Cafcit	Caffeine	Citric acid	Infantile apnoea	marketed
15.	Zafatek	trelagliptin	succinic acid	type 2 diabetes	marketed
16.	steglatro	Ertugliflozin	L-pyroglutamic acid	Diabetes	marketed
17.	Mayzent®	Siponimod	Fumaric acid	Treatment of relapsing forms of multiple sclerosis	marketed

Table1: Coformers Utilized in Cocrystal-Based Marketed Formulations

Additionally, coformers should be included in the FDA's "Everything Added to Food in the United States" (EAFUS) list or the GRAS list.

Following are the screening methods.

1) Hydrogen bonding propensity
2) Synthonic engineering
3) Supramolecular compatibility by CSD
4) pKa based models
5) Fabian's method
6) Lattice energy calculations
7) Conductor like screening model for real solvents (COSMO-RS)
8) Hansen solubility parameter
9) Virtual co-crystal screening (Based on Molecular Electrostatic Potential Surfaces MEPS)
10) Thermal analysis
11) Measuring saturation temperatures
12) Kofler contact method
13) Cocktail co-crystal method

2.1 PKa based model

Proton transfer refers to the process that takes place with salts. The equation used to predict the formation of co-crystals is.

$$\Delta pKa = [pKa(\text{base}) - pKa(\text{acid})]$$

The transfer of a proton is observable when the difference in pKa values exceeds 3. A ΔpKa value below zero suggests the potential formation of a co-crystal, whereas a ΔpKa value greater than 3 indicates the formation of salts. When the ΔpKa falls between 0 and 3, either a co-crystal or a salt may be anticipated. For example, succinic acid (pKa 4.2) can form a co-crystal with urea (pKa 0.1), while a salt is produced when L-lysine (pKa 9.5) is involved.

2.2 Cambridge structural database

The Cambridge Structural Database (CSD) serves as a validated, computer-based tool for identifying suitable co-crystal forming pairs, thereby streamlining the screening process and lowering experimental costs. It enables statistical analysis of packing characteristics and offers insights into various functional groups. Additionally, the CSD can be utilized to evaluate the potential for intermolecular hydrogen bonding among different molecules. Single crystal X-ray crystallography techniques can be applied to characterize the crystal structure of compounds, with the resolved structures being stored in the CSD. This information can be accessed, retrieved, and utilized at any time. Software such as 'Atoms' and 'Powder Cell' can be employed to visualize structures based on data obtained from the CSD.

2.3 Fabian's Method

The CSD was used to extract various sets of trustworthy co-crystal forming structures, and each molecule's single atom, bond and group counts, size and shape, surface area, and molecular electrostatics were calculated. The database described molecular pairs that might form co-crystals based on computed molecular characteristics. The shape and polarity of coformers showed the highest descriptive connection.

2.4 Lattice energy calculations

When ions joined to form a new compound, lattice energy was released from the substances. It is a measurement of the cohesive forces that hold ions together. The total of the absolute sublimation enthalpies of the pure components must be less than or equal to the lattice energy value of the two-component system (co-crystal). Strong hydrogen connections between hetero dimers and nearby molecules account for a smaller portion of the lattice energy than the hetero synthon, which contributes at least 50%.

$$\Delta H = (H_{API} + H_{co\text{-}former}) - H_{cc}$$

$$\Delta H = (H_A + H_B) - H_{AB}$$

Where A = API; B = co former; AB = Co-crystal and ΔH = Difference in lattice energy.

2.5 Virtual Co-crystal Screening

One computer method for finding new drugs is virtual screening. "A computer program that automatically evaluates very large libraries of compounds." The software used for the virtual screening was created by Professor Christopher Hunter and his colleagues. What combinations of APIs and co-formers are most likely to generate co-crystals could be predicted by this software. The virtual screening of co-crystals was founded on the idea that a crystalline solid's structure is determined by the hierarchical organization of functional group interactions. It indicates that the first best donor and acceptor form the strongest hydrogen bond, followed by the next best donor and acceptor, and so on, until all interaction sites (i, j) are met. The intermolecular interactions were predicted using Hunter's hydrogen bond parameters, such as α and β.

$$E = -\Sigma ij\alpha i\beta j,$$

where E stands for solid form energy.

The difference between the interaction site pairing energies of the cocrystal (ECC) and the two pure compounds E1 and E2 offers information on the probability of co-crystal formation because Hunters' method assumes that co-crystals only have attractive electrostatic interactions.

$$\Delta E = ECC - nE1 - mE2$$

where ΔE = Molecular Electrostatic Potential surfaces (MEPS) and n and m stand for the co-crystal stoichiometric ratio. The chance of co-crystal formation is at least 50% when the ΔE of any pair and two separate components is more than 11 KJ/mol.

2.6 Cocktail co-crystal method

Katsuhiko Yamamoto developed a novel, straightforward "cocktail grinding method" for the logical screening of co-crystal formation. For co-crystal synthesis, the grinding approach works better than any other solution-based test for crystallisation. Using this strategy, one mixture of coformers at a time was permitted to ground the API. They attempted the grinding procedure after selecting a large number of coformers with the same functional groups. This indicates that four coformers with the same functional group were ground concurrently with API in a ball mill. This kind of planning results in a 50% reduction in workload. The coformers' moieties will interact with API moieties to make synthons, such as homosynthons or heterosynthons, which ultimately produce a product that is either positive co-crystal or takes on various forms. In comparison to all other formulations, co-crystals of itraconazole made with succinic acid and serine using the cocktail grinding process yielded results with the highest in-vitro solubility and dissolution rate.

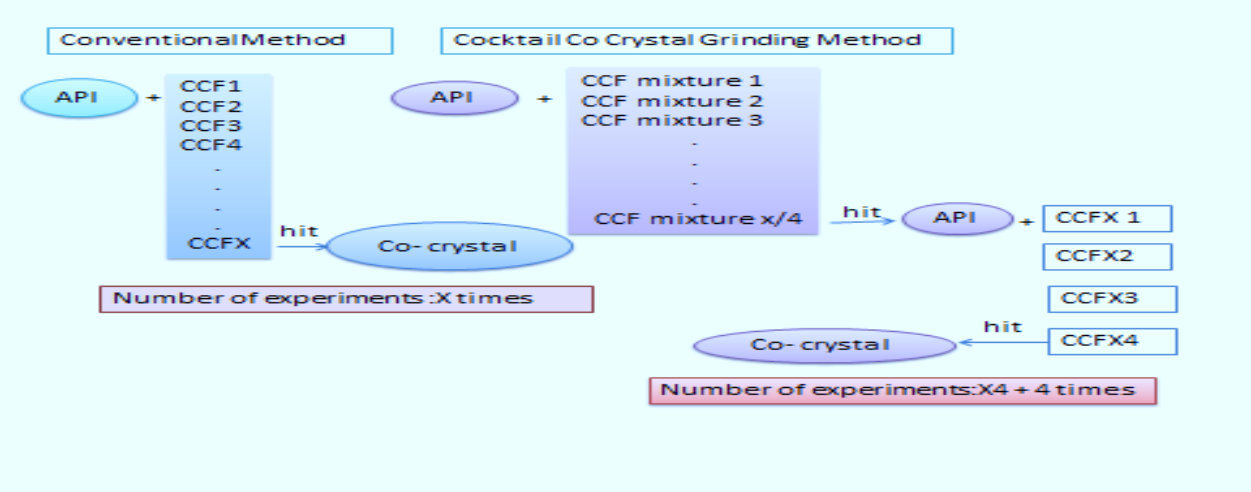


Fig 4: Cocktail co-crystal method

2.7 Hansen solubility parameter (HSP)

The use of Hansen Solubility Parameters (HSP) allows for the prediction of miscibility between a drug and its coformer, facilitating co-crystal formation. The group contribution method is frequently employed within HSP calculations, as it relies solely on the compound's structure. Commonly utilized group contribution methods include Fedors method, Hoy's method, and Van Krevelen's method. The theoretical framework for predicting co-crystal formation has been advanced by researchers Krevelen and Greenhalgh. Krevelen posits that co-crystals are likely to form when the solubility parameter deviation between the two components is ≤ 5 MPa1/2, while Greenhalgh indicates that a difference of ≤ 7 MPa1/2 also supports co-crystal formation.

Furthermore, Salem et al. have recently proposed a cut-off value of 8 MPa1/2, which is considered more reliable due to its relaxed criteria compared to earlier thresholds.

2.8 Hydrogen bonding

Research indicates that the hydrogen bond donors and acceptors present in the interacting partners facilitate the formation of hydrogen bonds. Furthermore, the most effective hydrogen bond donors and acceptors engage within the crystal structure, leading to the creation of co-crystals. The presence of hydrogen bonding can be verified through FTIR spectroscopy.

2.9 Supramolecular Synthon Approach

A pharmaceutical cocrystal can be engineered through crystal engineering to enhance the solid-state characteristics of an active pharmaceutical ingredient (API) while preserving its inherent structure. This approach provides a framework for the swift development of pharmaceutical cocrystals. Crystal engineering is defined as the application of supramolecular chemistry principles to the solid state, focusing on the concept that crystalline solids are tangible results of self-assembly. It is grounded in the fundamental principles of supramolecular chemistry, which extends beyond individual molecules to create new entities by manipulating non-covalent intermolecular interactions. Common interactions involved include hydrogen bonding, metal coordination, van der Waals forces, hydrophobic interactions, electrostatic effects, and pi-pi interactions. Additionally, crystal engineering is predicated on the comprehension of synthons' formation through non-covalent interactions. The term "synthon," introduced by Corey in organic chemistry, refers to "structural units within supermolecules that can be formed and/or assembled through known or potential intermolecular interactions." A supramolecular synthon represents a configuration made up of both molecular and supramolecular components. When these crystal patterns are regularly repeated, the interaction pattern is identified as a supramolecular synthon.

Supramolecular synthons can be classified into two main categories:

(a) supramolecular homosynthons, which consist of identical self-complementary functionalities, and

(b) supramolecular heterosynthons, which are made up of different yet complementary functionalities.

Supramolecular homosynthons can support single-component systems or compounds that contain the relevant functional groups, while supramolecular heterosynthons tend to prevail when other competing functional groups are present.

Supramolecular homosynthons involve interactions between two carboxylic acid groups, while supramolecular heterosynthons occur between a carboxylic acid group and an amide group. Common examples of supramolecular synthons include:

(1) A homosynthon created by the dimerization of carboxylic acids,
(2) A heterosynthon formed between a carboxylic acid and a pyridine group,
(3) A homosynthon resulting from amide dimerization,
(4) A heterosynthon between a carboxylic acid and an amide group, and
(5) A heterosynthon formed between an alcohol and an ether group.

Generally, heterosynthons exhibit greater stability compared to homosynthons; for instance, acid–amide heterosynthons are preferred over both carboxylic acid and amide homodimers.

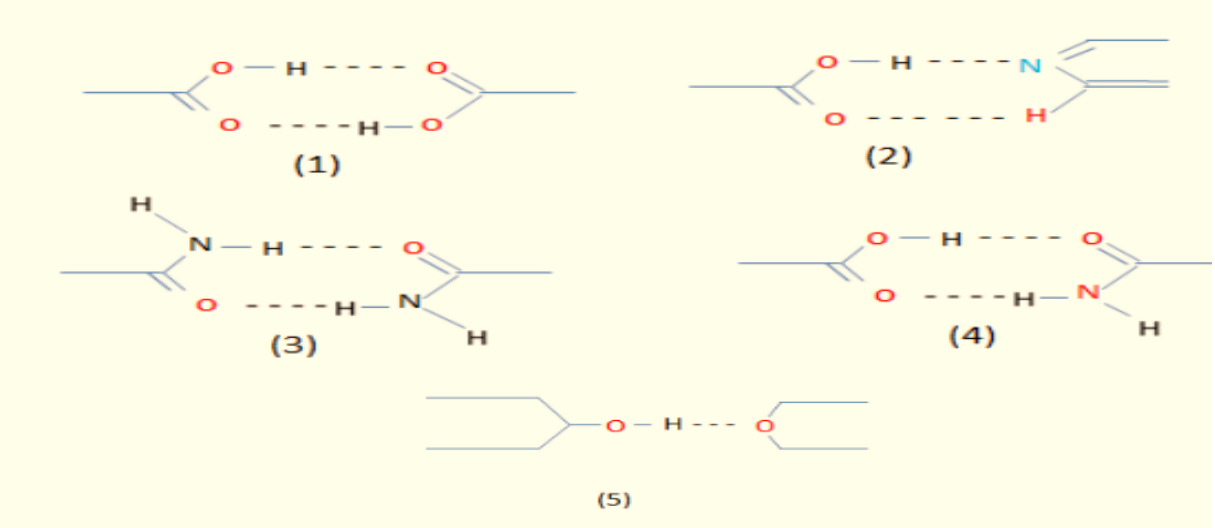


Fig 5:The most common supramolecular synthons in Crystal Engineering

Conductor-like screening model for real solvents (CSMO-RS)

CSMO-RS is a computational screening method that calculates the enthalpy of the active pharmaceutical ingredient (API) and its coformer, allowing for the ranking of coformers. The excess enthalpy of the API-coformer complex, compared to that of the individual components, indicates the potential for cocrystal formation. Abramov et al. have effectively utilized CSMO-RS theory for coformer screening with the aid of COSMO them software.[3,4,5]

CHARACTERIZATION OF CO-CRYSTALS

Various techniques are utilized for the characterization of co-crystals. Recent years have witnessed significant progress in the technology associated with characterization in this domain. The analysis of co-crystals can primarily be conducted through three principal methods: single crystal and powder X-ray diffraction (XRD and PXRD), thermal analysis techniques (including Differential Scanning Calorimetry and Hot Stage Microscopy), and spectroscopic methods (such as FTIR, Raman, and Solid-State NMR spectroscopy). This section of the review provides a concise overview of these characterization technologies along with several contemporary examples that employ these methods.

3.1 X-ray diffraction method (XRD) and powder X-ray diffraction method (PXRD) X-ray diffraction (XRD) is a leading and accurate technique for the identification and characterization of co-crystals. Typically, single-crystal XRD is employed for the structural analysis of larger crystals, which are usually produced through the solvent evaporation method. However, co-crystals formed via grinding cannot be analyzed using single-crystal XRD. Instead, powder X-ray diffraction (PXRD) is primarily utilized to identify the formation of co-crystals. In PXRD analysis, the co-crystals exhibit distinct changes in their characteristic peaks when compared to the individual components. Additionally, XRD methods are instrumental in determining the percentage yield of co-crystals by quantifying both the co-crystals and their components in the final product.

3.2 Thermal analysis method in thermal analysis, two primary methods are utilized for the characterization of co-crystals.

3.3 Differential scanning calorimetry (DSC) A simple and practical technique for characterising co-crystals is differential scanning calorimetry. When compared to pure components, co-crystals show a notable shift in their endothermic and exothermic peaks. By looking at the DSC peak of the physical mixture of co-crystal components, one can use the co-crystal DSC peak, which is located between the peaks of pure co-crystal components.

Nonetheless, there are many examples of co-crystals that have been formulated that have DSC peaks outside of the API and co-former range. This implies that the aforementioned rule cannot be applied universally to co-crystal formation conformation. DSC is a highly quick and effective way to characterise co-crystals. A very tiny amount of sample is needed to do a characterisation investigation using this solvent-free approach. Nine of the 16 co-crystals that Enxian Lu and colleagues examined using the DSC method are newly synthesised co-crystals that have not been documented in any prior literature.

A cocrystal of salicylic acid and coformer caffeine was created by Enxian Lu et al., and it has a lower melting point than both sa licylic acid and caffeine.According to the author, it is most likely because the mixture of two chemicals is eutectic.
For the purpose of choosing a coformer, more investigation and data gathering are required. and conformation of co-crystals. Furthermore, the heat energy reading can also be utilized for the conformation of formulated co-crystals as the heat energy of co-crystals tends to reduce as compared to utilized API.

3.4 Hot stage microscopy (HSM) HSM is widely recognized for its role in the characterization and screening of co-crystals. This technique enables users to monitor the recrystallization and crystal growth of the melted constituents of the co-crystal. The Kofler mixed fusion method can be employed for the characterization and screening of co-crystals. In this approach, the crystalline material is examined at the interface of the two components, indicating the potential for co-crystal formation between the constituents.

3.5 Spectroscopy The spectroscopic characterization of co-crystals can be categorized into two primary types. The first type is vibrational spectroscopy, while the second is nuclear magnetic resonance (NMR) spectroscopy. Vibrational spectroscopy is further divided into Fourier-transform infrared (FTIR) spectroscopy and Raman spectroscopy. FTIR spectroscopy operates based on the absorption mechanism, whereas Raman spectroscopy relies on the scattering mechanism. NMR spectroscopy serves as a highly effective technique for acquiring comprehensive structural information regarding multi-component systems.

3.6 Fourier transform infrared spectroscopy

FTIR spectroscopy serves as a highly effective method for identifying the formation of co-crystals. The confirmation of co-crystal formation is indicated by alterations in the vibrational energy peaks within the spectra, primarily resulting from the establishment of hydrogen bonds among the functional groups of the co-crystal constituents. A comparative analysis of the FTIR spectra of pure co-crystal components and the synthesized co-crystals is conducted to detect co-crystal formation and to elucidate their structure. Harry G. Brittain conducted an analysis of co-crystals formed from cinchona alkaloid and 5-nitro barbituric acid utilizing FTIR spectroscopy, noting variations in the absorption spectra between the co-crystal and its individual components.

3.7 Raman Spectroscopy

Raman spectroscopy serves as an effective in-situ technique for monitoring and confirming the formation of co-crystals. This method demonstrates superior accuracy, precision, and sensitivity compared to Fourier-transform infrared (FTIR) spectroscopy. It is capable of distinguishing between the co-crystal form and the ionic form within multi-component systems. The assessment of co-crystal formation involves analyzing the changes in the oscillation patterns of the co-crystals relative to their individual components. Yong Du and colleagues illustrated the potential of Raman spectroscopy in identifying the co-crystal formation between nitrofurantoin and 4-aminobenzoic acid. The data acquired through Raman spectroscopy is instrumental in differentiating various multi-component pharmaceutical solid systems. K. C. Mullers and associates employed color coding to analyze fixed crystal patterns, successfully identifying raw ibuprofen and nicotinamide within both the physical mixture and the co-crystals, as

well as any remaining co-former in the final product. The color-coded Raman spectroscopic image of the final product reveals the presence of formed co-crystals, residual co-former, and an absence of pure ibuprofen.

3.8 Solid-state NMR spectroscopy SSNMR possesses the capability to deliver comprehensive structural insights into organic and pharmaceutical co-crystals. It offers superior information content and high-yield data in comparison to vibrational spectroscopy and PXRD techniques. As a non-destructive approach, SSNMR requires only a minimal quantity of samples for effective data acquisition. Frederica G. Vogt and her colleagues investigated various molecular complexes and co-crystals to explore the potential of SSNMR. Their research highlights SSNMR's ability to confirm molecular associations and examine structural characteristics such as hydrogen bonding. Additionally, Li Zhao and his team showcased the advantages of the dynamic nuclear polarization-enhanced SSNMR technique for the characterization of co-crystals and salt forms. The NMR spectroscopy also provided more precise measurements of 1H–15N dipolar coupling constants and H–N bond lengths. These parameters facilitate a clear assignment of nitrogen protonation states and enable a definitive distinction between multicomponent systems as either co-crystals or salts. This methodology effectively addresses the prevalent confusion regarding the classification of the final product as co-crystals or salts.[6,7,8]

FORMATION OF CO CRYSTAL

4.1 Antisolvent crystallization

Antisolvent crystallization represents an alternative technique for the synthesis of high-quality co-crystals. In this method, a secondary liquid, which may be an organic solvent or a buffer, is introduced into the drug coformer medium to induce supersaturation. It is essential that the added liquid is miscible with the solvent to facilitate the precipitation of the co-crystal. However, a significant limitation of this approach is the necessity for a substantial volume of solvent during the preparation process.

4.2 Freeze Drying

The freeze-drying technique operates by first freezing the material and subsequently reducing the surrounding pressure, facilitating sublimation and resulting in a phase transition. This method is unique and offers numerous benefits compared to alternative techniques, particularly in large-scale production, as it addresses the challenges associated with variations in the solubility of the conformer. Research on the preparation of oxalic acid and theophylline cocrystals has demonstrated that freeze drying enables the creation of additional solid forms that are unattainable through conventional methods.

4.3 Solvent evaporation technique

The solvent evaporation technique is widely recognized as the most prevalent and dependable approach for the preparation of co-crystals. This method involves selecting the drug and coformer in an appropriate ratio and dissolving them in a shared solvent. Subsequently, the solvent is evaporated at ambient temperature to yield co-crystals. The solubility characteristics of both the drug and coformer are critical in determining the suitable solvent.

Intermolecular interactions, such as hydrogen bonding between the functional groups of the drug and coformer, facilitate the formation of co-crystals. A notable limitation of this method is the requirement for a larger volume of solvent compared to the liquid-assisted grinding (LAG) technique.[9]

Mounika et al. conducted a study on the preparation of fexofenadine-tartaric acid co-crystals using various methods and concluded that the solvent evaporation technique is straightforward, resulting in enhanced stability and solubility of the drug.

Additionally, this technique can also be employed to prepare multidrug co-crystals, such as sulfadimidine-aspirin. Savjani and Pathak explored the preparation of acyclovir co-crystals through solvent evaporation, wet grinding, and antisolvent addition, finding that the solvent evaporation method yielded superior results compared to the other techniques employed.

4.4 Neat grinding

Neat grinding is a solvent-free technique that involves the manual or mechanical pressing and crushing of a physical mixture of materials in a stoichiometric ratio, utilizing tools such as a mortar and pestle, ball mill, or vibrational mill. The process of co-crystal formulation relies on size reduction, which enhances the surface interactions between the co-crystal components. This interaction can facilitate the formation of covalent bonds or supramolecular reactivity between the target molecule and the co-former. Neat grinding serves as a practical alternative to solvent-based co-crystallization methods and, in certain instances, demonstrates greater selectivity than these traditional techniques. Typically, the grinding duration for this method ranges from 30 minutes to 1 hour. Neat grinding is recognized for its simplicity, speed, and convenience in the formation of co-crystals. Research conducted by Yuta Otsuka and colleagues successfully produced co-crystals of caffeine and oxalic acid using the neat grinding approach. Following approximately 10 minutes of mechanical grinding, the system reached chemical equilibrium. This investigation highlights that the rotation speed plays a more critical role than temperature in the co-crystal production process, with higher speeds correlating to an increased co-crystal yield.[10]

4.5 Solid-state grinding

Solid-state grinding, also referred to as dry grinding, involves the mixing and crushing of the drug and its coformers, typically utilizing a mortar and pestle or a milling device such as a ball mill. This method may encounter challenges in achieving successful co-crystal formation due to inadequate grinding, which can hinder the proper arrangement of crystals. Additionally, the heat

generated during the grinding process may compromise the stability of the materials involved. Consequently, drugs with high melting points are generally preferred for co-crystallization through mechanochemical grinding.

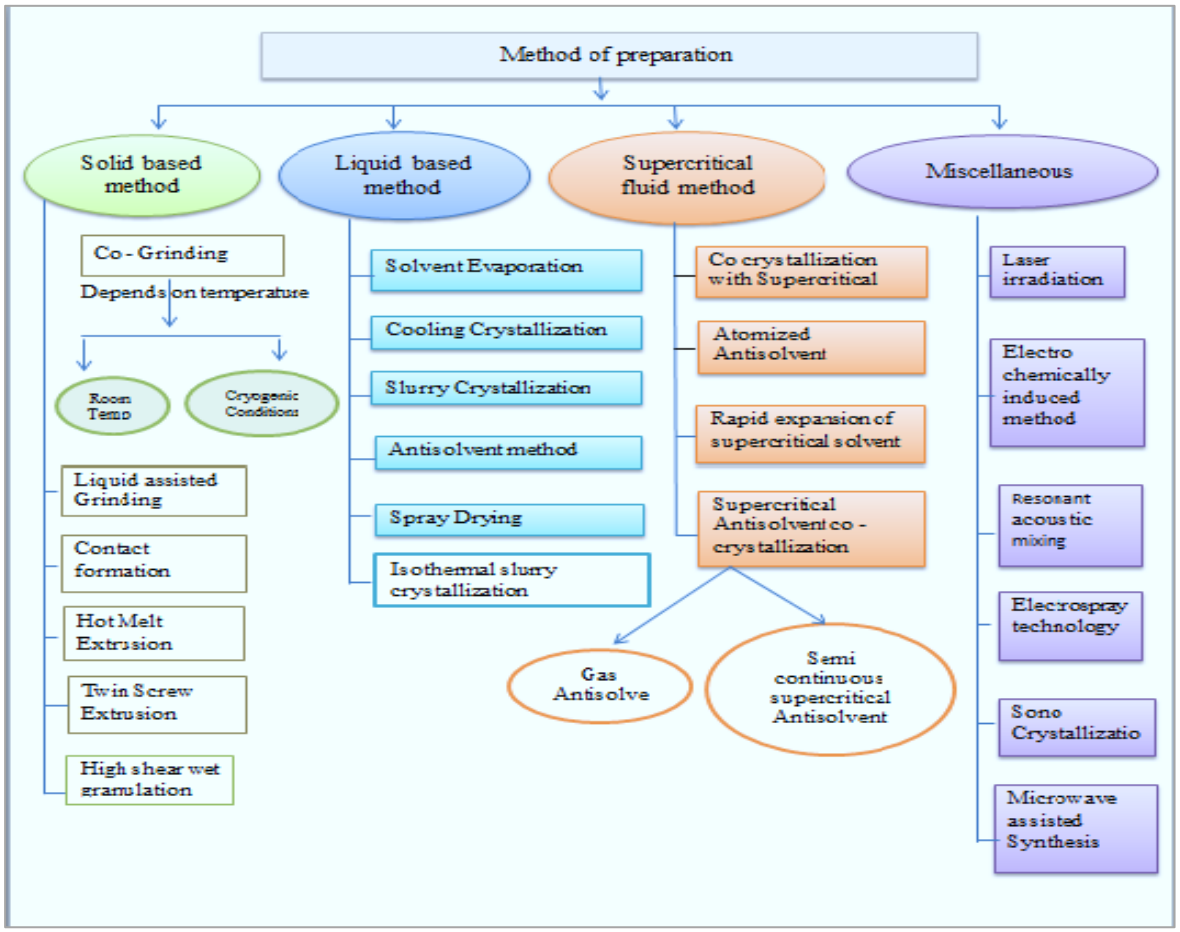


Fig6: Method of Preparation

Quashie et al. have successfully utilized mechanochemical synthesis to prepare co-crystals of sulfamethoxazole with 8-hydroxy-7-iodoquinoline-5-sulfonic acid as a coformer. Furthermore, Zaini et al. have validated the formation of a sulfamethoxazole-trimethoprim co-crystal through the milling process.

4.6 Microwave-assisted Co-crystallization:

The microwave-assisted co-crystallization technique is an efficient, cost-effective, rapid, and scalable approach. It offers enhanced yields by significantly reducing the reaction time when compared to traditional heating methods. Utilizing microwave energy as a heat source accelerates the formation of co-crystals relative to conventional heating processes. In this technique, the components of the co-crystal and solvents are subjected to microwave radiation within a reactor, maintained at appropriate temperatures and pressures for a designated duration to achieve the desired co-crystal product. Dipali Ahuja and colleagues successfully synthesized sulfamethazine co-crystals employing this microwave-assisted co-crystallization method. Their research indicates that the use of microwave heating notably increases the rate of co-crystal formation compared to standard heating methods. Furthermore, the study illustrates the feasibility of scaling the process from a production capacity of 0.2 grams to 20 grams without compromising product quality. These benefits can be leveraged in industrial applications to enhance formulation speed and ensure high-quality products.[11]

4.7 Electrospray method

Electron spraying is a concurrent process involving the formation of droplets and the generation of electric charge on those droplets. In this method of formulation, a solution containing co-crystal components is expelled from a capillary nozzle. The spray is subjected to a high electric potential, which leads to the elongation of the droplets, resulting in the formation of a jet. These droplets subsequently dry to produce powder particles, which are collected by a charged particle collector. Figure 1 illustrates the sequential steps involved in the electro spraying process and the generation of co-crystals using the electrospray technique.

4.8 Supercritical fluid processing

CO2 is the most used supercritical fluid in the preparation of co-crystals due to its penetration ability through the solids. The drug and coformer are added to a stainless-steel vessel by dissolving in CO2 and rapid expansion of the CO2 by gradually decreasing the pressure leads to the formation of co-crystals.40 The limited solubility of the drug and coformer in the supercritical fluid and less purity of the co-crystals are the main disadvantages of this method.[12]

4.9 Liquid-assisted grinding

Liquid-assisted grinding (LAG) represents a modification of the solid-state grinding technique, incorporating a small amount of solvent during the co-crystal development process. In this context, the introduced solvent serves as a catalyst for co-crystal formation. This approach offers several advantages over the solvent evaporation method, particularly in terms of reduced time requirements and lower solvent usage. Thenge et al. employed LAG to synthesize diacerein co-crystals using urea and tartaric acid. The coformer and the drug were combined in a 1:1 ratio within a mortar and pestle, and the mixture was ground for 90 minutes with the addition of a few drops of ethanol, constituting approximately 10% of the total weight.

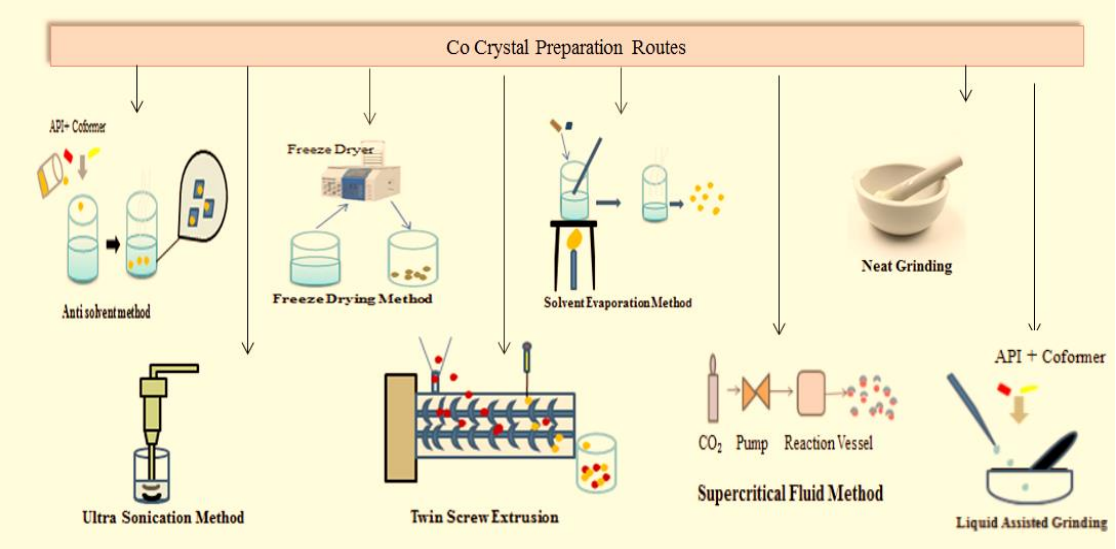


Fig7: Technique for cocrystal preparion

4.10 Hot melt extrusion (HME)

The method of melt extrusion represents a relatively novel approach to the preparation of cocrystals. This specialized technique involves the simultaneous melting and mixing of the target molecule and coformer through the utilization of a heated screw extruder. Typically, the initial materials are combined in a specific molar ratio and introduced into the heated extruder. As melting occurs, it promotes thorough mixing of the components. The cocrystal forms directly within the molten mixture, allowing for the continuous extraction of pure cocrystal extrudate from the extruder. This method offers several advantages, including the elimination of organic solvents, rapid processing times, improved conversion rates compared to solution-based techniques, reduced waste, and suitability for continuous pharmaceutical manufacturing. [13,14]

CHALLENGES ASSOCIATED IN THE DEVELOPMENT OF COCRYSTALS

The foremost obstacle in the advancement of pharmaceutical cocrystals lies in the identification of appropriate conformers. Theoretically, the potential number of conformers is exceedingly large, necessitating the creation of a screening tool capable of predicting likely conformers. Subsequently, these predicted conformers must undergo experimental screening to verify the formation of cocrystals. Given the heightened research activity in the domain of cocrystals over recent decades, a substantial amount of data has been gathered to facilitate the prediction of probable conformers. Various successful methodologies for conformer screening include hydrogen bond propensity, the Cambridge Structural Database, the supramolecular synthon approach, the pKa rule, and the Hansen solubility parameter. However, there remains a critical need for the development of more efficient screening tools to ensure the successful integration of cocrystallization within the pharmaceutical sector.[15]

PHYSICAL PROPERTIES OF CO-CRYSTALS

Melting Points of APIs, Coformers, and their Respective Cocrystals

The melting point, a key physical property of solids, serves as an important criterion for evaluating the purity of a product by analyzing the rate and range of its melting. A high melting point indicates that new materials possess thermodynamic stability; therefore, selecting a coformer with a higher melting point can enhance the thermal stability of an active pharmaceutical ingredient (API). In the case of thermolabile drugs, co-crystals with lower melting points may prove advantageous. Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA) are the predominant techniques employed for determining melting points and conducting.

API	API MP (°C)	coformer	coformer MP (°C)	cocrystal MP (°C)
AMG517	230			
AMG517		Trans-cinnamic acid	133	204
AMG517		2,5-dihydroxybenzoic acid	205	229
AMG517		2-hydroxybenzoic acid	61	130
AMG517		Glutaric acid	97	153
AMG517		Glycolic acid	78	141
AMG517		Sorbic acid	134	150
AMG517		Trans-2-hexanoic acid	34	127
AMG517		L-(+)-lactic acid	46	138
AMG517		Benzoic acid	122	146
AMG517		L-(+)-tartaric acid	171	198
Aspirin Aspirin	133-135			
		4,4′-bipyridine	111-114	91-96
Ethyl-Paraben	116- 39			
Ethyl-Paraben		Nicotinamide	128	107
Ibuprofen	77-78	4,4′-bipyridine	111-114	117-120
Ibuprofen				
Indomethacin	162 46			
Indomethacin		Saccharin	225-227	220
Norfloxacin	221 41	Isonicotinamide	155-157	180-185
Norfloxacin				
Piroxicam	198-220	Saccharin	225-227	220
Piroxicam				
Fluoxetine	157			
Fluoxetine HCL		Benzoic acid	122	132
Fluoxetine HCL		Succinic acid	185-187	134
Fluoxetine HCL		Fumaric acid	~287	161
Carbamazepine	190-192			
Carbamazepine		Succinic acid	187	189
Carbamazepine		Benzoic acid	122	123
Carbamazepine		Ketoglutaric acid, Form A	115	140
Carbamazepine		Ketoglutaric acid, Form B	115	134
Carbamazepine		Maleic acid	137	158
Carbamazepine		Glutaric acid	98	125
Carbamazepine		Malonic acid, Form A	136	143
Carbamazepine		Oxalic acid	189	158
Carbamazepine		Adipic acid	152	137
Carbamazepine		(+)-camphoric acid	186	156
Carbamazepine		4-hydroxybenzoic acid, Form A	2132	172
Carbamazepine		4-hydroxybenzoic acid, Form C	213	170
Carbamazepine		Salicylic acid	159	159
Carbamazepine		1-hydroxy-2-naphthoic acid	192	174
Carbamazepine		DL-tartaric acid, Form A	205	170
Carbamazepine		L-tartaric acid	169	160
Carbamazepine		Glycolic acid	149	139
Carbamazepine		Fumaric acid, Form B	287	189
Carbamazepine		Saccharin	225-227	174
Carbamazepine		Nicotinamide	128	151
Carbamazepine		Benzoquinone	113-115	170
Carbamazepine		Terephthalaldehyde	114-116	124
Carbamazepine		Trimesic acid	>300	278
Carbamazepine		5-nitroisophthalic acid	259-261	190

Table 2 : Physical properties (Melting Points of APIs, Conformers,) of co-crystals

thermal analyses. The melting point of medicinal co-crystals can be optimized through the careful selection of coformers. In a study involving ten co-crystals of the API AMG-517, the melting points were analyzed to assess the influence of different coformers. The results indicated a correlation between the melting points of co-crystals and their respective coformers, although this relationship was not linear with respect to solubility. It is recommended to use a high melting point coformer for high melting point co-crystals and vice versa. Numerous studies have reported similar findings, suggesting that the melting point of a coformer does not significantly affect solubility, while the melting point of the co-crystal is more determinative. The use of a less polar and hydrophobic coformer demonstrated that co-crystals exhibit lower water solubility compared to APIs alone. Co-crystals formed from similar hetero synthons displayed varying melting points due to differences in crystal packing. The melting point is a crucial consideration in the formulation of co-crystals, prompting extensive research into high melting point co-crystals with optimal solubility, as low melting co-crystals often face challenges related to stability, drying, and processing.[16,17,18]

Tabletability

The co-crystallization of pharmaceuticals with coformers can significantly influence tabletability, compaction, and crystal packing, all of which are essential considerations in formulation research. Studies have demonstrated that paracetamol co-crystals formed with trimethylglycine and oxalic acid exhibit superior compaction properties compared to the drug in its unmodified state. Furthermore, the co-crystallization of resveratrol with 4-aminobenzamide and isoniazid has been shown to markedly enhance tabletability. By altering the crystal packing during the co-crystallization process, it is feasible to modify the mechanical properties of active pharmaceutical ingredients (APIs), as evidenced by the co-crystals of vanillin isomers. Our recent research into the co-crystallization of isoniazid with various coformers has yielded improvements in mechanical characteristics.[19]

Fig8: Properties of co crystal

Solubility

Solubility represents a fundamental attribute of active pharmaceutical ingredients (APIs). Various studies have employed co-crystallization, alongside other techniques such as salt formation, solid dispersion, and particle size reduction, to enhance the solubility of pharmaceutical compounds. For instance, the solubility of the antifungal API ketoconazole was increased by 53 and 100 times through the synthesis of salts and co-crystals, respectively, demonstrating that co-crystals yield a more soluble formulation than salt formation.[20] In a comparative analysis, apixaban co-crystals exhibited a twofold enhancement in solubility and a more rapid dissolution rate relative to the pure drug. Additionally, the solubility of pterostilbene–piperazine co-crystals was augmented sixfold, while pterostilbene–glutaric acid co-crystals experienced rapid precipitation due to the high solubility of glutaric acid. Furthermore, co-crystals of 6-mercaptopurine with nicotinamide demonstrated a dissolution rate that was twice as fast as that of the drug alone.[21] Theoretical calculations of Keq are utilized to assess the solubility of co-crystals in a pure solvent, serving as a valuable resource for co-crystal selection and formulation. Keq has been characterized using a diverse array of over 40 co-crystal and solvent combinations.[22]

Stability

Conducting a stability study is essential for the development of new dosage formulations. Automated tests for water sorption and desorption are performed under conditions of relative humidity to evaluate the influence of water on the formulation. [23]The behavior of co-crystals under relative humidity stress has been examined by various researchers.[24] During these tests, indomethacin-saccharin co-crystals exhibited minimal water sorption, with no signs of dissociation or transformation occurring under the experimental conditions.[25] Theophylline co-crystals demonstrated stability across different relative humidity levels (0%, 43%, 75%, and 98%) over various durations (1 day, 3 days, 1 week, and 7 weeks). [26] The results indicated an enhancement in stability and physical properties, particularly in preventing the formation of hydrates.[27] Any alterations or chemical degradation in the formulation should be assessed during the chemical stability analysis, especially under accelerated stability conditions. Co-crystals of glutaric acid with an active pharmaceutical ingredient (API) displayed remarkable chemical stability over a two-month period at varying temperatures.[28] In different humidity conditions, carbamazepine and saccharin co-crystals

also exhibited good chemical stability over two months. Numerous studies have focused on thermal stability.[29] When subjected to differential scanning calorimetry (DSC), paracetamol co-crystals containing 4,4-bipyridine showed greater stability compared to other coformers.[30] Solution stability is a vital aspect in the formation of co-crystals, as it can be utilized to assess the stability of the solution. [31] Investigations into solution stability provide insights into the behavior of co-crystals in release media.[32] It was observed that when carbamazepine co-crystals were analyzed in water for 20 to 48 hours, coformers with high water solubility formed dihydrates, while those with low water solubility did not.[33] The caffeine/oxalic acid co-crystals remained physically unchanged after being slurried in water at room temperature for two days, demonstrating greater stability than other materials at all relative humidity levels up to 98% for a duration of seven days. [34]

The stability of carbamazepine and saccharine was evaluated by combining equal quantities of both compounds in water. [35] However, the powder X-ray diffraction (PXRD) analysis of the resulting solid indicated the exclusive formation of co-crystals. Research on photostability is conducted to investigate the impact of light on pharmaceuticals that are sensitive to illumination. [36] This type of research is essential for such medications, as many are prone to instability when exposed to light. There is a scarcity of literature addressing the chemical stability of co-crystals. [37] Notably, the photostability of nitrofurantoin co-crystals with various coformers was found to be superior to that of its pure form and physical mixtures. [38] After 168 hours, all co-crystals, except for one, exhibited minimal degradation (3%), suggesting that co-crystallization can effectively mitigate the photodegradation of light-sensitive drugs. [39]

Bioavailability

Bioavailability is defined as the rate and extent to which a medication enters the systemic circulation. The development of new drug formulations encounters significant obstacles due to low oral bioavailability.[40] Crystal engineering is essential in the design and synthesis of pharmaceutical co-crystals that enhance both oral bioavailability and aqueous solubility.[41] For example, a pharmacokinetics study involving beagle dogs revealed that apixaban–oxalic acid co-crystals demonstrated an oral bioavailability that was 2.7 times greater than that of the pure drug. [42] Another instance includes the formulation of co-crystals with nicotinamide, which significantly improved the oral bioavailability of baicalein. In studies conducted on rats, this improvement led to peak plasma concentrations (Cmax) and area under the curve (AUC) that were 2.49 and 2.80 times higher, respectively, compared to the pure drug. [43] Additionally, co-crystals of meloxicam and aspirin in rats showed a 12-fold quicker onset of action and enhanced oral bioavailability relative to the pure drug. [44] Moreover, co-crystals of 6-mercaptopurine, categorized as a BCS class-II medication, exhibited an oral bioavailability increase of 168.7% compared to the pure drug.[45]

Permeability

The ability of drugs to permeate cellular membranes is a critical determinant of their absorption and distribution.[46]When assessing the unmodified form of a drug, the permeability of pharmaceuticals primarily relies on the n-octanol/water partition coefficient, as indicated by log P and (C log P).[47] The permeability of hydrochlorothiazide and its co-crystals with various coformers was examined using Franz diffusion cells. With the exception of succinamide co-crystals, all other co-crystals exhibited higher drug flow rates compared to the pure drugs. [48] This enhancement in permeability for the co-crystals can be attributed to the formation of a heterosynthon between the drug and the coformer. [49]

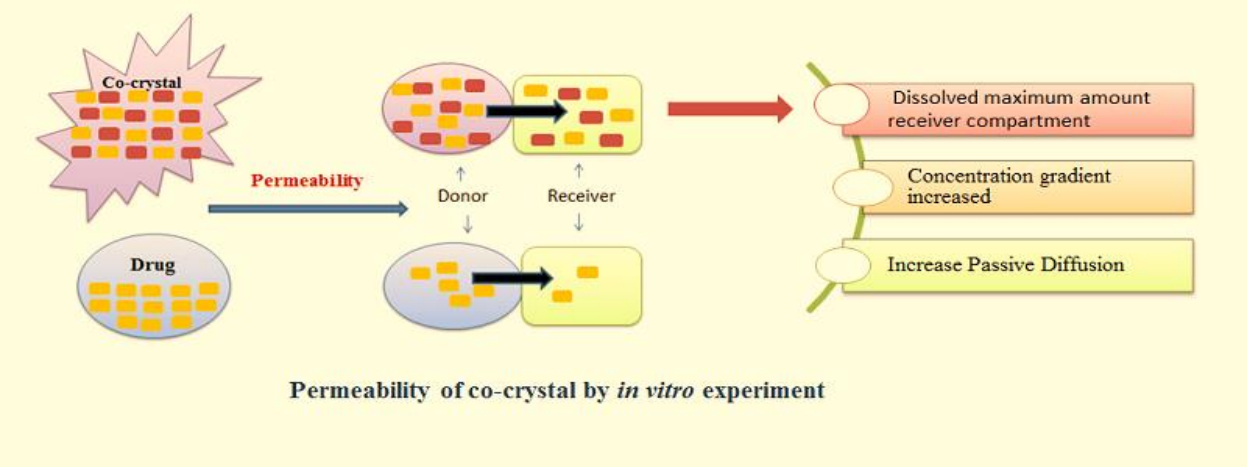


Fig 9: permeability of co crystal

TYPE OF CRYSTAL

7.1 Ionic cocrystals

In ionic cocrystals, hydrogen bonds between common donors and acceptors (OH, NH, O, N, etc.) may contribute to the dominating electrostatic interaction. [50] Ionic cocrystals of sodium chloride and carbohydrates are the best illustration of this. Childs et al. invented fluoxetine hydrochloride ICCs with a group of carboxylic acid coformer, and Childs et al. investigated organic cation halides based on ionic cocrystals. Examples of ICCs include streptomycin acid salts with alkaline earth metals, saxagliptin hydrochloride with enhanced stability, and tetracycline ICCs with enhanced performance.[51]

7.2 Molecular cocrystals

These cocrystals contain only conformer (neutral components).[52]

7.3 Multidrug cocrystals

Multidrug cocrystals, often referred to as drug-drug cocrystals, are crystalline solid solids composed of two or more medicinal compounds in a stoichiometric ratio. They have emerged as a more recent method for drug development.[53]

To determine an organic molecule's crystal structure from the chemical diagram, a number of crystal structure prediction tools were created.[54] Nonetheless, the presence of polymorphism—the emergence of distinct crystal forms that share a single molecule immediately demonstrates that certain crystal structures are not the most thermodynamically stable.[55] Molecules frequently crystallise in a metastable polymorph before changing into a stable state.[56]

REGULATION OF PHARMACEUTICAL CO-CRYSTALS

The regulation of pharmaceutical co-crystals and their formulations can significantly influence the strategies for development and quality control.[57] The US Food and Drug Administration (USFDA) defines co-crystals as "solids that are crystalline materials composed of two or more molecules within the same crystal lattice." The USFDA was the pioneer agency to provide guidance on the regulatory classification of pharmaceutical co-crystals.[58] These co-crystals are categorized as drug product intermediates (DPIs) that are anticipated to enhance the physicochemical properties of a drug. It is essential to demonstrate the extent of proton transfer in substances identified as co-crystals. [59] Furthermore, co-crystals must dissociate to regenerate the drug before it can exert its therapeutic effect. [60] The guidance outlines the necessary data for submission and discusses the implications of this classification for new drug applications and abbreviated new drug applications. [61] Notably, the recommendations from the USFDA do not pertain to pre-existing materials such as complexes, polymers, salts, or other non-crystalline forms. This guidance is specifically relevant to materials that have not been previously classified, such as pharmaceutical co-crystals.[62] Recently, co-crystals have been categorized as "new active substances," defined as "different salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives of an active substance shall be regarded as the same active substance unless they significantly differ in properties concerning safety and/or efficacy." Scientifically, solvates, including hydrates, may be viewed as a subgroup of co-crystals; however, the regulatory context may vary. [63] The European Medicines Agency (EMA) does not recognize multiple phase materials obtained through co-precipitation or physical mixing as co-crystals. [64] The EMA states that the documentation procedures for co-crystals and salts can be applied due to their conceptual similarities. In instances where a complex coformer is utilized, additional documentation may be necessary, following the scientific protocol.[65]

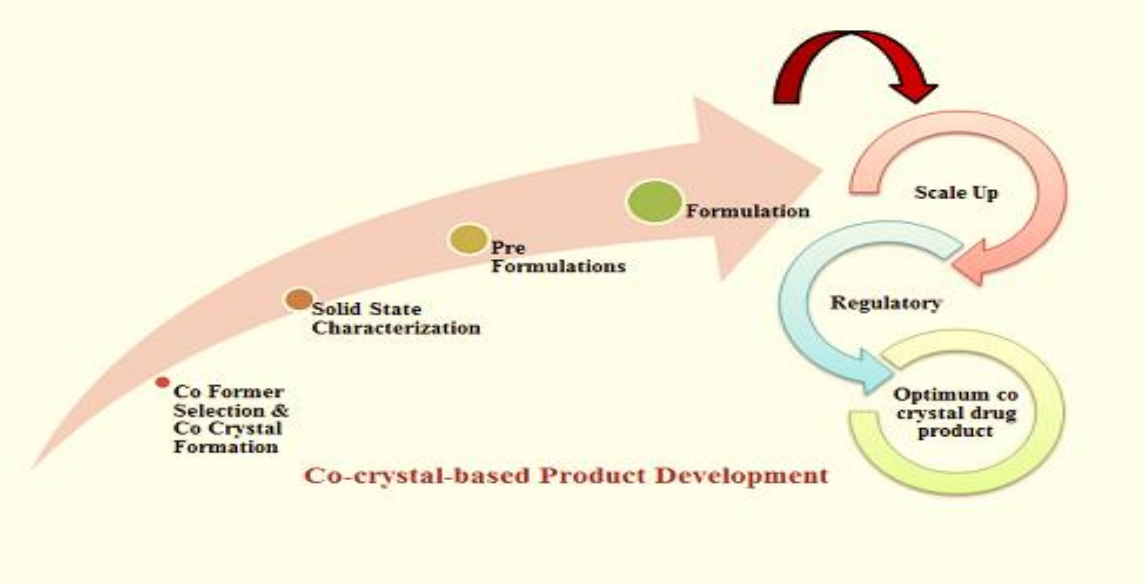


Fig10: cocrystal based product development

CONCLUSION

The design and development of a pharmaceutical cocrystal system to get beyond the physicochemical restrictions of the parent medication is successfully demonstrated in this work. Solid-state characterisation methods verified the production of the cocrystal, demonstrating the development of intermolecular interactions between the drug and conformer In comparison to the pure medication, the produced cocrystal showed notable improvements in solubility, dissolving rate, and o verall physicochemical stability, indicating that it may improve bioavailability.These results demonstrate cocrystallization's effi cacy as a viable approach to medication development, especially for poorly soluble molecules.Additionally, the cocrystal syste m's enhanced performance suggests that it could be used to increase therapeutic efficacy, particularly in disease models like can cer where drug delivery and absorption are critical.To prove its safety, effectiveness, and scalability for pharmaceutical applicat ions, more in vivo research and clinical assessments are necessary.

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