



## Review on Co-Crystals New Approach to Modify the Physicochemical Characteristics of API

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### ABSTRACT

The expansion of a novel product is constrained by an active medicinal ingredient's poor solubility in aqueous solutions and limited oral bioavailability. A novel strategy to improve the physicochemical characteristics of the active medicinal ingredient is co-crystal formation. The pharmacological action of the API is unaffected by co-crystallization with pharmaceutically acceptable molecules, although it can enhance the physical characteristics like solubility, stability, and dissolution rate. Cocrystals are multi-component systems comprising active medicinal ingredients that also contain a stoichiometric amount of a coformer that is acceptable to the pharmaceutical industry. The pharmaceutical business has a significant chance to create new medicinal products since producing pharmaceutical co-crystals can enhance a drug's physicochemical qualities. The most major benefit of co-crystals is their ability to produce novel medications with improved solubility, which increases the effectiveness and safety of the treatment. The thermodynamic stability of the co-crystal preparation is the key influencing factor. Co-crystal screening provides information on the chemical composition and connection between the active medicinal ingredient and the coformer. This review discusses the many co-crystal synthesis techniques, including hot-melt extrusion, slurring, antisolvent, grinding, and spray drying. Here is a quick explanation of the characterization methods frequently employed for co-crystals, as well as their uses in medicine. Here are some quick summaries of reported research on co-crystals that were evaluated in order to better grasp the notion of co-crystals.

**Keywords:** Pharmaceutical cocrystals, cocrystallization, solubility, stability, bioavailability, physicochemical property

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### INTRODUCTION

A drug's activity and effectiveness are significantly influenced by its solubility and dissolution rates. Early research into drug discovery was based on folk remedies or accidental discoveries. But over the last two decades, rational drug synthesis and design have become necessary of the development of drugs and the emergence of new diseases. There are numerous new drug targets that. The effectiveness of identified and potential drug molecules has been examined by synthesizing and using advanced methods like combinatorial chemistry and high-throughput screening. Pharmaceutical industry chemists and engineers typically aim to deliver crystalline forms of their active compounds due to the inherent stability of these forms of crystalline substances and the well-known process of crystallization's effect on filtration and isolation of chemical compounds raising awareness attention is now given to the effects of material properties on drug development and early drug discovery as the Drug ingredients are frequently extremely valuable

resources. The goal of the pharmaceutical sector is to quickly advance development initiatives with assurance so that formulation issues are less likely to occur, to increase a compound's therapeutic potential. This commentary aims to increase crystal's visibility. Form research and the newly popular subject of crystal by talking about engineering in pharmaceutical science the most recent developments in prescription crystals and by highlighting the potential outcomes for the future developments.

Numerous medications with low aqueous solubility have been found in the recent years. About 60-70 percent of these recently discovered drugs have been In relation to the BCS Class II (low toxicity) compounds IV (low solubility/low permeability) . Numerous potent pharmaceutical active ingredients (APIs) weren't created in formulations because they are poorly soluble in water which results in low drug bioavailability. The pH of the gastrointestinal tract varies

depending on parts, so medications administered orally have various solubility in digestive fluids at various pH, causing nonlinear and variable absorption quite frequently. Drug effectiveness and safety cannot be assessed properly. Due to this, a drug's limited solubility is a concern. Significant difficulty in creating oral dosage forms. The goal of the pharmaceutical industry is to confidently advance development programs quickly so that formulation issues are less likely to occur. to increase a compound's therapeutic potential. This commentary aims to increase crystal's visibility. Form research and the newly popular subject of crystal by talking about engineering in pharmaceutical science the most recent developments in pharmaceutical crystals and by highlighting the potential outcomes for the future developments. To increase a drug's solubility and increase its bioavailability, researchers have developed a number of strategies.

Reduction in size, salt formation, complexation of solids, self-emulsifying drug delivery system with nanoparticles (SEDDS), co-solvent addition, and nano-suspension and cocrystal formation, as well as emulsion. examples of the methods employed to increase solubility of drugs with poor water solubility. Each method has its own merits and shortcomings, as well as specific elements (like API characteristics, excipients chosen, and method used to develop and determine the makeup of a dosage form) should be borne in mind when choosing a technique. Among all of these methods, the crystal approach Unusual in that it has no impact on pharmacological effects the drug's properties, but it might enhance the drug's improved bioavailability and several of melting point, tabletability, solubility, stability, bioavailability, and permeability are examples of physicochemical properties. Various distinct solid forms, such as polymorphs, solvates, hydrates, salts, and co-crystals, are possible for pharmaceutical active ingredients (APIs). amorphous solids, etc. Every form displays a different physicochemical characteristic that have significant influence the manufacturing and bioavailability purification, consistency, and other abilities attributes of the drugs Design and discovery of solid forms are dependent on the characteristics of the target molecule and the difficulties in developing its physical properties. Typically, the preferred solid form is crystalline form of the substance that is thermodynamically most stable compound<sup>[3,4]</sup>. But the consistent crystal form of the Parent compound might not be very soluble or dissolution rate, which causes insufficient oral absorption, especially for compounds that are water-insoluble. That is In this instance, alternative solid forms might be

researched. Creating salt forms for ionizable compounds utilising acids and bases that are safe for use in medicine is a typical method for increasing bioavailability. Pharmaceutical salts may be similar to the parent compound in a variety of polymorphic, solvated, and/or hydrated forms. They are crucial in the development of new solids, particularly in the pharmaceutical industry. Amorphous forms, crystalline solid formulations, and lipid formulations can all be used to create the poorly water-soluble medications. to make them more soluble. A promising method for crystal engineering is cocrystallization addressing issues related to the drug.

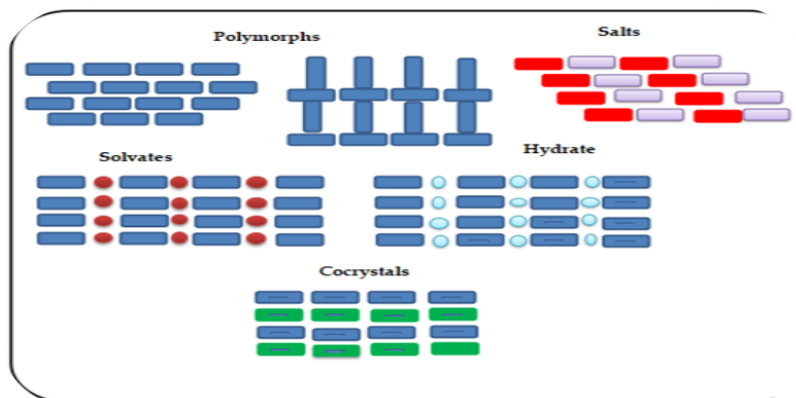
### Co-crystal

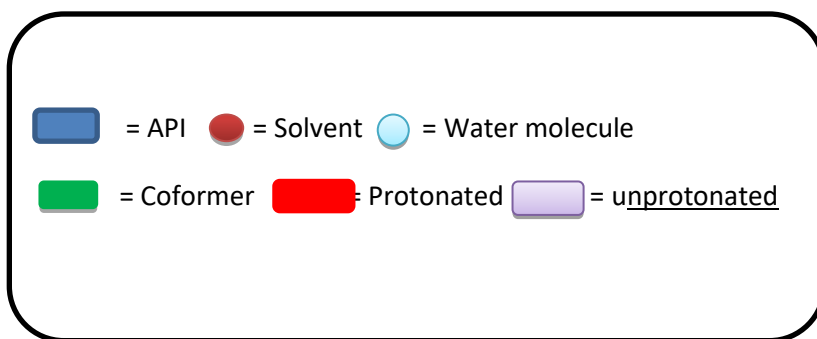
Etter was the first to report the term "cocrystal" and the design guidelines for hydrogen bonding in an organic cocrystal. The first person to give the was Desiraju Concept of hydrogen bond formation in crystal structures based on supramolecular synthon<sup>[1]</sup>.

Pharmaceutical co-crystals can be defined as crystalline materials comprised of an API and one or more unique co-crystal formers, which are solids at room temperature. P stacking, van der Waals forces, hydrogen-bonds, and other types of interaction can all be used to create co-crystals. and Solvates By this definition, hydrates of the API are not regarded as cocrystals. But co-crystals might include one or more molecules of the solvent or water in the Lattice of a crystal. Frequent<sup>[2]</sup>ly, API neutral molecules form hydrogen-bonded assemblies to form co-crystal and another element. The majority of reported cocrystals fall into the category of molecular cocrystals, which are made up of neutral or non-ionized cofomers in a stoichiometric ratio. Ionic cocrystals were created by charge-assisted hydrogen bonds and/or coordination bonds and contained ionized cofomers in a stoichiometric ratio<sup>[11]</sup>. Pharmaceutical cocrystals are those that contain an API as one component and a cofomer as another component in a stoichiometric ratio.<sup>[3]</sup>

### Cocrystals, Polymorphs, Solid Dispersions, Solvates (Hydrates), and Salts

In the draft guidance, USFDA defined cocrystal, salt, and polymorphs. Compounds that exist in various crystalline forms, such as solvates or hydrates (also referred to as pseudopolymorphs), as well as amorphous forms are referred to as polymorphs. Due to the different crystal lattice arrangements in polymorphs, they also have different physicochemical characteristics. The complete proton transfer from one acid to a base, salts and cocrystals can be distinguished from one another<sup>[4]</sup>.





**Figure 1:** Different solid forms of Active Pharmaceutical Ingredient

### Comparision between co- crystal and salt

Pharmaceutical co-crystallization has two inherent advantages over the salt form, despite the fact that it has only recently attracted widespread attention as a method of altering the physicochemical properties of APIs. The first reason is that co-crystal formation might be used with any API, including basic, acidic, and nonionisable molecules.<sup>[5]</sup> The second reason is that there are a lot of potential "counter molecules" that might be considered non-toxic, broadening the application of pharmaceutical co-crystallization over salt forms. When salt is formed for toxicological reasons, only acidic or basic counter-ions are investigated in the typical API salt form, but when cocrystals are screened, a wide variety of potential cocrystal cofomers that are unrestricted by toxicology are available. The US Food and Drug Administration has kept a list of thousands of substances that are frequently used as potential co-formers for pharmaceutical cocrystals (i.e., the FDA's "generally recognized as safe" (GRAS) list: a list of substances generally recognized as safe). Cocrystals are made up of an API and a neutral molecule (coformer compound), as opposed to polymorphs, which have just one API in the crystal lattice.<sup>[6]</sup>

### Comparison of Co-crystal and Solvent

Based on the physical state of the constituents, co-crystals and solvates can be distinguished from one another. Solvates are substances that are liquefiable at room temperature, while co-crystals are substances that are solid at room temperature.<sup>[7]</sup>

### Comparison of Co-crystal and Hydrate

Hydrates are solvates that have water as a solvent within their crystal lattice. Solvates and hydrates can change the physicochemical properties of APIs and are frequently formed during cocrystallization via solution or liquid assisted grinding. 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 low humidity levels during storage, as well as the different physiochemical characteristics between hydrated and dehydrated forms, solvates/hydrates are quite unstable.<sup>[8]</sup>

### CONSIDERATIONS OF CO-CRYSTALS

Advantages of co-crystals include their stable crystalline form (as opposed to amorphous solids), the absence of the need to form or break covalent bonds, the theoretical ability of all types of API molecules to form co-crystals (weakly ionizable/non-ionizable), the presence of a large number of potential counter-molecules (food additives, preservatives,

pharmaceutical excipients, and other APIs), the unique solid form<sup>[9]</sup>

### Design of Co-crystals:

Various theoretical methods have been described for the mechanism of co-crystals, including hydrogen bonding propensity, the Cambridge Structure Database, supramolecular synthon, pKa values, and Hansen solubility parameters.<sup>[10,11]</sup>

Typically, the experimental work is followed by a survey of the Cambridge Structural Database (CSD) for the crystal engineering experiment. Co-crystals built on the supramolecular synthesis principle offer a strong strategy for the proactive discovery of new pharmaceutical solid phases. Multiple components come together in co-crystals in a specific stoichiometric ratio, and various molecular species interact both through hydrogen bonds and other types of bonds.

### Hydrogen bonding :

Graph sets, synthons, and hydrogen bonding rules can all be used to help with the design and analysis of co-crystal systems. In general, though, it is currently necessary to use empirical methods to determine whether co-crystallization will take place. By taking into account the potential interactions between the hydrogen bond donors and acceptors of the materials that will be co-crystallized, the co-crystal formation can be explained. Following a thorough investigation of hydrogen bond patterns and preferential packing preferences in a variety of organic crystals,<sup>[12]</sup> Etter and colleagues proposed the rules to make the deliberate design of hydrogen-bonded solids easier. Six-membered ring intermolecular hydrogen bonds form more frequently than intermolecular hydrogen bonds because they are the best proton donors and acceptors for hydrogen bonding. Intermolecular hydrogen bonds will form between the best proton donor and acceptors that are still present after intermolecular hydrogen bond formation (but not all acceptors will necessarily interact with donors). These findings contribute to resolving the problem of competing hydrogen bond assemblies that was seen when using a specific cocrystallizing agent.<sup>[12]</sup>

### CSD:

CSD is a validated tool that makes it easier to analyze packing motifs statistically and thereby reveal information about typical functional groups. Based on the functional group that interacts with supramolecular synthons, CSD is used to

provide information about the molecular association of drugs and Coformer. CSD can create a library of appropriate Coformer for an API. This method for locating suitable co-crystal forming pairs uses computers and cuts down on both research time and experimental expense.<sup>[13]</sup>

#### pKa value :

A proton transfer between an acid and a base can be used to predict the crystallization of co-crystals or salts. The pKa value of an acid and a base can be used to predict the formation of salt or co-crystals. If the value of pKa [pKa (base) - pKa (acid)] is greater than 2 or 3, salt formation typically occurs between acid and base. A smaller value of pKa (less than 0) will almost certainly lead to the formation of co-crystals, but the intermediate value of pKa (between 0 and 3) was unable to distinguish clearly between co-crystals and salts. There is a co-crystal to salt continuum between pKa values of 0 and 3.<sup>[14]</sup>

#### Hansen solubility parameter

Another crucial method for assessing the miscibility of drugs and Coformer used in co-crystal systems is the Hansen solubility parameter. The formation of co-crystals may be predicted by the miscibility of the components in the solid state. The use of components with similar miscibility increased the success rate of the co-crystal synthesis . It was

shown that the two elements ought to mix if the total HSPs differ was immiscible otherwise, was 7MPa n0.5. If the difference between two substances that are supposed to form co-crystals is less than 5 MP0.5, another method calculates the miscibility of two components .<sup>[15]</sup>

#### Methods of Preparation of Cocrystals<sup>[16,17,18,19,20]</sup>

The literature's descriptions of co-crystal formation show the notoriously challenging situation these systems present in terms of preparation. A single co-crystal of good enough quality for a single X-ray diffraction analysis has been known to require six months of preparation. This is in part because a heteromeric system of this kind can only come into existence if the noncovalent forces between two or more molecules are stronger than those in the corresponding homomeric crystals between the molecules. Co-crystal design strategies are still being investigated, and the formation mechanism is still not fully understood.<sup>[33]</sup>

Both solvent-based and solid-based methods can be used to prepare co-crystals. Slurry conversion, solvent evaporation, cooling, crystallization, and precipitation are all components of the solvent-based processes.<sup>[21]</sup>

Net grinding, solvent-assisted grinding, and sonication between 80 and 85 degrees are the solid-based methods.

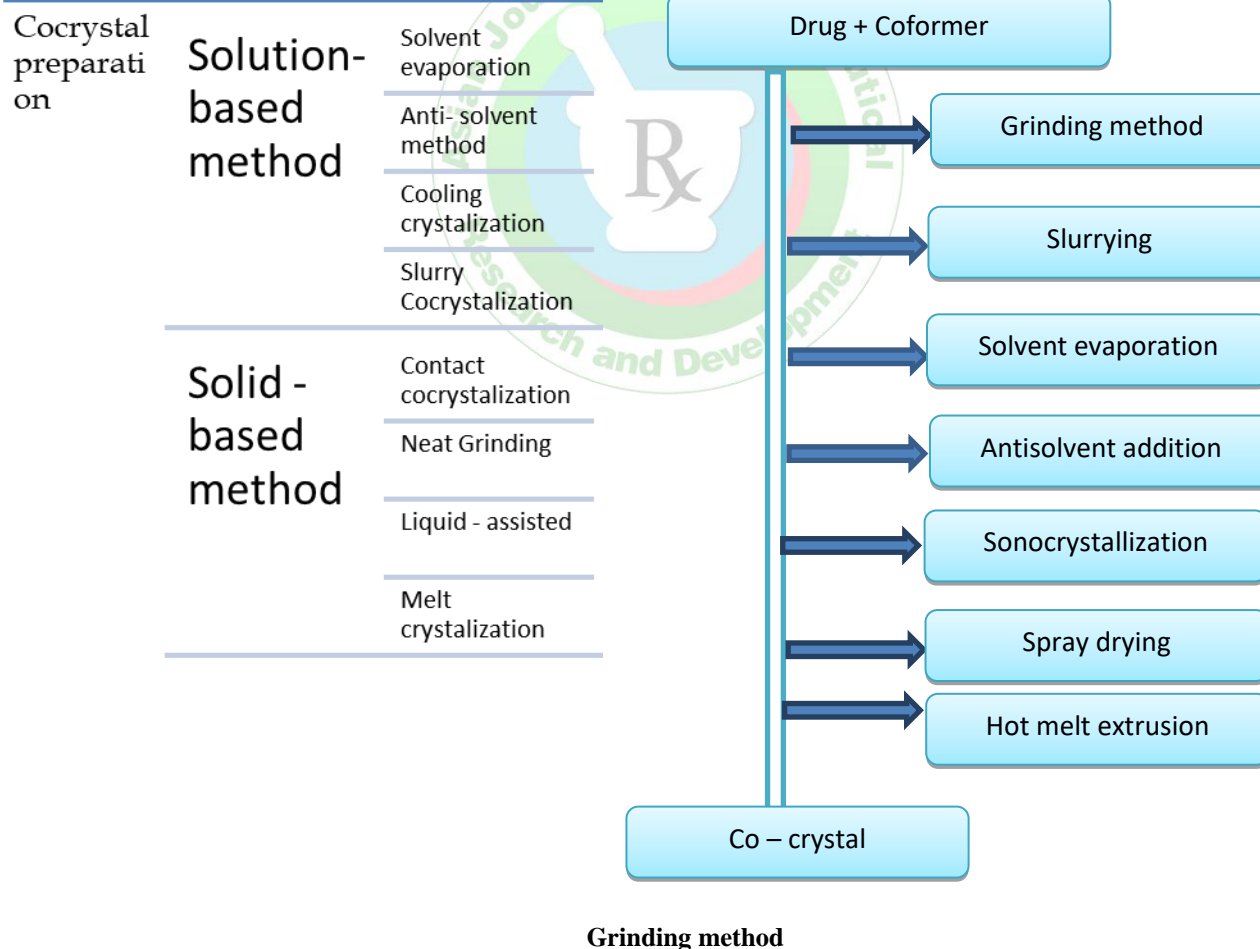
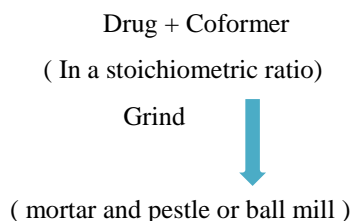


Figure 2: Common method for co-crystal Preparation<sup>[22,23]</sup>

Grinding methods have been widely used for co-crystal production in recent years and have been found to be superior to other approaches (solution or melt). There are two sorts of grinding techniques: dry grinding and wet grinding.<sup>[24]</sup>

## 1. Dry grinding (solid-state grinding)



It is also known as mechanochemical grinding or solid-state grinding. Dry grinding can be accomplished in a variety of ways, including mechanical grinding with a ball mill mixture, vibratory milling, or manual grinding with a motor and pestle. Prabhakar et al. employed a dry grinding process to create co-crystals of Piroxicam with sodium acetate as a coformer.<sup>[25]</sup>

The dry grinding procedure results in the creation of co-crystals. The author indicated that the properties of piroxicam co-crystal and formed orodispersible tablets had been adjusted, resulting in faster disintegration and a higher dissolution rate.

## 2. Wet grinding (Liquid- assisted grinding)

Drug + Coformer

(In a stoichiometric ratio )

Grind ( mortar and pestle or ball mill )

Addition of some drops of solvent in the mixture

The diagram shows the same initial steps as dry grinding, but with a blue box containing the text 'Addition of some drops of solvent in the mixture' and a downward arrow pointing to the grinding step.

Liquid-assisted grinding (LAG) is a modification of the solid-state grinding procedure that involves the addition of a small amount of solvent. The additional solvent acts as a catalyst in the creation of co-crystals. When compared to the solvent evaporation approach, this method is more favorable because it requires less time and less solvent.<sup>[9]</sup> Panzade et al. developed Zaltoprofen Nicotinamide co-crystals using LAG. To create co-crystals, the drug and coformer were mixed separately in mortar and pestle in different molar ratios (1:1 and 1:2) for 45 minutes.<sup>[26]</sup>

This is one way for producing high-quality co-crystals. During this procedure, the coformers are dissolved in various solvents, including organic solvents, and the API is disseminated in the coformer solution using a dispersion homogenizer<sup>[28]</sup>. The coformer on the medication is then precipitated by adding this solution to distilled water or another appropriate solution. The disadvantage of this procedure is that it requires a large amount of solvent for preparation.

## 3. Slurrying

Slurry crystallization is a simple technique that involves adding solvent to the API as well as a suitable coformer. The physical stability of the crystallization solvent to co-crystals and its solid former mostly influences the choice of this procedure. The creation of co-crystals is accomplished by adding coformer to the solution and stirring it. The solvent is subsequently evaporated at room temperature to obtain co-crystals, which can then be characterized by PXRD. Prafulla et al. used ultrasound-assisted slurry co-crystallization procedures to create a caffeine/maleic acid co-crystal.<sup>[27]</sup> Rahman et al. performed a grinding and slurry technique comparison research of acyclovir and succinic acid co-crystals. The results show that the generated co-crystals prepared by the slurry approach have a high crystalline structure. Instead of grinding, the X-ray diffraction approach produced the highest diffraction peak intensity and dissolving efficiency at 15 minutes. The main downside of this approach is that it uses a lot of solvent.

## 4. Antisolvent inclusion

## 5. Hot - melt Extrusion

It's also known as the solvent drop extrusion method. Hot-melt extrusion is frequently used as an infinite manufacturing method in a single step for the preparation of co-crystals. The choice of this approach is primarily determined by the compound's thermodynamic stability. It entails the production of co-crystals without the need of a solvent, resulting in high efficiency mixing and better surface contact. The co-crystals are generated in this process by applying<sup>[29]</sup> high-intensity mixing to the drug and coformer to make them miscible in the molten state. The drug and coformer must be miscible at the molten stage for this approach to work.

## 6. Sonocrystallization

This method was created for the creation of very small co-crystals, also known as nanocrystals. In this process, the drug and coformer are dissolved in a shared solvent and held at a consistent temperature for sonication. Cold water is made available to keep the sonicator at a consistent temperature and prevent fragmentation. The solution is left to dry overnight. The creation of cocrystals is caused by further evaporation of the solvent. This process yields pure co-crystals, and the<sup>[30]</sup>

purity of co-crystals may be determined using an X-ray diffraction analysis.

## 7. Spray drying<sup>[34]</sup>

Spray dryers are employed in the production of co-crystals. It is a continuous, one-step procedure for converting liquids (solutions, suspensions, and slurries) to solid powders. To make good cocrystals, dissolve the medication and coformer solution in a common evaporating solvent and spray it into a hot stream of air for evaporation of the solvent. This is the most commonly used technique since it is a rapid, continuous, and one-step process. As a result, the spray drying procedure will provide a one-of-a-kind environment. Urano et al. used spray drying to create co-crystals of Cilostazol-Hydroxybenzoic Acid (CLZ-HBA). The author compared the properties of CLZ-HBA co-crystals produced by solvent evaporation, slurry, and spray drying. The findings indicate that the spray drying approach is effective and coformer dissolution was improved. This suggests that the spray drying

process could be used to successfully manufacture poorly water-soluble pharmacological co-crystals.

## 8. Solvent evaporation technique<sup>[35]</sup>

This is the most common and dependable procedure for producing co-crystals. The medication and coformer are chosen and dissolved in a shared solvent at an appropriate stoichiometric ratio before being evaporated at room temperature to produce co-crystals. The solubility of medications and coformers influences the choice of a common solvent. Intermolecular interactions such as Hbonding occur between the functional groups of medicines and coformers, resulting in thermodynamically preferred products. To achieve the best outcomes during evaporation, the thermodynamic stability of molecules should constantly be taken into account. The main disadvantage of this approach is that it does not work on a wide scale. Setyawan et al. used solvent evaporation and a slurry technique to create co-crystals of artesunate (AR) and nicotinamide (NI)

## Characterization of Cocrystals :<sup>[36,37,38,39]</sup>

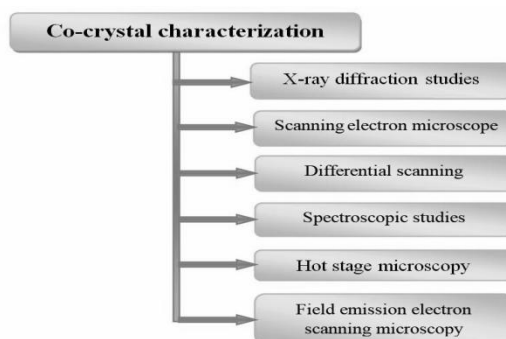


Figure 2: Methods for characterization of co-crystals.

### 1. X-Ray Diffraction (XRD studies) – Powder XRD and Single crystal XRD

This analytical method is used to determine the phase of co-crystal-related unit cells. PXRD is a method that is commonly used to characterise co-crystals.<sup>[40]</sup> For the purpose of assessing the structure of co-crystals, the PXRD patterns acquired from the diffractometer were compared to one another. The different PXRD patterns of co-crystals from their constituents serve as indicators of co-crystal formation. The material is triturated to create a consistent, fine powder before XRD analysis. For analysis, the chosen sample must adhere to Bragg's law ( $n=2d \sin \theta$ ). The primary issue with single crystal XRD is the challenge of crystal acquisition. PXRD is therefore used increasingly to verify the formation of cocrystals.

### 2. Scanning Electron Microscope (SEM)

An electron microscope called a SEM<sup>[41]</sup> scans the material using an electron beam. The atoms that make up the sample interact with the electrons to produce signals that provide information about the surface topography of the sample. Using double-sided tape and a vacuum, specimens were placed to a metal sample holder with a 12 mm diameter and coated with gold-palladium. The co-crystal micrograph and particle size are calculated using it.

### 3. Differential Scanning Calorimetry (DSC)

The characterization of co-crystals in the pharmaceutical industry has lately employed DSC as a technique.<sup>[43]</sup> It is preferred for acquiring melting point information as well as thermal information like melting enthalpy. Heat capacity, heat of transition, and heat of fusion are all measured by DSC. DSC can assess how crystalline something is. The co-crystal and pure components are heated in this method at a regulated pace, and the resulting thermogram is examined to determine whether co-crystal formation is likely. Regardless of the ratio of medication to coformer, the eutectic melt produced by slow heating rates recrystallizes and ultimately melts throughout this cocrystal formation process. The DSC technique to screen co-crystals of hydroxybenzamides and derivatives of benzoic acid. In 18 systems, the effectiveness of several co-crystal screening approaches was compared, and it was discovered that DSC screening has adequate accuracy and permits screening over a short period of time.

### 4. Spectroscopic studies

Co-crystals are characterised using spectroscopic techniques such as vibrational spectroscopy and Nuclear Magnetic Resonance (NMR).<sup>[42]</sup> The energy absorbed by the chemical bonds in co-crystals will differ from that of the pure components in vibrational spectroscopy (infrared and Raman), allowing for the determination of the co-crystals'

structural behaviour. A method for observing the crystallisation process is Raman spectroscopy. It is used to distinguish between salts, co-crystals, solid solutions, polymorphs, and those that have been hydrated. Co-crystals exhibit a different range of bands in infrared spectroscopy than the pure drug and coformer owing to the development of hydrogen bonds between them. The structure of pharmaceutical co-crystals and complexes may be fully described using the NMR, a potent characterization technique. Since this approach can determine the amount of proton transfer, it is utilised to distinguish between cocrystals and salts. The instrument's lack of sensitivity is one of the method's biggest drawbacks.

### 5. Hot stage microscopy

The hot stage microscopy research incorporates heat analysis together with microscopy. It is used to characterise co-crystals in relation to time and temperature. When heating a co-crystal sample that is put on a glass slide beneath a microscope, thermal changes like freezing point, crystalline transformations, etc. are frequently visualised using hot stage microscopy. It has increased the optical collecting capacity when utilised with DSC.

### 6. Field Emission Scanning Electron Microscopy (FESEM)

In order to evaluate the surface morphology of co-crystals, topography or FESEM are used. It offers topographical and elemental features at 10x–300,000x magnifications. FESEM produces pictures that are clearer and less electrostatically distorted as compared to conventional (SEM). For the comparison, micrographs of the parts and co-crystals from the FESEM experiments are employed. Heat is not employed in the emission microscope; instead, a so-called "cold" source used. Electrons are emitted from the conductor's surface using a high electric field. As a cathode, a tungsten filament with a tip diameter of 10 to 100 nm is employed. A scanning microscope is connected to the field emission source to take co-crystal micrographs.

### Applications of Co-crystals in Pharmaceutical Industry

Due to their straightforward manufacture, co-crystals have a number of advantages over other solid-state drug modification procedures including complexation, solid dispersion, micelle solubilization, cosolvency, etc. in the pharmaceutical sector. Experts think that the co-crystallization technique may have positive effects on the pharmaceutical industry's intellectual property landscape. To speed up the dissolution rate, co-crystallization utilising sugar-based coformers can be an option. Using sucrose as a coformer, hydrochlorothiazide co-crystals were produced. A co-crystal that was produced benefited from both improved dissolving rates and flavour masking. Nutraceuticals, which have health benefits, can be used as coformers with APIs to provide superior overall health benefits. Recent times have also seen an increase in interest among pharmaceutical scientists in Multi-Drug Co-crystal (MDC). MDC might be superior to pure pharmacological components in some situations. Described the MDC of two antidiabetic medicines Glimepiride (Gli) and Metformin (Met), which were made using the solvent evaporation process, including better solubility, bioavailability, and potential to stabilise unstable APIs via

intermolecular interactions. A superior solubility and dissolution rate than Glimepiride, as well as reduced hygroscopicity and stronger accelerated stability than the parent medication Met, were among the striking physicochemical alterations shown by the studies. Co-crystals are also utilised to separate and purify the API as it is being processed. Co-crystallization methods are commonly used on medications with a weak ionisation nature. Co-crystals can also act as a crystallisation inhibitor, prolonging the time that supersaturation is maintained during dissolution. In turn, this aids in boosting the drug's bioavailability and controlling its release.

### CASE STUDIES OF PHARMACEUTICAL CO-CRYSTALS

#### Pharmaceutical co-crystals of sildenafil (Viagra®)

The drug sildenafil is used to treat conditions like peripheral vascular disease, atherosclerosis, pulmonary arterial hypertension, congestive heart failure, and decreased blood vessel potency in addition to treating male erectile dysfunction and female sexual difficulties.<sup>[43]</sup> Sildenafil particularly inhibits the phosphodiesterase type 5 enzyme that degrades cyclic guanosine monophosphate (cGMP) in the corpus cavernosum. As a result, the smooth muscle in that area relaxes, increasing blood flow and resulting in an erection. It has a moderate water solubility, and Pfizer has developed and commercialised sildenafil citrate for use in human medicine. It is offered under the Viagra® brand name. Pharmaceutical cocrystals of sildenafil have been reported to improve the API's solubility in acidic conditions. Additionally, the orally administrable form of sildenafil may profit notably from this improvement in solubility. Sildenafil and acetylsalicylic acid can crystallise together well in a slurry or under reflux conditions (1:1 molar ratio). The cocrystal of sildenafil and acetylsalicylic acid's crystal structure was determined by single crystal X-ray diffraction, and the material's composition was confirmed by powder X-ray diffraction and infrared spectroscopy. Additionally, thermogravimetric and differential scanning calorimetric studies show that the cocrystal is thermodynamically stable up to 165 degrees and has a melting point of about 143 degrees. According to an intrinsic dissolving research in simulated gastric body fluid (pH 1.2), the sildenafil: acetylsalicylic acid cocrystal had an intrinsic dissolution rate (IDR) of approximately 11.75 mg/min/cm as opposed to 6.64 mg/min/cm for sildenafil citrate under the same conditions.

#### Co-crystals of aceclofenac:

The phenyl acetic acid category of drugs includes the nonsteroidal anti-inflammatory drug (NSAID) aceclofenac, which can be used orally. It possesses outstanding antipyretic, analgesic, and anti-inflammatory properties. Due to its low water solubility,<sup>[44]</sup> aceclofenac has a restricted bioavailability when taken orally. Mutalic<sup>[39]</sup> employed chitosan to make aceclofenac co-crystals using a simple solvent change process. Experts believe that chitosan is one of the most promising biopolymers for the delivery of medications. Chitosan is made from D-glucosamine, a linear hydrophilic polysaccharide polymer. The bacteria in the colon degrade a naturally occurring, non-toxic polycationic polymer. It can be found in the exoskeleton of crustaceans like crabs and shrimp and is widely distributed in the natural

environment. It has been demonstrated that chitosan works well as a drug carrier to increase the bioavailability and dissolving properties of pharmaceuticals. Chitosan was precipitated on aceclofenac crystals using sodium citrate as a salting out agent. Characterizations of the prepared co-crystals with different concentrations (0.05 to 0.6%) and the pure drug included solubility, drug content, particle size, thermal behaviour (differential scanning calorimetry, DSC), X-ray diffraction (X-RD), morphology, in vitro drug release, stability, and pharmacokinetic study. The formation mechanism was observed to drastically lower the particle size of co-crystals. A decrease in melting enthalpy, detected by the DSC, suggests crystallinity disorder. XRD also revealed crystallinity disorder. Comparing the dissolving analysis to pure drug, a much higher solubility rate was found. The considerable dissolving rate of aceclofenac from the optimised crystal formulation was believed to be caused by the wetting effect of chitosan, decreased drug crystallinity, modified shape, and micronization. Under accelerated conditions, the enhanced crystals shown outstanding storage stability. An in-vivo study revealed that the crystals quickly elicited a pharmacological response in mice and rats and improved pharmacokinetic properties in rats.

## CONCLUSION:

One of the most promising methods to improve the physicochemical characteristics of APIs is co-crystallization. One of the most alluring aspects of co-crystallized APIs is the improved solubility and chemical and physical stability it offers. Co-crystal organisation possibilities range widely, from standard lab-scale synthesis techniques to perhaps large-scale continuous production techniques. This study provides a typical overview of the numerous techniques that can be used to create co-crystals, followed by an explanation of each method's characteristics. The range of all established application areas for pharmaceutical co-crystals is covered in this study as co-crystals continue to attract attention and demonstrate their worth. Co-crystals are anticipated to play a significant role in the development of new drugs because they have enhanced drug delivery performance, are more stable, and play an important intellectual property status.

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