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# Exploring cocrystals and polymorphism in pharmaceutical science: A comprehensive review

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## Abstract

The pharmaceutical industry has been working hard in recent years to find ways to control polymorphism, which involves many solid drug forms due to their various physical and chemical characteristics. Creating cocrystals and salts of active pharmaceutical ingredients (APIs) is one potential research direction. These substances have drawn a lot of attention because they can improve crucial pharmacological features without reducing therapeutic efficacy. It is significant to note that not all compounds having multiple hydrogen bond donor/acceptor groups and polymorphism properties will form cocrystals; this behavior varies. Pharmaceutical firms and researchers alter APIs, frequently by generating cocrystals, salts, or polymorphs. This review discusses analytical approaches for solids drug forms such as diffraction, spectroscopy, thermal analysis, and pharmaceutical characterization. These techniques enable us to investigate solid APIs thoroughly, from their bulk characteristics to their molecular composition. They offer vital details regarding the composition, attributes, purity, and probable changes of the substance. These technologies are also useful for continuous monitoring and analysis of drug development physical procedures.

**Keywords:** Active Pharmaceutical Ingredients; Polymorphs; PXRD (Power X-Ray Diffraction); FTIR (Fourier Transform Infrared Spectroscopy); Drug Development

## 1. Introduction

The development of a medicine with the best chemistry, pharmaceutical usage, and effectiveness is the major objective of drug development. As new medications have been discovered less frequently lately, researchers have turned to altering already-existing ones to enhance their properties and lengthen their half-lives [1]. Enhancing medication solubility is a major difficulty, particularly because many authorized and in-development treatments suffer from this problem. A popular strategy is to create salts of the medicine, which can dramatically increase solubility. Cocrystals and polymorphs can also be helpful. An acid-base reaction results in the creation of salt, whereas non-covalent interactions between neutral substances result in cocrystals. These changes are made to improve drug qualities and get around restrictions. Because they provide higher solubility and stability for medications with poor solubility, cocrystals have grown in favor, particularly in the pharmaceutical industry. Additionally, they can enhance mechanical qualities [2]. This is crucial for medications that fall under Classes II and IV of the Biopharmaceutical Classification System (BCS). Some cocrystals have been licensed for use and can prolong the shelf life of older medications.

Another important characteristic is a substance's ability to exist in several crystalline forms, known as polymorphism. It is estimated that more than 50 % of medications exist in numerous polymorphic forms, each with unique characteristics including solubility, melting point, and bioavailability. The processing and production of pharmaceuticals are impacted by polymorphs' effects on physical and mechanical features [1,2]. It can be difficult to find the ideal cocrystals, salts, or polymorphic forms for medications because of things like chemical incompatibility,

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contaminants, and variations in solubility. For salts and polymorphs, stability and solubility are essential because they affect the effectiveness and quality of the drugs. Spectroscopy, thermal analysis, biological testing, and pharmaceutical investigations are a few of the cutting-edge methods employed to forecast and comprehend drug modification qualities. The technique of scaling up is crucial in the creation of therapeutic modifications. Active pharmaceutical ingredients (APIs) are often formulated as multicomponent crystals with different shapes and characteristics, such as salts and hydrates. Drugs are hydrated by adding water molecules, which is important because many medications already include water [3]. On the other hand, salts are widely utilized and are used to give more than half of all drugs now available. The API must, however, have an appropriate ionizable site (either basic or acidic) for this strategy to function. The new subject of pharmacological co-crystals, however, takes a different tack. Multiple constituents kept together by reversible, non-covalent interactions make up co-crystals. Any API, whether it comprises acidic, basic, or ionizable groups, can produce co-crystals, which is what makes it special [4].

## 2. History

Co-crystals and polymorphism in the pharmaceutical business have an interesting history that has had a big impact on formulation, intellectual property, and medication development. Let's examine the major turning points in the study of polymorphism in medicines and the development of co-crystals:

### 2.1. Polymorphism

Early Observations: Polymorphism has been observed for millennia, although it was not fully understood until modern crystallography was developed. "Polymorph" is derived from the Greek terms "poly" (many) and "morph" (shape). Eilhard Mitscherlich, a German chemist, is widely credited with discovering polymorphism in the 1840s. He discovered that some chemical compounds, despite having the same chemical makeup, might exist in various crystalline forms with differing characteristics [5]. One of his significant discoveries was the chemical potassium sulfate.

Late nineteenth century: Advances in crystallography, such as Auguste Bravais' work, assisted scholars in better understanding the structural variations between polymorphs. Scientists gained a more precise understanding of the atomic and molecular configurations in distinct polymorphs with the introduction of X-ray crystallography in the early twentieth century. This enabled a more systematic investigation of polymorphism. Polymorphism is still a topic of active research in chemistry and materials science today. It is significant in drug development because distinct polymorphs of a pharmaceutical molecule can have varied solubilities and bio availabilities.

### 2.2. Co-crystals

Early Observations: Co-crystals have a long history, with early observations dating back to the late 1800s. Researchers discovered that certain chemicals could create crystalline structures with other molecules, which frequently involved hydrogen bonding.

When researchers began carefully examining the formation and properties of these substances in the 1970s, the name "co-crystal" became more commonly recognized [6]. During this time, understanding of co-crystals as a different class of materials began to emerge.

Polymorphism and co-crystals have long histories dating back to the early findings of scientists in the nineteenth century. Since then, these notions have been key in understanding the behavior of solid-state materials, having significant ramifications in domains such as chemistry, materials science, and medicines. Ongoing research in these areas is expanding our understanding and uses of polymorphism and co-crystals. Co-crystals and polymorphism research and development are still advancing [5,6]. Co-crystal strategies are actively being pursued by pharmaceutical companies to improve the performance of their medication prospects. The use of co-crystals to produce innovative formulations for generic medications is also being investigated.

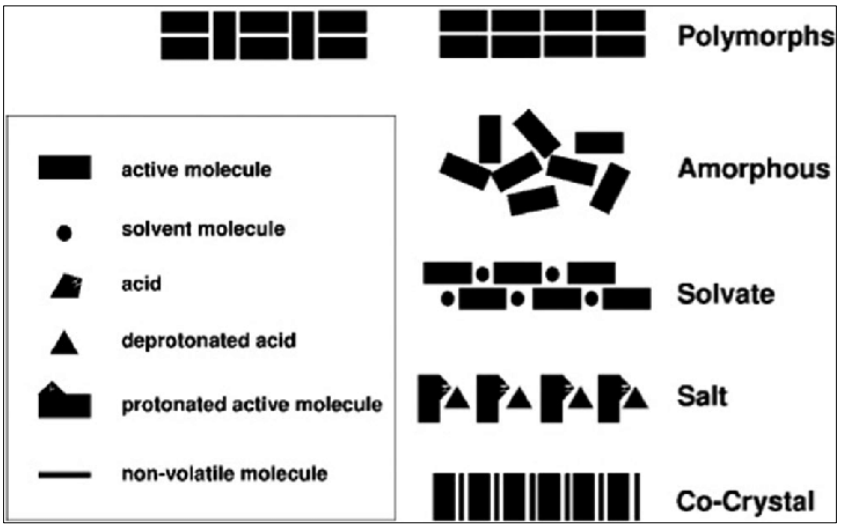


**Figure 1** Different types of polymorphs and pseudo polymorphs of a molecule [7]

## 3. Polymorphism

A solid can be either crystalline or amorphous. We refer to substances that have different crystal shapes as polymorphs, and this phenomenon is known as polymorphism. Greek is the origin of the word "polymorph", where "poly" means numerous, and "morph" implies form [7]. Different types of polymorphs and pseudo polymorphs of a molecule are shown in figure 1. Therefore, polymorphism describes several chemical substances' structural configurations.

One of these several crystal formations is typically more stable than the others under most circumstances. One polymorph of a chemical may, however, be stable only within a narrow range of temperature and pressure, whereas another polymorph may be stable only under different circumstances. It is known that more than 59 % of chemicals can exist in different crystal forms, 38 % of them can change into polymorphs, 30 % into hydrates, and 12 % into solvates. The arrangement of molecules in a crystal determines the physical and chemical properties of a medicine [8]. The effectiveness of the medicine is significantly influenced by these characteristics, also referred to as physicochemical features. Different pharmaceutical procedures like manufacturing, mixing, separating, washing, drying, tablet-making, and dissolution can be impacted by the form and structure of a solid medicine.

Crystalline solids can be polymorphs, hydrates, solvates, or occasionally a mix of these [9]. Packing polymorphism, which modifies how molecules are organized in space, and conformational polymorphism, which modifies how flexible molecules twist into different forms, are the two methods by which organic molecules can create diverse crystal structures.

## 4. Properties Of Co-Crystals

Understanding and regulating the actual features of pharmacological cocrystals using a variety of depiction techniques is essential for product quality. Compound arrangements are relatively simple to analyze and manipulate. The cocrystal nature and level of improvement are determined by the required data and logical techniques [1, 3]. In the early stages of development, the robust structure and genuine properties of cocrystals are frequently depicted at the milligram scale. Determining the number of truly differentiable minor components in pharmaceutical crystal manufacturing remains a challenge [10]. Differential filtering calorimetry (DSC) and warm gravimetry (TG) can provide significant information regarding cocrystals such as their softening temperature, enthalpy of combination, warm progress temperature, crystallinity, and solvate or hydrate arrangement. Some cocrystals dissolve at different temperatures than the equivalent API and conformer components. Warm outputs from temperature-controlled PXRD or concurrent DSC-PXRD frameworks discriminate easily between actual and estimated changes. These alterations are explained through synthetic examination of thermally changed materials using logical techniques including HPLC, Raman, and FT-IR. Solvatization and hydrate representation work with TG and residual water estimations. Stage charts that show the relationship between organizations and melting points provide insight into certain goods and a rational cycle plan. Predicting the capacity solidity of cocrystals and their plans also benefits from understanding melting and heated variations. Drug cocrystal strength and clinical performance are significantly influenced by crystallinity [11]. PXRD and DSC are the primary controlling factors for the measurement of target cocrystal in solids. PXRD designs that included

cocrystal dissolving enthalpy and diffraction top powers explicit to the objective cocrystal were used to analyze the crystallinity of CBZ-saccharin and indomethacin-saccharin cocrystals.[12]. Additionally, crystallinity is thought to measure cocrystal stability. For complex strong plans involving excipients, precise crystallinity conclusions to increase drug cocrystal utilization can be testing.

### 4.1. Production Of Co-Crystals

The two main types of cocrystal manufacturing methods are solid-state and solution based. Strong state procedures are ones that utilize little to no dissolvable, whereas arrangement-based approaches are those that employ a lot of dissolvable and require an additional confinement stage to separate the transparent product from the mother alcohol.

The API and conformer properties, necessary cocrystal sum, projected plan, and improvement stage all influence drug cocrystal preparation procedures. The quantities of cocrystal required varies from milligrams for basic early phase visualizations to multi-kilogram clumps for company formation [13]. To file objects of a specific nature, various ways are utilized. Specialized enhancements should also change the correct processes for creating pharmaceutical crystals.

#### *4.1.1. Solution crystallization*

Cocrystals are typically created by crystallizing conformer and active component solutions in aqueous or organic solvent solutions. Chilling, antisolvent addition, and seed crystal addition crystallization techniques have been proved to be cost-effective and scalable. The resulting high purity cocrystals have a larger dispersion and can be employed in formulations for other API crystals [14]. This method has drawbacks since some constituents are less soluble than the equivalent cocrystals, which frequently results in precipitation. Phase diagrams that reflect temperature and crystal development variations make it easier to produce cocrystals.

Low-stability components cannot crystallize because reaction-crystallization creates cocrystals with non-equivalent solubility [15]. Process control is aided by the identification of changing solute compositions using spectroscopic techniques. Some strategies have been developed to reduce the amount of inorganic solvent necessary to form cocrystals. The gas antisolvent (GAS) approach successfully induces the production and precipitation of itraconazole-succinic acid cocrystals from aqueous solutions.

#### *4.1.2. Spray- and freeze-drying methods*

Splash drying or freeze-drying API-conformer arrangements, such as CBZ-nicotinamide (94), can also be used to shape cocrystals. Throughout these cycles, solute cementing occurs faster than crystallization in watery arrangements, which may enhance cocrystal formation by minimizing stage detachment and precipitation of low-solvency components [16]. They are also viable with growth and the addition of a third industry, such as a building specialist, that deals with pharmacological properties. Shower drying is required to work with the large scope production of drug crystals by rapid, practical dissolvable disappearance. Freeze-drying is excellent for the aseptic manufacturing of injectable strong details. In any case, these techniques have a few downsides [17]. They need the material solvents, mainly water and t-butanol, to be sufficiently soluble in API and conformers. Additionally, the rapid hardening may result in less stable formless solids or metastable valuable stones.

#### *4.1.3. Hot-melt extrusion and grinding*

Grinding and hot-melt extrusion, which are adaptable to a wide range of chemicals, have proven to be useful in the production of medical cocrystals. The process of neat grinding is carried out in a mill or mortar with or without a little amount of solvent. Some chemical combinations, such as citric acid and piracetam, can be ground cleanly to form cocrystals. To adjust particle size and crystal form, solvent addition speeds up cocrystal formation considerably compared to neat grinding. The dissolving of the API and conformer on the solid surface is what causes these solvent effects. With increasing grinding force, cocrystal formation occurs more quickly. However, due to its sensitivity to the quality of the raw materials and different process parameters, grinding frequently runs into problems during scale-up [12, 13].

Related technologies like polymer-assisted grinding and grinding with solvent and high shear have also been investigated. A scalable mechanochemical technique for making cocrystals is hot-melt extrusion. One of numerous modified techniques has been reported to include matrix polymers, such as the polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer. Process analytical methods such as Raman and near-IR spectroscopies, which enable in-situ tracking of product alterations, are used to manage mechanical production operations [14]. Hot-melt extrusion is now possible with higher cocrystal purity thanks to recent advancements in screw assembly design and operating temperature management, which also lessen component deterioration brought on via shear and heat.

*4.1.4. Other methods*

Ultrasound, melt mixture cooling with a supercritical fluid, microwave heating, and other methods can also be used to create pharmaceutical cocrystals. The final solids' physical characteristics and purity, as well as process reproducibility, all play a role in the choice of production techniques. Some techniques can only be used with cocrystals made of materials with low melting points and chemical stability [15]. It is believed that a process will produce formulations continuously if it meets the goal product profile.

### 4.2. Characterization Of Co-Crystals

Pharmaceutical cocrystals have been characterized using a variety of techniques, and intermolecular interactions have been clarified.

*4.2.1. X-ray diffraction of single crystals and powders (XRD)*

The XRD method is the most used technique for cocrystals characterizing. Single-crystal XRD is commonly employed to solve the arrangement of cocrystals, whereas powder XRD (PXRD) is typically utilized for recognition. Predella et al., who formulated and applied this technique to investigate the development of indomethacin-saccharin cocrystals by mechanochemistry, also reported on the measurement of cocrystals in the crystallization mixture using PXRD [16]. Thanks to software tools like DIFFRAC.TOPAS (Bruker AXS, Karlsruhe, Germany), arrangement deduction and refinement based on Rietveld analysis are now possible.

They are commonly used to analyze the yield of co-crystallization since they can compute the proportion of cocrystals along with their constituent parts in a combination [17]. Several thermal and spectroscopic methods are used concurrently to characterize and compute potential new cocrystals.

*4.2.2. Thermal examination*

The phrase "thermal analysis" mentions a set of methodologies that, in a controlled environment and with a programmed temperature change (e.g., heating, cooling, alternating, or maintaining a constant temperature), reports the chemical or physical changes in the thermal effects of a sample over time. Mass, enthalpy, heat flow, heat and other properties can be measured. The most useful procedures for cocrystal characterization are differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA), as well as hot-stage microscopy (HSM).

The following is an outline of the application of DSC and HSM in the characterization of cocrystals: DSC is advantageous for creating binary phase diagrams for cocrystals when screening for cocrystal production or the presence of eutectic mixes or eutectic impurities that lower the melting point. All of the heats of fusion, solid-solid transition heats, and heat capacities are calculated. It is also possible to measure the degree of crystallinity by measuring the sample's enthalpy of fusion and comparing it to the worth of a totally crystalline substance. Binary phase diagrams reveal the emergence and steadiness of the cocrystal. Sharp endothermic peaks appear at lower temperatures than sharp endothermic peaks do for the individual components in the cocrystal, which has a melting point that differs from the individual components' melting points. When chemicals remain as impurities, the main melting peak can continue as a second peak. DSC is used to demonstrate the presence of cocrystals at a melting temperature which is typically between the melting points of pure substances. It is also used in in situ cocrystal production [17, 18]. When two cocrystal-forming materials are mixed and heated, an endothermic peak is followed by an exothermic peak, indicating cocrystal formation. In mixture that do not produce cocrystals, there will be only one endothermic peak seen near the eutectic point. In-situ creation kinetics of the carbamazepine-nicotinamide cocrystal from equimolar ingredients in an amorphous form after melting is one example of how DSC has been used to research the cocrystal formation mechanism. Because of the amorphous state's great molecular mobility, molecular cocrystal formation is conceivable [19]. Rapid-heating DSC was employed to separate and distinguish the metastable carbamazepine-nicotinamide cocrystal form II, which was generated in situ by heating at a rate of 500 °C per minute.

*4.2.3. Spectroscopy*

Vibrational spectroscopy and nuclear magnetic resonance (NMR) are the two types of spectroscopic approaches that can be used to display cocrystals. Furthermore, vibrational spectroscopy can be identified as having a place with either a retention (infrared, IR) or a dispersion (Raman) method. The infrared range is labeled as mid-IR (4000-400 cm1), near-IR (NIR: 14,000-4000 cm1), and far-IR (400-10 cm1). NMR is an excellent representation instrument that can supply exact information on the composition of natural pharmacological cocrystals and structures [20]. In terms of changing FTIR, the study of the constituent spectra of cocrystals and their final mix with polymer lattices, and so on, is

a key tool in identifying cocrystal arrangement and in explaining their constructions. Because of the presence of hydrogen bonds, the range of the cocrystal differs from that of the components combined. This is particularly true when a carboxylic corrosive is used as a conformer and an impartial hydrogen link O-H- N forms between a corrosive and a base. The IR spectra of an unbiased carboxylic corrosive functional group and a carboxylic anion differ significantly. Due to coordination, the carboxylic anion (- COO-) exhibits a strain band of C-O in the distinct finger impression district (1000-1400 cm-1), whereas the impartial carboxylate (- COOH-) exhibits a solid strain band of C=O at about 1700 cm-1 and a more fragile pressure band of C-O at about 1200 cm-1. If an unbiased hydrogen bond O-H- N is established between the components, two enlarged zones will be observed at about 2450 cm-1 and 1950 cm-1. Solid hydrogen bonds are framed in (NH-O), (OH-O), (- NH-N), and (OH-N), as opposed to weak hydrogen bonds, which are framed in (-CH-O) and (CH-O=C). Glasslike structure, polymorphisms, and cocrystal identification are all affected by IR changes [21]. The solid ingestion of excipients or other example components makes detecting cocrystals by IR difficult. This is due to the fact that most excipients have high dipole-second structural securities, and different retentions provide the impression that they can only be segregated and allocated to each segment with a great deal of effort. Under comparable settings, NIR was used as a scientific technique to evaluate the cocrystal arrangement of ibuprofen and nicotinamide through a pivoting double screw extruder. The technique was eventually presented for the regulation of cocrystal immaculateness on a modern scale, however it was deemed fragile due to the appearance of new tops in the region 4800-5200 cm -1. However, Raman has more accuracy and applicability, and it has been employed in situ to analyze arrangements and confirm co crystallization, either alone or in conjunction with NIR [22]. Raman spectroscopy was used to investigate the crystallization cycle. It is an excellent perceptual strategy for discriminating between polymorphs, salts, cocrystals, strong arrangements, and hydrated salts since it requires less example planning and only consumes a tiny amount of information. Furthermore, the approach utilized to portray blends is safe due to the low strength of the Raman dispersed radiation. Because cocrystal movements differ from those of the beginning materials, Raman spectra are particularly relevant for co-crystallization in measuring cocrystal growth [23]. They also determine whether the investigated combination is a cocrystal or an ionized molecule. When amino and carboxyl groups create cocrystals, the unique zones that corelate to the bowing and extending vibrations of these groups are transferred to lower frequencies, and any increase in bond length is due to hydrogen holding. Fourier-change Raman is particularly important for the identification and quantitative research of polymorphic structures and cocrystals due to its minimum planning needs and lower danger of advancement in a metastable polymorphic structure. Furthermore, the spatial purpose is simpler, and the test design has less impact. Nonetheless, Raman has several disadvantages. Unlike fluorescent examples, which can absorb heat and generate spectra of worse quality as a result of the foundation, can even consume the example, or result in polymorphic progress (in the insane), signal force may be constrained by the size of the molecule. There are probably systems that can mitigate these issues. For example, using the typical range derived from spectra gathered at various sites throughout the example. When the pressing factor is employed and the API is not changed into another polymorphic structure, the issue of huge cocrystals is overcome by employing a mortar [21, 22]. Ibuprofen and nicotinamide cocrystals were created using supercritical liquid and then quantitatively characterized utilizing a range of logical strong state techniques. The DSC and Mid-IR methods were inadequate for measuring the separate elements of the combination. The average forecasting inaccuracy was 15%. Overall, the PXRD and Raman procedures yielded the best findings. Using the partial least squares (PLS) multivariate model, Raman can forecast how cocrystals and conformers will centralize rapidly and precisely. Because they revealed an overall error rate for the forecast of the focus of less than 5%, these approaches prompted an alignment model to evaluate the virtue of the cocrystal following its merger.

### 4.3. Application Of Co-Crystals

Rules pertaining to medication cocrystals have an unanticipated impact on how forward-thinking and non-exclusive ideas evolve. The QbD strategy of plan detailing, and careful evaluation of the ensuing definitions should have enough details to allow for various province guideline regulations in the advancement of cocrystals including new dynamic particles. According to Schultheis et al., choosing the ideal drug crystal for a standard improvement measure requires consideration of a variety of factors, including softening point, dissolvability, stability, and adaptability [24]. They advocated for early real-life depiction throughout product development. Another upcoming methodology by creative organizations is the use of cocrystals to the lifecycle the board of their registered API to work on the items and to construct new organization courses. The application of cocrystal developments to off-patent APIs in regular medicine programs is gaining popularity. Cocrystals may be used as a replacement for other specialized innovations used in reference trend-setter products, such as disintegration assistance, to achieve clinical execution, thereby avoiding violation of protected innovation rights [25]. A proper portrayal of real features and execution is intended to ensure advantageous identicalness and lessen the potential hazards of medicine cocrystals in conventional details. Recognizing local differences in rules for cocrystals and conventional commodities should be reasonable outcomes.

## 5. Conclusion

Drug cocrystals have a tremendous potential for improving API physical and biological properties, and as a result, this field of research is undergoing fast transformation now. There are a few methods for their arrangement and physicochemical representation, and efforts are underway to develop theoretical together with experimental techniques for the anticipation of cocrystal development; these efforts have, up until now, been hampered by the dearth of adequate knowledge of the cocrystal development tool. As our knowledge of the intermolecular partnerships that characterize cocrystal formation and solidity grows, hypothetical approaches for predicting cocrystal arrangement may become an important tool for supporting cocrystal-based measurement structure planning. Furthermore, the development of modern methods for their production, as well as they must soon become more significant as options to deal with salt development or API polymorph selection, as well as the building of a clear and effective administrative framework, are required.

## Compliance with ethical standards

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No conflict of interest to be disclosed.

### *Author contributions*

- Archana Rao P: Conceptualization, paper writing and corresponding author
- Harichandana T, Naga Praneeth, Srujan Reddy, Navya: Collection of literature, paper writing

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