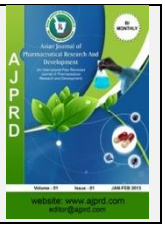
Available online on 15.6.2025 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

Pharmaceutical Cocrystals: An Overview

Jagdish Kumar Rawal, Dr. Anshu Sharma

Bhupal Noble's College of Pharmacy, Bhupal Noble's University, Udaipur

A B S T R A C T

Poor aqueous solubility and low oral bioavailability of an active pharmaceutical ingredient are the major constraints during the development of new product. Various approaches have been used for enhancement of solubility of poorly aqueous soluble drugs, but success of these approaches depends on physical and chemical nature of molecules being developed. Cocrystallization of drug substances offers a great opportunity for the development of new drug products with superior physicochemical such as melting point, tabletability, solubility, stability, bioavailability and permeability, while preserving the pharmacological properties of the active pharmaceutical ingredient. Cocrystals are multicomponent systems in which two components, an active pharmaceutical ingredient and a coformer were present in stoichiometric ratio and bonded together with non-covalent interactions in the crystal lattice. This review article presents a systematic overview of pharmaceutical cocrystals. Differences between cocrystals with salts, solvates and hydrates are summarized along with the advantages of cocrystals with examples. The theoretical parameters underlying the selection of coformers and screening of cocrystals have been summarized and different methods of cocrystal formation and evaluation have been explained.

Keywords: Pharmaceutical cocrystals, cocrystallization, solubility, stability, bioavailability, supramolecular synthons

A R T I C L E I N F O: Received 01 Jan. 2025; Review Complete 26 March. 2025; Accepted 28 April 2025. ; Available online15 June. 2025

Cite this article as:

Rawal JK, Sharma A, Pharmaceutical Cocrystals: An Overview , Asian Journal of Pharmaceutical Research and Development. 2025; 13(3):208-217, DOI: http://dx.doi.org/10.22270/ajprd.v13i3.1580

*Address for Correspondence:

Jagdish Kumar Rawal, Bhupal Nobles College of Pharmacy, Bhupal Noble's University, Udaipur

INTRODUCTION

The Organic Solid State

Within an organic solid, molecules are held together by intermolecular forces (e.g. hydrogen bonds) that limit or restrict mobility (1-4). The aggregation of molecules in solids creates a single entity termed supermolecule. The structural arrangement or packing within the crystal is influenced by the sizes (5,6), shapes (7), and functionalities of organic molecules (1,8). Indeed, strategies based on principles of crystal engineering, which involves the understanding and investigation of fundamental properties that dictate molecular arrangement, is essential for the rational design, control, and useful applications of organic solids (9-10).

A means to design a target supermolecule is with the use of a supramolecular synthon (11). Supramolecular synthons provide adhesive forces in the form of non-covalent bonds that establish specific connectivity between molecules in organic solids. These relatively robust interactions commonly impose directionality on molecular assemblies (12). There are two types of synthons: the homosynthon and the heterosynthon. The former is comprised of self-complementary functional groups (Figure 1.1) and the latter is composed of complementary groups that differ in functionality (Figure 1.2) (13,14).

In the solid state the supramolecular synthons allow crystal engineers to predict the structural outcome within a solid to a reasonable degree. In the case of the benzene carboxylic acids such as benzoic, terephthalic, and trimesic acid, the molecules self-assemble to form multidimensional assemblies based on the positions of the carboxylic acid groups (3). Benzoic acidcontaining one carboxyl group forms a discrete assembly while terephthalic acid functionalized with carboxyl groups at the para positions forms a linear one-dimensional (1D) assembly. Similarly, trimesic acid with carboxyl groups at the 1, 3, 5-positions forms a three-connected honeycomb-like architecture. Similarly, a linear hydrogen-bonded 1D chain of isonicotinic acid is sustained by pyridyl-carboxylic acid interactions (15). The examples

above provide a few examples of supramolecular assemblies that can be constructed by design.

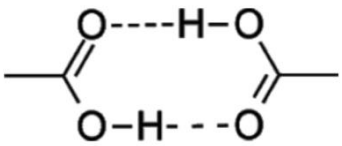


Figure 1: Schematic representation of complementary hydrogen-bonded supramolecular homosynthons: carboxyl-carboxyl synthon.

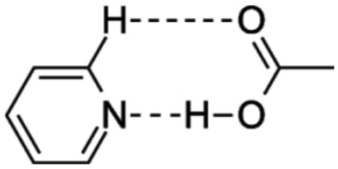


Figure 2: Schematic representation of complementary hydrogen-bonded supramolecular heterosynthons: carboxyl-pyridyl synthon.

Emergence of Co-crystals: Definitions, Applications, and Preparation

Having established that functional groups form homo- and heterosynthons,chemists have started to rationally design multiple-component assemblies in the form of co-crystals. A co-crystal can be defined as a crystalline solid composed of two or more molecules that are solids at ambient temperatures that interact via charge neutral non-covalent bonds (16,17). Another interpretation of a co-crystal is a case wherein a target molecule is co-crystallized with a crystallizing agent called a co-crystal former (CCF). The intermolecular interactions within a co-crystal govern the molecular arrangement of the components in the solid.

A co-crystal exhibits modularity. A CCF, depending on the nature of the interactions with the target molecule, can be exchanged without compromising the covalent linkage and/or arrangement of the target molecule. Consequently,this alters the composition and, thereby, can change the bulk properties of the solid (i.e. melting point, solubility) (18). The modularity has inspired applications of co-crystals in solid-state organic synthesis, organic semiconductors (22), structural determination of small organic molecules (20-22), and materials science particularly in the area of pharmaceutics (23). An example of how co-crystals are currently being applied is in the area of pharmaceutics (24-27).

A common approach of modifying or altering the physiochemical properties of an active pharmaceutical ingredient (API) is to create a salt. Salt formation, however is limited to an API with an acid or base ionizable site (28). Co-crystals represent a viable alternative to salt formation in pharmaceutics.

The emergence of applications of co-crystal solids have motivated solid state chemists to develop alternative or efficient means of preparation (29). Traditionally, a co-crystal has been prepared by dissolving the solid components in a solution and allowing co-crystallization via slow evaporation or sublimation (30). It is well established that solution-based crystallization provides well-defined and highly-ordered crystals with excellent opportunity for purification; however, there are disadvantages associated with the conventional routes. Solution crystallizations may sometimes require toxic solvents, which can have a harmful impact on the environment as well as generate costly expenses from the use and waste disposal. Moreover, the solvent can also form solvates with the individual components rather than form the pure co-crystal or lead to undesired metastable polymorphs (24,31).

To circumvent the disadvantages of solution-based crystallizations, mechanochemical methods have been employed to generate co-crystals with little or no use of solvent (29). Mechanochemistry is the act of grinding or milling solids to induce the formation or breaking of a chemical bond (32). Typically, the grinding is carried out using a mortar and pestle or an automated ball and mill.Substantial increases in heat and pressure are exerted on the solids. For a co- crystal formation, non-covalent interactions are, thus, formed and broken. Moreover, given the significance of co-crystals, obtaining these highly useful materials with little or no use of solvent makes the materials appealing from numerous perspectives. However, the application of mechanochemistry, in the context of co-crystal synthesis, remains in its infancy.

Introduction to Cocrystals

Co crystals are defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions. Co-crystallisation is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single component crystals and their polymorphs) or with different molecular components (multiple component crystals or co-crystals) in the crystalline state (33).

The components in a co-crystal exist in a definite stoichiometric ratio, and assemble via non covalent interactions such as hydrogen bonds, ionic bonds, and π-π or van der Waals interactions rather than by ion pairing (34).Generally co-crystals in their pure states are solids at room temperature and by convention, these normally excludes salts. Co-crystals can have different properties than the crystals of individual components. Further, co-crystals have different crystal structures than the pure components, contain different intermolecular spacing patterns, and as such they often exhibit widely different physical properties than the pure components. Co- crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionization sites in the API (35,36).

The key benefits associated with co-crystallisation approach to modifying properties of pharmaceutical solids including weakly ionisable and non-ionisable, to form co-crystals, and the existence of numerous potential counter-molecules including food additives preservatives, pharmaceutical excipients as well as other APIs, for co-crystal synthesis. Additional valuable advantages that co-crystal formation may offer for the pharmaceutical industry are the opportunity of

intellectual property protection and the possibility of extending the life cycles of old APIs.

Pharmaceutical cocrystals

Pharmaceutical cocrystals offer an alternative method to alter the dissolution rate and solubility of BCS Class II drugs. Cocrystals consist of an API and a generally regarded as safe (GRAS) molecule, with specific stoichiometric compositions (Figure 1.4). However, there is no single definition as to what a pharmaceutical cocrystal is. Multiple definitions appear in the literature, but a common definition is "a stoichiometric multi- component system connected by non-covalent interactions where all the components present are solid under ambient conditions" (34,37,38). As both the API and coformer in a cocrystal must be solid on their own under ambient conditions, solvates and hydrates are not classed as cocrystals. However, other restrictive definitions define a cocrystal as "a crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, often including hydrogen bonding" (37). This definition specifies that the API and coformer must be in the neutral form. However, there are many reports of "ionic cocrystals" in the literature, where themolecules in the crystal lattice interact via ionic bonds as well as hydrogen bonding (39-40). An article authored by 46 researchers in the area of cocrystals have proposed an inclusive definition of cocrystals, defining cocrystals as "solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts" (32).

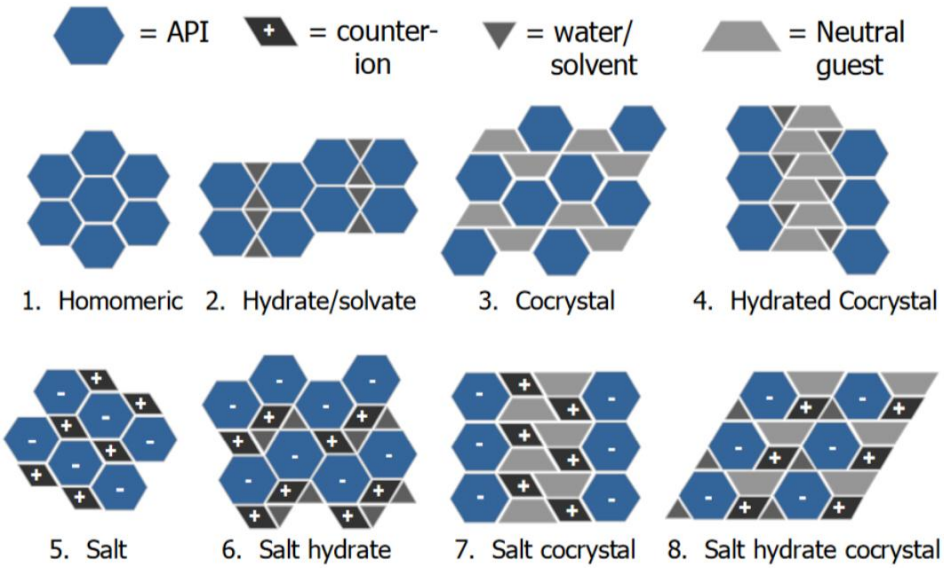


Figure 3: Multi Component Cocrystals

Classification of Cocrystals (42)

The following classification has been proposed by the FDA: Co- crystals should be classified within the Agency's current regulatory framework as dissociable "API-excipient" molecular complexes. They may then be treated as a "drug product intermediate" rather than as a drug.

Should this classification be adopted, then there are several implications:

- Cocrystal containing drug products will not be considered to contain new APIs.
- New drug applications, NDAs, and abbreviated NDAs, ANDAs, claiming to contain a cocrystal form will have to prove the extent of proton transfer.
- The cocrystal must be shown to dissociate in vivo prior to reaching its active site. The nature and location of the putative active site varies greatly between different drug classes, such that there is significant ambiguity about how to address the dissociation requirement, especially in the case of topically active drugs (applied on skin or orally active within the GI tract, for instance).
- The API cocrystal which by definition is a crystalline multicomponent chemical compound would be considered analogous to the "API-excipient" blend that overwhelmingly represents a physical mixture of an API and excipient(s

Method of Production of Cocrystals

Cocrystal production routes can be broadly categorized as solid-state or solution based. Solid-state methods can be differentiated as methods using very little or no solvent, with solution based methods representing production routes that involve a large excess of solvent necessitating a subsequent isolation stage to separate the crystalline product from the mother liquor.

Solid State Methods.

Contact Formation.

The spontaneous formation of cocrystals via mixing of pure API and coformer under a controlled atmospheric environment has been reported (33-36). In this method, no mechanical forces are applied during cocrystallization (37,38). However, in some cases, brief grinding of pure components individually before mixing has been done. The mechanism of cocrystallization in the presence of moisture at deliquescent conditions consists of three stages of (1) moisture uptake, (2) dissolution of reactants, and (3) cocrystal nucleation and growth (40).

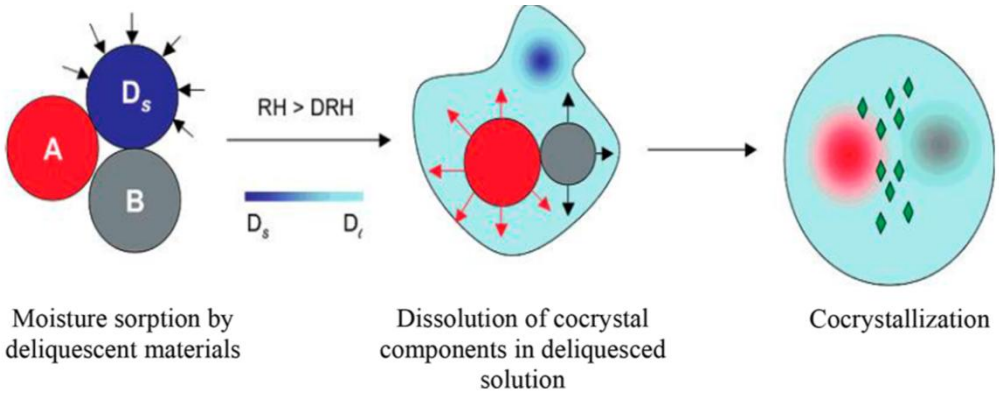


Figure 4: Illustration of the moisture uptake process leading to deliquescence, reactant dissolution, and cocrystal formation

Solid State Grinding

Solid state grinding methods have been used successfully to generate cocrystal powder samples. Two formats are practiced: neat (dry) grinding and liquid assisted grinding. Neat grinding involves the combina- tion of the target molecule and coformer in their dry solid forms with the application of pressure through manual (mortar and pestle) or mechanical (automated ball mill) means. Dry grinding is distinct from melt crystallization as the solid starting materials are not expected to melt during grinding. The temperature achieved during grinding is often monitored to ensure the same, and will often be reported. Two sulphathiazole:carboxylic acid cocrystals were prepared by grinding stoichiometric equivalents of sulphathiazole with the required carboxylic acid for 90 min in a Retsch mixer mill at a 25 Hz frequency with the temperature not allowed to exceed 37 °C (20).

Hot Melt Extrusion.

There is an efficiency associated with solid state grinding, relative to solution based methods, in that yield is not lost to the solvent due to solubility (21).

Twin Screw Extrusion.

Distinct from Hot Melt Extrusion (HME), Twin Screw Extrusion (TSE) operates at temperatures below the melting point of either starting material and takes place in a distinct piece of equipmentan aptly named twin screw extruder. This unit consists of two co-/counter-rotating screws in a single barrel. Screw action provides simultaneous mixing and movement of material along the length of the barrel. In a study, the authors compared an AMG-157:saccharin cocrystal prepared from TSE and solution crystallization (22). Cocrystals from TSE were shown to have improved surface area, bulk density, and flow properties relative to those produced from solution crystallization.

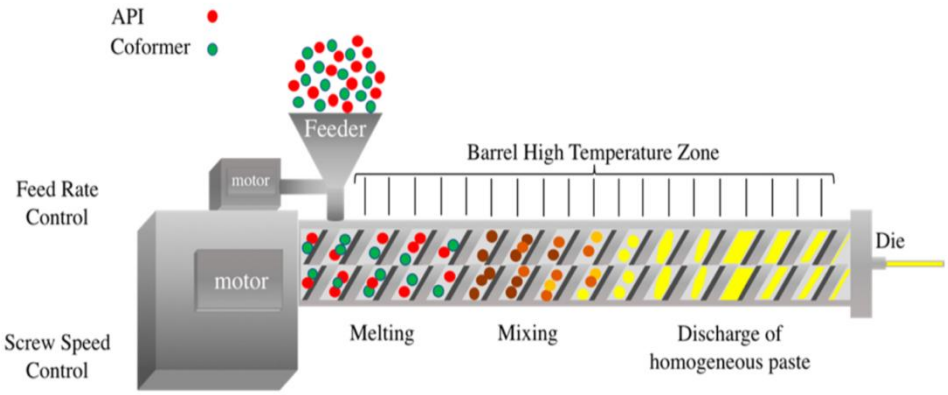


Figure 5: Schematic representation of a typical HME instrument

Hot melt extrusion (HME) is a relatively recent addition to cocrystal preparation options. This specialist technique combines simultaneous melting and mixing of the target molecule and coformer via the use of a heated screw extruder (Figure 1.5). Typically, the starting materials are mixed in a molar ratio and fed to the heated extruder. Melting occurs, facilitating intimate mixing of the starting materials. The cocrystal nucleates directly in the melt, and pure cocrystal extrudate is isolated from the extruder continuously. The advantages of the method are elimination of the use of organic solvents, fast operating times, increased conversion relative to solution based methods, reduced waste, and the technology lending itself well to continuous pharmaceutical processing.

High Shear Wet Granulation.

Typically employed for drug product formulation, high shear wet granulation has been investigated as a route to cocrystal preparation. This technique involves the agglomeration of powder particles via a liquid medium in the presence of a binder. Technically, the procedure is carried out in a high shear granulator, whichmparts shear on the powder mixture through impellers and choppers. The mechanism of cocrystal formation by high shear granulation is not exactly known but suspected to be either similar to liquid assisted grinding or slurry transformation. Granules containing a 1:1 piracetam:tartaric acid cocrystal were successfully produced from a mixture of piracetam, tartaric acid, and a variety of excipients in the presence of water using a Bohle mini granulator (23). The extent of cocrystal formation was impacted by the volume of granulation liquid used, impeller speed, and the excipient mixture used, with 95% conversion achieved within 5 min.

Solution Based Methods.

Evaporative Cocrystallization.

Evaporative cocrystal- lization is a common method of generating cocrystals, typically employed for generating single crystal cocrystals suitable for diffraction studies to elucidate cocrystal structure. The technique involves the nucleation and growth of a cocrystal from a solution of both coformers in a solvent, with supersaturation provided by removal of the solvent from the solution via evaporation. Individual cocrystals, or the bulk crystal sample, should be harvested before the solution evaporates to dryness to ensure recovery of a clean crystal(s). A slow rate of evaporation is usually desired so as to ensure formation of a small number of larger crystals as opposed to a high number of smaller crystals. As crystal structure identification is a necessary step in the discovery of new cocrystal forms, evaporative cocrystallization is evident in the majority of cocrystal related research papers, and there are countless examples of it in the literature. Moreover, the synthesized cocrystals presented higher tabletability and less absorbed humidity compared to the individual precursors (24).

Cooling Crystallization.

A designed seeded cooling crystallization was used to prepare cocrystals of carbamazepi- ne:nicotinamide from ethanol, in an effort to establish a scalable solution cocrystallization strategy (25). Solvent selection, identification of the thermodynamically stable cocrystal operating range, and desupersaturation kinetics were consid-ered in design of the process, which was demonstrated at 1 L scale with 90% yield and 14 L kg^{-1} throughout. A similar approach was taken by Holaň et al . in the preparation of agomelatine:citric acid cocrystals, and the impact of cooling rate and seed amount on the crystal size distribution in the final product was assessed (26).

Reaction Cocrystallization.

Reaction cocrystallization was used to produce cocrystals of carbamazepine:saccharin by combining individual feed solutions of either of the starting materials (27). The method was informed by the ternary phase diagram and illustrated a robust operating range for cocrystal formation and demonstrated the expected relationship between supersaturation and induction time. Formation of a carbamazepine:nicotinamide cocrystal was also done by reaction cocrystallization under ambient conditions (28).

Isothermal Slurry Conversion.

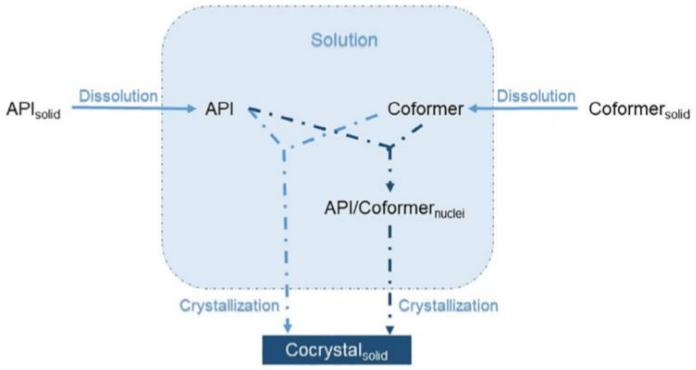


Figure 6: Scheme of solution mediated phase transformation (SMPT) process that is the base of the slurry cocrystallization technique.

This technique involves the suspension of the target molecule and coformer, usually in a fixed molar ratio, in a solvent with the solid fraction always remaining in excess. In practical terms, the technique can also operate by adding the target molecule to a solution or suspension of coformer in solvent. While this is a solutionbased method, it does not require generation of a clear (fully dissolved) starting solution.

Supercritical Fluid Methods.

Cocrystallization with Supercritical Solvent.

The Cocrystallization with Supercritical Solvent (CSS) technique uses the solvent power of supercritical CO_2 to suspend the API and the coformer as a slurry in liquid or supercritical CO_2, avoiding the use of toxic organic solvents. By controlling the thermodynamic conditions of CO_2 (e.g., temperature, pressure), it is possible to fine-tune its density and solvent power, which provides control over the cocrystallization between cocrystal components. Subra-Paternault et al. have compared the cocrystallization outcome of distinct APIs (e.g., indomethacin, theophylline, carbamazepine, caffeine, sulfame- thazine, and acetylsalicylic acid) with saccharin in liquid and supercritical CO_2 (29). Those authors have suggested that despite the usual low solubility of most cocrystal components (API and coformer) in CO_2, cocrystallization is mediated by their dissolution in it.

Rapid Expansion of Supercritical Solvents.

The Rapid Expansion of Supercritical Solvents (RESS) technique consists of the saturation of the supercritical fluid (supercritical CO_2) with a solid substrate (API and coformer in the case of producing cocrystals) prior to the depressurization of the CO_2 phase through a nozzle into a drying chamber at atmospheric pressure . Müllers et al . have used this process to produce microparticles of ibuprofen-nicotinamide cocrystals. The main drawback of this technique is that the starting components (API and coformer) have to be soluble in supercritical CO_2, as unfortunately most pharmaceutical molecules have a very low solubility in it.

Supercritical Antisolvent Cocrystallization.

Using supercritical CO_2 as an antisolvent for cocrystallization works on the principle that solubility of API and the coformer is reduced in supercritical CO_2, allowing them to precipitate together in a cocrystalline structure. This approach has the potential to control the polymorphic form of the API or cocrystals produced. It has been used for the production of cocrystals by two distinct techniques: (1) a batch gasantisolvent (GAS) process which involves saturating a solution containing the dissolved API and coformer inside a high pressure vessel with CO_2 until cocrystallization occurs and (2) a semicontinuous supercritical antisolvent (SAS) process which involves forcing a solution containing the dissolved API and coformer molecules through a nozzle into a high pressure vessel containing supercritical CO_2. In both techniques, the CO_2 dissolves in the solvent simultaneously expanding its volume and reducing it solubilizing ability, ultimately resulting in precipitation.

Supercritical CO2-Assisted Spray Drying.

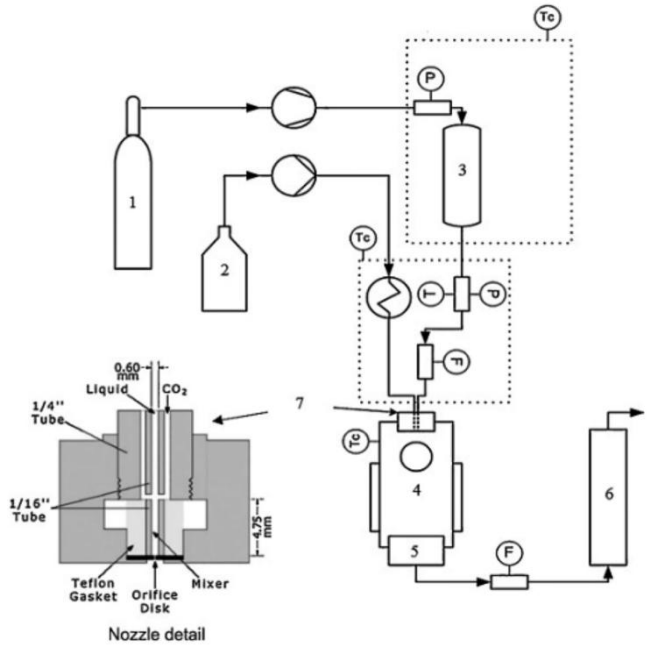


Figure 7: Schematic diagram of the SEA apparatus. (1) CO_2 cylinder; (2) liquid solution flask; (3) temperature

Using supercritical CO_2 as an atomization enhancer is based on the supercritical fluids' ability to enhance the breakup of liquid jets into fine droplets when depressurized simultaneously with liquid solutions (Figure 1.6). This is a single-step process which consists of spraying a solution containing the dissolved starting cocrystal components through a nozzle with supercritical CO_2 into a drying chamber at atmospheric pressure. Padrela et al. have used the Supercritical Enhanced Atomization (SEA) technique to produce micro- to nanosized cocrystals of theophylline with several coformers and fine-tune the cocrystal particles' morphology and dissolution properties.88,89 Interest- ingly, this technique was also successfully used to generate microcomposites of theophylline-saccharin cocrystals dispersed in hydrogenated palm oil as a controlled release formulation.

ControlledCO2 storage cylinder; (4) precipitator; (5) filter; (6) solvent trap; (7) detail of the nozzle cap. P, T, F: instruments for, respectively, pressure, temperature, and flow measurements. T_c is for temperature control and measurement

Miscellaneous Cocrystal Preparation.

Laser Irradiation.

This method consists of using a high-power CO_2 laser to irradiate powder blends of cocrystal formers and induce their recrystallization to a cocrystal structure. Titapiwatanakun et al. have used this method to produce caffeine cocrystals with oxalic acid and malonic acid. Interestingly, these authors have found that the cocrystal formers need to sublime to a considerable extent for the cocrystallization to take place, which indicated that the mechanism of the molecular rearrangement between API and coformer molecules and the nucleation of the cocrystal is likely to take place in the vapor phase.

Electrochemically Induced Cocrystallization.

Ur- banus et al. demonstrated the potential of using cocrystalliza- tion combined with electrochemistry for in situ product removal of carboxylic acids. Proof-of-principle was estab- lished using a cinnamic acid and 3-nitrobenzamide cocrystal system. This work showed that electrochemistry can be used to locally shift the pH to obtain neutral carboxylic acids and generate a local driving force for cocrystallization.

Resonant Acoustic Mixing.

Resonant acoustic mixing has been used to mix the target molecule and coformer in the presence of a liquid to form a cocrystal in the absence of any grinding media. In this method, mechanical energy is transferred acoustically into a wetted powder mixture, encouraging intimate mixing of the components. A range of carbamazepine cocrystals were successfully produced using a labRAM resonant acoustic mixer operating at 80−100G and 60 Hz. The cocrystal products were isolated at a range of laboratory scales, 100 mg and 1.5 and 22 g, and the technology appeared amenable to scale-up.

Spray Drying.

Spray drying is a continuous single-step method of transformation of liquids (solutions, suspensions, slurries) to solid powders. It is advantageous due to its continuous, highly controllable, and fast process. Although spray drying has been widely used in formulating amorphous solid dispersions because of the fast solidification process, it has also been employed in synthesis of cocrystals (21).Alhalaweh and Velaga spray dried several combinations of API-coformer with the aim of cocrystallization. They claim that cocrystalliza- tion has been observed in highly supersaturated regions of the drug due to the rapid solvent evaporation, presence of the coformer, or interaction between the drug and coformer in liquid form (22).

Freeze-Drying.

Freeze-drying, technically known as lyophilization, has been mostly used as a processing technique to preserve a wide variety of products, which include food and pharmaceuticals. This process works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase. It has also has been demonstrated recently to be a feasible method for the preparation of new solid forms of cocrystal systems (23). Eddleston et al. prepared a new form of the theophylline:oxalic acid cocrystal using freeze-drying. Cocrystallization takes place via an amorphous phase that is generated as solvent sublimes during the freeze-drying process.

Electrospray Technology.

Electrospraying is a process of simultaneous droplet generation and charging by means of an electric field. In this process, a solution containing the dissolved substances flows out from a capillary nozzle, which is maintained at high potential, through an electric field, which causes elongation of the solution droplets to form a jet. The solution jet is dried, and the generated particles are collected on a charged powder collector. Patil et al. demonstrated the potential of this process to generate cocrystals of carbamaze- pine and itraconazole with different coformers (24).

Microwave assisted cocrystallization

Cocrystallization by microwave radiation is based in the improvement of molecular mobility, caused by the interaction between the microwave radiation and rotating dipoles of the molecule, which promotes molecular excitation. Dielectric heating caused by microwaves induces acceleration and maintenance of the saturated solution state of the reacting compounds at the crystal interface leading to fast cocrystallization (Figure 1.8). Dielectric heating depends on the dielectric proprieties of the material and reflects the capability of a substance to convert microwave energy into heat at a certain frequency and temperature. When solvent is used, the cocrystal supersaturation promotes crystallization out from the solution. Therefore, the degree of reacting compounds in the solution decreases, which limits their formation rate. The overall process and the final cocrystal form are determined by solubility of components and the dielectric properties (25). Cocrystallization using microwave is a viable technique to produce cocrystals in a faster and greener way and without exposing the compounds to any shear forces as in other techniques.

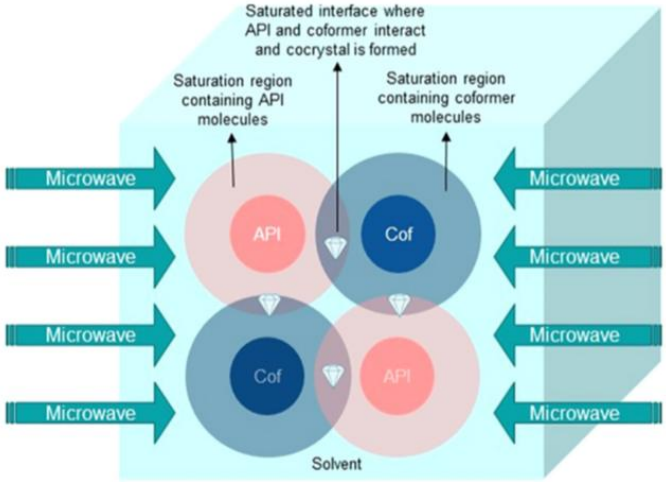


Figure 8: Schematic representation of the saturation region of the cocrystallization assisted by microwave radiation.

Effect on Drug Properties by Cocrystallization

Melting Point.

The melting point is a fundamental physical property, which is determined by the temperature at which the solid phase is at equilibrium with the liquid phase. Since melting point is a thermodynamic process where the free energy of transition is equal to zero, the value is determined by the ratio of change in the enthalpy of fusion over the change in the entropy of fusion (36, 37). If available, differential scanning calorimetry (DSC) is the preferred technique for obtaining comprehensive melting point data, over a standard melting point apparatus or Kofler method, because additional thermal data such as the enthalpy of fusion can be determined. For example, the melting point and heat of fusion, both determined from DSC, are necessary when attempting to characterize a polymorphic pair of compounds as monotropic or enantiotropic (38)

Stability.

Stability is a heavily studied parameter during the development of a new chemical entity. Different types of stability need to be considered depending on the structure and characteristics of the molecule. Chemical and physical stability data are commonly obtained at accelerated stability conditionsto determine developability and shelf life (39).

Relative Humidity Stress.

As with other solid forms, changes over a wide relative humidity (RH) range are a key consideration when developing a cocrystal (80,81). Automated moisture sorption/desorption studies are commonly performed to determine problem areas and to provide direction for more detailed studies when the need arises. X-ray powder diffraction (XRPD) data collected on the solid at the end of the moisture balance experiment provides information on the final form, but not necessarily on any form conversions that may have occurred during the experiment. Significant moisture uptake during the course of the experiment may warrant longer exposure at a specific relative humidity using a relative humidity chamber and subsequent analysis of the sample after equilibration.

Thermal Stress.

High temperature stress is another common condition used to determine chemical and physical stability based on accelerated stability conditions. Very few reports discuss thermal stress experiments on cocrystals. For the cocrystal of a monophosphate salt with phosphoric acid an 8-week exposure at 60 °C resulted in no detectable degradation or form change (32).

Chemical Stability.

Chemical stability is commonly investigated early in the development of a new compound and during formulation studies in order to minimize any chemical degradation that may occur. Accelerated stability conditions, such as 40 °C/75% RH and 60 °C/75% RH, are commonly used for early studies on solid materials. Very few reports of chemical stability of cocrystals were found when reviewing the literature.

Solution Stability.

Solution stability for this discussion is defined as the ability of the cocrystal components to stay in solution and not readily crystallize. Solution stability can be an important parameter to assess during development, not only for solutions or suspensions, but also for solid dosage forms that will dissolve in the GI tract. A variety of vehicles can be used, including water, simulated gastric fluid (SGF), simulated intestinal fluid (SIF), formulation vehicles, and buffered solutions. In many instances, these experiments can be coupled with solubility or dissolution experiments to get a more complete picture of the behavior and the solid form remaining at the end of the experiment. Because dissociation of a cocrystal can occur, solution stability can be a key consideration for development. However, the results should always be weighed with other properties and needs.

Solubility.

One of the main reasons to investigate cocrystals is to increase the solubility of a poorly soluble compound. For neutral molecules, cocrystals can certainly expand the solid forms possible for development. For a free acid or free base, both salts and cocrystals can be used to improve the solubility; however, it is not always straightforward to determine whether a salt or a cocrystal has been formed and a variety of techniques may be needed to understand the system (33).

Intrinsic Dissolution.

Intrinsic dissolution measures the rate of dissolution without the effect of particle size. This is accomplished by pressing a disk or pellet, commonly using a Woods apparatus in a dissolution vessel (34). Solution concentra- tion is measured over time to determine the dissolution rate (in mg/cm2·min). The disk needs to remain intact during the experiment, so compression pressures may be critical for poorly compressible powders. It is also important that there is no form change upon pressing the pellet or during the dissolution study. XRPD data can be obtained on the initial disk and the remainingdisk after completion of the experiment to determine any major form changes that may affect the dissolution data.

Bioavailability.

Bioavailability is a measurement of the rate and extent of the active drug that reaches systemic circulation (35). Animal bioavailability is an important parameter to consider when preparing new forms of a compound, and studies can be set up in a number of different ways to obtain specific information for development. Species for animal studies can include rodents, rabbits, dogs, pigs, and primates. These studies are usually performed during early development and can be small studies (4-6 animals) to determine pharmacokinetic data quickly on a new form. Usually the same animals are used for all forms/formulations with a washout period, typically, a week in length, between the doses. This gives a direct comparison within the same animals for all the materials in the study.

Characterization of co-crystals

- Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase (36). Melting point

of pure API, co-formers and cocrystals are obtained by capillary method using liquid paraffin (37) or DSC is the preferred for obtaining melting point data and thermal data such as enthalpy of melting. DSC has recently been used as a tool for rapid cocrystal screening (38).

- SEM is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is used to determine the cocrystal micrograph and particle size (38-40).
- Single X-ray diffraction (SXRD) is a technique for determination of the solid-state structure of cocrystals at an atomic level. The problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, powder X-ray diffraction (PXRD) are utilised more frequently to verify the formation of cocrystals.
- Raman spectroscopy is used to study vibrational, rotational, and other low frequency modes in a system. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products (38-40).

Advantages of cocrystal approach

- Co-crystals having several advantages such as no necessitate to make or break covalent bonds, as compared to amorphous solids it is stable crystalline form, theoretical ability of all types of drug molecules such as weakly ionizable/non-ionizable to form co- crystals, the existence of numerous potential counter molecules such as food preservatives, pharmaceutical excipients, additives, and other APIs, the only solid form that is designable via crystal engineering patentable expanding IP portfolios and can be produced using solid-state synthesis green technologies high yield, no solvent or by-products.
- Compared to other solid-state modification techniques employed by pharmaceutical industry, cocrystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization.

Application

A key question concerning the practical application of a cocrystal of a commercial API is whether the cocrystal is in some sense a physical mixture and hence might fall within current compendial guidelines, or whether the cocrystal should be regarded as a new chemical entity with all the concomitant safety and toxicological testing such substances require. The USA Food and Drug Administration (FDA) have released draft guidance on the regulatory classification of pharmaceutical cocrystals for applicants for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). The FDA defines cocrystals as "solids that are crystalline materials composed of two or more molecules in the same crystal lattice" - the implication is that it is two or more types of molecules that are referred to here.

The FDA also regards cocrystals as dissociable "API-excipient" complexes, blurring the boundary between cocrystals and physical mixtures. This guidance has generated a strong response from some researchers in the cocrystal field who propose alternative, yet also potentially controversial definitions that distinguish multicomponent APIs and their cocrystals from solvates and hydrates.

Among many recent patents relating to potential commercial cocrystal products, the possibility of combining two active ingredients in a single cocrystal is an interesting one and has been claimed in the cocrystallization of quercetin (a plant-derived flavonoid, used as a nutritional supplement and reputed to offer some anti-cancer properties) with antidiabetic agents such as metformin or tolazamide. The combination drug has been suggested to have physical properties and biological activity that are distinct from the individual properties of the two components. Interesting research pointing the way to applications of cocrystals in the modification of drug pharmacological action has been reported for insulin, a peptide hormone used for the treatment of diabetic patients. Insulin has poor oral bioavailability and is commonly injected. Human insulin has been cocrystallised with lipophilically modified, closely related insulin analogue octanoyl-N-LysB29-human insulin. The lipophilic formulation was designed to provide a slow release profile compatible with an improved physiological insulin profile.

REFERENCES:

1. Desiraju GR. Supramolecular synthons in crystal engineering—a new organic synthesis. Angewandte Chemie International Edition in English. 1995 Nov 17;34(21):2311-27.
2. Desiraju GR. Crystal engineering: a holistic view. Angewandte Chemie International Edition. 2007 Nov 12; 46(44):8342-56.
3. Desiraju GR. Chemistry beyond the molecule. Nature. 2001 Jul; 412(6845):397-400.
4. Steed JW, Atwood JL. Supramolecular chemistry. John Wiley & Sons; 2013 May 21.
5. Gavezzotti A. Crystal packing of hydrocarbons. Effects of molecular size, shape and stoichiometry. Acta Crystallographica Section B: Structural Science. 1990 Apr 1; 46(2):275-83.
6. Anderson KM, Probert MR, Goeta AE, Steed JW. Size does matter—the contribution of molecular volume, shape and flexibility to the formation of co-crystals and structures with Z'> 1. CrystEngComm. 2011;13(1):83-7.
7. Dunitz JD, Filippini G, Gavezzotti A. Molecular shape and crystal packing: a study of C12H12 isomers, real and imaginary. Helvetica Chimica Acta. 2000 Sep 6;83(9):2317-35.
8. Gavezzotti A, Filippini G. Self-organization of small organic molecules in liquids, solutions and crystals: static and dynamic calculations. Chemical Communications. 1998(3):287-94.
9. Aakeröy CB, Sinha AS, Epa KN, Chopade PD, Smith MM, Desper J. Structural chemistry of oximes. Crystal growth & design. 2013 Jun 5;13(6):2687-95.
10. Adams CJ, Haddow MF, Lusi M, Orpen AG. Crystal engineering of lattice metrics of perhalometallate salts and MOFs. Proceedings of the National Academy of Sciences. 2010 Sep 14;107(37):16033-8.

11. Merz K, Vasylyeva V. Development and boundaries in the field of supramolecular synthons. CrystEngComm. 2010;12(12):3989-4002.
12. Kavuru P, Aboarayes D, Arora KK, Clarke HD, Kennedy A, Marshall L, Ong TT, Perman J, Pujari T, Wojtas Ł, Zaworotko MJ. Hierarchy of supramolecular synthons: persistent hydrogen bonds between carboxylates and weakly acidic hydroxyl moieties in cocrystals of zwitterions. Crystal growth & design. 2010 Aug 4;10(8):3568-84.
13. Shattock TR, Arora KK, Vishweshwar P, Zaworotko MJ. Hierarchy of supramolecular synthons: persistent carboxylic acid⋯ pyridine hydrogen bonds in cocrystals that also contain a hydroxyl moiety. Crystal growth and design. 2008 Dec 3;8(12):4533-45.
14. Khan M, Enkelmann V, Brunklaus G. O− H⋯ N heterosynthon: a robust supramolecular unit for crystal engineering. Crystal Growth and Design. 2009 May 6;9(5):2354-62.
15. Takusagawa F, Shimada A. Isonicotinic acid. Acta Crystallographica Section B: Structural Crystallography and Crystal Chemistry. 1976 Jun 15;32(6):1925-7.
16. Desiraju GR. Crystal and co-crystal. CrystEngComm. 2003 Nov 14;5(82):466-7.
17. Dunitz JD. Crystal and co-crystal: a second opinion. CrystEngComm. 2003 Dec 9;5(91):506-.
18. Friščić T, MacGillivray LR. Modularity in organic solid state and supramolecular chemistry. Croatica chemica acta. 2006 Jul 19;79(2):327-33.
19. Sokolov AN, Friščić T, MacGillivray LR. Enforced face-to-face stacking of organic semiconductor building blocks within hydrogen-bonded molecular cocrystals. Journal of the American Chemical Society. 2006 Mar 8;128(9):2806-7.
20. Eger C, Norton DA. Androgenic steroid complexes with p-Bromophenol. Nature. 1965 Dec;208(5014):997-9.
21. Bhatt PM, Desiraju GR. Co-crystal formation and the determination of absolute configuration. CrystEngComm. 2008;10(12):1747-9.
22. Eccles KS, Deasy RE, Fábián L, Maguire AR, Lawrence SE. The use of co-crystals for the determination of absolute stereochemistry: An alternative to salt formation. The Journal of organic chemistry. 2011 Feb 18;76(4):1159-62.
23. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Crystal growth and design. 2009 Jun 3;9(6):2950-67.
24. Vishweshwar P, McMahon JA, Peterson ML, Hickey MB, Shattock TR, Zaworotko MJ. Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. Chemical communications. 2005(36):4601-3.
25. Bucar DK, Henry RF, Lou X, Duerst RW, MacGillivray LR, Zhang GG. Cocrystals of caffeine and hydroxybenzoic acids composed of multiple supramolecular heterosynthons: screening via solution-mediated phase transformation and structural characterization. Crystal Growth and Design. 2009 Apr 1;9(4):1932-43.
26. Blagden N, Berry DJ, Parkin A, Javed H, Ibrahim A, Gavan PT, De Matos LL, Seaton CC. Current directions in co-crystal growth. New Journal of Chemistry. 2008;32(10):1659-72.
27. Babu NJ, Nangia A. Solubility advantage of amorphous drugs and pharmaceutical cocrystals. Crystal Growth & Design. 2011 Jul 6;11(7):2662-79.
28. Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. Crystal growth and design. 2009 Jun 3;9(6):2950-67.
29. Trask AV, Jones W. Crystal engineering of organic cocrystals by the solid-state grinding approach. InOrganic solid state reactions 2005 Jan 1 (pp. 41-70). Springer, Berlin, Heidelberg.
30. Weyna DR, Shattock T, Vishweshwar P, Zaworotko MJ. Synthesis and structural characterization of cocrystals and pharmaceutical cocrystals: mechanochemistry vs slow evaporation from solution. Crystal Growth and Design. 2009 Feb 4;9(2):1106-23.
31. Chen J, Sarma B, Evans JM, Myerson AS. Pharmaceutical crystallization. Crystal growth & design. 2011 Apr 6;11(4):887-95.
32. Braga D, Giaffreda SL, Grepioni F, Pettersen A, Maini L, Curzi M, Polito M. Mechanochemical preparation of molecular and supramolecular organometallic materials and coordination networks. Dalton transactions. 2006(10):1249-63.
33. Jayasankar A, Somwangthanaroj A, Shao ZJ, Rodríguez-Hornedo N. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. Pharmaceutical research. 2006 Oct 1;23(10):2381-92.
34. Aakery CB, Salmon DJ. Building co-crystals with molecular sense and supramolecular sensibility. CrystEngComm, 2005, 7(72), 439–448
35. Miroshnyk I, Mirza S, Sandler N. Pharmaceutical co-crystals–an opportunity for drug product enhancement. Expert opinion on drug delivery. 2009 Apr 1;6(4):333-41.
36. McMohan JA. Crystal engineering of novel pharmaceutical forms. Master of Science thesis, Department of Chemistry, University of South Florida, USA, 2006.
37. Jones W, Motherwell WS, Trask AV. Pharmaceutical cocrystals: an emerging approach to physical property enhancement. MRS bulletin. 2006 Nov;31(11):875-9.
38. Bhogala BR, Nangia A. Ternary and quaternary co-crystals of 1, 3-cis, 5-cis-cyclohexanetricarboxylic acid and 4, 4′-bipyridines. New Journal of Chemistry. 2008; 32(5):800-7.
39. Yao J, Chen JM, Xu YB, Lu TB. Enhancing the solubility of 6-mercaptopurine by formation of ionic cocrystal with zinc trifluoromethanesul fonate: single-crystal-to-single-crystal transformation. Crystal growth & design. 2014 Oct 1; 14(10):5019-25.
40. Braga D, Grepioni F, Maini L, Prosperi S, Gobetto R, Chierotti MR. From unexpected reactions to a new family of ionic co-crystals: the case of barbituric acid with alkali bromides and caesium iodide. Chemical communications. 2010 Oct 12; 46(41):7715-7.