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

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Abstract

Pharmaceutical cocrystals are crystalline materials made up of a neutral co-former and an active pharmaceutical ingredient (API) in a specific stoichiometric ratio. These materials are held together by non-covalent interactions like van der Waals forces, hydrogen bonding, and π–π stacking. A successful crystal engineering technique for enhancing the physicochemical and biopharmaceutical characteristics of poorly soluble medications without changing their pharmacological activity is cocrystallization. Cocrystals provide more flexibility in altering drug properties like solubility, dissolution rate, stability, hygroscopicity, compressibility, and bioavailability than traditional solid forms like salts and polymorphs. Solvent evaporation, grinding techniques, slurry conversion, melt crystallization, spray drying, hot-melt extrusion, and supercritical fluid technology are some of the methods used to prepare cocrystals. Analytical methods like differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and dissolution studies are frequently used to characterize and evaluate cocrystals. Pharmaceutical cocrystals have drawn a lot of attention lately because of their potential to solve formulation issues with poorly water-soluble medications. A number of cocrystal-based products have also made it to the pharmaceutical market, indicating their significance in both industry and medicine. In order to improve drug performance and patient compliance, co-crystallization is a promising and adaptable approach in contemporary drug development.

Keywords

co-crystallization, van der Waals forces, hydrogen bonding

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INTRODUCTION

Pharmaceutical cocrystals are multicomponent crystalline systems made up of a pharmaceutically acceptable co-former and an active pharmaceutical ingredient (API) in a specific stoichiometric ratio, joined by non-covalent interactions like hydrogen bonds. Cocrystallization has become a significant crystal engineering technique in recent years for enhancing the physicochemical and biopharmaceutical characteristics of medications, especially those that are poorly soluble in water. Cocrystals, in contrast to salts, can form with neutral molecules without changing the drug's pharmacological activity or molecular structure. Pharmaceutical compounds' solubility, dissolution rate, stability, bioavailability, compressibility, and

mechanical properties can all be improved by the formation of cocrystals. Pharmaceutical cocrystals have drawn a lot of interest in drug development and formulation research because of these benefits, which present a viable way to get around the drawbacks of traditional dosage forms.

PHYSICAL PROPERTIES OF CO CRYSTALS:

Cocrystals are multicomponent crystalline systems composed of an active pharmaceutical ingredient (API) and a coformer, typically held together by non-covalent interactions such as hydrogen bonding, π–π stacking, and van der Waals forces. These interactions significantly modify the physical properties of the parent drug(1–3).

1. **Solubility:** Enhancing solubility is a key goal in the creation of cocrystals. Cocrystals can improve aqueous solubility by lowering lattice energy and altering crystal arrangement. The solubility is influenced by the characteristics of the coformer and its interactions with the solvent. In certain instances, cocrystals may exhibit supersaturation behavior, leading to enhanced drug absorption(4). Asenapine maleate is an atypical antipsychotic drug belonging to BCS class II, characterized by low solubility and high permeability, which limits its bioavailability. To improve the solubility and dissolution rate of Asenapine maleate, cocrystals were prepared using the solvent evaporation method. Various coformers, such as nicotinamide, urea, succinic acid, benzoic acid, and citric acid, were evaluated in different ratios. The optimized cocrystals was obtained with nicotinamide in a 1:3 drug-to-coformer ratio. Asenapine maleate cocrystals were successfully prepared and characterized. The optimized cocrystal significantly improved solubility and dissolution, which is expected to enhance the bioavailability of Asenapine (5).
2. **Melting Point:** Cocrystals display melting points that are distinct from those of the individual active pharmaceutical ingredient (API) and coformer. An elevated melting point typically signifies stronger intermolecular interactions and enhanced lattice stability. A reduced melting point might be associated with better solubility and dissolution. Melting characteristics are important for processing, storage, and formulation stability. Aripiprazole cocrystals with catechol and resorcinol showed different melting points due to variations in hydrogen-bonding networks. High-melting cocrystals exhibited strong 3-dimensional hydrogen bonding, whereas low-melting cocrystals formed two-dimensional layered structures. The aripiprazole cocrystal are ISO structure different in melting point due to variation in their hydrogen bond network(6).
3. **Bioavailability:** Cocrystals improve bioavailability mainly by increasing the solubility and dissolution rate of poorly soluble medications while maintaining their chemical structure. Genistein exhibits poor solubility and bioavailability. Genistein piperazine cocrystals, prepared by solvent-assisted grinding, significantly improved solubility and bioavailability. Genistein is a cocrystal with genistein _piperazine formed to overcome poor bioavailability(7).
4. **Mechanical properties:** Cocrystals often show improved compressibility, compactibility, and flowability. In the production of tablets, this is advantageous for direct compression. Intermolecular interactions and crystal packing determine mechanical strength. Paracetamol cocrystals with 5-nitroisophthalic acid(5-NIP), prepared by solvent evaporation, demonstrated improved mechanical strength and stability under accelerated storage conditions(8).
5. **Density**: The effectiveness of crystal packing is changed by cocrystal formation. This has an impact on mechanical behavior, porosity, and bulk density. In general, better stability results from efficient packing. HNIW-TNT cocrystals synthesized using ethanol exhibited higher density and improved crystal packing, confirmed by powder X-ray diffraction studies. Pharmaceutical cocrystal of paracetamol with 5-nitroisopthalic acid(5-NIP) 1:1 molar ratio using solvent evaporation this confirm that they PCA 5-NIP core crystals strategy enhance Mechanical properties. Increase the density in in this proper cocrystal HNIW (2,4,6,8,10,) hexanitro (2,4,6,8,10,12) hexazaisowurtzitane often refer to as (L_20) with TNT (2,4,6 trinitro tolune) where synthesizer using ethanol in a green method the cocrystals is formulated as C_{13}, H_{11}, N_{15}, O_{18} and possessive high density poses a new crystal powder extra diffraction the result the structure of new HNIW/TNT cocrystal. In this proper cocrystal HNIW (2,4,6,8,10,12) the cocrystal was formatted has C_{13}, H_{11}, N_{15}, O_{18} and used to overcome poor density(8).
6. **Dissolution Rate:** When compared to pure medications, cocrystals frequently show quicker rates of dissolution. Enhanced dissolving is a result of decreased particle agglomeration and increased wettability.

Increased bioavailability results from this, particularly for poorly soluble medications (BCS Class II and IV). Carbamazepine-glutaric acid cocrystals showed enhanced solubility and dissolution rate. Excess glutaric acid reduced drug precipitation by lowering supersaturation levels, leading to improved dissolution performance. A highly soluble carabamazepine cocrystal with glutaric acid impact of excess GLA on solubility and Intersinic dissolution rate GLA solution was also measured solid form of powders and pellets was examined using powder extra diffraction cocrystal and GLA Mixture indifferent ratio where to identify suitable formation for maintaining high dissolution of CBZ GLA Aqueous environment. The excessive GLA increased solubility of CBZ to H2O and they're by reduce the precipitation of CBZ H2O during the solution by lowering the degree of supersaturation this allowed development of a CBZ GLA formulation resolution rate than CBZ GLA(9).

METHODS OF PREPARATION OF COCRYSTALS: With the advancement in drug development, various methods are being used for preparation of multicomponent, solid forms as cocrystal, co-solvates, polymorph, hydrates/salts & eutectics. Solvent selection, API and co-formers are the important parameters for such preparations(10,11).
The various kinds of methods that are most commonly used are: -

Solid state methods: -They use little or no solvent; rely on mechanical or thermal activation. It generally includes solid phase grinding, melt, extrusion and melt crystallization.

1. Contact Formation
2. Solid State Grinding
3. Neat (Dry)Grinding,
4. Liquid-Assisted Grinding.
5. Twin Screw Extrusion (TSE)
6. Hot Melt Extrusion (HME)
7. High Shear Wet Granulation

Solution or liquid based methods: -These Rely on super saturation in a solvent, require recovery of crystalline solid from mother liquor.

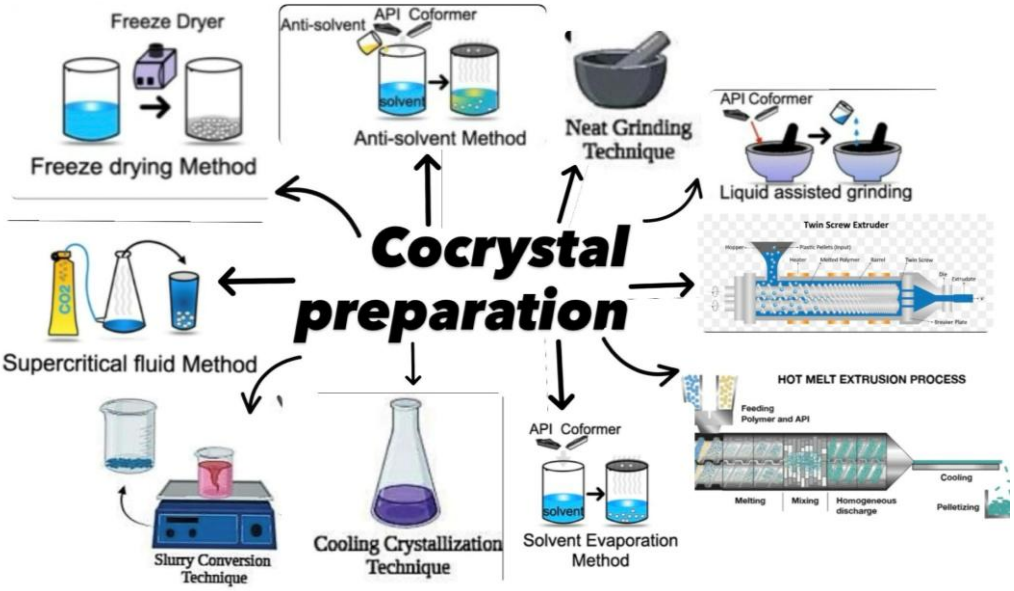
1. Evaporative Co- Crystallization
2. Cooling Crystallization Method
3. Reaction Co Crystallization Method
4. Slurry Method

Supercritical Fluid Method:

1. Co- Crystallization with Supercritical Solvent (CSS)
2. Rapid Expansion of Supercritical Solvent (RESS)
3. Supercritical Antisolvent Co- Crystallization
4. GAS (Gas Antisolvent Method)
5. SAS (Supercritical Antisolvent Method)
6. Supercritical CO2-Assisted Spray Drying

(d)Miscellaneous Co-Crystallization Preparation Method:

1. Laser Irradiation
2. Electrochemically Induced Crystallization
3. Resonant Acoustic Mixing (RAM)
4. Spray Drying
5. Freeze- drying (Lyophilization)
6. Microwave-Assisted Co- crystallization
7. Electrospray Technology.



(A) SOLID STATE METHODS: In this method, API & coformer are melted and mixed together, resulting in the cocrystal formation in a fixed stoichiometric ratio. It is basically not suitable for thermolabile moiety, but it is easy, scalable and continuous process.

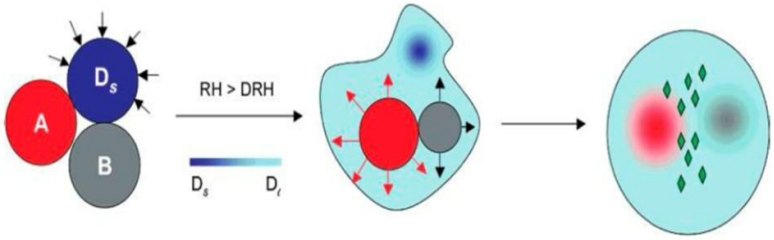
1.Contact Formation

A method where API and co-former are simply brought into contact under controlled conditions without mechanical force. Cocrystals form spontaneously via moisture uptake, dissolution under deliquescent condition and recrystallisation. Pre-milling reduces particle size and increases surface energy(12). High temperature and RH significantly speed up formation. Smaller particle size (<45 micrometers) accelerates conversion without amorphous intermediates(13).

Mechanism:

1. Moisture uspdate
2. Deliquescent dissolution of reactants, &
3. Nucleation and growth of cocrystals.

Screening tools: - Hot stage microscopy/ kofler method to map phase behaviour Identify possible cocrystal zones between components.



Examples:

a) Pre-milling of starting material on the crystallization rate of Carbamazepine and Nicotinamide(14,15). The crystallization rate in the case of pre-mild reactant was markedly faster than unmoved reactants(16).

b) Studied the effect of the particle size of starting material on spontaneous crystallization of Urea and 2-methoxy benzamide. It has been shown that smaller particle size distribution lead to faster cocrystal formation(17).

2. Solid-State Grinding

One of the most widely used methods.

1) Neat (dry) grinding &

2) Liquid-Assisted grinding (LAG)

1)Neat (dry) grinding:

It is most widely and commonly used technique for cocrystal formation, in which API and coformer are mingled in a stoichiometric proportion using mortar and pestle. This method is simple, easy to perform, eco-friendly, and highly productive but is mechanical and time consuming. Efficient because no solubility loss to solvent(17). Nowadays, plain tarry milling systems are also available in laboratory scale.

Examples:

a) Cocrystals of Caffeine and Oxalic acid by neat grinding method. The study suggests that the importance of rotation speed is more than that of the temperature for the production of cocrystals. With the increase in speed, cocrystal content also increases(18).

b) Two Sulphathiazole: Carboxylic acid cocrystals where successfully prepared by grinding stoichiometric using a Retsch mixer at 35 HZ for 90 minutes, ensuring temperature did not exceed set limits(19). Higher efficiency compared to solution methods, and yield is not lost to the solvent due to solubility(20).

2)Liquid-Assisted grinding (LAG):

A small number of liquid acts as catalytic (the solvent remains only for the duration of grinding and does not act as a reactant)(21). Its primary role is to enhance interaction between the starting materials by wetting their surfaces, which accelerates and promotes cocrystal formation(22). This method provides higher efficiency and better co crystallisation outcomes because of this solvent mediated surface activation.

Mechanical insights. Molecular diffusion (solid-state vapor or surface diffusion), Eutectic formation, Amorphous intermediate formation.

Examples:

a) Ketoconazole (KTZ) blends or combined with different diabolic acids namely fumaric acid (FA) and succinic acid (SA) via neat or liquid assisted grinding, immediately after preparation, solid samples were analyzed using thermal analysis, spectroscopy, power x-ray diffraction (PXRD). The Cocrystals showed enhanced dissolution rates compared to the pure drug in LAG, where as in neat and dry grinding it shows poor dissolution rates, time dependent analysis showed that cocrystals formed rapidly under LAG conditions.

LAG was applied to generate highly water soluble cocrystals of poorly soluble

nutraceuticals hesperetin (HESP) with different co-formers such as: Picolinic acid (PICO), Nicotinamide (NICO) & Caffeine (CAFF). It has led to optimization of the pharmacokinetics properties by improving the bioavailability and dissolution studies showed hesperetin concentration increased 4 to 5 times/X compared to pure drug(23).

3.Twin-Screw Extrusion (TSW)

This method operates a temperature below the melting point of either starting material and take place in distant piece of equipment-an aptly named twin-screw extruder(24).

Mechanochemical continuous manufacturing technique involving two screws in a barrel. Screw action provides simultaneously mixing and movement of material along the length of barrel.

Daurio et al. reported on the formation of four model cocrystals using a 16mm twin screw extruder with four control temperature zones(25).

Advantages: High shear mixing, no solvent, continuous process, enhance the physical properties (flexibility, density). Temperature influence varies by system, Higher mixing intensity and residence time-greater purity, successful for systems like carbamazepine: saccharin, caffeine: oxalic acid, ibuprofen: nicotinamide, etc.

Examples:

a) Ibuprofen: Nicotinamide cocrystals via TSE, produced by continuous process, purity determined via PXRD varied from 20-99%depending on execution settings. This study showed that extrusion temperature, screw configuration and screw rotation speed are the three critical parameters to determine cocrystal purity, optimal conditions for high purity, high residence time (low screw speed), high processing temperature and intensive screw mixing(25).

b) Caffeine and AMG-517 first successful demonstration of this cocrystal via TSE. This study proved that TSE helps to have a highly efficient mixing, tighter component packing and enhanced surface contact between reactant. Consequently, cocrystals formation will be facilitated without adding any solvent(26).

4. Hot melt Excretion (HME)

In this technique, API & coformers are transferred into a fixed controlled temperature system where they are melted and form cocrystals of new moiety. This technique is not suitable for thermolabile drugs because both drug and coformer should be mixed in a molten state(27). In this method, API and coformer should be mixed in their molten state to enhance their surface contact without the use of solution(solvent). Crystalline drugs are converted to Amorphous Solid Dispersion (ASDS).

Examples:

a) Hydrochlorothiazide: Nicotinamide (HCT: NIC) cocrystals are prepared by HME. HCT: NIC cocrystal transitioned to an amorphous form during HME processing forming flexible and printable filaments. The mechanical properties of the obtained tablets and release profile of the drug from the AM tablets were enhanced as compared to the materials obtained using conventional method i.e., tableting & encapsulation. Improve solubility & diffusion characteristics(28).

b) Dhumal et al. manufactured the agglomerated cocrystal of Ibuprofen & Nicotinamide by HME. The barrel temperature must be above the eutectic point of physical mixture. Also, in order to get the purer cocrystal, the highest sheer screw configuration should be applied(24).

Advantages: No solvent, fast and scalable, suitable for continuous manufacturing and can protect heat sensitive APIs co-crystallization (lower melting cocrystal protects drug). Key parameters include temperature profile, Screw speed and Feed rate.

5. High Shear Wet Granulation

Granulation with liquid binder in high shear environment. Mechanism: similar to LAG, slurry transformation(29). key observation: Conversion depends on type or amount of granulation liquid, impeller speed. Ethanol can promote cocrystallisation where water fails(30) (eg:Vabradine HCL-Mandelic acid).

Examples:

a) A 1:1 Piracetam: Tartaric acid cocrystal was successfully produced from a mixture of piracetam, tartaric acid, & a variety of excipients in the presence of water using a Bohle mini granulator. The Extent of cocrystal formation was impacted by volume of granulation liquid used, impeller speed, & the exicipent mixture used, with 95% conversion achieved within 5min(30).

b) Ivabradine hydrochloride(s)- Mandelic acid cocrystal (ICISM) Evaluated the Effect or different granulation liquids on cocrystal formation, two granulation liquids tested are: water and ethanol & whereas lactose monohydrate added as excipient along with API and co-former. No cocrystal formation occurred with water, even in the presence of lactose monohydrate. Ethanol successfully facilitated cocrystal formation, confirmed through PXRD showing characteristic peaks.

(B)Solution or Liquid Based Methods

Cocrystal form when solution concentration of API and co-former exceed co-crystal solubility, generating super saturation relative to the cocrystal.

1.Evaporative Co-crystallization

Evaporative co-crystallization is a widely used method for forming cocrystals, especially single crystals suitable for diffraction & structural analysis.(31)

The process involves: - Dissolving both the API & coformer in a suitable solvent. Allowing the solvent to evaporate slowly to induce supersaturation. Promoting nucleation and growth of cocrystals during solvent loss. Crystals must be collected before complete dryness to avoid contamination or undesired crystal forms. A slow evaporation rate is preferred because: - It leads to fewer but larger & better-quality crystals.

Rapid Evaporation tends to produce many small crystals. Structural confirmation (eg: Using X-ray diffraction) is essential to determine whether the obtained solid is cocrystal, salt, hydrate, Polymorph(32).

Example:

a) Norfloxacin+ Nicotinamide dissolved in 8ML chloroform (0.1 mmol each). Slow evaporation at room temperature produced rod shaped single crystals(33).
b) Cocrystal of Baicalein with Theophylline co-former by the solvent evaporation method. Obtained cocrystal exhibits a significant increase in performance in in-vitro as well as in-vivo evaluation(34).

2.Cooling Crystallization Method

It is less frequently applied method for the cocrystal formation. It is generally slow and time-consuming process as compared to other techniques(35).

Example:

a) Succinic acid cocrystal.
In this, there is an improvement in solubility, dissolution and micrometric properties than its individual drug darunavir(36).
b) Used to produce Carbamazepine-Nicotinamide cocrystal from ethanol. Solvent selection, identification of the thermodynamically stable cocrystal operating range and supersaturation kinetics(37).
c) Preparing Agomelatine: Citric acid cocrystals. The impact of cooling rate and seed amount on the crystal size distribution in the final product was assessed.

3)Reaction Cocrystallization Method

This technique is mainly employed for quick formation of cocrystals at the macroscopic & microscopic level at a room temperature in which cocrystallization & nucleation are based on their solubility and cocrystal formation. Drug & coformer are solvated separately in either methanol or other suitable solvent and finally mixed together for crystal formation under its solubility limit. To determine stoichiometry of the complex, precipitates are examined by high performance liquid chromatography(38).

Examples:

a) Used to produce Cocrystals of Carbamazepine-Saccharin by combining individual feed solutions of either of the starting materials. Process development was guided by a Ternary Phase Diagram, which helped define a robust operating range for cocrystal formation. The process demonstrated the expected correlation between supersaturation level & induction time(39,40).
b) Formation of Carbamazepine-Nicotinamide Cocrystals. Process is done under ambient conditions(41).

4.Slurry Method

It is also one of the easiest techniques for the crystallization process where cocrystal formation takes place(42). The selected drug & coformer are dissolved into a suitable solvent forming a suspension & are finally stirred, filtered & dried(43). Celecoxib-Venlafaxine Cocrystal (non-steroidal anti-inflammatory drugs (NSAIDS] + antidepressant) drug was prepared & patented using slurry technique of crystallization.

The (Celecoxib (BCS class II and Venlafaxine (BCS class I]). Solubility issue are overcome by the use of high solubility BCS class I drug(44). In this technique, a slurry of API & coformer is prepared in a suitable solvent, stirred properly with glass rod/magnetic stirrer & solvent is allowed to cool slowly at room temperature until cocrystal formation takes place.

Examples:

a) Zhang et al- Studied Theophylline: Glutaric acid (1:1) cocrystal. Times ranging from 15 min to 5h were recorder for complete conversion depending on solution concentration solvent selection. The transformation time to cocrystal decreases with increasing solubility in a given solvent(45).

b) Jayasankar et al. directly investigated the impact of coformer concentration of Carbamazepine:4-Aminobenzoic acid(4-ABA) system, forming two cocrystals (1:1&2:1). The yield is productivity of isothermal slurry conversion can vary widely based on operating conditions and concentrations and can also be optimized through use of the TPD(46).

(C)Supercritical Fluid Method

Cocrystals have been successfully produced using supercritical fluid technology, primary with the use of supercritical CO2, by three different approaches which flows on distant supercritical CO2 properties: solvent, anti-solvent, and atomization enhancement.

1.Cocrystallisation with Supercritical Solvent (CSS)
Uses supercritical CO2 as a solvent to disperse the API and co-former as a slurry. Eliminates the need for toxic organic solvents(47). The solvent strength of CO2 can be controlled by adjusting temperature and pressure, allowing precise manipulation of the crystallization process. Researchers (Subra-Daternault Et al.) tested several APIs (Indomethacin; Theophylline, Carbamazepine, Caffeine, Sulfamethazine, Acetylsalicylic acid) with saccharin using liquid & supercritical CO2(48). Although most APIs & coformers have low solubility in CO_2, cocrystal formation still occurs through limited dissolution. Increasing the concentration of components in CO_2 accelerates cocrystal formation. Stirring enhances mass transfer through convection & is crucial for achieving complete conversion into pure cocrystals, without leftover raw materials(49).
Examples:
a) Cocrystals of Curcumin-N-Acetylcysteine by using supercritical fluid technology. It results in high purity, high-quality cocrystals(50)
b) Cocrystals of various drugs using SEA technology, resulting in particle sizes ranges from 0.3 to 10 micrometers. The study highlights the strong potential of supercritical fluid technology for cocrystal screening and formulation(51).
2.Rapid Expansion of Supercritical Solvent (RESS)
Involves dissolving the API and co-former in super critical CO2.The loaded supercritical fluid is then rapidly depressurized through a nozzle into a chamber at atmospheric pressure. The sudden pressure drop causes instant precipitation, forming crystals(52).
– Main drawback: Most pharmaceutical molecules have very poor solubility, CO2, making this method applicable only to specific cases(53).
3.Supercritical Antisolvent Crystallization
Two main strategies:
A) GAS (Gas Antisolvent Method):
API and coformer are dissolved in a solvent inside a vessel.CO_2 are slowly introduced until crystallization begins.
Examples:
a) Itraconazole-Succinic acid cocrystals for successfully formed using GAS. Using GAS, Itraconazole- Succinic acid cocrystals showed differences in agglomeration behavior depending on preparation routes(54).
b) Prepared Mefenamic Acid-Nicotinamide cocrystals using the gas anti-solvent method. The study suggests the ratio of drug and co-former and the percentage of drug saturation had a significant effect on cocrystal dissolution time.

B) SAS (Supercritical Antisolvent Method)
A solution of API and co-former is sprayed through a nozzle into supercritical CO2.
CO2 mixes with the solvent, rapidly expanding the volume and reducing solvent strength, causing both components to precipitate together as a cocrystal. The shape and size of the produced particles can be controlled (eg: micron sized needles or block like particles)(55).
Examples:
a) Indomethacin- Saccharin cocrystals were first prepared by Gomes de Azevedo. Likewise, Piracetam-salicylic acid cocrystals, diflunisal-nicotinamide cocrystal, paracetamol-dipicolinic acid, & naproxen-Nicotinamide cocrystal are some of the it's prepared by this method. CO_2 (non-polar compound) is the best supercritical fluid applied in the pharmaceutical fields due to its advantages such as non-toxic, non-flammable, economical & easily available(56).
CO2-to-solution flow ratio strongly affects purity and crystal quality in SAS processing.
3.Supercritical Co2-Assisted Spray Drying
This method takes advantage of the ability of supercritical CO2 to improve atomization, meaning it helps break a solution into extremely fine droplets when both the liquid solution and CO2 are depressurized together. It is a single step process.
A liquid solution containing the API and co-former (both dissolved) is spray through a specially designed nozzle along with supercritical CO2.When released into a chamber at atmospheric pressure, rapid depressurization results in:-formation of fine droplets, fast solvent evaporation, precipitation of cocrystals.
Applications & outcomes: The Supercritical Enhanced Atomization (SEA) technique has been successfully used to produce Micro-Sized to nanosized cocrystals, controlled crystal shape & morphology, improved dissolution behavior.
Examples:
a) Used to produce micro to Nano sized cocrystal of theophylline with various co-former successfully applied to form micro composites of Theophylline-Saccharin cocrystals dispersed in hydrogenated palm oil. Enables fine-tuning of particle morphology and dissolution characteristics and designed for controlled release formulation(57).
b) These methods represent standard approaches to cocrystal formation, newer and less common preparation. Fast removal of solvent from an undersaturated solution of both co-former by dispersing it through a nozzle using supercritical CO_2.

(D) Miscellaneous Cocrystal Preparation Methods

1.Laser Irradiation

A high-power CO2 laser is used to heat powder mixtures of the API and co-former. The heat promotes recrystallisation directly into a cocrystal phase. Studies showed that the method works best when both components can partially sublime, suggesting that cocrystal formation occurs through molecular rearrangement in the vapor phase.

Example: Varin Titapiwatanakun and coworkers demonstrated the potential of the LI method for synthesis of Caffeine-Oxalic acid cocrystals, this experiment used a CO2 laser for imparting radiation energy to cocrystal components. The study observed that the speed and power of the laser is the main factor that affects the production of high-quality cocrystals(58).

2.Electochemical Induced Co-crystallization

These technique combines electrochemistry with co-crystallization. This shift provides a local supersaturation trigger, enabling cocrystal nucleation and growth.

Example: Demonstrated successfully using a Cinnamic acid and 3-nitrobenzamide cocrystal system as proof of concept. The electrical input creates localized shifts in pH, converting ionized to forms (eg: carboxylates) into neutral species(59).

3.Resonate Acoustic Mixing (RAM)

Uses acoustic energy (no grinding media required) to mix API and co-former in the presence of a small amount of solvent. Produces intimate mixing and promote cocrystallization under wet condition. Successful preparation reported for several carbamazepine cocrystals using a lab RAM mixer at 80-100 G force and 60HZ.Products were reproducible from small (100mg) to larger (22g) batches, showing good scale-up potential(60).

4.Spray Drying

Spray drying is a continuous, single step technique used to convert liquid systems (solutions, suspensions, or slurries) into dry solid powder. It is preferred because the process is fast, easily controlled and suitable for large scale (industrial) production. Use in cocrystal preparation. Although commonly used to make amorphous solid dispersions, spray drying is now also applied to produce pharmaceutical cocrystals. Studies by Alhalaweh and Velaga showed that spray drying multiple API-coformer pairs can successfully form coke crystals. Cocrystallization during spray drying occurs due to rapid solvent evaporation, high supersaturation and molecular interaction between API and co-former in solution(61).

Examples and Applications: The method was successfully used to prepare Carbamazepine Nicotinamide (1:1) Ternary Phase Diagram (TPD) have proven helpful for predicting and optimizing spray drying parameters for industrial scale cocrystal production(62).

Co spray drying with excipients: spray drying can embed cocrystals within a carrier excipient, improving flow and tablets behavior. Walsh et al. demonstrated this approach using sulphadimidine 4-aminosalicyclic acid. Flow rate, heating temperature are critically for producing high-quality cocrystals. When the Hansen solubility parameter (HSP) mismatch between cocrystal and excipient is larger, cocrystal formation is promoted because the components separate from the excipient, but remain able to crystallize together.

Co-Spray dried sample showed better compaction properties, reduce sticking during processing and improved handling compared to samples produced without excipient(63).

5.Freeze-Drying (Lyophilization)

Traditionally used for preservation of pharmaceuticals and food products. Works by first freezing the material and then lowering the pressure so that the frozen solvent (usually water) sublimes directly from solid to vapor(64). Recently applied to cocrystal preparation, demonstrating its usefulness in generating new solid forms. Eddleston et al. successfully produced a new form of the Theophylline-Oxalic acid cocrystal using this method. The co-crystal is thought to form through an intermediate amorphous phase, which appears as the solvent gradually sublimes during drying(65).

6.Microwave-Assisted Cocrystallization

This method is clean, economically, fast and scalable method. Produces higher yields in shorter reaction time compared to conventional heating. Microwave radiation, accelerate cocrystal formation due to rapid and uniform energy transfer(66). Cocrystal components and solvents are placed in a micro radiation reactor at suitable temperature and pressure for a specific time to obtain the desired cocrystal product(67).

Example: Deepali Ahuja and co-workers prepared Sulfamethazine cocrystal using this technique. This study suggests that microwave as a heating source increases the rate of cocrystal formation in comparison with the conventional heating process. The study demonstrates the potential of microwave assisted cocrystallization for scaling up the process from 0.2-20gm production capacity without altering product quality. These advantages can be utilized in industries for faster formulation, speed and for obtaining a good quality product(68).

7.Electrospray Technology

This method generates charged droplets and dries them simultaneously using a strong electric field. The dissolved API and co-former are pumped through a capillary nozzle held at a high voltage, forming a thin jet due to electrostatic forces. As the jet dries, solid particles form and are collected on a charged surface. These droplets undergo evaporation, fission and drying(69).

Mechanism: Flow of co-crystal solution→ formation of jet → droplet breakup → evaporation → crystallization → charged particle collection.

Examples: Sharvil Patil & co-workers prepared Forskolin-Nicotinamide cocrystals using the electrospray technique. There is a significant reduction in particle size & increase in solubility compared to pure Forskolin. This study suggests needle shape of cocrystal provides an enormous increase in surface area and reduced particle size by this method resulting is increase in dissolution of Forskolin- Nicotinamide cocrystals in comparison with cocrystals obtained by other methods(70).

b) Shahram Emami & co-workers formulated Naproxen Nicotinamide cocrystals using Electrospray. NPX-NIC cocrystals were formulated in 2:1, 1=1, 1:2 ratios. Only NPX-NIC Cocrystal with a ratio of 2: 1 was successfully formulated with high purity. Other ratios of cocrystal components give a product containing a high amount of impurities(71).

EVALUATION TECHNIQUES OF COCRYSTALS:

The determination of physiochemical properties of co crystals is an important part of the research, and therefore, the combination of techniques is employed for the cocrystal characterization, as no single method can fully elucidate their structure and properties. The characterization techniques for the structure determination include(72)

1.THERMAL ANALYSIS

a. Differential Scanning Calorimetry (DSC) method

The thermal Analysis technique utilizes Q1000 DSC instrument and it's containing a cooling system. The small amount of drug, coformer and cocrystals are heated in a DSC instrument. The instrument records the melting point, heat flow and glass transition properties.

Uses:

It is used to check the thermal stability.
It is determining the purity.
Melting point indicates the crystal formation.
It is used to solid state confirmation.

b. Thermogravimetric Analysis (TGA) method

Thermogravimetric analysis was carried out on Netzsch TG 209 F3 equipment. Sample is placed in the open aluminum oxide pans. It is heated at 10°C to 400°C.Nitrogen is used as purge gas 20 ml. Heat gradually in control atmosphere to measure weight changes.

Uses:

Thermal stability

Detects the solvent evaporation and decomposition of temperature Presence of hydrated solvents.

C. Hot - Stage Microscopy method

A small amount of the cocrystals sample is placed in a clean glass slide. Slide is hot stage and which can be heated at a control rate (1-10°c). The sample is observed in microscope throughout heating. Physically changes such as melting, color changing, recrystallization or phase transitions, is visually record. Temperature at which change occurs thermal behavior.

Uses:

Determine the melting points visually.
Evaluate thermal stability.

2. SPECTROSCOPY

a. Fourier Transforms Infrared (FTIR)method

Cocrystal sample is mixed with dried KBr and ground using mortar and pestle. The mixture is compressed into a pellet using a hydraulic press. Pellet is scan in IR spectrometer in the range 4000—400 cm -1.

Uses:

To detect the hydrogen bonding and functional group changes.
Differentiate cocrystal from physical mixtures.
Formation of new supra molecular structure.

b. Raman Spectroscopy method

A small amount of sample is placed under Raman laser without special preparations. Laser beam is passed over the sample. Laser excites molecular vibration.

Uses:

Detects changes in bond vibration.
It confirms new crystalline form.
Differentiate polymers, salts hydrated and cocrystals.

C. Terahertz Time Domain Spectroscopy (THz–TDS) method

This technique similar to the powder x-ray diffraction for the characterization and identification of a cocrystals. The sample reflects the terahertz waves depending on how is molecular arranged. The detector collects the transmit are reflect terahertz overtime. This instrument converts this time signal into a frequency spectrum using Fourier transform.

Uses:
Detect the hydrates, solvents or impurities and new lattice vibration models.
To identify polymorphs and impurities.
Used to quality control and solid-state forms.
3.X–RAY DIFFRACTION

a. Powder X-Ray Diffraction (PXRD) method

It gives crystal finger print pattern. A sample of powder diffractometer with Cu Ka radiation is used for obtaining the X ray pattern of co crystals. The slit and anti-scattering slit for light through a 20 mm sample. The specimen are scanned from 5-40°using Cu Ka radiation. It exposes to x ray beam and detector collect diffraction.

Uses:
It is used to determine the crystalline dimension, purity and structure.
It provides unique crystal finger print distinct from API and co former.
Formation of cocrystals reliable method.

b. Single Crystal X–Ray Diffraction method

It shows the exact the 3D structure of a cocrystals. A single crystal is placed in instrument. The X–ray determines atom positions in the lattice.

Uses:
It gives accurate structure, bonding and stoichiometry.
It proves cocrystal formation.
Exact molecular arrangement.
4. MICROSCOPIC & MORPHOLOGICAL TECHNIQUES

a. Scanning Electron Microscopy method

Electron beam with high intensity is scan across a sample using a scanning electron microscopy. Signals that are produced when the electrons are interact with the sample. It explains the visualize surface and particle morphology. The sample is coated with gold and scanned using an electron beam under high vacuum.

Uses:
Used to surface morphology.
It determines the particle size and shape.
It supports cocrystal formation visually.

b. Solid state nuclear magnetic resonance (SS-NMR) method

Take a cocrystal sample and it's placed in an NMR rotor. Analyze under solid state NMR conditions.

Uses:
Differentiate salt and co crystals.
Generally used to identification and characterization of various solid forms pharmaceutical products.
It detecting local confirmation changes.

C. Polarized light microscopy method

It performs in hot stage system. Sample of cocrystals are absorbed under polarized light. This method uses the hot stage microscope cocrystals. Use USP dissolution apparatus, maintain medium at 37°c and rotate basket/ paddle. withdrawal sample at intervals and measure drug release.

Uses:
It is used to the screening studies.
Differentiate crystalline and amorphous.
Identification of crystals formation.

5. PHYSIO-CHEMICAL STUDIES

a. Solubility studies method

It explains how much cocrystals are dissolved in water. Take and shake excess amount of cocrystals in solvent for 24 hours. Filter it and measure concentration via UV. It shows solubility improvement and compare to pure drug.

Uses:
It confirms solubility improvement.
It helps for better absorption.
Predicts bioavailability.

b. Dissolution study method

It helps to measure how quickly the drug is released from the cocrystals.

Uses:
Predict the in vivo performance.
Confirms enhancement in dissolution due to cocrystal formation.
Dissolution rate improvement.

c. Stability study method

This test explains the how stable the cocrystal is over time. the sample are store at different temperatures humidity for months. Check the drug content, dis dissolution, PXRD etc.

Uses:
Determine shelf life.
Ensures no conversion to another form.
It shows physical and chemical stability.
Dissolution rate improvement.

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