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PHARMACEUTICAL CO-CRYSTALS: A NOVEL STRATEGY FOR ENHANCING DRUG PERFORMANCE

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ABSTRACT
Pharmaceutical co-crystals have attracted significant attention as a novel approach to enhancing the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients (APIs) without altering their chemical identity. Such co-crystals, synthesized through non-covalent interactions between an API and a suitable co-former, can hopefully improve solubility, dissolution rate, permeability, stability, and mechanical strength and hence overcome major drug development challenges such as poor bioavailability. A broad range of preparation methods—ranging from solid-state methods like grinding as well as hot-melt extrusion to solution methods like solvent evaporation as well as slurry crystallization—has been utilized, supported by advanced methods like ultrasound-assisted crystallization and supercritical fluid atomization. Regulatory guideline-defined specifications, as well as experimental screening protocols and computational modelling, guide the choice of co-formers. Approved by the FDA and EMA as novel solid-state phases but not new chemical entities, co-crystals facilitate drug development with efficacy and safety. Overall, they are a green, scalable, and versatile method for modern drug formulation.

1. INTRODUCTION
Cocrystals, as defined by the United States Food and Drug Administration (FDA), are "crystalline materials composed of more than one molecule within the same crystal lattice". [1] In 2011, 46 scientists presented a widely accepted definition of cocrystals at an Indo-US meeting, defining them as crystalline single phase materials formed by two or more distinctive molecular and/or ionic compounds in a stoichiometric ratio that are neither solvates nor simple salts.[2] Pharmaceutical cocrystals are defined as having at least one API and another pharmaceutically acceptable coformer.[3,4] Pharmaceutical cocrystals are mostly generated by non-covalent interactions that consist of hydrogen bonding, co-ordinate attachment, van der Waal forces, or p-p stacking interactions between two crystallized substances in specific stoichiometric ratios. [5]

Co-crystals were originally identified in 1844, but their structure was not fully understood until 1958. Etter was the first to coin the term "cocrystal" and describe the design guidelines for hydrogen bonding in an organic cocrystal. [6,7] The word "cocrystal" was not used until 1967, when it was proposed to characterize a complex of hydrogen bonds generated by 9-methyl adenine and 1-methyl thymine. Desiraju, the first researcher to introduce the supramolecular synthon notion of hydrogen bond creation in crystal formations, popularized the term in the 1990s.[8] Stahly reported on the history of cocrystals previous to 2000, and this examination included the discovery

and history of organic components, as well as instances to illustrate the concepts of cocrystal chemistry.[9] The argument over cocrystals began in 2003, when Desiraju sent a controversial letter outlining his choice for the term "a multi-component system held together by non-covalent interactions." Dunitz responded, pointing out that the word includes solid solutions, encapsulated chemicals, and amorphous solids. [10]

Pharmaceutical experts are continually working on modifying the physicochemical properties of Active Pharmaceutical Ingredients (APIs) in order to increase the therapeutic efficacy of medications. Making various solid dosage forms of an API can improve its physicochemical qualities (such as melting point, solubility, stability, permeability, bioavailability, tabletability, and so on).[11] One of the greatest challenges in developing oral formulations of an API is its low bioavailability, which is mostly determined by the drug's solubility and permeability. [12,13]Researchers have developed a variety of approaches to increase API solubility, including the formation of pro drugs[14], solid dispersions[15], size reduction[16], inclusion complexes with cyclodextrins[17], polymorphs[18], nanoparticles[19], and the use of multicomponent molecular crystals[20]. All of the approaches mentioned above have advantages and disadvantages, but the success rate is mostly determined by the unique physicochemical features of the APIs and polymers.[21] The development of prodrugs necessitates synthetic techniques and the insertion of additional steps during the production stage. This will result in higher costs and a longer lead time for pharma product development. Similar to the prodrug method, cocrystallization is widely employed in drug product development to improve the biophysical and pharmacokinetics properties of APIs. [22]

Table 1: Classification of co crystals[22]

Class	Description
Binary Co-Crystals	Two components (typically API and co-former).
Ternary/Quaternary	Three or four elements in the stoichiometric ratio.
Polymorphic Co-Crystals	Co-crystals with distinct crystalline shapes
Salt Co-Crystals	Include ionic connections; bridge amongst salts and neutral co-crystals.
Solvated/Hydrated	Include liquid or water in the crystal lattice.
Other Outcomes	Non-co-crystal forms include eutectics, gel-like substances, solid dispersions, and ionic liquids.

2. FUNDAMENTAL APPROACH OF CO CRYSTALS

Table 2: Physical Forms of co-crystal

Type	Physical State	Formation Conditions/Characteristics	References
Co-crystals	Solid at ambient temperature.	Formed when pKa difference < 0	[23,24]
Salts	Solid at room temperature	Formed when pKa difference > 3	[23,24]
Solvates	includes liquid component.	May form during liquid-assisted grinding.	[5,25–27]
Hydrates	Contain water in the lattice	Less stable due to water loss during storage	[25,26]
Polymorphs	Can be solid or amorphous	Show different physicochemical properties due to different lattice arrangements	[28,29]

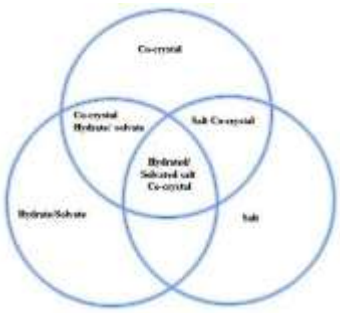

Figure1: Physical Form with physical state

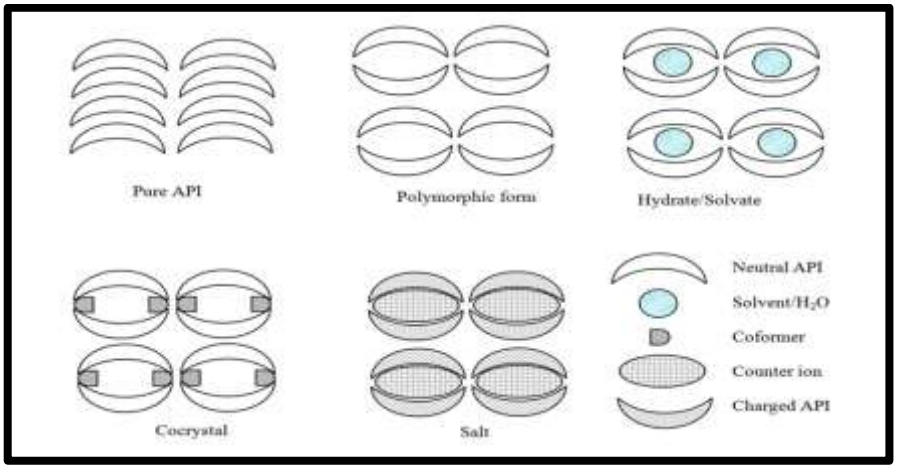

Figure 2: illustration of salt, co-crystal and polymorph[30]

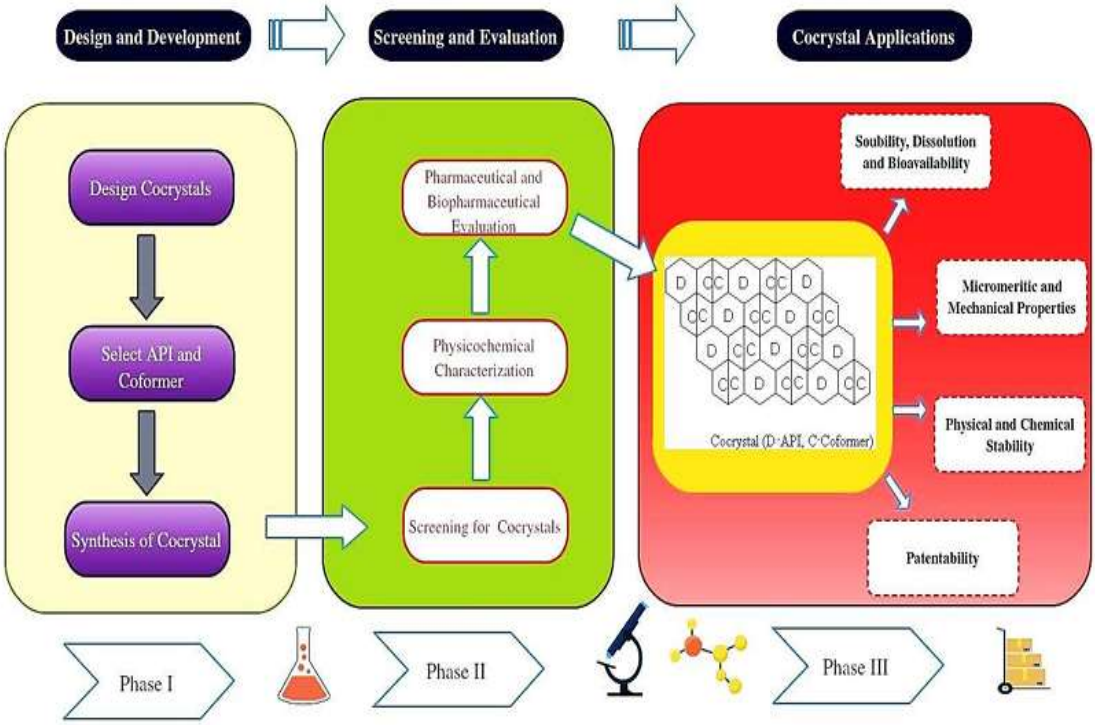

Figure3: Process for cocrystal development, screening and application[30]

3. PHYSICOCHEMICAL PROPERTIES AND CHEMICAL PROPERTIES IMPROVED BY COCRYSTALS

3.1 Physical stability

Solid-state materials have physical qualities such as the point of melting, hygroscopicity, solubility, hardness, elasticity, and elasticity. Co-crystallization is a strong strategy for increasing physical properties and maintaining the structural integrity of drugs.[31,32]

3.2 Melting points

Some medications exist in liquid form at room temperature due to their low melting temperatures. Cocrystallization has the ability to change the melting point of liquid pharmaceuticals by introducing a suitable coformer into the crystalline lattices.[33]

3.3 Hygroscopicity

The hygroscopicity of a drug ingredient must be thoroughly examined since it may affect its physicochemical qualities, such as solubility, dissolving rate, stability, bioavailability, and mechanical properties. As a result, one of the most difficult aspects of medication development is

maintaining the anhydrate form's hygroscopic stability. Several solutions have been used to address this issue, including incorporating appropriate excipients into the formulation, using adequate packing to reduce moisture uptake, and covering the medication product with enteric polymers.[34]

3.4 Chemical stability

Chemical degradation of pharmacological ingredients occurs during the manufacturing and storage stages, complicating the development of a stable pharmaceutical formulation. It is vital to devise an effective approach for eliminating or reducing medication degradants. Recently, pharmaceutical cocrystals have emerged as a promising strategy to address the chemical instability of APIs in the solid form.[35,36]
Example: Nitrofurantoin drug -4-Hydroxybenzoic acid cofomer.[37]

3.5 Mechanical properties

The mechanical properties of crystalline materials are crucial in a variety of solid dosage form manufacturing processes, including blending, milling, granulation, tableting and coating. Solid materials' mechanical deformation mechanisms include elastic, plastic, viscoelastic, and fragmentation. In general, materials with better plasticity qualities may exhibit improved compressibility, which is permanent and irreversible once tension is removed. However, many organic substances have weak mechanical characteristics, making it difficult to develop tablet formulations. Cocrystallization has been shown to efficiently improve the mechanical characteristics of pharmaceuticals by changing crystal packing.[38,39][40]

3.6 Optical properties

The optical characteristics of medications may be useful in biomedical applications. For example, medicines with high fluorescence can be utilized as biocompatible probes for bioimaging and lipid droplet imaging in cells and tissue slices. Molecular stacking, crystal packing arrangement, and intermolecular interactions all play essential roles in solid materials' optical characteristics.[41,42]Recently, cocrystal engineering has demonstrated the ability to change the optical characteristics of pharmaceuticals.[43,44]

4. PREPARATION METHODS

Over time, researchers have experimented with several cocrystal preparation procedures. Traditional procedures, including solvent evaporation and grinding, have been combined with solvent-based and solid-state approaches. Different methodologies have been used, including crystallization techniques, suspension conversion, solvent evaporation, anti-solvent addition, and reaction crystallization. Recently, newer approaches have arisen, including as ultrasound-assisted procedures, supercritical fluid atomizing, spray drying, and hot melt extrusion.[45]

Table3: Solid-State Based Methods

Sr. No.	Method	Description
1	Contact Formation	API and coformer are directly mixed without external effort; spontaneously cocrystal formation occurs under controlled conditions. [46]
2	Solid-State Grinding	Includes neat (dry) and liquid-assisted grinding, which improves interaction between molecules. [47]
3	Hot Melt Extrusion (HME)	API and coformer are heated together to generate cocrystals that do not require solvents; this process is scalable and continuous. [48]
4	Resonant Acoustic Mixing	Mixes solids using sonic energy (60 Hz, 80-100 G); suited for large-scale production. [49]

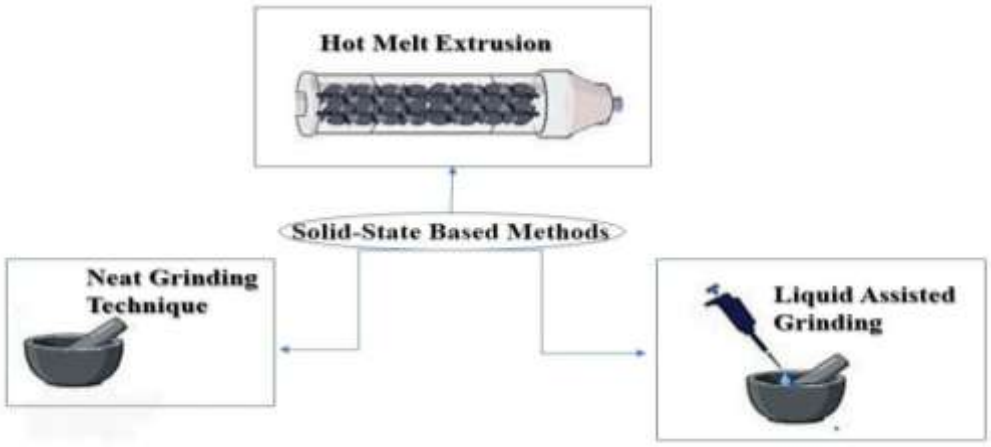

Figure 4:Techniques for Co-crystal formation Using solid-state methods

Table 4: Solution-Based Methods

Sr. No.	Method	Description
5	Slurry Crystallization	suspends API and coformer in solvent, which is subsequently withdrawn and the solid dried. [50,51]
6	Evaporative Crystallization	Drug and coformer are dissolved in a shared solvent; gradual evaporation produces cocrystals. [51]
7	Cooling Crystallization	Cocrystals are formed by seeding and chilling a saturated solution under controlled conditions. [51–53]
8	Anti-Solvent Method	Antisolvent was added to induce overabundance and cocrystal precipitation. [53]
9	Reaction Crystallization	Based on the solubility difference, add coformer below the limit of solubility to precipitate clear cocrystal. [54]
10	Ultrasound-Aided Crystallization	Sonication improves nucleation and crystal development; utilized in nanocrystal production. [52,54]
11	Spray Drying	Converts liquids or slurries to dry powders and embeds cocrystals in matrix. [55]
12	Supercritical Fluid Atomization	Fine cocrystal particles precipitate when a supercritical CO_2 solution is rapidly depressurized. [56]
13	Spray Flash Evaporation	To promote fast crystallization, superheated low-boiling solvents are used in conjunction with pressure drops. [48]

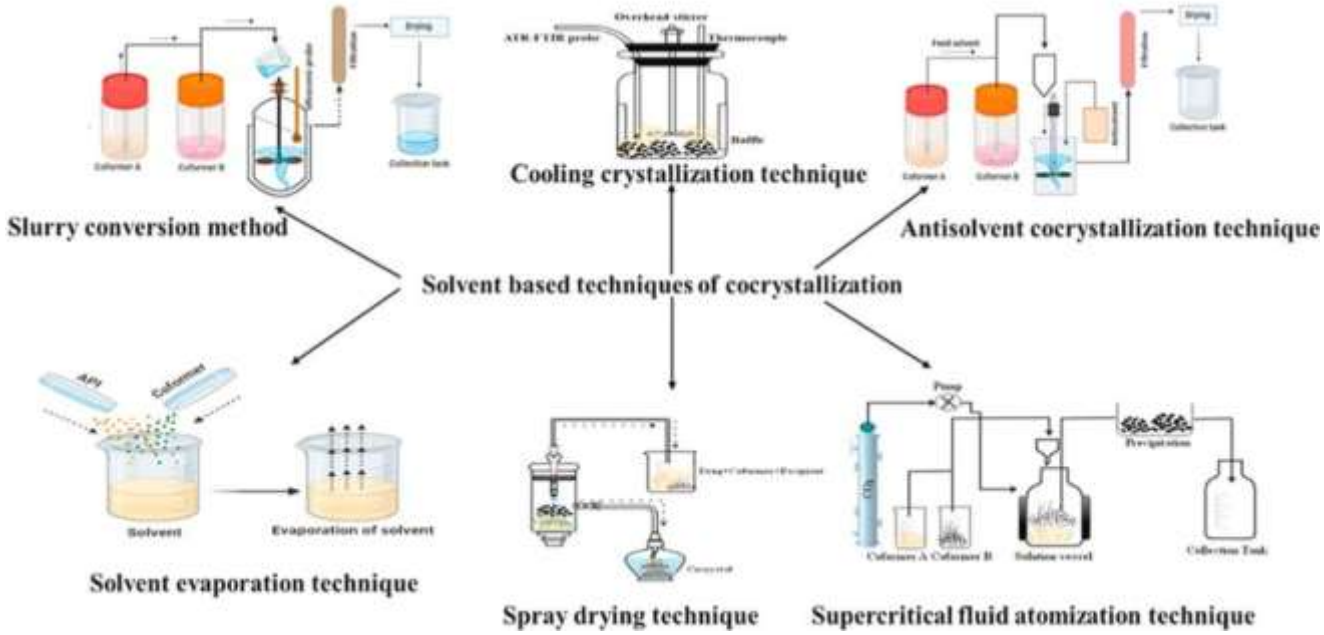

Figure 5: Solvent-Based Co-crystallization Approaches

Table 5: Miscellaneous / Emerging Techniques

Sr. No.	Method	Description
14	Laser Irradiation	Cocrystal formation is facilitated by CO_2 lasers through vapor-phase nucleation and sublimation. [57]
15	Freeze Drying (Lyophilization)	Freezing followed by sublimation under vacuum; suitable for cocrystal formation. [58]
16	Electro-spraying	A high-voltage electric field forms and dries solution droplets, resulting in cocrystal particles. [58]
17	Microfluidic and Jet Dispensing	Allows for combinatorial screening on chips, resulting in accurate mixing and reproducible cocrystal formation.[45]

4.1 COMPARISON BETWEEN SOLUTION CO-CRYSTALLIZATION AND SOLID-STATE CO-CRYSTALLIZATION [59]

Table 5

	Solution Co-crystallization	**Solid-State Co-crystallization**
General Characteristics	• Solvent is used to cocrystallize. • Supersaturation is necessary as the driving force. • Techniques such as chilling, evaporation, antisolvents, and slurry crystallization are examples.	• Very little or no solvent is used during crystallization. • Shear mixing or melting and re-solidification are two methods that force the production of crystals. • Techniques such as spray congealing, extrusion, and grinding are examples.
Advantages	• Well-established equipment and methodology. • Crystal size, shape, and polymorphism form can be reasonably controlled. • The cocrystals are very pure. Both batch and continuous modes can be easily scaled, and screening is effective. • Developed monitoring PAT (process analytical technology) instruments.	• Green approach because no solvent is used. • Prevents solvate production. • One-step procedure.
Disadvantages	• Crystals are separated from the parent liquor. • Recycling or disposing of solvents.	• Inadequate control over crystal characteristics. • PAT is difficult to use for real-time monitoring; it is not suitable for medications that are thermally labile.

5. CO-FORMERS SELECTION AND SCREENING OF CO-CRYSTALS

An API and a co-crystal former combine to generate pharmaceutical cocrystals in both neutral and solid form. The co-crystal former may be another API or an excipient. The non-API component used as a coformer needs to be safe and have no negative impacts. It is desirable for the co-crystal former to be approved as generally recognized as safe (GRAS).[60] The selection of a coformer for an API is crucial for the production and screening of co-crystals. The trial-and-error method is usually used for all kinds of coformers for an API, and it is costly and time-consuming. A number of methods, including the Cambridge Structure Database (CSD), synthon engineering, lattice energy calculation, thermal analysis, and the Kofler contact method, can be used to choose the coformer to create the co-crystals.[61,62]

Hydrogen bonding propensity, Fabian's method, pKa rule, Hansen solubility parameters,[63] Conductor-like Screening Model for Real Solvents (COSMO-RS), Molecular Electrostatic Potential

Surface (MEPS), ML-based cocrystal virtual screening approaches, Tactless Cocrystal Screening.[64]

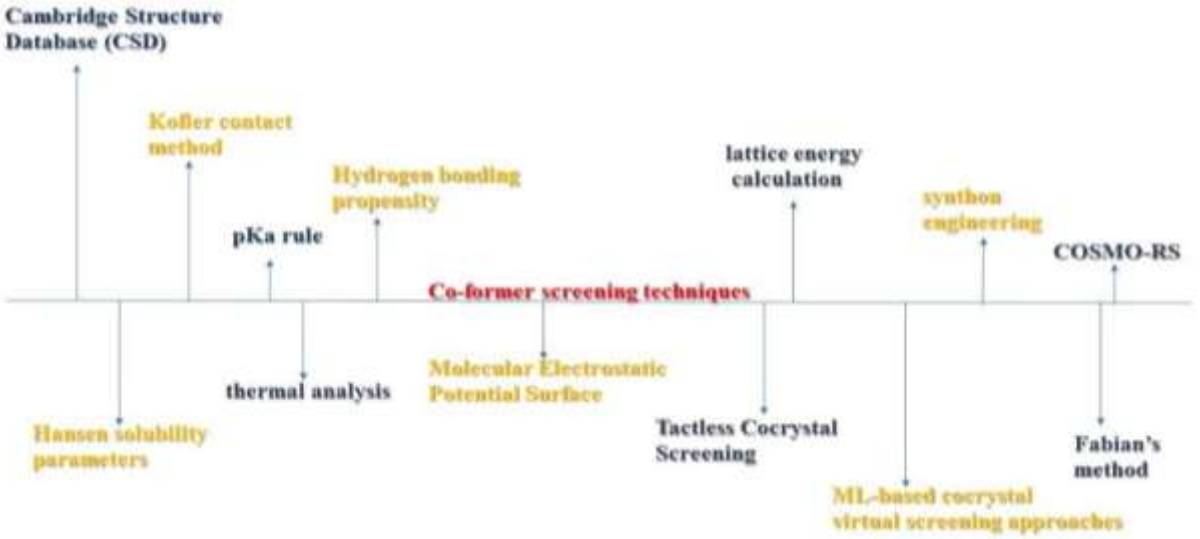

Figure 6 : Different Co-former screening techniques for pharmaceutical Co-crystals[65]

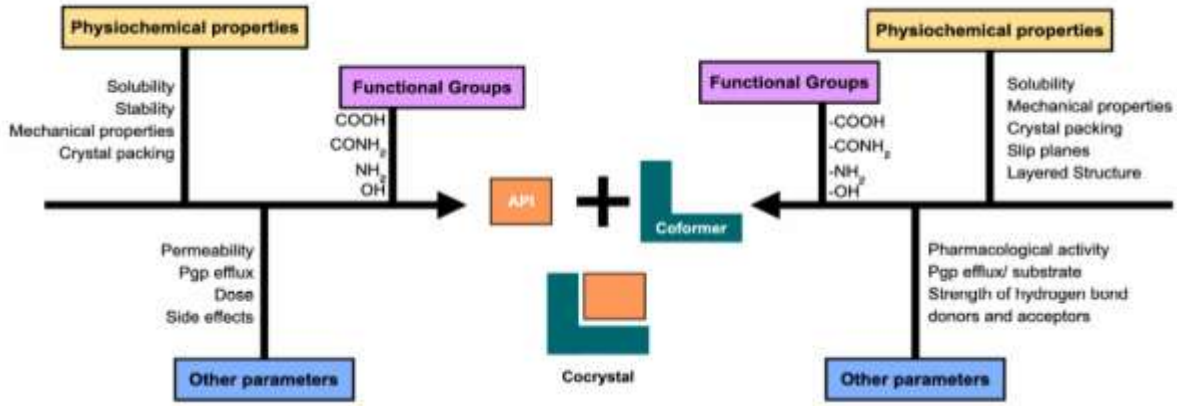

Figure 7: Illustrating properties of Co-former and drug to be considered while designing the cocrystal[65]

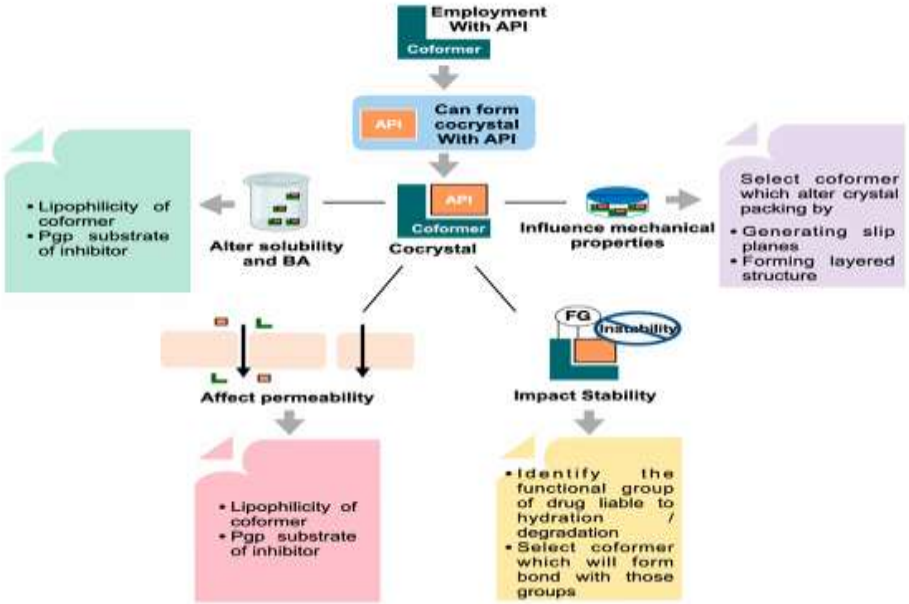

Figure 8: Pharmaceutical attributes affected by co-crystal formation and its relation to co-former[65]

Table 6: Examples of studies reporting on co-formers effect on Solubility, Bioavailability, Permeability, Stability, and Dissolution rate.

API Name	Co-former Name	Result
Modafinil	Sodium acetate (2022)	enhanced solubility and dissolution (highest performer)[66]
5-Fluorouracil	L-Proline (2022)	improved permeation (3.89x), bioavailability, and solubility (4.6x). [67]
Roxadustat	Nicotinamide(2023)	enhanced general physicochemical characteristics and photochemical stability. [68]
Ketoprofen	Fumaric acid(2022)	Improved solubility and anti-inflammatory properties in vivo.[69]
Fluconazole	Benzoic acid(2025)	Better mechanical and flow qualities, a 13x increase in solubility.[70]
Citric acid	Nicotinamide	enhanced stability and decreased hygroscopicity in effervescent formulations. [71]
Amiodarone HCl	Glutamine, Urea, Citric acid, Ascorbic acid (2020)	Co-crystallization leads to increased solubility. enhanced solubility and use in the production of tablets used to improve solubility, assessed for improving solubility through co-crystallization.[72]
piroxicam	sucralose	Co-crystals utilized in buccal films have demonstrated improved drug release and bioavailability, as well as six times more solubility. [73]
Curcumin	Ascorbic acid (2020)	enhanced solubility and antioxidant activity; stable co-crystal formed.[74]
Telmisartan	Hydrochlorothiazide (2023)	Solubility, moisture stability, and bioavailability were all enhanced by drug-drug cocrystals.[75]
Ivermectin	Cinnamic acid (2023)	enhanced medication release and solubility; prepared into tablets.[76]
RS-Ofloxacin	L-(+)-Tartaric acid(2025)	increased enantiomeric purity and successful chiral resolution using diastereomeric co-crystal formation.[77]
8-Hydroxyquinoline	Acetone-(2,4-dinitrophenyl)hydrazine (2024)	creation of a new supramolecular co-crystal with π–π stacking, strong hydrogen bonds, and possible antioxidant properties.[78]
Ketoprofen	p-Aminobenzoic acid (2021)	better physicochemical characteristics and increased solubility.[79]
5-Fluorouracil	Cinnamic acid	enhanced anticancer growth inhibition capacity at 100 μgmL−1 by 67.30% in comparison to API.[80]
Allopurinol	Piperazine/2,4-dihydroxybenzoic acid	Compared to API, the ALP-24DHBZA cocrystal's solubility was 50% better and the ALP-PIP cocrystal's diffusion was 41% better after 8 hours.[81]
Sulfathiazole	Amantadine hydrochloride	improved penetrability by two times and water solubility by 1.83–5.23 times.[82]
Ambrisentan	Syringic acid	1.8 times the intrinsic dissolving rate and 4.8 times the solubility when compared to API.[83]
Berberine chloride	Myricetin	reduced moisture absorption of 1.5% water up to 95% relative humidity and enhanced hygroscopicity.[84]
Bumetanide	Caprolactam	enhanced solubility by 1.7 times and intrinsic dissolving rate by 1.4 times in comparison to API.[85]
Donepezil	1,3-Diiodotetrafluorobenzene	melting point that is 20 °C higher than API 1.6-fold increase in solubility over API.[86]
Ethenzamide	Glutaric acid/malonic acid/maleic acid	melting point that is 20 °C higher than API 1.6-fold increase in solubility over API.[87]
Ethionamide	Salicylic acid	Increased ETH content in cocrystal form with a dissolving rate of 10 mg L−1.[88]
Famotidine	Theophylline	As opposed to the observed phase shifts of form A famotidine within 1 hour, the cocrystal maintains its original peak position even after 24 hours, indicating improved stability in pH 1.2.[89]
Febuxostat	Piroxicam	2.8 times better dissolution than pure piroxicam and 1.5 times better solubility in pH 6.8 buffer and 1.24 times better solubility in pH 7.4 buffer as compared to pure febuxostat.[90]
Isoniazid	Resveratrol	86 percent less permeability than API.[91]

Itraconazole	Suberic acid	39-fold improvements in dissolving performance over API.[92]
Urea	Various organic co-formers (not specified in snippet)	Depending on the type of co-former, many urea co-crystals with enhanced physicochemical characteristics can form. [93]
Rivaroxaban	Niacinamide	Co-crystals with molar ratios of 1:1 and 1:2 enhanced compressibility and flowability upon excipient addition; appropriate for direct compression.[94]
Daidzein	Piperazine	When compared to the parent drug, the daidzein–piperazine co-crystal's formation greatly increased stability, solubility (up to 60.8× in various conditions), permeability (4.8×), and bioavailability (3.2×). [95]
Formononetin	Imidazole	In comparison to pure FMN, the FMN–IMD co-crystal exhibited good physical stability over a 6-month period, as well as 2–3× higher solubility, 4.93× increase in Cmax, and 3.58× increase in AUC.[96]
Ibuprofen (IBF)	Nicotinamide (NA)	THz and FT-IR spectroscopy revealed the formation of an IBF/NA cocrystal; the reaction rate was highly reliant on humidity; the solubility and bioavailability were enhanced. [97]

6. CHARACTERIZATION OF CO-CRYSTALS

Co-crystals are characterized using a variety of techniques. Characterization technology has advanced significantly in this field in recent years. Three primary analysis techniques can be used to characterize co-crystals: FTIR, Raman, and solid-state NMR spectroscopy; thermal analysis techniques (Differential scanning calorimetry and Hot Stage Microscopy); and single crystal and powder X-ray diffraction techniques (XRD & PXRD). A brief overview of characterization technologies and many recent examples that make use of these techniques are covered in this portion of the paper.[98]

6.1 X-ray diffraction method (XRD) and powder X-ray diffraction method (PXRD)

One popular and accurate technique for identifying and classifying co-crystals is XRD. Large-size crystals, which are often generated by the solvent evaporation process, are typically structurally identified by single-crystal XRD. Single-crystal XRD is unable to characterize co-crystals produced by the grinding process. Because of this, PXRD technology is mostly employed to identify cocrystal formation. Co-crystals exhibit a shift in characterisation peaks in PXRD when compared to their constituent parts. By measuring the proportion of co-crystals and co-crystal components in the final product, XRD techniques are also utilized to determine the percentage yield of co-crystals.[99]

6.2 Thermal analysis method

6.2.1 Differential scanning calorimetry (DSC)

A simple and practical technique for characterizing co-crystals is differential scanning calorimetry [3].[100] The endothermic and exothermic peaks of co-crystals differ significantly from those of pure components. Co-crystals can be screened by looking at the DSC peak of the physical mixture of co-crystal components, which is located between the peaks of pure co-crystal components.[101]

6.2.2 Hot stage microscopy (HSM)

HSM is well-known for its ability to characterize and screen co-crystals. Users may see the recrystallization and crystal development of melted co-crystal components using HSM. The Kofler mixed fusion method can be used to characterize and screen co-crystals.[102]

6.3 Fourier transform infrared spectroscopy

One extremely effective method for determining the creation of co-crystals is FTIR spectroscopy. A shift in vibrational energy peaks in spectra, mostly as a result of hydrogen bonding forming in the functional group of co-crystal components, verifies the creation of co-crystals. To identify co-

crystal formation and clarify its structure, FTIR spectra of formed co-crystals and pure co-crystal components are compared.[103]

6.4 Raman spectroscopy

An in-situ monitoring and characterisation technique for confirming co-crystal formation is Raman spectroscopy. Compared to the FTIR approach, Raman spectroscopy shows superior accuracy, precision, and sensitivity. Multi-component systems can be distinguished between their ionic and co-crystal forms using Raman spectroscopy. By comparing the shift in co-crystal oscillation to that of co-crystal components, the production of co-crystals is evaluated.[104,105]

6.5 Solid-state NMR spectroscopy

SSNMR may be able to offer comprehensive structural details on pharmaceutical and organic co-crystals. Compared to vibrational spectroscopy and PXRD techniques, SSNMR offers richer information content and high-yield data. SSNMR is a non-destructive technique that collects data using a relatively small number of samples. In order to comprehend the capabilities of SSNMR, Frederica G. Vogt and colleagues looked at a number of molecular complexes and co-crystals. This study assesses SSNMR's capacity to observe structural characteristics such as hydrogen bonds and demonstrate molecular connection.[106]

6.6 Dissolution study

Using the proper dissolution equipment and media as outlined by official compendia, in-vitro dissolution tests are carried out to assess the dissolution efficiency of manufactured pharmaceuticals. Samples are taken at predetermined intervals and subjected to ultraviolet (UV) spectrophotometry or HPLC analysis.[107]

6.7 Stability study

When assessing cocrystals, stability is a crucial metric that offers information on how various environmental elements, including temperature, light, and humidity, as well as climatic storage circumstances, impact a medication's or drug product's shelf life. To evaluate the shelf life of cocrystal products under different storage circumstances, stability experiments are conducted over predefined time periods under particular temperature and humidity conditions.[108]

6.8 Hansen solubility study

The cohesion energy linked to the Hansen parameter is used to predict physicochemical properties like melting point and solubility, and it is a crucial tool for predicting the miscibility of a drug and its coformer in a cocrystal formation as well as the compatibility of pharmaceutical materials.[109]

Figure 9: Marketed cocrystals and ones in phases of clinical trials.[110]

REGULATORY UNDERSTANDING OF PHARMACEUTICAL CO-CRYSTALS

The US FDA's definition Solid crystalline solids made up of two or more molecules arranged in a single crystal lattice are known as co-crystals. Without changing the chemical structure of the API, they change advantageous therapeutic properties (such as dissolving, solubility, and solid-state behavior). According to the pKa Difference Rule, complete proton transfer is indicated when ΔpKa is greater than one, which is expected to result in salt production. Co-crystal formation is expected to result from non-ionic interactions when ΔpKa is less than 1. The US FDA's classification of regulations Rather than being unique APIs, co-crystals are categorized as biologic intermediate molecules. Before arriving at the operation site, the degree of proton transfer and in vivo dissociation must be proven. Because complete clinical studies are not necessary, development can proceed more quickly (provided safety and efficacy are comparable to the parent API).[111]

Co-crystals are homogenous, single-phase crystalline structures with a specific stoichiometric ratio, according to the EMA definition. Unlike salts, it is not reliant on ionic bonding. Regulatory Implications: Co-crystals are not considered novel pharmaceuticals if they are just as safe and effective as the parent API. The same marketing authority that is available for the parent API may be requested by applicants. Considerations for Manufacturing and Approval: GMP (Good Manufacturing Practices) might not apply if co-crystals are formed in situ. The Active Substance Master Record can be used by both the co-crystal and the API. Performance and security of the co-former must be demonstrated. Co-crystals containing multiple APIs need to have their dosage ratio justified and their biological and therapeutic effects evaluated.[111]

CONCLUSION

Pharmaceutical co-crystals represent a new and versatile solution to issues of active pharmaceutical ingredient poor solubility, stability, and bioavailability. By the use of non-covalent interactions to produce stable crystalline solids with suitable co-formers, co-crystals significantly improve physicochemical, mechanical, and pharmacokinetic properties with preservation of the native chemical structure of the medicine. Advances in preparation technologies—ranging from traditional methods such as solvent evaporation and grinding to newer methods such as hot melt extrusion, supercritical fluid atomization, and microfluidics—have opened up opportunities for co-crystal formulation for many APIs.

The judicious selection and evaluation of co-formers are still paramount to the optimization of therapeutic activity, as next-generation characterization techniques like XRD, DSC, FTIR, Raman spectroscopy, and solid-state NMR offer proficient means of structural and functional assessment. Additionally, the FDA and EMA's regulatory policies recognize co-crystals as unique solid forms and not new chemical entities, thus opening an expedited path to clinical and commercial acceptance.

Generally, co-crystallization is an inexpensive, scalable, and environmentally friendly method of improving drug design and formulation. With mounting evidence of their capacity to enhance solubility, dissolution, permeability, and stability, pharmaceutical co-crystals represent great promise for drug delivery system design and the resolution of unmet clinical needs. Further research, aided by rational co-former selection and computer screening, will increasingly leverage their utility in contemporary pharmaceutical development.

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