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An approach for enhancing pharmaceutical properties using crystal engineering

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ABSTRACT:

The purpose of this work is to investigate the possibility of "Co crystallization" in emergent an aqueous soluble co crystal'. This technique may provide the synergistic enhancement in aqueous solubility of poorly water-soluble drugs having low aqueous solubility and bioavailability to overcome these problems there is a need to alter the property of the drug. Crystal engineering is a technique to modify the physicochemical properties of the active pharmaceutical ingredients and maintain the intrinsic activity of the drug molecule. Such as solubility, melting point, stability, and bioavailability. The purpose of this review article is to focus on crystallization techniques like solvent evaporation, slow cooling, and vapor diffusion, The article's main feature on co-crystallization, its methods, and its significance.

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INTRODUCTION:

The ability to deliver the drug to the patient in a safe, efficient, and cost-effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid-state [1]. Chemists and engineers in the pharmaceutical industry generally seek to deliver crystalline forms of their active compounds, mainly due to the inherent stability of crystalline materials and the well-established impact of crystallization processes on the purification and isolation of chemical substances. Increasing attention is now being paid to the impact of material properties on drug discovery and early development as the drug substances tend to be very valuable materials [2]. The pharmaceutical industry's mission is to rapidly advance development programs with good confidence so that

formulation problems are unlikely to arise and to maximize the potential of a compound as a therapeutic shown in Fig 1 [3]. This commentary seeks to raise the profile of crystal form studies and the emerging topic of crystal engineering in pharmaceutical science by discussing the state-of-the-art relating to pharmaceutical crystals and by expanding on possibilities that exist for future developments [4].

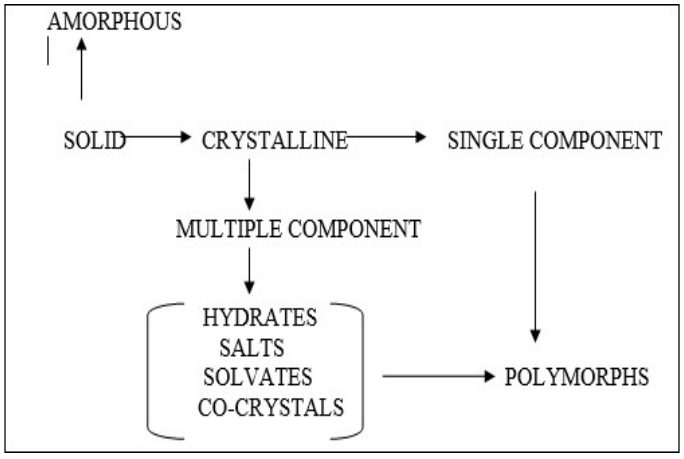

Fig 1. API solid form classification based on structure and composition [4].

Challenges of Co-crystallization [5-8]:

- Poorly soluble, difficult to crystallize, or problematic with respect to physicochemical properties for successful development.
- Crystal engineering has been identified by pharmaceutical scientists as a means of improving and tailoring the physicochemical properties of API.
- Improved properties like shelf life, dissolution rate, and bioavailability.

Co-crystals:

A co-crystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form [9,10]. These components co-exist as a stoichiometric ratio of a target molecule or ion and a neutral molecular co-crystal former(s)'. It can be argued that liquids and gases can also serve as co-crystal formers, and this is appropriate from a supramolecular perspective. For example, solvates or hydrates; there is a design or crystal engineering aspect of co-crystals that distinguishes them from solvates and single-component molecular solids [11,12]. Co-crystallization with pharmaceutically acceptable (GRAS) compounds does not affect the pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, and compaction behavior [13].

Co-crystals relevant:

Co-crystals offer opportunities to modify the composition of matter and the chemical and/or physical properties of a molecular species without the need to make or break covalent bonds [15]. This has already resulted in two applications for co-crystals;

- Non-covalent derivatization [16].
- Solid-state synthesis offers great potential in the context of green chemistry (high yield, region/stereo specificity, no solvent or by-products) [17].

Mechanism of co-crystal synthesis:

When solid mixtures with co-crystal reactants were exposed to deliquescent conditions involve;

- Moisture uptake [18].
- Co-crystal aqueous solubility [19].
- Solubility and dissolution of co-crystal reactants [20].
- Transition concentration [21].

Nucleation and growth of co-crystals were directed by the effect of the co-crystal components on reducing the solubility of the molecular complex to be crystallized [21]. A molecular-level mechanism for two cases of mechanochemical co-crystallization via halogen bonds was reported and was based on the observation and structural characterization of intermediates that appeared in the early stages of the reaction [22]. The mechanism arises from the competition of strong and weak intermolecular halogen bonds of the N...I and S...I type and involve the initial formation of finite molecular assemblies, held together via N...I bonds that subsequently polymerize into infinite chains by cross-linking through S...I bonds [23].

Co-crystallizations of exemestane and megestrol acetate improved initial dissolution rates compared to the respective original crystals [24]. The mechanism of dissolution enhancement varied [25]. With exemestane/maleic acid co-crystal, fine particle formation resulted in enhancement, whereas with megestrol acetate /saccharin co-crystal, enhancement was due to the maintenance of the co-crystal form and rapid dissolution before transformation to the original crystal [25].

The mechanisms of conversion of crystalline drugs to co-crystals and factors affecting co-crystal stability were reported [26]. Co-former solution concentration controlled the formation and stability of different stoichiometry co-crystals. Co-crystallization also occurred in solid mixtures of co-crystal reactants [27].

Nano-pharmaceutical co-crystal [25-27]:

A nanocrystal refers to any nanomaterial with at least one dimension ≤ 100 nm and it should be single crystalline. The production of drug nanocrystals by bottom-up techniques (with the main focus on particle diminution by high-pressure homogenization) for many new chemical entities of very low solubility has been reported. The transfer of the liquid nanosuspensions to the patient in convenient oral dosage forms such as tablets and capsules has also been reported. Under microwave irradiation, nonlinear optical nano-cocrystals of aminonitropyridines with benzenesulfonic acids were reported. Single-component crystalline nanorods, composed of 9-methylanthracene (9-MA) and exposed to a suspension of 1, 2, 4, 5-tetracyanobenzene (TCNB) in water formed a 1:1 charge-transfer complex within the rods, which are transformed from crystalline 9-MA into co-crystalline 9-MA/TCNB. The co-crystal nanorods were characterized by electron microscopy, X-ray diffraction, and optical spectroscopy. These studies demonstrated the importance of organic nanostructures for supporting structure-preserving chemical transformations that were not possible in larger crystals. Nanostructured co-crystals exhibiting single-crystal to single-crystal chemical reactivity were constructed by Sonochemistry.

Screening of co-crystal: COF CO-CRYTST

The ultimate goal of co-crystal screens is to discover a solid form of an API with improved physical properties. From this perspective, an efficient co-crystal screening protocol can be split into 3 phases as below in Fig 2 [28].

- Co-crystal design.
- Co-crystal screening.
- Co-crystal selection.

Crystallization techniques:

Commonly used techniques include solvent evaporation; slow cooling of the solution, solvent/ non-solvent diffusion, vapor diffusion, sublimation, and many variations on these themes. The choice of technique may be dictated by the amount of sample [28].

Solvent evaporation:

This is the simplest technique for air-stable samples. A near-saturated solution is prepared in a suitable solvent [28]. The sample can then be left in a sample vial that has a perforated cap. The size of the perforations is an experimental variable that depends to some extent on the volatility of the sample. It is desirable to incline the tube so that some of the crystals grow on the side of the tube. This facilitates the easier removal of delicate crystals without damage [29]. Other variations of this method are to transfer some of the solutions to a crystallization dish and covering with perforated aluminium foil or to trap some of the solvents between microscope slides.

Slow cooling:

This is good for less soluble solute-solvent systems where the boiling point of the solvent is in the range of 30 to 90 ºC. Prepare a saturated solution where the solvent is heated to just below the boiling point. Transfer the solution to a stoppered tube and this tube to a Dewar containing water at a temperature also just below the boiling point of the solvent (be very sure this temperature is below the boiling point.). The water level should exceed the solvent level but be below the stopper. The Dewar should be capped and left for several days. Both the above techniques may be improved by using solvent mixtures. Better crystals may form or be induced where none were formed from single solvent solutions. The method may also be used to tailor crystal form. Very fine needles or extremely thin plates give poor diffraction data. Variation of solvent composition may inhibit or promote the growth of particular crystal faces and hence yield crystals of suitable morphology [30].

Solvent diffusion:

This method is applicable to mg quantities of the sample that are air and/or solvent sensitive. A solution is placed in a sample tube then a second less dense solvent is carefully dripped down the side of the tube using either a pipette or a syringe to form a discreet layer. A good solvent combination is CH_2Cl_2/ EtOH provided the sample is near insoluble in the ether. Crystals form at the boundary where the solvents slowly diffuse [31].

Vapour diffusion:

This method is similar to the previous method and also applicable to mg quantities of sample. In this case, a solution of the sample contained in a small sample tube is placed in a larger tube containing a second less efficient solvent, and this tube is then sealed. The method works best if the solution solvent is less volatile and thus predominately the second solvent diffuses into the sample solution [32].

Vacuum sublimation:

A large number of compounds can be sublimed to form excellent crystals. There are numerous variations of this method using either static or dynamic vacuum.

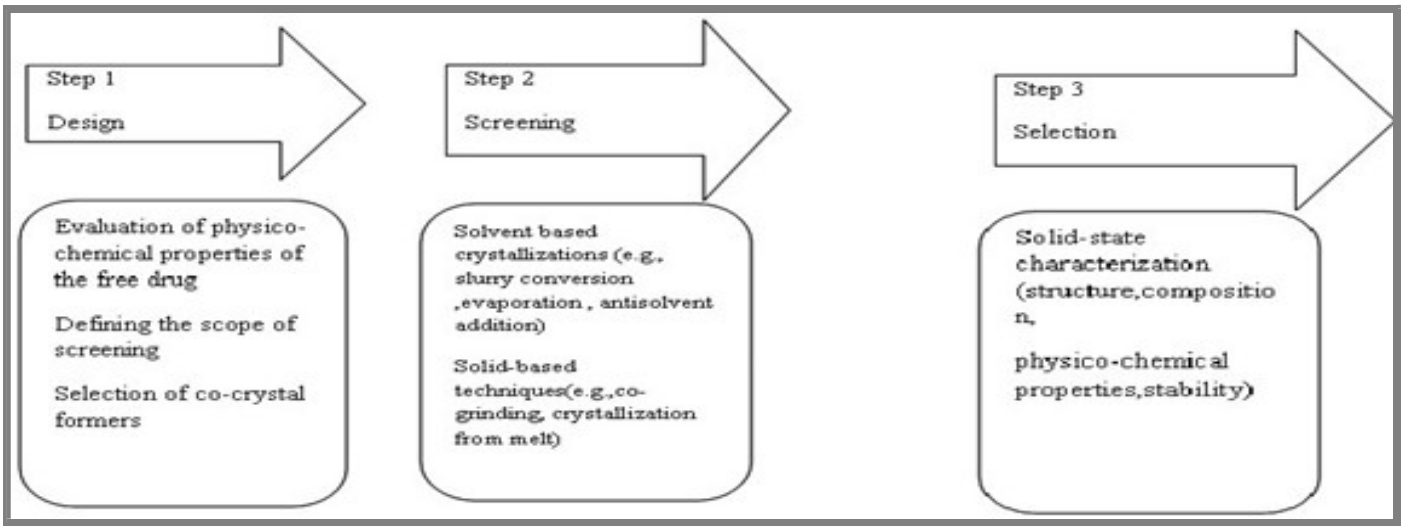

Fig 2. A general guideline for co-crystal design and screening.

A small amount of sample sealed under vacuum in a Pyrex tube can be subject to a temperature gradient in any number of ways. A simple method that often succeeds is to put the tube in a warm oven. The small temperature gradient can be sufficient to produce crystals in hours or possibly weeks depending on the volatility of the sample and the quality of the vacuum. The dynamic vacuum works better for less volatile samples. Vacuum sublimation is ideal for very air-sensitive compounds as the tubes can be loaded in dry boxes [33].

BIOPHARMACEUTICAL PERFORMANCE OF COCRYSTAL [34-38]:

Solubility:

Solubility of the active pharmaceutical ingredient is one of the important factors taken into Consideration while developing its dosage form. Co-crystals can be made ionizable as well as Nonionizable drugs. For ionizable drugs, numbers of suitable co-crystal formers are available which implies that there is great potential to form highly soluble and stable pharmaceutical co-crystals. Co-crystal solubility is proven to be dependent on the concentration of co-former in solution.

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. Within pharmaceutical sciences, the melting point is also very valuable due to its correlations to aqueous solubility and vapor pressure.

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 conditions to determine developability and shelf life. In the case of cocrystals and salts, solution stability may be a factor due to dissociation of the material resulting in precipitation of the less soluble parent compound or a less soluble form (such as a hydrate in aqueous media).

Relative humidity stress:

As with other solid forms, changes over a wide relative humidity (RH) range are a key consideration when developing a co-crystal. 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. Limited water sorption/desorption data were found in the literature for co-crystals. Longer-term co-crystal stability studies with respect to RH have been reported for a small number of co-crystal systems and a range of parameters have been used.

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 co-crystals. For the co-crystal of a monophosphate salt with phosphoric acid, an 8-week exposure at 60 °C resulted in no detectable degradation of form change. Two other studies discuss DSC data and the effect of temperature on stability.

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 the chemical stability of co-crystals were found when reviewing the literature. In one example, a pharmaceutical co-crystal of a monophosphate salt with phosphoric acid was reported to have no detectable degradation after 8 weeks of storage at 40 °C/ 75 % RH and 60 °C. Samples of a glutaric acid co-crystal of 2-[4-(4-chloro-2-fluorphenoxy)phenyl]pyrimidine-4-carbox amide were placed under the same conditions for 2 months, and HPLC impurity analysis did not show any significant increases in known degradants.

Physical stability in solution

Solution stability is defined as the ability of the co-crystal 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 co-crystal can occur, solution stability can be a key consideration for development. However, the results should always be weighed with other properties and needs. Studies of co-crystals in water can give an indication of possible dissociation and precipitation of another form such as a hydrate.

Dissolution:

The co-crystal dissolution profile is compared with the active pharmaceutical ingredient of the original in crystal form. Particle size is generally an important and controllable parameter of API forms, including co-crystals, which influence dissolution behavior. Little is known about the effect of the particle size on the dissolution and transformation behavior of a co-crystal. Dissolution studies for pharmaceutical co-crystals were carried out by preparing different co-crystals of the same API with different sizes.

Powder x-ray diffraction (PXRD) and polarization microscopy are used to study the mechanisms of dissolution improvement from co-crystallization, and the transformation behavior of each co-crystal in an aqueous suspension. The paddle apparatus is used to study the dissolution rate in fasted-state simulated fluid (FaSSIF) at 37 ºC.

The transformation behavior can be studied by suspending co-crystals of all sizes in FaSSIF at 37 ºC. Intrinsic dissolution tests are conducted to compare the dissolution rate of a co-crystal with its host crystal. The sink condition is maintained to study the dissolution rate of API and its co-crystals of different sizes. According to the Noyes Whitney equation, the smaller particle sizes dissolved at a higher rate. The dissolution rates for all sizes of co-crystals are nearly similar to that of fine.

Bioavailability:

Bioavailability is a measurement of the rate and extent of the active drug that reaches systemic circulation. A study with both the parent material and the co-crystal will give a direct assessment of bioavailability improvements due to the co-crystal. A limited number of animal bioavailability studies have been reported using co-crystals. One study on the pharmaceutical co-crystal of a mono phosphate salt with phosphoric acid mentions that excellent *in vivo* performance was observed.

CONCLUSION:

Co-crystallization is a multi-component method that significantly enhances the solubility of hydrophobic drugs. In the circumstances of crystal engineering bioavailability and dissolution rate give frequent responses and their contribution, in the study of the micro merits is quite better compared to another technique. Hence improving the solubility of APIs, structure-property studies are still very few.

At present, crystal engineering is an opportunity for overcoming the solubility challenge with APIs. This will lead to better design and engineering of pharmaceutical co-crystals with the desired properties.

Table 1. Reported Methods of co-crystals [38-40].

Drug	Co-former	Method used to prepare
Felodipine	Xylitol	Wet co-grinding
Darunavir	Succinic acid	Cooling crystallization
Aceclofenac	Sodium Saccharin	Solvent-drop grinding method
Clarithromycin	Urea	Solvent evaporation
Paracetamol	Caffeine	Dry grinding, liquid assisted grinding (lag), solvent evaporation (se), and anti-solvent addition
Myricetin	Proline	Solution crystallization based on the ternary phase diagram principle
Fenofibrate	Nicotinamide	Kneading, solution crystallization, antisolvent addition, and solvent drop grinding methods

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