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CO-CRYSTALLIZATION- A TECHNIQUE FOR SOLUBILITY ENHANCEMENT

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ABSTRACT: Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former. Pharmaceutical Co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, stability, and bioavailability in pharmaceutical development without changing the chemical composition of the API. Cocrystal is a crystalline entity formed by two different or more molecular entities where the intermolecular interactions are weak forces like hydrogen bonding and π - π stacking. Super porous systems, biodegradable hydrogel systems. Co-crystallization alters the molecular interactions and composition of pharmaceutical materials and is considered a better alternative to optimize drug properties. Co-crystals offer a different pathway, where any API, regardless of acidic, basic, or ionizable groups, could potentially be co-crystallized. This aspect also helps complement existing methods by reintroducing molecules that had limited pharmaceutical profiles based on their nonionizable functional groups. The article gives a brief review of the co-crystallization, its difference from other states and its importance as an alternative over salt formation. The review also highlights the current FDA notice on Guidance on co-crystallization, the various methods of preparing cocrystals and their characterization. The article also gives a list of the various cocrystals which have been worked on, thus highlighting their importance in the current trend for enhancing various physical, chemical, and pharmacological properties.

INTRODUCTION: The most common state of delivering dosage form is solid such as tablets, capsules, *etc.*¹ Various other states exist which allow delivering the API faster than the solid state. But this state provides API in the most convenient, compact and stable format to store. Thus, an important part of drug development becomes the understanding and controlling of the solid-state chemistry. Many times an API cannot be formulated in its pure form due to various issues of instability.

Thus, they are converted to solid forms such as polymorphs, salts, solvates, hydrates, amorphous, and co-crystals. Each of them imparts a different physiochemical property and affects other performance characteristics stability, bioavailability, purification, and manufacturability of the drug in their own better way. Taking this into consideration, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

The maximum development and interest area are being diverted to co-crystallization. Co-crystallization can be achieved only when the physiochemical properties (Hygroscopicity, solubility, and compaction behavior) of the formulation as a whole is improved. Co-crystals consists of two components that are the API and the former.

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Now, the former can be any other excipient or API which, when given in combination, reduces the dose and also the side effects. Hence, even if the API is the same changing the former will also change the pharmaceutical properties (chemical stability, bioavailability, solubility, melting point, moisture uptake, dissolution, *etc*).

As mentioned earlier, co-crystallization is the most dynamically developing group of solid pharmaceutical substances; it is a very vast area. Hence, they can be divided into cocrystal anhydrates, cocrystal hydrates (solvates), anhydrates of cocrystals of salts and hydrates (solvates) of cocrystals of salts.

According to the BCS classification, the API belonging to class II and IV have always posed a challenge in case of enhancing the solubility. Hence, one such option is crystallization. Thus the knowledge of crystal engineering along with the molecular properties of active pharmaceutical ingredients can pose a great option. Co-crystals consist of two or more molecules with a hydrogen bonding. The most appropriate co-crystal can be selected using various analytical techniques and rational physicochemical studies that include investigations of solubility and stability.

An example of hydrogen bond co-crystallization is the co-crystals of aspirin, rac-ibuprofen, and rac-flurbiprofen. These were prepared by disrupting the carboxylic acid dimers using 4,4V-bipyridine. These structures are formally molecular compounds (or co-crystals) but do not involve the formation of covalent bonds or charge transfer from or to the active substance. Hence to understand this in detail, high-throughput (HT) crystallization systems have recently been developed. This is a combinatorial approach using various conditions and compositions. Experiments are performed at a small scale to reduce the material demand and to afford the largest number of conditions possible. A more refined definition of a co-crystal can be "multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule.

Co-crystals often contain self-assembly units based on supramolecular synthons that are derived from motifs that are commonly found in crystal

structures. Generally in the case of pharmaceutical co-crystals, at least one of the components must be an API, while the additional co-crystal former(s) should be a pharmaceutically acceptable entity such as frequently used food additives and excipients.

Co-crystallization against Ionization: ² There are many other techniques except co-crystallization, which may enhance the solubility. One such technique is the formation of salts or crystalline ionic complexes but this form poses several inherent drawbacks. The most important requirement for salt formation is the existence of an ionic center of an API of interest. Hence in case of APIs which are non-ionizable, these are incapable of salt formation and provide great risk in terms of pharmaceutical profiles.

In case of forming a salt form the number of pharmaceutically acceptable, non-toxic acids and bases are relatively small. Though many API does exist in the salt form a survey carried out revealed that the number of salt-forming acidic counter ions were only 10 with a market usage rate of over 1% and the number of salt-forming basic counter ions are comparatively even less.

If taken into consideration the technique of co-crystallization the scenario is different. As co-crystallization involves the conversion of the molecule to a neutral form, it does not matter whether the API is ionic, non-ionic, and acidic or basic. The former or the counter molecule used in co-crystallization may be considered non-toxic, thus increasing the scope of co-crystallization over the salt formation. The counter molecule may be an excipient, food additive, preservatives, vitamins, minerals, amino acids, and other biomolecules or another API.

To design a co-crystallization experiment, two aspects should be kept in mind the first one being the evaluation of the robustness of the potential intermolecular interactions and considering the hydrogen bonding rules. Robustness can be checked by analyzing the trends within the Cambridge Structural Database (CSD) or by retrospective data.

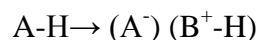
In a co-crystal, there exists hydrogen bond which imparts a robust and directional nature to it. Hence in the case where hydrogen bonding plays

importance, this rule should be considered, which says that strong hydrogen bond donor tends to interact with the best hydrogen bond acceptor in a given crystal structure. This 'best-donor–best-acceptor' rule can be of great utility in the design of specific hydrogen bonding interactions.

Co-crystal Versus Solvates: ^{2, 3, 4} The only difference between solvates and cocrystals is the physical state of the components. If one of the components is liquid and the other is solid, then it is termed as solvates but on the other hand, if both exist in the solid form then they are termed as cocrystals.

Co-crystal Versus Salt Formation: ^{4, 5} Salt formation and co-crystallization must not be confused with. Though salt formation and co-crystallization is used for enhancing solubility, stability, and other aspects of the API or formulation there is a difference between both.

While salt formation needs an API charge to form its salt form, co-crystallization doesn't need any such criteria. Hence, co-crystallization offers an option for API which doesn't carry a charge and needs to be enhanced for solubility or stability, etc. While crystallization includes a conformer and API, salt formation includes three components an acid (A), a base (B) and a solvent. The salt formation can be explained by a simple reaction.



The proton transfer depends on the pKa value. The hydrogen packing rule leads to salt formation. When no such proton transfer is observed but the crystal exists as a neutral entity then it is considered as cocrystal, which is a two-component system. The different solid forms are shown in **Fig. 1** represents the different types of crystal forms, while **Fig. 2** gives the idea of co-crystal formation.

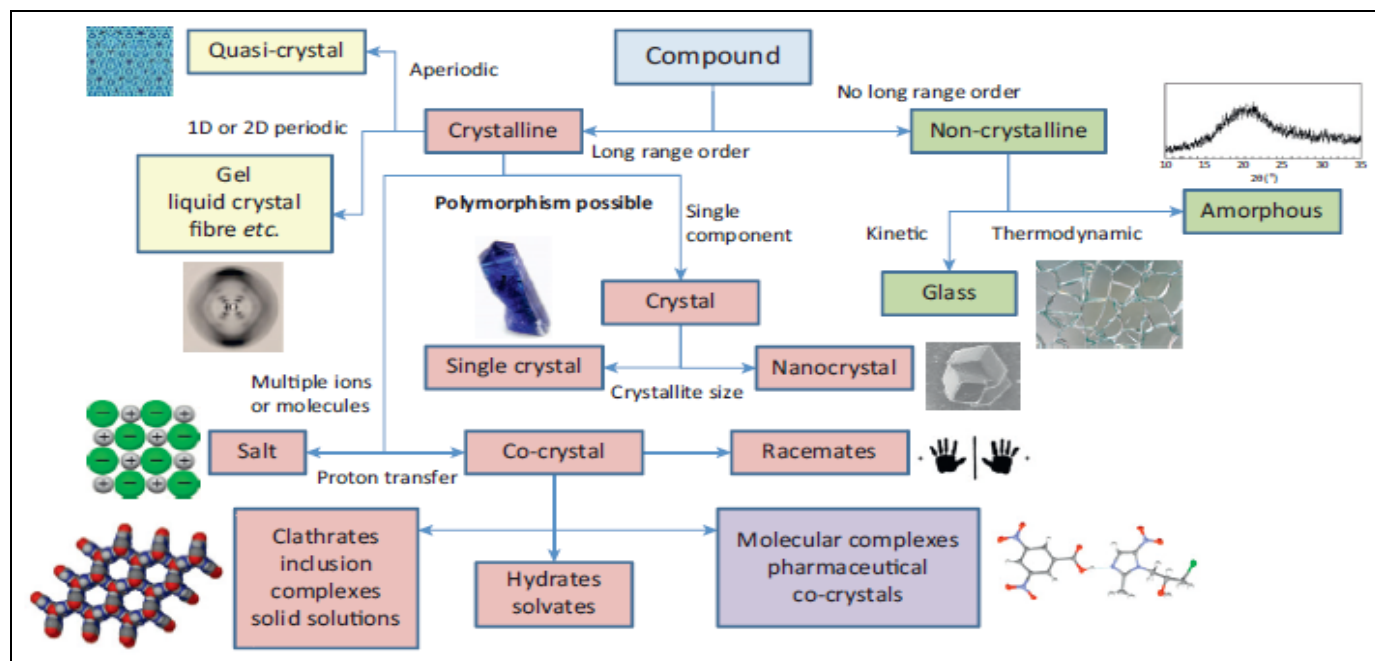


FIG. 1: THE DIFFERENT SOLID FORMS ¹⁸

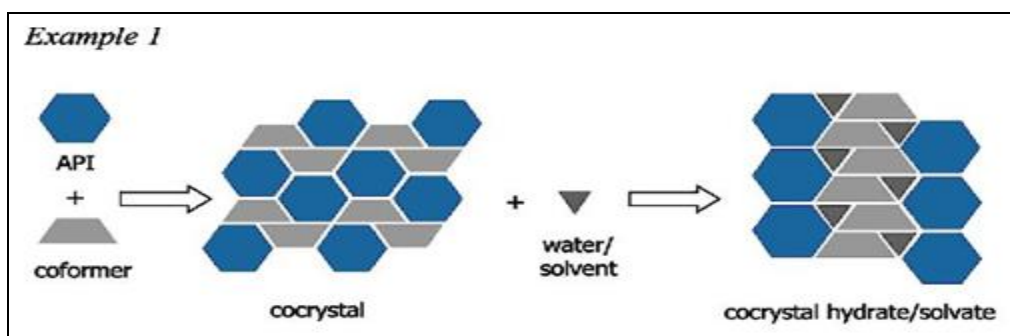


FIG. 2: POSSIBLE MULTICOMPONENT CO-CRYSTAL

Different Techniques of Co-crystallization:^{6,7} In case of discovery focused pharmaceutical companies enhancement of solubility in case of API with limited aqueous solubility are becoming increasingly prevalent in the research and development portfolios. Such molecules pose a great challenge in the pharmaceutical development as it leads to slow insufficient and inconsistent systemic exposure, consequent sub-optimal efficacy in patients and dissolution in biological fluids, particularly when delivered via the oral route of administration. The various approaches of increasing the solubility includes micronization where reducing the particle size increases the surface area and also the dissolution rate, converting to salt form with enhanced dissolution profile, solubilization of the drug in co-solvents or micellar solutions, complexation with various complexing agents such as cyclodextrin, *etc.* and use of lipophilic systems to deliver the various lipophilic drugs.

Although these techniques are established and enhances the solubility success of these approaches depends at times on the specific physiochemical nature of the molecule under study. Even though the dissolution increases by such techniques, it does not necessarily assure sufficient bioavailability. In the case of micronization, the excess size reduction can increase the van der Waals interactions and electrostatic attraction, which may reduce the effective surface area for dissolution and therefore limit improvements in the bioavailability.

Solvent Evaporation: Solvent evaporation is the most convenient method in the case of crystallization. In this technique, the material is mixed with the common solvent and evaporated completely. In the evaporation stage, the solution of molecules is expected to undergo various hydrogen bonding reactions. But in the case of co-crystallization, which consists of API and conformers solubility of both in the selected solvent plays a great role. If the solubility of the two is not similar, then the one with low solubility than the other will precipitate out. This does not mean that solubility alone is the criteria for success. Considering the polymorphism of the compound of interest is also very necessary. If the polymorphism existed, then the chances are that the compound after co-crystallization may convert into a form

which can bridge with the co-former. But the main point to be considered is the ability of the molecule to participate in the intermolecular interaction to form a co-crystal. The intrinsic dissolution rate was increased of Fluoxetine hydrochloride by using multiple conformers like succinic acid, fumaric acid, and benzoic acid. Norfloxacin cocrystals were synthesized with Isonicotinamide, Malonic acid, and maleic acid as conformer. The major disadvantage of this method is that it requires a large amount of solvent.

Solvent-free:⁸

Grinding: Solid state grinding is where the materials are mixed, pressed and crushed in a mortar and pestle or mill. In general aspects, this technique provides particle size reduction, but in case of co-crystallization, these have proved to be a viable method for solid-state grinding along with liquid state grinding. One such example of solid-state grinding is where Caira and co-workers study it on six pharmaceutical co-crystals of sulpha drug sulfadimidine with various carboxylic acids, including anthranilic acid (AA) and salicylic acid (SA). Out of which remarkable preference was demonstrated for one particular co-crystal, the sulfadimidine: AA co-crystal. In grinding competition experiment, the sulfadimidine: SA was ground in the presence of AA. The after grinding SA was replaced by the AA as the co-crystal partner of sulfadimidine. The replacement took place because of the common hydrogen bonding pattern in both co-crystals. This concluded that such solid state grinding competitions could help determine the stability of the given pharmaceutical co-crystal material in the presence of excipients.

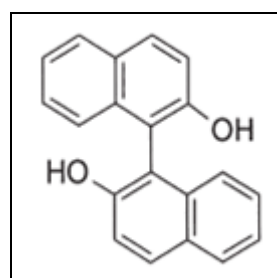


FIG. 3

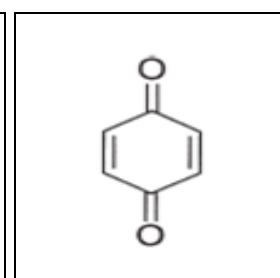


FIG. 4

Kuroda and his co-workers in their work proved that different methods of co-crystallization lead to distinct cocrystals. The co-crystallization of racemic bis-*b*-naphthol (BN) **Fig. 3** and benzoquinone (BQ) **Fig. 4** with different co-

crystallization methods lead to three forms. Form I was formed by simple solid-state grinding of BN: BQ in mortar pestle in a ratio of 1:1.5. When another method was used where cocrystals were prepared by solvent evaporation method to lead to Form II. In this, a solution of ether and hexane was used with BN: BQ in a ratio of 1:1. When the mixture of BN: BQ was cooled from the melt form III was observed.

Solvent- Reduced:

Slurrying: Slurry crystallization is a simple process which includes the addition of crystallization solvent in the API along with its acceptable former. The selection of this process mainly depends upon the physical stability of the crystallization solution to co-crystals and its solid former. While preparation of cocrystals for Trimethoprim and sulfamethoxazole through slurry technique, simple distilled water is used as a solvent. Cocrystals designed with 4, 4-Dipyridil of aspirin as a co-former by using slurry crystallization method. However, the yield obtained was not sufficient as compared with the solvent drop grinding method. The major disadvantage of this method is that it requires a large amount of solvent.

Solvent Drop Grinding: Modification of solid grinding technique is this technique where two materials can be ground by adding a minor quantity of solvent. The criteria of this technique being the solvent added are in very minute quantity which, when added acts as a catalyst but do not form a part of the end product. The usefulness of solvent-drop grinding was first demonstrated in the context of co-crystallization rate enhancement in a system

involving several cocrystals of nitrogenous bases with a cyclohexane tricarboxylic acid derivative, all of which were initially prepared by solution growth. It was found that some cocrystals could be readily prepared by solid-state grinding, whereas others exhibited only minor cocrystal content after grinding together starting materials for a significant time. For those that did not proceed to completion upon solid-state grinding, it was found that solvent-drop grinding could be used to prepare an essentially phase-pure cocrystal material after significantly reduced periods.

High Throughput Co-Crystallization:⁹ High throughput crystallization includes three steps: designing of the experiment, execution of protocol, and analysis of data. The design of experiments includes hardware and software. These enable to analyze the data, drive conclusions, store them, and retrieve them when required. Though this high throughput screening has already made a mark in the pharmaceutical industry, its existence in case of drug discovery, especially in the solid screening area is emerging.

Hence, it is important to distinguish both of them. First, the goal of HT screening is to get a small number of successful outcomes, which are then passed on to the next stage of development. Little effort is typically made to learn why certain outcomes were positive and why others were negative. In contrast, HT experimentation, such as HT crystallization, is carried out to have each point in the experiment produce multiple types of data that can be interpreted, and the interpretation used to guide the experimental process to a successful conclusion.

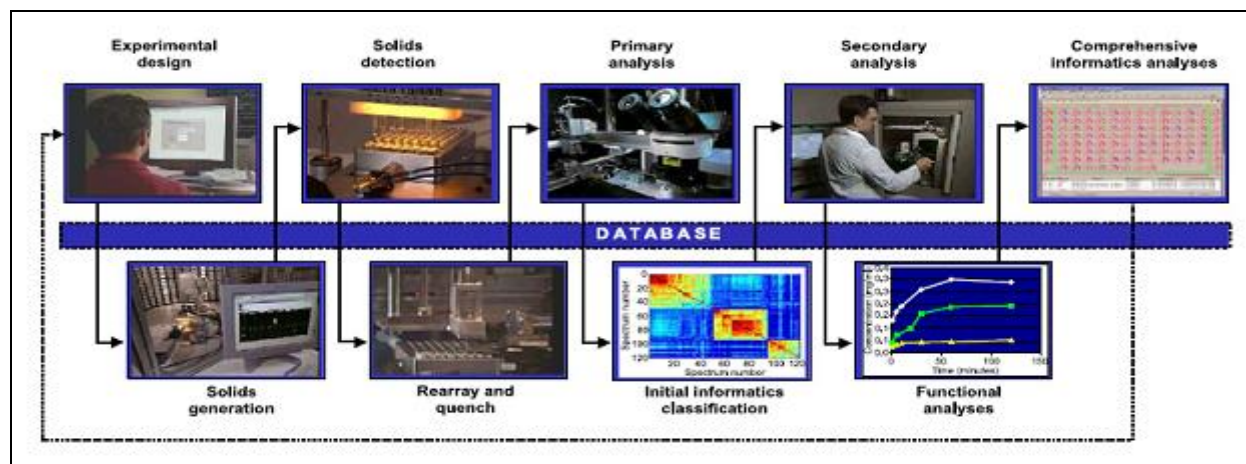


FIG. 5: SCHEMATIC REPRESENTATION OF THE HT CRYSTALLIZATION PROCESS

Second, unlike traditional HT screening assays where experiments are generally conducted under constant experimental conditions, HT crystallization experiments for solid form discovery are best conducted using a variety of process methods, each having varying experimental conditions (e.g., temperature variations as a function of time) throughout the experiment.

HT crystallization experiments can yield hit rates ranging from tens of percents to nearly 100%, depending on the type of experiment and the process mode(s) used. A fully integrated HT crystallization system consists of several components, including experimental design and handling hardware, robotic dispensing and execution software, automated highspeed micro-analytical tools, end-to-end sample tracking and integrated cheminformatics analysis software for data visualization, modeling, and mining. **Fig. 5** shows how the process of HT crystallization takes place.

Hot Melt Extrusion:¹⁰ Extrusion is a useful method for synthesis of cocrystals; it involves highly efficient mixing and improved surface contacts, Cocrystals are prepared without the use of solvent. The selection of this method primarily depends on the thermodynamic stability of the compound. This method was studied with the use of four models for cocrystal formation. Solvent drop extrusion technique used to optimize and make the process more flexible. Solvent drop extrusion technique gives the advantage to carry out the process at a lower temperature. Hot melt extrusion method was used in the synthesis of Carbamazepine-nicotinamide cocrystals with polymer as former. Continuous co-crystallization, API, and co-former poured in the twin extruder. As a result of the continuous addition of mixture, the barrel temperature also increases.

Sonocrystallization Method:¹¹ The development of the sonochemical method for the preparation of organic cocrystals of finite size has been done. This method was primarily developed for the preparation of nanocrystals. Caffeine- maleic acid cocrystal preparation commenced with the use of the ultrasound method. The comparative study of the method of preparation of caffeine and theophylline as API and L-tartaric acid as co-

former by Solvent drop grinding method and sonochemical method has been commenced. The results of the methods were consistent; hence, sonocrystallization proves to be a significant approach.

FDA Says:¹² US Food and Drug Administration (FDA) has now finalized guidance on Regulatory Classification of Pharmaceutical Co-Crystals. The guidance provides both the data required for submission as well as its implications of the classification for the new drug applications (NDAs) and abbreviated new drug applications (ANDAs). The recommendation does not apply to the already existing materials like complexes, polymers, salts, or other noncrystalline forms. The guidance applies to the materials which have not been determined previously like the pharmaceutical cocrystal. These are solids with crystal lattice having two or more molecules.

The solid-state polymorphs of an API can be classified as hydrate, crystalline, solvate or amorphous forms. The guidance or regulatory norms for these solid-state polymorphs already exists. But cocrystals are very different for these solid-state polymorphs. These pharmaceutical cocrystals have opened a new area of opportunity where the bioavailability of the product, as well as the solubility and process stability, can be enhanced.

“No formal regulatory policy exists at present on the classification of pharmaceutical co-crystals. Hence to combat this guidance provides the appropriate classification of co-crystal solid-state forms. But the requirement is that the data should be in polymorphic to support the classification. As stated earlier, the cocrystal is a crystal lattice having the API and the conformer where only the API reaches the site of action while the other part dissociates. This is because of the non-ionic charges which exist between them unlike the ionic interaction required for the salt form of an API. Considering all these reasons, the current regulatory framework has classified co-crystals as dissociable.”

For the parties interested in filing NDA and ANDAs for the pharmaceutical cocrystal it is necessary to prove that the API and excipient

dissociate before reaching the site of action and also are neutral and have no interaction that can alter the bioavailability of the API in any sense. The cocrystal is not classified or considered as a new API by the regulatory but instead as a new product intermediate.

The type and extent of characterization and release testing performed on the active pharmaceutical ingredient, the co-crystal intermediate, or both should be sufficient to ensure the identity, strength, quality, and purity of the active ingredient, critical process intermediates, and the drug product. Regardless of whether the co-crystal is manufactured in an API manufacturing facility or in one typically used to manufacture a drug dosage form, the co-crystal should be manufactured in a facility that operates by current good manufacturing practice (CGMP), stated the guideline.

Physicochemical Properties and Characterization:

1. Solubility:¹³⁻¹⁶ Co-crystallization is a technique most frequently used when the main aim is to enhance the solubility. Thus the co-crystals usually increase the solubility, which is not possible in case if an individual molecule. For example, Telmisartan is a class II drug which means it has low solubility. Thus formulating it needs to overcome the problem of its low solubility. In such cases, co-crystals pose a better option. Consider one more example were two novel cocrystals were prepared by solution method of different particle size which was of exemestane/maleic acids (EX/MAL) and megestrol acetate/saccharin (MA/SA) to improve the solubility of two APIs exemestane (EX) and megestrol acetate (MA). Co-crystallization of EX and MA enhanced the dissolution compared to individual API.

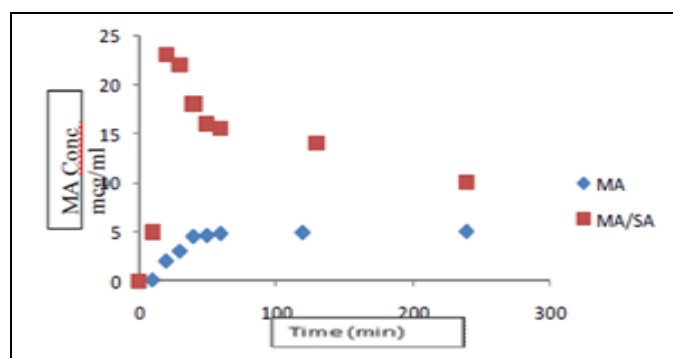


FIG. 6: DISSOLUTION PROFILE OF MEGESTROL ACETATE AND MEGESTROL ACETATE / SACCHARIN

In the case of EX/MAL, it showed a high dissolution rate even in large particles size. While MA/SA cocrystals showed supersaturation in fine particles. But when compared to the pure MA, the supersaturation of cocrystals in 15 min was increased by eight times as and 2 times in 4 h. **Fig. 6** shows the dissolution profile of pure MA with that of its cocrystals.

2. Maximum Wavelength: When the co-crystal solution is allowed for UV scan, the scan gives the peak showing maximum wavelength of the API. If the conformer is also an API the scan will show two peaks of lambda max of both the API. This leads to the conclusion that the co-crystals are formed and that they both are present in the solution.

3. Stability: It is an important parameter to be considered for any formulation. Hence in case of cocrystals, it is also important to ensure the chemical stability, solution stability, thermal stability, and relative humidity stability. The relative humidity stability of the cocrystals can be analyzed by water absorption/desorption experiments. For example, when cocrystals of 2-[4-(4-chloro-2-fluorophenoxy) phenyl] pyrimidine-4-carboxamide and glutaric acid were exposed to this absorption/desorption cycle, the crystals showed less than 0.08% water content up to 95% relative humidity. The results obtained from such experiments showed that the cocrystals are stable in terms of relative humidity. There are no much studies done on chemical and thermal stability.

4. Intrinsic Dissolution: Co-crystallization is a new technique for solubility enhancement mainly used in case of BCS class II drugs. One cocrystal example, a low solubility API, 2-[4-(4-chloro-2 fluorophenoxy) phenyl] pyrimidine-4-carboxamide, was cocrystallized with glutaric acid to achieve 18 times higher intrinsic dissolution rate.

5. Bioavailability:¹⁶ Bioavailability is the measurement of the extent to which the drug reaches the systemic circulation. Studies were done on the dog to find out the bioavailability enhancement of glutaric acid and 2-[4-(4-chloro- 2 fluorophenoxy) phenyl]-pyrimidine-4-carboxamide (PPPA) cocrystals. It was observed that the AUC was increased three times when the API was

formulated in cocrystal form. **Table 1** below gives the comparison of mean pharmacokinetic parameters for PPPA and PPPA-glutaric acid cocrystals.

TABLE 1: COMPARISON OF MEAN PHARMACOKINETIC PARAMETERS FOR PPPA AND PPPA-GLUTARIC ACID COCRYSTAL'S

Dose Group	Tmax (hr)	C max (ng/ml)	AUC (ng h/ml)
5 mg/kg PPPA	13 ± 12	25.4 ± 11.4	374 ± 192
5 mg/kg PPPA Glutaric acid Cocrystal	6 ± 9	89.2 ± 57.7	1234 ± 634
50 mg/kg PPPA	13 ± 14	89.2 ± 68.7	889 ± 740
50 mg/kg PPPA Glutaric Cocrystal	2 ± 0	278 ± 70.5	2230 ± 824

6. Melting Point:¹⁷ Melting point is amongst the physicochemical properties of co-crystals. It is the temperature of solid and liquid phase equilibrium. When the co-crystals are formed the melting point changes and comes in between the melting point of two individual molecules. If such results are obtained, it can be confirmed that the co-crystals are formed.

This can be explained by considering the example of two systems of cocrystals one is the optically active form, and the other is the racemic form of 2-phenyl butyric acid and 2-phenyl propionic acid. These two are co-crystallized with isonicotinamide. On carrying the melting point detection, it was found that the racemic group had a higher melting point than the optically active form. This result can be correlated with the denser packing arrangement inherent in centrosymmetric space groups.

7. Melt (Hot stage microscopy):^{18, 19} Hot stage microscopy, also known as MELT, is an analytical technique which can be used for cocrystal characterization. Characterization of cocrystals properties is done as a function of time and temperature. As the name suggests, this analytical technique is a combination of the feature of microscopy along with thermal analysis. The added features in this which offer greater possibilities of characterization of materials are image manipulation software, high-resolution color cameras, and video-enhanced microscopy. The other characterization techniques, along with the hot stage microscopy, are used in a variety of ways to confirm transitions.

Hot-stage microscopy in the pharmaceutical industry is used in a variety of ways to confirm transitions observed using other techniques. Hot stage microscopy may be used for the evaluation of crystal forms and hydrates [14 ± 19], solid-state

characterization of bulk drugs and other physicochemical properties. Hot melt is a visual technique; hence, when used with other characterization techniques such as DSC has expanded the visual collection capabilities. This visual technique is also required to confirm transitions such as melts and recrystallization.

8. Scanning Calorimetry (DSC):²⁰ In this characterization technique, the two specimens in which one is the sample, and the other is the reference subjected to identical temperature and an environment which is heated or cooled at a controlled rate. The energy required to obtain a zero temperature difference between the two specimens is plotted, and the results are interpreted. There are two types of DSC which are commonly used. The first one is the power compensation DSC where the two specimens are kept in different identical furnaces. The temperature of both is made identical by varying the power input. Thus the energy is interpreted in terms of heat capacity or the enthalpy. Another type of DSC is where both are kept in the same furnace where both the sample holders are connected by a low-resistance heat flow path. Rest of the interpretation part is same.

9. XRD:²¹ This analytical technique is used to provide the unit cell dimension information by phase identification. This is obtained by constructive diffraction of the monochromatic X-ray and the crystalline sample. The monochromatic ray is produced by cathode ray tube which is filtered and collimated to produce monochromatic radiation and then directed towards the sample. In the case of the sample preparation, the sample is finely grounded such that a homogeneous sample is produced and the average bulk composition is analyzed. The sample is analyzed in terms of d-spacing. As the sample is posed to the random

orientation, it gives a set of d-spacing. As each mineral has a different set of d-spacing, the sample is thus analyzed. For all this to happen, the most important thing is that the sample must obey Bragg's law ($n\lambda=2d \sin \theta$) which relates the wavelength of the electromagnetic radiation to the diffraction angle 2θ .

10. Vibrational spectroscopy (IR and Raman):²²

Electromagnetic radiation has been one of the strongest tools for organic structure determination with frequencies between 4000 and 400 cm^{-1} . This electromagnetic radiation in organic chemistry is termed as infrared (IR) radiation and as IR spectroscopy for its application. The radiations bombarded are absorbed by the interatomic bonds. Thus a specific chemical bond will absorb varying radiations and at varying frequencies in different environments. Thus their absorption information which is given in the form of a spectrum helps draw some conclusion of what the structure may be.

Various examples:^{23, 25}

Caffeine and Methyl gallate:²⁴ The cocrystals of caffeine and methyl gallate were prepared in 1:1 ratio. The reason for going for the cocrystals of these two was because it was found the cocrystallization improved the powder compaction properties. Earlier when these two were individually compressed the problem of lamination was observed. In the case of methyl gallate, the tablet tensile strength was very poor (<0.5 MPa) within the whole range of compaction pressure. Due to this severe sticking and lamination was observed in almost all tablets. In the case of caffeine, the tablet ability was acceptable, but when increased to more than 180 MPa severe lamination was suddenly observed. But in case of the cocrystals of these two in the ratio of 1:1 suspended in ethanol, the tensile strength increased two times. Poor tablet tensile strength was always associated with high elastic recovery and low elasticity. The good plasticity and tablet ability of the cocrystal validated the selection criterion for the presence of slip planes in the crystal structure.

Danazol Cocrystal with Controlled Supersaturation:²⁵ The cocrystals of danazol: vanillin (1:1) was prepared to overcome the solubility issues with danazol. The neat aqueous

suspension, when prepared gave an increase in area under the curve by 1.7 times higher **Fig. 7** than the poorly soluble crystals of danazol. But there was a more marked difference in the bioavailability, which increased almost 10 times when the aqueous suspension was prepared by using 2% Klucel LF Pharm hydroxyl propyl cellulose and 1% vitamin E-TPGS (TPGS). Thus, in this case, the cocrystals increased the bioavailability, but when used in the form of supersaturated formulation, it was able to overcome limited solubility bioavailability by creating the conditions required for increasing the cocrystal solubility.

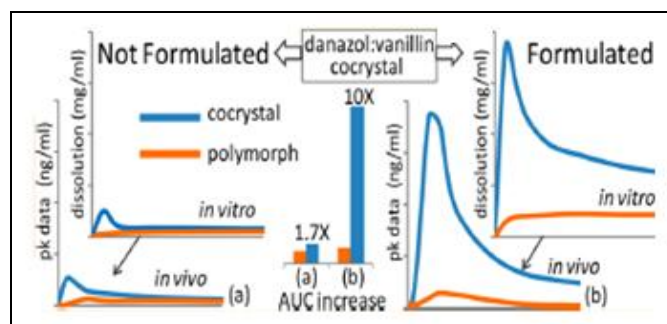


FIG. 7: COMPARATIVE AUC OF DANAZOL: VANILLIN COCRYSTALS IN NON FORMULATED AND FORMULATED FORM

Carbamazepine (Tegretol®) and Saccharin:

Crystallization does offer better properties than the individual API or its anhydrous form. But it may not always guarantee the same stability. Hence in case of carbamazepine: saccharin cocrystals only this form was found to be stable after various form screening equivalent to the amorphous form. This cocrystal offers better physical stability. On further studies on dog models, these cocrystals showed improved pharmacokinetics, dissolution properties, and suspension stability. On comparing the pharmacokinetic studies of the cocrystals with the marketed tablet of Carbamazepine (Tegretol®), it appeared that the cocrystals exhibited higher C_{\max} and comparable T_{\max} .

Co-crystals of Fluoxetine Hydrochloride (Prozac®):

Co-crystals of Fluoxetine Hydrochloride was found to demonstrate better physical properties with the hydrochloride salt remaining as a stable entity. Fluoxetine hydrochloride was Co-crystallized with fumaric acid (2:1), succinic acid (2:1) and benzoic acid (1:1) by using the evaporation technique. The reaction took place as an acid-base reaction where

there was proton transportation between the carboxylic acid and the chloride ion. This now interacted with the protonated amide, known as amine hydrochloride salt hydrogen bonding to an additional neutral molecule. When all the three cocrystals were crystallized, it was found that each showed a different dissolution profile by powder dissolution experiments. In the case of fluoxetine HCl: fumaric acid cocrystal, it had shown only a slight increase in aqueous solubility. In the second one, fluoxetine HCl: benzoic acid, the aqueous solubility was reduced by 50%. However, the third cocrystal that was of fluoxetine HCl: succinic acid cocrystal exhibited a two-fold increase in aqueous solubility after only 5 min.

Co-crystals of Sildenafil (Viagra®): Sildenafil has solubility issues; hence, it was thought of that its co-crystallization with acid could overcome this issue. Hence, sildenafil was Co-crystallized with acetylsalicylic acid in 1:1 molar ratio under reflux or slurry method. The co-crystallization of sildenafil in acidic conditions was advantageous in case of its oral administration. The cocrystals were characterized by XRD, DSC, IR, etc. In case of dissolution studies which were done under stimulated gastric fluid pH, 1.2 shows that the dissolution rate was increased almost two-fold as compared to sildenafil citrate (*i.e.*, from 6.64 mg/min/cm to 11.75 mg/min/cm. thermal analysis showed that the melting point of the cocrystals was 145 °C, but the cocrystals were thermodynamically stable up to 165 °C.

Co-crystals of Theophylline: The cocrystals of theophylline were prepared by solvent evaporation method with four different conformers, glutaric acid, malonic acid, maleic acid, and oxalic acid. The stability of these four cocrystals was compared by exposing them to different relative humidity (0%, 43%, 75% and 98% RH) and different time points (1 day, 3 day, 1 and 7 weeks). After 7 weeks it was found that the cocrystals at 75% RH and below, theophylline anhydrate converted into theophylline monohydrate. No formation of theophylline hydrate was found in any case. Out of the four cocrystals, the oxalic acid cocrystal was the most stable one.

Co-crystals of Aceclofenac with Chitosan: Aceclofenac, which is slightly soluble in water

when formulated for oral administration, showed poor bioavailability. Hence, its co-crystallization was done with chitosan. Chitosan was precipitated on Aceclofenac by salting out method. When the cocrystals were prepared, it was analyzed for various parameters like solubility, *in vivo* dissolution, XRD, DSC, particle size, stability, morphology, etc.

The cocrystals analysis results were compared to the pure Aceclofenac API. When done, so the following observation was found. In the case of particle size, the cocrystals particle size was reduced during formulation. In case of dissolution studies, there was a marked increase. Also, there were morphological changes. Stability was also improved at accelerated conditions.

Curcumin & Methylparaben Cocrystals: ²⁶ Curcumin obtained from *Curcuma longa* belonging to the family of, Zingiberaceae is proved to have preventive and chemotherapeutic action. Thus it can act as an alternative treatment of many diseases. The basic need for co-crystallization of curcumin was because of its low solubility, poor bioavailability, slow dissolution rate, and low absorption. Curcumin was Co-crystallized with methylparaben (1:1) by using solvent grinding. The grinding was done for 30 minutes manually in mortar pestle where 5 to 6 drops of ethanol was added. The cocrystals were characterized by using PXRD, DSC, FT-IR, and SEM. The pure curcumin having dose 100 mg/kg and the cocrystals were evaluated for inhibitory studies. It was found that the inhibitory activity in case of curcumin was 4.65% and that of cocrystals was 66.67%.

CONCLUSION: Pharmaceuticals are the pillar of the healthcare industry. Hence it poses a great challenge in formulating a new type of delivery system or altering the API form to enhance or improve the characteristics which hinder its acceptability. Hence in case, of co-crystallization, it is a new method which can be used to overcome various physical, chemical, or physiological drawbacks of an API. In the case of formulation aspect, the co-crystallization offers a new area to develop a new method of preparation, characterization of API. Hence it can act as opportunities for industries who want to claim for an Intellectual property. Another challenging area

is the new techniques for screening these API. According to the various papers reviewed the liquid-assisted grinding and neat grinding a method of choice as compared to solvent-based approaches. Cocrystals are the best alternative for APIs which cannot be converted into its salt form. This is because of the absence of any ionic charge. Hence, in the case of co-crystallization, which consists of simply an API and conformers, can be used to enhance various properties of the API. Whether it is enhancing solubility, pharmacokinetic properties, or improving the stability co-crystallization has established its presence.

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