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CO- CRYSTALLIZATION: A TECHNIQUE FOR SOLUBILITY ENHANCEMENT

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Abstract:

API and a stoichiometric amount of a pharmaceutically approved co-crystal former are combined to generate co-crystals. Pharmaceutical Co-crystals are nonionic supramolecular complexes that can be employed in pharmaceutical development to solve physical property challenges such as solubility, stability, and bioavailability without affecting the chemical makeup of the API. A cocrystal is a crystalline entity generated by two or more molecular entities with weak intermolecular interactions such as hydrogen bonding and - stacking. Biodegradable hydrogel systems, super porous systems. Co-crystallization changes the molecular interactions and composition of medicinal materials and is thought to be a better option for optimising therapeutic characteristics. Co-crystals provide an alternative method in which any API with acidic, basic, or ionizable groups could potentially be co-crystallized. This aspect also contributes to the complementarity of existing approaches by reintroducing compounds with limited pharmacological profiles due to nonionizable functional groups. The article provides a brief overview of co-crystallization, how it differs from other states, and why it is important as an alternative to slat formation. The page also includes a summary of the numerous cocrystals that have been studied, emphasising their significance in the current trend of improving various physical, chemical, and medicinal properties.

Index term: Co-crystals, supramolecular complexes, nonionizable Functional groups

INTRODUCTION:

The most frequent method of dosage delivery is solid, such as tablets, capsules, and so on.[1] Other states exist that allow the API to be delivered faster than the solid state. However, this state exposes API in the most convenient, compact, and stable storage format. As a result, understanding and managing solid-state chemistry has become a key element of medication development. Many times, an API cannot be defined in its pure form due to instability difficulties. As a result, they are transformed into solid forms such as polymorphs, salts, solvates, hydrates, amorphous, and co-crystals. Each of them transmits a particular physiochemical property and influences the drug's other performance qualities such as stability, bioavailability, purification, and manufacturability in a different way. Given this, it is vital to comprehend the relationship between a compound's specific solid structure and its functional qualities. The majority of development and interest is being directed toward co-crystallization. Co-crystallization is only possible if the formulation's overall physiochemical qualities (hygroscopicity, solubility, and compaction behaviour) are enhanced. Co-crystals are made up of two parts: the API and the former.

Now, the former can be any other excipient or API that, when combined, minimises the dose as well as the negative effects. As a result, even if the API remains the same, changing the former will alter the pharmacological characteristics (chemical stability, bioavailability, solubility, melting point, moisture uptake, dissolution, etc). As previously said, co-crystallization is the most rapidly evolving group of solid medicinal compounds; it is a broad field. As a result, they can be classified as cocrystal anhydrates, cocrystal hydrates (solvates), cocrystal salt anhydrates, and cocrystal salt hydrates (solvates). API belonging to classes II and IV, according to the BCS classification, have always offered a problem in terms of increasing solubility. As a result, crystallisation is one such alternative. Thus, understanding crystal engineering as well as the molecular characteristics of active pharmaceutical components can be a huge asset. Co-crystals are made up of two or more molecules that are linked together by a hydrogen bond. Various analytical techniques and reasonable physicochemical studies, including tests of solubility and stability, can be used to choose the best appropriate co-crystal. Aspirin, rac-ibuprofen, and rac-flurbiprofen co-crystals are examples of hydrogen bond co-crystallization. The carboxylic acid dimers were disrupted with 4,4V-bipyridine to create these. These structures are officially molecular compounds (or co-crystals),

but they do not include covalent bond formation or charge transfer from or to the active substance. As a result, high-throughput (HT) crystallisation techniques have recently been created to better comprehend this. This is a combinatorial method that employs a variety of conditions and compositions. Experiments are carried out on a modest scale in order to limit material demand and provide the greatest variety of situations conceivable. A co-crystal is a "multicomponent crystal created between two substances that are solids under ambient conditions, with at least one component being an acceptable ion or molecule." Co-crystals frequently contain self-assembly units based on supramolecular synthons formed from motifs found in crystal formations. In the case of pharmaceutical co-crystals, at least one of the components must be an API, with the remaining co-crystal former(s) being a pharmaceutically acceptable item such as commonly used food additives and excipients.

CO-CRYSTALLIZATION AGAINST IONIZATION:[2]

Apart from co-crystallization, there are other ways that may improve solubility. The creation of salts or crystalline ionic complexes is one such approach, although it has significant limitations. The presence of an ionic centre of an API of interest is the most significant condition for salt production. As a result, non-ionizable APIs are incapable of salt production and pose a significant danger in terms of pharmacological profiles. In the case of salt formation, the number of pharmaceutically acceptable, non-toxic acids and bases is relatively limited. Despite the fact that numerous APIs exist in salt form, a survey conducted found that the number of salt-forming acidic counter ions was only 10 with a market utilisation rate of more than 1%, and the number of salt-forming basic counter ions was much lower. The scenario changes when the process of co-crystallization is considered. Because co-crystallization requires the molecule to be converted to a neutral state, it makes no difference whether the API is ionic, non-ionic, acidic, or basic. The former or counter molecule utilised in co-crystallization may be non-toxic, expanding the scope of co-crystallization over salt production. Excipients, food additives, preservatives, vitamins, minerals, amino acids, and other biomolecules, as well as other APIs, may be used as the counter molecule.

Two considerations should be kept in mind when designing a co-crystallization experiment. The first is evaluating the robustness of probable intermolecular interactions and considering hydrogen bonding principles. The robustness of a system can be determined by studying trends in the Cambridge Structural Database (CSD) or by using retrospective data.

A hydrogen bond exists in a co-crystal, which gives it a strong and directed nature. As a result, in the instance when hydrogen bonding is involved This rule, which states that string hydrogen bond donors tend to interact with the best hydrogen bond acceptor in a particular crystal structure, should be addressed. This ‘best-donor–best-acceptor' criteria can be quite useful in designing specialised hydrogen bonding interactions.

CO-CRYSTAL VERSUS SOLVATES: [2, 3, 4]

The only distinction between solvates and cocrystals is their physical condition. If one of the components is liquid and the other is solid, they are referred to as solvates; however, if both are solid, they are referred to as cocrystals.

CO-CRYSTAL VERSUS SALT FORMATION:[4, 5]

Salt production and Co-crystallization are not the same thing. Though salt production and co- crystallisation are both employed to improve solubility, stability, and other properties of the API or formulation, there is a distinction between the two. While salt production requires an API charge to create its salt form, co-crystallization does not. As a result, co-crystallization provides an option for API that does not carry a charge and needs to be improved for solubility or stability, among other things. While crystallisation requires a conformer and an API, salt production requires three ingredients: an acid (A), a base (B), and a solvent. A simple process can explain the production of salt.

$$A\text{-}H \rightarrow (A^-)\ (B^+\text{-}H)$$

The proton transfer is affected by the pKa value. Salt is formed as a result of the hydrogen packing rule. When no such proton transfer is detected but the crystal still exists as a neutral entity, it is referred to as a cocrystal, which is a two-component system. Figure 1 depicts the various sorts of crystal shapes, whereas Figure 2 depicts the concept of co-crystal formation.

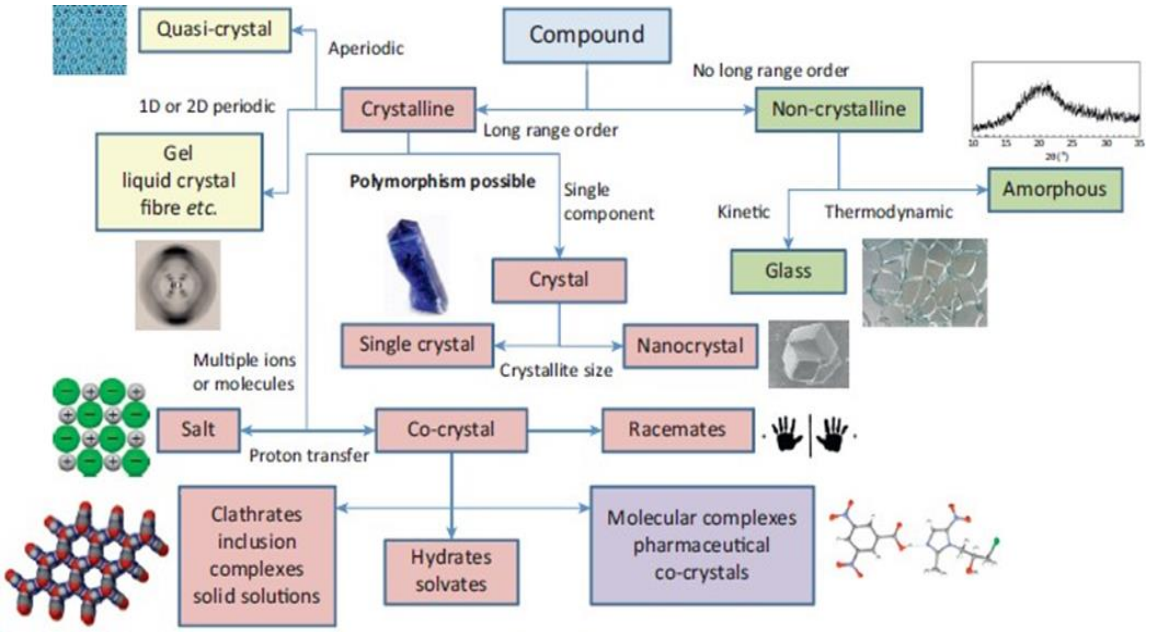

Fig. 1: The Different Solid Forms [18]

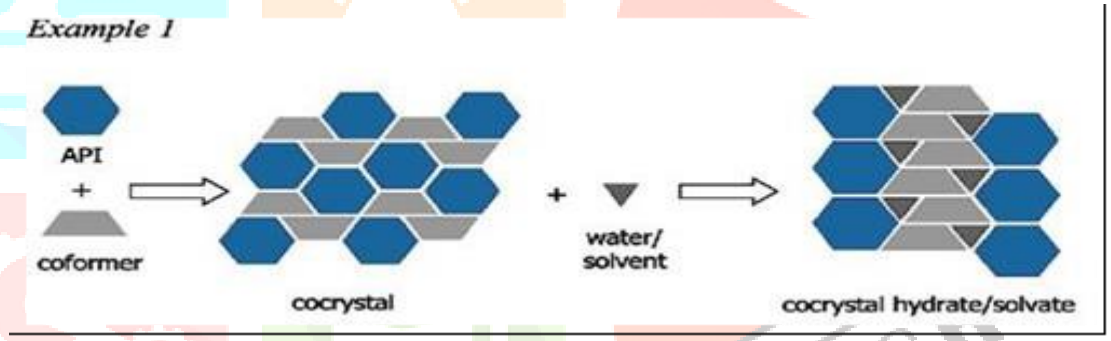

Fig. 2: Possible Multicomponent Co-Crystal

DIFFERENT TECHNIQUES OF CO-CRYSTALLIZATION:[6, 7]

Enhancement of solubility in case of API with poor water solubility is becoming increasingly widespread in the research and development portfolios of discovery-focused pharmaceutical businesses. Such compounds present a significant problem in pharmaceutical development since they cause sluggish, inadequate, and inconsistent systemic exposure, resulting in sub-optimal efficacy in patients and solubility in biological fluids, particularly when administered orally. Micronization, which reduces particle size and thus increases surface area and 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 drug. Although these procedures are well-established and improve solubility, their efficacy is sometimes dependent on the precise physiochemical characteristics of the molecule under study. Even though such approaches promote solubility, they do not always ensure adequate bioavailability. In the case of micronization, the increased van der Waals interactions and electrostatic attraction may restrict the effective surface area for dissolving and thus limit bioavailability increases.

SOLVENT EVAPORATION:

In the case of crystallisation, the most convenient procedure is solvent evaporation. The substance is combined with a common solvent and totally evaporated in this procedure. The solution of molecules is predicted to undergo numerous hydrogen bonding events during the evaporation stage. However, in the case of co-crystallization, which involves both API and conformers, the solubility of both in the chosen solvent is critical. If the two have different solubilities, the one with a lower solubility will precipitate out. This is not to say that solubility is the only criterion for success. It is also critical to consider the polymorphism of the chemical of interest. If the polymorphism exists, the compound may convert into a form that can bridge with the co-former following co-crystallization. The essential element to examine is the molecule's ability to participate in the intermolecular interaction and create a co-crystal. Fluoxetine hydrochloride's intrinsic dissolving rate was boosted by utilising several conformers such as succinic acid, fumaric acid, and benzoic acid. Isonicotinamide,

Malonic acid, and Maleic acid were used as conformers to create norfloxacin cocrystals. The main downside of this procedure is that it uses a lot of solvent.

SOLVENT-FREE: [8]

Grinding:

Solid state grinding is the process of mixing, pressing, and crushing materials in a mortar and pestle or mill. In general, this process reduces particle size, but in the case of co-crystallization, it has proven to be a viable way for solid-state grinding in addition to liquid-state grinding. Caira and colleagues investigated solid-state grinding on six pharmaceutical co-crystals of the sulfa medication sulfadimidine with various carboxylic acids, including anthranilic acid (AA) and salicylic acid (SA). One particular co-crystal, the sulfadimidine, was shown to have a striking preference: Co-crystal of AA. The sulfadimidine: SA was pulverised in the presence of AA in a grinding competition experiment. After grinding, the SA was replaced as the co-crystal partner of sulfadimidine by the AA. Because of the shared hydrogen bonding pattern in both co-crystals, the replacement occurred. This resulted in the conclusion that such solid state grinding competitions could aid in determining the stability of a specific pharmaceutical co-crystal material in the presence of excipients.

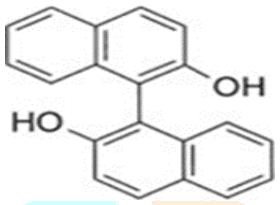

Fig. 3

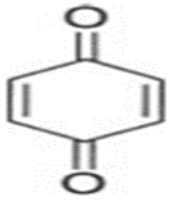

Fig. 4

Kuroda and his colleagues demonstrated in their work that different methods of co-crystallization result in distinct cocrystals. Co-crystallization of racemic bis-b-naphthol (BN) Fig. 3 and benzoquinone (BQ) Fig. 4 results in three forms. Form I was created through simple solid-state grinding of BN:BQ in a mortar pestle in a 1:1.5 ratio. When another approach was utilised to create cocrystals by solvent evaporation, Form II resulted. A 1:1 BN:BQ solution of ether and hexane was utilised in this experiment. When the BN:BQ mixture was cooled from the melt phase, III was noticed.

SOLVENT- REDUCED:

Slurrying: Slurry crystallisation is a straightforward procedure that involves the addition of crystallisation solvent to the API as well as an appropriate former. The physical stability of the crystallisation solution to co-crystals and its solid former is the primary determinant in the choice of this technique. Simple distilled water is employed as a solvent in the slurry process for the manufacture of cocrystals for trimethoprim and sulfamethoxazole. Slurry crystallisation was used to create cocrystals with 4, 4-Dipyridil of aspirin as a co-former. However, when compared to the solvent drop grinding process, the yield obtained was insufficient. The main downside of this procedure is that it uses a lot of solvent.

SOLVENT DROP GRINDING:

This technique is a modification of the solid grinding process in which two materials can be ground by introducing a little amount of solvent. The characteristics of this procedure are that the solvent used is in very small quantities, which act as a catalyst but do not form part of the finished product. The utility of solvent-drop grinding was originally proven in the context of increasing the pace of co-crystallization in a system involving numerous cocrystals of nitrogenous bases with a cyclohexane tricarboxylic acid derivative, all of which were generated through solution growth. Some cocrystals were discovered to be easily generated by solid-state grinding, whilst others had only minimal cocrystal content after grinding together starting materials for an extended period of time. For those who did not complete solid-state grinding, it was discovered that solvent-drop grinding may be employed to make an essentially phase-pure cocrystal material in much less time.

HIGH THROUGHPUT CO-CRYSTALLIZATION:[9]

High throughput crystallisation consists of three steps: experiment design, protocol execution, and data processing. Experiment design encompasses both hardware and software. These allow data to be analysed, conclusions drawn, data to be stored, and data to be retrieved when needed. Though high throughput screening has already created a name for itself in the pharmaceutical sector, its use in drug development, particularly in the solid screening domain, is still in its early stages. As a result, it is critical to distinguish between the two. First and foremost, the purpose of HT screening is to obtain a small number of effective outcomes that are subsequently advanced to the next stage of development. Typically, little effort is taken to determine why certain results were positive and others were negative. In contrast, HT experimentation, such as HT crystallisation, is carried out with the goal of producing many types of data that may be evaluated and used to drive the experimental process to a successful finish.

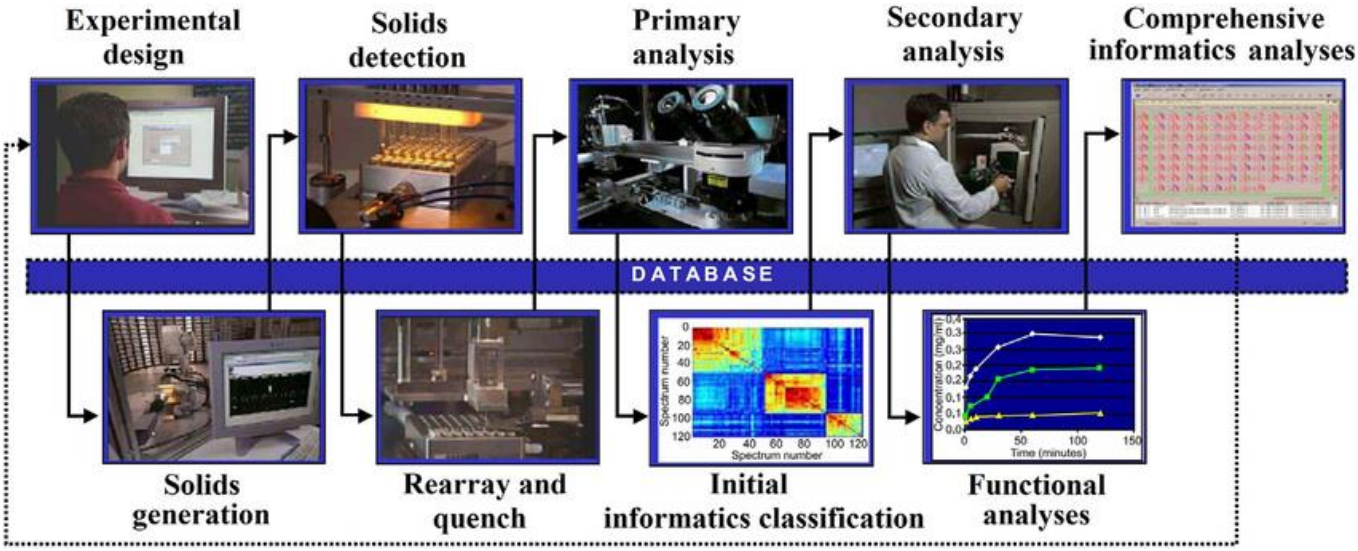

Fig. 5. Schematic Representation of The Ht Crystallization Process

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

HT crystallisation experiments can provide hit rates ranging from tens to almost one hundred percent, depending on the type of experiment and process mode(s) used. A fully integrated HT crystallisation system includes several components such as experimental design and handling hardware, robotic dispensing and execution software, automated high-speed micro-analytical tools, end-to-end sample tracking, and integrated cheminformatics analysis software for data visualisation, modelling, and mining. The process of HT crystallisation is depicted in Fig. 5.

HOT MELT EXTRUSION:[10]

Extrusion is a suitable approach for preparing cocrystals because it involves very effective mixing and better surface interactions. Cocrystals are prepared without the need of a solvent. The choice of this approach is mostly determined by the compound's thermodynamic stability. This approach was investigated using four cocrystal formation models. To optimise and make the process more flexible, the solvent drop extrusion technique was adopted. The solvent drop extrusion technique allows the procedure to be carried out at a lower temperature. Carbamazepine-nicotinamide cocrystals were synthesised using a hot melt extrusion process with polymer as a former. In the twin extruder, continuous co-crystallization, API, and co-former are poured. The barrel temperature rises as a result of the constant adding of mixture.

SONOCRYSTALLIZATION METHOD:[11]

The sonochemical approach for the fabrication of organic cocrystals of finite size has been developed. This approach was created particularly for the preparation of nanocrystals. The ultrasound approach was used to create caffeine-maleic acid cocrystals. A comparative investigation of the methods for preparing caffeine and theophylline as API and L-tartaric acid as co-former using the solvent drop grinding method and the sonochemical approach has begun. The results of the approaches were consistent, indicating that sonocrystallization is an important approach.

FDA SAYS:[12]

The US Food and Drug Administration (FDA) has recently published final advice on the Regulatory Classification of Pharmaceutical Co-Crystals. The guidance includes both the data required for submission as well as the categorization implications for new drug applications (NDAs) and abbreviated new drug applications (ANDAs) (ANDAs). The advice does not apply to pre-existing materials such as complexes, polymers, salts, and other noncrystalline forms. The guidance applies to materials that have not previously been determined, such as medicinal cocrystals. These are solids with two or more molecules in their crystal lattice. API solid-state polymorphs are characterised as hydrate, crystalline, solvate, or amorphous. There are currently guidelines or regulatory standards in place for these solid-state polymorphs. Cocrystals, on the other hand, are quite different for these solid-state polymorphs. These pharmaceutical cocrystals have opened up a new area of possibility for increasing product bioavailability, as well as solubility and process stability.

"At the moment, there is no official regulatory regulation on the classification of medicinal co-crystals. As a result, in order to resist this instruction, the appropriate classification of co-crystal solid-state forms is provided. However, the data must be polymorphic in order to enable the classification. As previously stated, a cocrystal is a crystal lattice composed of the API and the conformer, with only the API reaching the site of action while the other component dissociates. This is due to the non-ionic charges that exist between them, as opposed to the ionic contact required for an API's salt form. Given all of these considerations, the existing regulatory framework classifies co-crystals as dissociable."

Parties interested in filing NDAs and ANDAs for pharmaceutical cocrystals must demonstrate that the API and excipient dissociate before reaching the site of action, are neutral, and have no interaction that can modify the API's bioavailability in any way. The cocrystal is not classed or considered by the regulatory as a new API, but rather as a new product intermediate. The type and extent of characterization and release testing performed on the active pharmaceutical ingredient, co-crystal intermediate, or both should be sufficient to ensure the active ingredient's identity, strength, quality, and purity, as well as critical process intermediates and the drug product. The co-crystal should be created in a facility that follows current good manufacturing practise (CGMP), regardless of whether it is manufactured in an API manufacturing facility or one that is generally used to make a medicinal dosage form, according to the recommendation.

PHYSICOCHEMICAL PROPERTIES AND CHARACTERIZATION:

1. Solubility: [13-16]

Co-crystallization is a process that is commonly employed when the primary goal is to increase solubility. Thus, co-crystals frequently increase solubility, which is not achievable with a single molecule. Telmisartan, for example, is a class II medication with limited solubility. In order to solve the difficulty of its low solubility, it must be formulated. Co-crystals are a superior option in such instances. Consider another example in which two unique cocrystals of exemestane/maleic acids (EX/MAL) and megestrol acetate/saccharin (MA/SA) were synthesised by solution technique to improve the solubility of two APIs exemestane (EX) and megestrol acetate (MA/SA) (MA). When compared to solitary API, co-crystallization of EX and MA improved solubility.

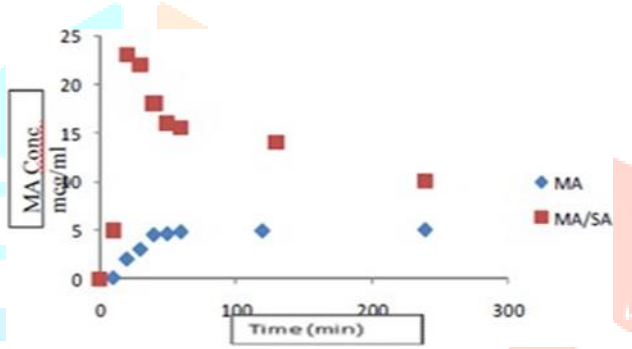

Fig. 6: Dissolution Profile of Megestrol Acetate and Megestrol Acetate / Saccharin

Even with huge particle sizes, EX/MAL demonstrated a high dissolving rate. In fine particles, MA/SA cocrystals displayed supersaturation. However, when compared to pure MA, the supersaturation of cocrystals in 15 minutes was enhanced by eight times, and by two times in 4 hours. Figure 6 compares the dissolution profiles of pure MA and its cocrystals.

2. Maximum Wavelength:

When the co-crystal solution is permitted for UV scanning, the scan produces a peak indicating the maximum wavelength of the API. If the conformer is also an API, the scan will show two lambda max peaks from both APIs. This implies that the co-crystals have formed and that they are both present in the solution.

3. Stability:

It is an important parameter to consider while developing any formulation. As a result, it is critical to assure chemical stability, solution stability, temperature stability, and relative humidity stability in the case of cocrystals. Water absorption/desorption studies can be used to assess the relative humidity stability of cocrystals. Cocrystals of 2-[4- (4-chloro-2-fluorphenoxy) phenyl] pyrimidine-4-carboxamide and glutaric acid, for example, showed less than 0.08 percent water content up to 95 percent relative humidity when exposed to this absorption/desorption cycle. The results of such trials revealed that the cocrystals are relative humidity stable. There haven't been many investigations on chemical and thermal stability.

4. Intrinsic Dissolution:

Co-crystallization is a new technology for increasing solubility that is mostly employed in the case of BCS class II pharmaceuticals. A low solubility API, 2-[4-(4-chloro-2 fluorophenoxy) phenyl] pyrimidine-4-carboxamide, was cocrystallized with glutaric acid to generate an 18-fold increase in intrinsic dissolution rate.

5. Bioavailability:[16]

The extent to which a medicine reaches the systemic circulation is measured by its bioavailability. The bioavailability increase of glutaric acid and 2-[4-(4-chloro-2 fluorphenoxy) phenyl]-pyrimidine-4-carboxamide (PPPA) cocrystals was studied in dogs. The AUC was found to be three times higher when the API was formulated in cocrystal form.

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 one of co-crystals' physicochemical qualities. It is the temperature at which the solid and liquid phases are in balance. When co-crystals develop, the melting point shifts and converges on the melting point of two separate molecules. If such data are obtained, the formation of co-crystals can be confirmed. This can be explained by using the examples of two cocrystal systems: the optically active form and the racemic form of 2-phenyl butyric acid and 2-phenyl propionic acid. These two compounds have been co-crystallized with isonicotinamide. When the melting point was measured, it was discovered that the racemic group had a greater melting point than the optically active form. This finding is consistent with the denser packing arrangement found in centrosymmetric space groups.

7. Melt (Hot stage microscopy): [18, 19]

Hot stage microscopy, commonly known as MELT, is an analytical technique that can be used to characterise cocrystals. The properties of cocrystals are characterised as a function of time and temperature. This analytical approach combines the features of microscopy and heat analysis, as the name implies. Image editing software, high-resolution colour cameras, and video-enhanced microscopy are some of the additional characteristics that allow for greater material characterisation. Other characterisation techniques, in addition to hot stage microscopy, are employed to validate transitions in a variety of ways. In the pharmaceutical business, hot-stage microscopy is used to confirm transitions detected using other techniques in a variety of ways. Hot stage microscopy can be utilised to evaluate crystal forms and hydrates as well as solid-state characterization of bulk medicines and other physiochemical properties. Because hot melt is a visual approach, its usage in conjunction with other characterization techniques such as DSC has increased the visual collecting possibilities. This visual approach is also essential to confirm transitions such as melts and recrystallization.

8. Scanning Calorimetry (DSC): [20]

In this characterization procedure, two specimens, one as the sample and one as the reference, are subjected to identical temperatures and an atmosphere that is heated or cooled at a regulated rate. The amount of energy necessary to achieve a temperature differential of zero between the two specimens is plotted and the results are evaluated. There are two kinds of DSC that are widely utilised. The first is the power compensation DSC, which keeps the two specimens in distinct identical furnaces. By adjusting the power input, the temperatures of both are rendered identical. As a result, energy is interpreted in terms of heat capacity or enthalpy. Another sort of DSC is where both sample containers are retained in the same furnace and are connected by a low-resistance heat flow route. The rest of the interpretation is the same.

9. XRD: [21]

This analytical technique employs phase identification to obtain unit cell dimension information. This is achieved through the constructive diffraction of a monochromatic X-ray and a crystalline material. The monochromatic beam is created by a cathode ray tube that has been filtered and collimated to produce monochromatic radiation before being directed towards the sample. In the case of sample preparation, the sample is finely processed to form a homogeneous sample and the average bulk composition is determined. In terms of d- spacing, the sample is examined. When a sample is presented in a random orientation, it produces a set of d-spacing. Because each mineral has a unique set of d-spacing, the sample is evaluated. The most critical need for all of this to occur is that the sample satisfy Bragg's law (n=2d sin), which connects the wavelength of electromagnetic radiation to the diffraction angle 2θ.

10. Vibrational spectroscopy (IR and Raman): [22]

With frequencies ranging from 4000 to 400 cm-1, electromagnetic radiation has been one of the most powerful techniques for determining organic structure. In organic chemistry, this electromagnetic radiation is known as infrared (IR) radiation, and its use is known as IR spectroscopy. The blasted radiations are absorbed by the interatomic bonds. As a result, in

different surroundings, a specific chemical bond will absorb varying radiations and at varying frequencies. As a result, their absorption information, which is presented in the form of a spectrum, aids in drawing some conclusions about what the structure may be.

VARIOUS EXAMPLES: [23, 25]

Caffeine and Methyl gallate: [24]

Caffeine and methyl gallate cocrystals were produced in a 1:1 ratio. The cocrystalization of these two was chosen since it was discovered that co-crystallization increased powder compaction qualities. Previously, when these two were crushed separately, the problem of lamination was discovered. In the instance of methyl gallate, the tablet tensile strength was very low (0.5 MPa) across the whole compaction pressure range. Almost all tablets have serious sticking and lamination as a result of this. Caffeine tablet ability was adequate, however when pressure was increased to more beyond 180 MPa, severe lamination was found. However, when these two cocrystals were suspended in ethanol in a 1:1 ratio, the tensile strength rose twofold. High elastic recovery and low elasticity were consistently related with poor tablet tensile strength. The cocrystal's high flexibility and tablet ability validated the selection criterion for the existence of slip planes in the crystal structure.

Carbamazepine (Tegretol®) and Saccharin:

The properties of crystallisation are superior to those of the individual API or its anhydrous state. However, it may not necessarily guarantee the same level of stability. As a result, only this form of carbamazepine: saccharin cocrystals was determined to be stable after various form screening, equivalent to the amorphous form. This cocrystal provides more physical stability. Further research on dog models revealed that these cocrysrals had enhanced pharmacokinetics, dissolving characteristics, and suspension stability. When the pharmacokinetic tests of the cocrystals were compared to the marketed tablet of Carbamazepine (Tegretol®), the cocrystals appeared to have a greater Cmax and comparable Tmax.

Co-crystals of Theophylline:

Theophylline cocrystals were created using a solvent evaporation process and four distinct conformers: glutaric acid, malonic acid, maleic acid, and oxalic acid. The stability of these four cocrystals was compared by exposing them to varying relative humidity (0, 43, 75, and 98 percent RH) and time points (1 day, 3 day, 1 and 7 weeks). After 7 weeks, it was discovered that theophylline anhydrate changed into theophylline monohydrate in cocrystals at 75% RH and lower. In any case, no theophylline hydrate was formed. The oxalic acid cocrystal was the least stable of the four cocrystals.

Curcumin & Methylparaben Cocrystals:[26]

Curcumin, derived from the Zingiberaceae family's Curcuma longa, has been shown to have anti-inflammatory and anti-cancer properties. As a result, it can be used as an alternate treatment for a variety of disorders. Curcumin's limited solubility, poor bioavailability, sluggish dissolving rate, and low absorption necessitated co-crystallization. Using solvent grinding, curcumin was co-crystallized (1:1) with methylparaben. The grinding was done manually in a mortar pestle for 30 minutes with 5 to 6 drops of ethanol added. PXRD, DSC, FT-IR, and SEM were used to characterise the cocrystals. For inhibitory investigations, pure curcumin at a dosage of 100 mg/kg and cocrystals were used. Curcumin had a 4.65 percent inhibitory activity, while cocrystals had a 66.67 percent inhibitory activity.

CONCLUSION:

Pharmaceuticals are a cornerstone of the healthcare business. As a result, developing a new type of delivery method or changing the API form to enhance or improve the qualities that impede its adoption presents a significant problem. As a result, in the instance of co-crystallization, it is a novel technology that can be utilised to overcome numerous physical, chemical, or physiological shortcomings in an API. In terms of formulation, co-crystallization provides a new field for developing a new way of preparation and characterization of API. As a result, it may present chances for industries seeking to assert intellectual property rights. Another difficult topic is the development of new strategies for filtering these API. According to the numerous publications evaluated, liquid-assisted grinding and neat grinding are preferred methods over solvent-based procedures. For APIs that cannot be transformed into salt form, cocrystals are the best choice. This is due to the lack of any ionic charge. As a result, in the situation of co-crystallization, which consists of only an API and conformers, can be utilised to improve the API's numerous features. Co-crystallization has established its presence in a variety of applications, including increasing solubility, pharmacokinetic characteristics, and stability.

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