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Stability and Bioavailability Enhancement of Drugs by Cocrystallization

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ABSTRACT
The main obstacles to the development of a novel product are the active pharmaceutical ingredient's poor water solubility and low oral bioavailability. Several strategies have been attempted to improve the solubility of medications that are poorly soluble in water, but the effectiveness of these strategies depends on the physical and chemical properties of the molecules being created. The development of new drug products with superior physicochemical properties, such as melting point, tablet ability, solubility, stability, bioavailability, and permeability, while preserving the pharmacological characteristics of the active pharmaceutical ingredient, is greatly facilitated by cocrystallization of drug substances. A coformer and an active medicinal ingredient are two components that are present in a cocrystal in a stoichiometric ratio and are linked by non-covalentinteractions.

Drug-drug cocrystal is becoming more and more popular nowadays. It provides a low-risk, low-cost, but high-reward path to developing new and improved medications, and it may enhance a drug's physiochemical and biologic capabilities by adding an appropriate therapeutic component without undergoingand chemical alteration.

KEYWORDS
Pharmaceutical Cocrystals , Cocrystallization , Solubility , Stability , Bioavailability**.**

I. INTRODUCTION

Several medications with limited aqueous solubility have been found in the recent years. About 60–70% of the molecules in these recently found medications belong to BCS Classes II (low solubility/high permeability) and IV (low solubility/poor permeability)[1,2]. Low water solubility of active pharmaceutical ingredients (APIs), which results in limited bioavailability of medications, has prevented the development of several APIs in formulations [3]. The gastrointestinal tract has different pH levels in each section, so drugs administered orally have varying degrees of solubility in gastrointestinal fluids at varying pH levels. As a result, the effectiveness and safety of medications cannot be properly assessed. Because of this, developing oral dosage forms is a significant problem due to the low solubility of drugs [4].

To increase a drug's solubility and increase its bioavailability, researchers have developed a number of strategies. Some methods for improving solubility include size reduction, solid dispersion, complexation, salt generation, nanoparticles, self-emulsifying drug delivery systems (SEDDS), inclusion of co-solvents, nano-suspension and emulsion, and cocrystalformation.of medicines with limited water solubility. Each methodology has advantages and disadvantages, and when choosing one, it is important to consider things like the qualities of the active pharmaceutical ingredient (API), the nature of the chosen excipients, the method of development, and the nature of the dosage form [5]. The cocrystals approach stands out from the rest of these methods because it does not alter the drug's pharmacological properties while potentially enhancing its bioavailability and a number of physicochemical properties, including melting point, tablet ability, solubility, stability, bioavailability, and permeability.

II. DIFFERENCE BETWEEN COCRYSTALS, SALTS, SOLVENTS AND HYDRATES

The cocrystal, salt, and polymorphs were denounced by the USFDA in the draught advice. The substances that exist in several crystalline forms, such

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as solvates or hydrates (sometimes referred to as pseudo polymorphs), as well as amorphous forms are referred to as polymorphs. Due to the varied crystal lattice arrangements in polymorphs, they also exhibit different physicochemical characteristics. The full proton transfer from one chemical to another is how salts are formed[18]. By transferring a proton from an acid to a base, salts and cocrystals can be distinguished from one another. Non-covalent interactions, such as hydrogen bonds, -stacking, and van der Waal forces, hold two components to one another.

The pKa value can be used to forecast whether cocrystals will form or not. It is generally agreed upon that cocrystals will develop when the pKa value is less than 0 and salts will form when the pKa value is greater than 3. Between pKa values of 0 and 3, this parameter cannot accurately predict the formation of cocrystals in solids, but as pKa rises, the likelihood of salt production increases[19,20]. Based on the physical state of the constituents, cocrystals and solvates can be distinguished from one another. Solvates are substances that are liquid at ambient temperature as opposed to those substances.

Solvates are substances that are liquid at room temperature, whereas cocrystals are substances that are solid at room temperature. Hydrates are solvates that have water as a solvent within their crystal lattice[21]. Solvates and hydrates can change the physicochemical properties of APIs and are frequently generated during cocrystallization via solution or liquid aided grinding[9]. Due to the solvent's presence in the crystal lattice, solvates have a different level of stability than unsolved forms. Due to the solvent/water loss at high temperatures and low humidity levels during storage, as well as the variable physiochemical characteristics between hydrated and dehydrated forms, solvates/hydrates are extremely unstable[22–24]. The solvated versions of spironolactone increased the drug's rate of dissolution[25]. Liquid aided grinding was used to create several polymorphic cocrystals and solvates of caffeine and anthranilic acid using various solvents[26].

- **ADVANTAGES**

Several methods, including as salt creation, micronization, solid dispersion, amorphous medicines, and encapsulation, can be used to customise the physicochemical properties of medications. Cocrystals should have the benefit of being in a stable crystalline state and not requiring additional excipients or additives in formulations among all of these[21]. The characteristics of APIs and coformers, the type of molecular interaction that occurs between them, and the synthetic techniques used all have a significant impact on the physicochemical attributes. The main benefit of creating cocrystals is that, although maintaining their pharmacological effects, the APIs' physicochemical properties will be improved due to the inclusion of the conformer in the crystal structure which is a part that alters property. The effect on the API's physicochemical qualities depends on the conformer that is available [16, 24, 27, and 28].

The fact that cocrystals can be created for complex pharmaceuticals with sensitive functional groups that might not withstand the harsh reaction conditions of strong acids or bases [12,28] and for non-ionisable APIs gives them an additional edge over the more prevalent salts. The creation of cocrystals has a number of other primary benefits. The time it takes for APIs to produce new drugs may be sped up using cocrystals. Reduced costs as a result of shortened development timeframes appeal to pharmaceutical corporations.

Cocrystal solid-state synthesis processes can be categorised as green chemistry because they have a high yield, don't utilise solvents, and produce few by-products. Pharmaceutical cocrystals differ structurally from their bulk counterparts, and they may be patented as a new crystal form together with existing APIs. As examples of various pharmaceutical cocrystal formulations on the market, mention should be made of Viagra (Pzer), which is used to treat erectile dysfunction and pulmonary arterial hypertension, Entresto (Novartis), which is used to treat chronic heart failure, and some other formulations that are still in the clinical development stage[12,14,16,24,28]. These properties are highlighted here with appropriate examples. Pharmaceutical cocrystals can improve the physicochemical characteristics of drugs, such as melting point, tablet ability, solubility, stability, bioavailability, and permeability.

- **SOLUBILITY**

To examine the formulations of poorly soluble medications, solubility is a key characteristic. Cocrystallization has been utilised by various researchers[37-41] among other methods to increase the solubility of pharmaceuticals, including salt creation, solid dispersion, particle size reduction, and others[23]. By synthesising salts and cocrystals instead of the antifungal drug ketoconazole, solubility was increased by 53 and 100 times, respectively. As a

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result, co-crystal formulation produced a higher solubility of the drug than salt formulation [37].

The amount of apixaban crystals was increased by about two times, and crystals demonstrated quicker dissolution than pure drug[38]. The solubility of pterostilbene-piperazine cocrystals was increased six times, whereas the drug quickly precipitated in pterostilbene-glutaric acid cocrystals due to the high solubility of glutaric acid[39]. 6-mercaptopurine cocrystals with nicotinamide had a two-fold greater rate of dissolution than the medication alone[40]. The solubility of cocrystals in pure solvent was determined using a theoretical method based on Keu (the ratio of solution concentrations of cocrystal components at the eutectic point), which is also a useful tool for cocrystal selection and formulation without the material and time requirements of conventional methods[42].the cocrystals solubility ratio and solution chemistry by using a set of more than 40 cocrystals and solvent combinations[43]. In one work, equations for cocrystals with acidic, basic, amphoteric, and zwitter-ionic competents were derived [12, 44] that explain cocrystal solubility in terms of product solubility, cocrystal component ionisation constants, and solution ph.

- **STABILITY**

An in-depth analysis of solubility is crucial when creating new dosage forms. Many stability tests, including relative humidity stress, chemical stability, thermal stability, solution stability, and photo stability study, should be carried out throughout the creation of pharmaceutical cocrystals. Automated water sorption/desorption tests are carried out under relative humidity stress to ascertain the impact of water on the formulation. Cocrystal behaviour under relative humidity stress conditions was investigated by several researchers[41,45–47]. Cocrystals of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide and glutaric acid displayed 0.08% moisture at high 95% RH and were proven to be stable under various circumstances[41]. Little water sorption was observed in indomethacin-saccharin cocrystals during relative humidity experiments, and no dissociation or transformation took place under experimental conditions[45].Theophylline cocrystals with several coformers (oxalic acid, malonic acid, maleic acid, and glutaric acid) showed relative humidity stability behaviour at various RH (0, 43, 75, and 98%) during various time periods (1 d, 3 d, 1 w and 7 w). The outcomes demonstrated an improvement in the stability and physical properties, particularly by preventing hydrate formation[47].

Any alteration or chemical deterioration should be noted during chemical stability studies be examined primarily under accelerated stability conditions in the formulation. The literature contains very few reports on the chemical stability of cocrystals. Cocrystals of glutaric with an API did not degrade and shown excellent chemical stability over a two-month period at various temperatures (40°/75% RH and 60°)[41]. At varied circumstances (5, 40, and 60° at ambient humidity and high RH stability at 25°/60% and 40°/75% RH) for 2 mo., carbamazepine and saccharin cocrystals demonstrated good chemical stability[48]. Based on accelerated stability conditions, high temperature stress can also be used to predict the physical and chemical stability. Thermal stability was a topic that few researchers explored[49,50]. When heated by DSC, paracetamol cocrystals containing 4,4-bipyridine displayed greater stability than other coformers[49].At several stoichiometries ranging from 0.3:1.0 to 0.9:1.0, the thermal stability of cocrystals (L-883555, a phosphodiesterase IV inhibitor) with tartaric acid was investigated. Since acid content can occupy the crystal's channels and create various binding modes, cocrystals with stoichiometries of 0.5:1.0 were discovered to be the most stable[50].

Solution stability is a crucial factor in the formation of cocrystals since it may be used to gauge the stability of the solution. Studies on solution stability help to better understand how cocrystals behave in release media[16]. A 20–48 hour study of the behaviour of carbamazepine cocrystals in water revealed that the cocrystals with high water soluble coformers transformed into dihydrates, whilst the cocrystals with low water soluble coformers remained as such in the solution[51].When materials were slurried in water at room temperature for two days, no significant change in their physical form was noticed[52]. Caffeine/oxalic acid cocrystals also displayed better stability than others at all RH up to 98% for seven days. By mixing equal amounts of the two substances in water, the stability of the cocrystals of carbamazepine and saccharine was tested. After 24 hours, powder X-ray diffraction (PXRD) analysis revealed that only the cocrystals were present in the solution; no other form was found[48]. A photo stability research is conducted to examine how light affects medications that are sensitive to light. For these kinds of medications, photo stability research is crucial because many pharmaceuticals are unstable under light. The literature contains very few reports on the chemical stability of cocrystals. In comparison

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to the pure drug and physical mixture, the photo stability of nitrofurantoin cocrystals with various coformers was higher. After 168 hours, all but one of the cocrystals showed minimal degradation (3%), indicating that cocrystallization can stop the photo degradation of light-sensitive drugs.

- **BIOAVAILABILITY**

The amount and pace at which a pure medicine enters systemic circulation is known as bioavailability[54]. The creation of novel formulations faces a significant hurdle due to the low oral bioavailability of APIs. The principal application of crystal engineering is the design and synthesis of pharmaceutical cocrystals with improved oral bioavailability and aqueous solubility. The oral bioavailability of apixaban-oxalic acid cocrystals was shown to be 2.7 times higher than that of the pure drug in a pharmacokinetics investigation in beagle dogs[38]. By creating cocrystals with nicotinamide, baicalein's oral bioavailability was increased. Rats treated with cocrystals had 2.49 times higher peak plasma concentrations (Cmax) and 2.80 times higher areas under the curve (AUC) than those treated with the drug alone[55].

In rats, meloxicam cocrystals with aspirin demonstrated a 12 times faster onset of action than the pure drug and had a better oral bioavailability than the pure drug[56]. Rats' oral bioavailability of 6-mercaptopurine, a BCS Class-II medication, was higher in cocrystals, at 168.7%, than in pure drug[40].

- **PERMEABILITY**

Drug permeability across the cellular membrane is a major factor in drug absorption and distribution. Drug permeability is primarily influenced by the n-octanol/water partition coefficient, which may be calculated using log P and (C log P) for the drug's unmodified form[28]. The cocrystallization of a BCS class-III medication, 5-uorouracil, with various coformers, such as 3-hydroxybenzoic acid, 4-aminobenzoic acid, and cinnamic acid, increased the drug's permeability[57]. Permeability study of hydrochlorothiazide and cocrystals with different coformers was studied by using Franz diffusion cells. With the exception of succinamide crystals, all cocrystals contained more drug ux than the pure substance. Because of the creation of a heterosynthon between the drug and coformer, the permeability of cocrystals was increased[58].

III. SELECTION OF COFORMERS AND SCREENING OF COCRYSTALS

An API and a co-crystal former are two neutral molecules that are combined into a single crystalline solid to form a pharmaceutical co-crystal. An excipient or another medication could be the co-crystal former[59]. A list of thousands of substances that could be used as potential coformers for pharmaceutical cocrystals has been kept on file by the USFDA[60]. The non-API component that is employed as a coformer must be non-toxic and free from side effects.

The cocrystal former should ideally be authorised as generallyregarded as Safe (GRAS) or be listed on the US FDA's "Everything added to food in the United States" (EAFUS) list, which contains approximately 3000 compounds that are appropriate as food additives [61]. The choice of a coformer for an API is crucial for developing and screening cocrystals. The two methods used to select coformers are experimental methods and knowledge-based methods. All sorts of coformers for an API and to confirm the structure of cocrystals are typically utilised in a hit-and-miss manner; they are distinguished by acceptable procedures. This method is time- and money-consuming. Researchers have employed a variety of knowledge-based strategies for the selection of appropriate coformers and the screening of cocrystals, including the following ones: the hydrogen-bonding propensity, syntonic engineering, supramolecular compatibility by Cambridge Structure Database (CSD), pKa based models, Fabian's method, Lattice energy calculation, the conductor-like screening model for real solvents (COSMO-RS), Hansen solubility parameter, and virtual cocrystal screening (based upon molecular electrostatic potential surfaces-MEPS), thermal analysis, measuring saturation temperature, Kofler contact method and matching[10,62].

Van der Waal forces, hydrogen bonds, and other non-covalent bonding mechanisms are used to interact between cocrystals, API, and coformers. Among all of these, API-coformer hydrogen bonding is crucial for the development of cocrystals[7,8]. Every hydrogen molecule that is acidic in nature will be present in bond formation, all hydrogen bond acceptors will be used when there are hydrogen bond acceptors available, and hydrogen bonds will be formed when there will be the best hydrogen bond donors and hydrogen bond acceptors, according to Etter's description of a graph-set notation system[6].

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Etter also proposed three rules for preferable hydrogen bond formation.

IV. SYNTHONIC ENGINEERING

The "synthon approach" for the selection of coformers which formed a supermolecule.

By using specie molecular fragments within the cocrystal to establish "supramolecular synthons" [8]. A coformer with the appropriate functional group will be employed for a certain API, and the functional groups present in the API and coformer will play a significant role in the creation of cocrystals. Super molecules contain synthons, which are fundamental structural elements connected by non-covalent bonds. There are two different types of supramolecular synthon approaches: supramolecular homosynthons and supramolecular heterosynthons. In contrast to supramolecular heterosynthons, which are created by distinct functional groups like carboxylic acid-amide heterosynthons and acid-pyridine heterosynthons, supramolecular homosynthons are made up of the same functional groups that are present in API and coformer. In general, supramolecular heterosynthons are preferred over homosynthons; for example, acid-amide and acid-pyridine heterosynthons are more frequently utilised than carboxylic acid and homodimers [22].

V. HYDROGEN BONDING PROPENSITY

API and coformers interact with one another in cocrystals by non-covalent interaction, such as hydrogen bonds and van der Waal forces. Among all of these, API-coformer hydrogen bonding is crucial for the development of cocrystals[7,8]. Every hydrogen molecule that is acidic in nature will be present in bond formation, all hydrogen bond acceptors will be used when there are hydrogen bond acceptors available, and hydrogen bonds will be formed when there will be the best hydrogen bond donors and hydrogen bond acceptors, according to Etter's description of a graph-set notation system[6]. Etter also proposed three rules for preferable hydrogen bond formation. A value between 0 and 1 was assigned to the quantitative measurement of hydrogen bond creation between donor and acceptor functional groups contained in indomethacin and isonicotinamide, and a greater value indicated the establishment of a hydrogen bond[63].A value between 0 and 1 was assigned to the quantitative measurement of hydrogen bond creation between donor and acceptor functional groups contained in indomethacin and isonicotinamide, and a greater value indicated the establishment of a hydrogen bond[63].

VI. PKA VALUE

Proton transfer between an acid and a base can be used to anticipate the development of crystals or salts. By calculating the pKa=[pKa (base)-pKa (acid)], salt or cocrystal formation can be predicted. It is generally agreed that if the difference between the pKa values is higher than 2 or 3, proton transfer will take place from acid to base. Cocrystals develop when the pKa value is lower (less than 0), whereas salts form when the value is greater (more than 2 or 3)[19,20]. By analysing 6465 cocrystals from the CSD, the pKa rule was validated and quantified, and it described a linear link between the pKa value and the likelihood of proton transfer between acid-base pairs. When pKa-1 was calculated, it was determined that a non-ionized complex should develop; an ionised complex is formed when the value of $\Delta pKa<4$ and the possibility of formation of ionized complex increase by 17% by increase in ΔpKa by one unit from 10% at $\Delta pKa=-1$ to 95% at $\Delta pKa=4$. By determining the ΔpKa value, the possibility of formation of cocrystals and salts can be determined. This is a simple and less time-consuming method for the preparation of cocrystals[64].

VII. HANSEN SOLUBILITY PARAMETERS

Another crucial method for assessing the miscibility of drugs and coformers used in cocrystal systems is the Hansen solubility parameter. The development of cocrystals may be predicted by the miscibility of the components in the solid state. The use of components with similar miscibility increased the success rate of the cocrystal synthesis[67]. It was demonstrated that the two components should be miscible if total HSPs difference2017was <7MPa0.5, otherwise immiscible[68]. Another method estimates the miscibility of two components if the difference is ≤5 MP0.5 between two substances which are supposed to be cocrystal formation[69,70].

VIII. DIFFERENT METHODS OF COCRYSTALS FORMATION

Researchers have documented a variety of strategies for creating cocrystals up to this point. For the production of cocrystals, only a few conventional techniques based on solution and grinding were reported[81]. Cocrystals are created using the solution process and an appropriate type of solvent. With appropriate examples, many solution methods are reviewed, including solvent evaporation[76], solution crystallisation technique[41], antisolvent addition[82], slurry conversion method[83], and reaction

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crystallisation method[84]. There are two different types of grinding processes: plain grinding and solvent drop grinding[85, 86]. Ultrasound aided solution method[87,88], supercritical uid atomization technique[46,89], spray drying technique[90,91], and hot melt extrusion technique[92,93] are some recently developed techniques utilised to create cocrystals.

IX. SOLUTION - BASED METHOD

In the solvent evaporation approach, the coformer and API are both dissolved in an appropriate solvent, and the solvent is then gently evaporated from the solution. The functional groups in the medication and conformer engage with one another during dissolution to create hydrogen bonds[89]. Researchers most frequently use this technique to create cocrystals[79,94]. Drugs and coformers are dissolved in a solvent that is boiling while being stirred, and the boiling of the solution is continued until the volume of the solution becomes minimal.

The boiling solution crystallises quickly after cooling for about 15 minutes. Cocrystals are divided by filtration and dried in an oven or in the open air[41,95]. The process of creating slurry through the addition of various solvents to a mixture of an API and suitable coformers is known as slurry crystallisation. After the solvent has been decanted, the solid material is dried and subjected to various evaluation techniques. When the drug and coformer need to be stable in the solvent, this approach is chosen for the creation of cocrystals[29,83,96,and 97]. In the antisolvent addition approach, API is distributed in the coformer solution using a dispersion homogenizer after the coformers have been dissolved in various solvents, such as organic solvents. This solution is then added to distilled water or suitable solution to precipitate the coformer on the drug[82,98,and 99].

The quick creation of cocrystals at microscopic and macroscopic scales using the reaction crystallisation method relies on the solubility of the cocrystal components for cocrystallization and nucleation. The more soluble component (coformer) is added in a quantity that is just below its solubility limit after the saturated solution of the less soluble component (drug) has been created in methanol and altered. The intention is to avoid starting solutions that contain any extra medication or coformer that can be mistaken for a cocrystal. The cocrystals that precipitate out of solution are also pure since they do not exceed the solubility limits of the constituents. Throughout the crystallisation process, solution concentrations are measured by HPLC to determine whether the solid that was seen looked to be a complex of the reactants (cocrystals). Moreover, the solid precipitates are gathered and subjected to HPLC analysis to ascertain the complex's stoichiometry. DSC, TGA, and PXRD are used to further describe the solid if the HPLC results indicated that it appeared to be a cocrystal[84,100,101].

X. GRINDING METHOD

Over the past few years, grinding techniques have been used extensively for the formation of cocrystals and have been found to be superior to other techniques (solution or melt)[85, 86]. There are two different sorts of grinding methods: neat or dry grinding and wet grinding. In dry grinding, the medication and the coformer are combined in a stoichiometric ratio and pulverised using a ball mill or a mortar and pestle[102]. By adding a few drops of solvent to the mixture, wet grinding was carried out similarly to neat grinding[103,104].

XI. ULTRASOUND ASSISTED SOLUTION COCRYSTALLIZATION

For the creation of Nano crystals, or cocrystals of extremely small size, a son chemical approach has been developed[87]. The API and cocrystal former are dissolved together in a solvent in this process, and the resulting solution is then maintained in a son reactor to make it turbid. To keep the sonicator's temperature consistent and avoid fragmentation, cold water is provided during sonication. The solution is allowed to dry overnight. This technique produced pure cocrystals, and X-ray diffraction analysis can be used to evaluate the purity of cocrystals[88]. Supercritical atomization method: In the supercritical atomization method, the drug and coformers are combined by using x-ray diffraction study [88].

XII. SUPERCRITICAL FLUID AUTOMIZATION TECHNIQUE

In the supercritical atomization process, CO2, a highly compressed supercritical fluid, is used to combine the medication and coformers. By atomizing this solution with an atomizer, cocrystals are created. In the supercritical antisolvent (SAS) approach, the antisolvent action of the supercritical fluid is used to form cocrystals from solution[46,89,105].

XIII. SPRAY DRYING TECHNIQUE

Cocrystals are made via spray drying, which involves evaporating the solvent from a solution or suspension containing the medication and the coformer. This technology is the most popular since it

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uses a quick, continuous, and one-step approach. In order to prepare and scale up cocrystals, a special environment will be provided by the spray drying process[90,91].

XIV. HOT MELT EXTRUSION TECHNIQUE

By heating the drug and coformers while vigorously combining, the hot melt extrusion approach produces cocrystals that have better surface interactions without the use of a solvent. The coformer and API both need to be miscible in molten form for this approach to work properly, therefore thermo labile medicines cannot be used[29,92,93].

XV. EVALUATION OF COCRYSTALS

The compatibility research between drugs and coformers and intermolecular interactions are predicted using FTIR spectroscopy. The prediction of compounds' chemical conformation is frequently done using this method. By analysing the role of the carboxylic acid in the creation of the hydrogen bond, Aakeroy et al.[106] employed FTIR to identify cocrystals from salts. FTIR is used to analyse pure drugs, coformers, physical mixtures, and cocrystals in the 400–4000 cm-1 range. For the purpose of screening the cocrystals, FTIR study is also performed in conjunction with other methods like DSC or XRD[12,76,107].

Cocrystal formation screening has been done using DSC. The presence of an exothermic peak followed by an endothermic peak in the DSC spectrum can be used to screen for the production of cocrystals. These peaks in the physical admixture of the constituents suggest the potential for cocrystal formation. Weighed out (1.5-2.5 mg) in aluminium pans, the pure drug, coformer, physical combination, and cocrystals were then analysed at heating speeds ranging from 5 to 30 degrees using a corresponding empty pan as a reference. The inert atmosphere was maintained by nitrogen gas flowing at a rate of 50 ml/min. DSC can be used to determine endothermic or exothermic behaviour, melting point, glass transition temperature, polymorphic character, heat of fusion, and more[73,75,98].

Thermal analysis is used to determine the physical and chemical properties of solids as a function of temperature increase (with constant heating rate) or as a function of time (with constant temperature and/or constant mass loss). The temperature of sublimation or decomposition as well as the presence of volatile components can all be determined using the TGA technique. TGA analysis helps forecast cocrystal purity, thermal stability, and compatibility. The weight decrease of the sample mass during TGA analysis is a sign of volatile component loss or cocrystal decomposition[61,108].

For the characterization of cocrystals, terahertz time-domain spectroscopy (THz-TDS) is an alternate method to PXRD. Terahertz spectroscopy can discriminate between racemic and chiral supramolecular structures[12]. Theophylline cocrystals with several coformers, including malic acid and tartaric acid, which were present in chiral and racemic forms, were distinguished using terahertz spectroscopy[109].

Solid phases that cannot be examined by SXRD are characterised using solid-state NMR (SSNMR)[12]. SSNMR was utilised to examine the complexity of the complex by measuring the proton transfer rate. In order to identify crystals or salt, SSNMR is a crucial instrument. By calculating hydrogen bonds and local conformational changes caused by couplings, SSNMR can also be employed to assess the cocrystal structure[110,111]. For screening and determining cocrystal structure, PXRD is frequently used[89]. For the purpose of analysing the structure of cocrystals, the PXRD patterns produced from diffractometers were compared to one another.

The different PXRD pattern of cocrystals from their components is the indication of cocrystal formation [103,112].

Cocrystal single crystal X-ray diffraction is used to determine the atomic level crystal structure of substances (SXRD). The main issue with this method is that it is typically unable to produce a single cocrystal that is acceptable for SXRD analysis[12]. Cocrystal morphology examination and particle size determination are done using a scanning electron microscope. Atoms that contain information about the topography of the sample surface are scanned by high intensity electron beams[12,45,46].

Dissolution studies are used to calculate the rate of drug release over time in the dissolution medium and forecast how well the formulation will work in vivo. The dissolution apparatus can be used to carry out cocrystal dissolution research. The appropriate dissolution medium is given in the drug protocol of the relevant pharmacopoeia, and this is where the cocrystal dissolution studies can be carried out. The drug samples can be collected in an appropriate amount at a predefined interval and evaluated using the appropriate tools, such as HPLC or UV [113,114].

The Higuchi and Connors method for solubility determination can be used to evaluate solubility studies. It is possible to determine the

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solubility of pure drugs, physical mixtures, and Cocrystals in water or other suitable media listed in the referred pharmacopoeia. The drug sample and medium should be combined in a conical flask, and the flask should be agitated on a rotary shaker for 24 hours at room temperature. If the medicine is light-sensitive, the entire sample should be shielded from light by wrapping it in aluminium foil. Samples are filtered using Whatman filter paper after 24 hours, and aliquots are then appropriately diluted and tested using HPLC or UV light at the appropriate wavelength [115,116].

Information on the shelf life of pharmaceutical items under various storage settings is provided via stability studies. The storage of pharmaceutical goods in glass vials under varying environmental conditions (such as humidity, temperature, and light) for varying lengths of time is recommended. The samples are next examined for thermal analysis, drug release analysis, XRD analysis, and FTIR analysis, and the results are compared to those from the stability research that came before [98].

XVI. APPLICATION

The physicochemical qualities of medications can be improved through cocrystallization without affecting their molecular structure. The API and particular project will determine whether Cocrystals or salts will have the desired characteristics.

In some cases, salts offer superior physicochemical characteristics over Cocrystals, such as salts having a higher inherent solubility in water. When dissolved, Cocrystals with negative pKa values will produce non-ionized drugs while salt will produce ionised API, which is more water soluble. Cocrystals can be preferable to salt forms of drugs when dissolution rate rather than equilibrium solubility should be a consideration. A different method to improve the solubility and bioavailability of pharmaceuticals that are poorly water soluble is cocrystallization, especially for substances that are neutral or weakly ionised in nature [12, 20, and 37]. Moreover, as described in earlier sections, cocrystallization offers the potential to change and improve the melting point, tablet ability, solubility, stability, bioavailability, and permeability.

XVII. FUTURE PERSPECTIVES AND CHALLENGES

The increase of the physicochemical properties of pharmaceuticals while conserving the pharmacological qualities of the API can be accomplished through crystallisation. One of the main obstacles in the creation of pharmaceutical cocrystals is the selection of coformer's thafuture perspectives and challengesselection and cocrystal screening have been done in a variety of ways, but each method has drawbacks. These substances, which are recognised as GRAS by the USFDA and the EAFUS database, should primarily be employed as coformers, albeit the GRAS designation does not ensure their usage as cocrystal forming agents. In the development of cocrystals, stability in the presence of excipients is also a problem; at the moment, this is an unknown area.

The scaling up of the manufacture of high purity cocrystals has certain significant drawbacks that make it an unappealing option for industry. Guidelines for the pharmaceutical sector on the patenting of cocrystals were published by the US-FDA in 2011. The FDA classified cocrystals as a drug product intermediate, not a novel API, but rather as an "API excipients" molecular complex. Nonetheless, according to EMA, cocrystals should follow the same rules for documentation as salt. As a result, even if the US-FDA and EMA have distinct regulatory philosophies, it does show the growing interest in using pharmaceutical cocrystals as prospective marketable pharmaceuticals. It takes a lot of time and effort to develop, test, and evaluate new drug cocrystals; however, as mentioned in other sections [10, 24,116], some researchers have employed knowledge-based methodologies for conformer selection, crystal design, and screening. Pharmaceutical cocrystals can only be expected to strengthen their hold on medication development as cocrystal research continues to expand and new drug products based on it hit the market.

Low medication bioavailability and poor water solubility are important obstacles in the development of oral formulations. Among the many methods for overcoming these difficulties, the use of cocrystals has the distinct advantage of maintaining the drug's pharmacological qualities while gaining the benefits of the conformer's physicochemical properties. The main benefit of using cocrystals over salts is that they can be utilised for medications that are either poorly or never ionisable by nature. Therefore, in addition to straight forward formulation techniques, cocrystals have the potential to improve melting point, tablet ability, solubility, stability, bioavailability, and permeability. A combination of knowledge-based and experimental methods for conformer selection offer a new era in cocrystal formation because the cocrystals approach has not yet

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received much attention. Due to their improved pharmacological benefits and shortened medication development time, pharmaceutical crystals are gaining increasing industrial interest.

XVIII. CONCLUSION

By carefully choosing coformers, crystallisation is one of the noble methods for increasing the many aspects of active medicinal substances, including stability, solubility, micrometric properties, dissolution bioavailability, and pharmacokinetic properties. According to the United States Food and Drug Administration's guidelines, the coformers chosen must not have any toxic effects on the drug. The methods utilised to manufacture cocrystals must be simple, secure, marketable, environmentally friendly, and effective. Moreover, cocrystals offer important qualities including an increase in the permeability of medications with low solubility and a better tableting capability for drugs with weak tablet forming properties.

XIX. ACKNOWLEDGMENT

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