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RECENT ADVANCES IN THE SYNTHESIS AND APPLICATIONS OF PHARMACEUTICAL CO-CRYSTALS: A COMPREHENSIVE REVIEW

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ABSTRACT

Pharmaceutical cocrystals have become a cutting-edge field of study, providing creative ways to improve medication qualities and get around formulation problems. The use of pharmaceutical cocrystals to modify the physicochemical properties has drawn attention in recent years due to the prevalence of poorly soluble APIs that exhibit poor and inconsistent bioavailability. In order to successfully develop the formulation with the desired pharmacokinetic profile, co-crystallization approach was established for adjusting the solubility, permeability, and processability of APIs by introducing another compatible molecule or molecules into the crystal structure without affecting its therapeutic efficacy. Co-crystals are multi-component systems in which a coformer and an active medicinal ingredient are bonded together in the crystal lattice by non-covalent interactions and are present in a stoichiometric ratio. The cocrystals exhibited improved solubility, dissolution rate and bioavailability indicating of potential of co-crystallization as a strategy to improve the therapeutics efficacy of the API.

KEYWORDS: Co-crystals, Physiochemical properties, Coformer.

INTRODUCTION

Creating a novel dosage form from a novel chemical entity is a difficult procedure. It includes both exploratory and strategic research in the choice and creation of medical products. On the other hand, for the molecule to meet the necessary requirements, it must pass several developmental phases. Prior to clinical trials, incomplete knowledge about its characteristics and pharmaceutical production capabilities may result in difficult and expensive issues later on. In these situations, it was discovered that enhancing the current molecules was more advantageous than creating a new one. The majority of Active Pharmaceutical Ingredients (APIs) in solid state exist primarily in two morphological forms: crystalline and amorphous.[1] Because crystalline materials are naturally stable and because crystallisation processes have a reported effect on the purification and isolation of chemical substances, chemists and engineers working in the pharmaceutical industry typically aim to supply crystalline forms of their active compounds.[2] It is commonly recognised that the molecular arrangement within crystalline materials determines its basic physical properties. Changing the location or the interactions between these molecules can, and typically does, directly affect the specific solid's properties. To change the chemical and physical solid-state characteristics of APIs, solid-state chemists currently employ a range of diverse tactics, including the creation of salts, polymorphs, hydrates, solvates, and cocrystals.[3] A drug's solubility and rate of dissolution play a significant role in determining its effectiveness and activity. These screens have led to the discovery of progressively bigger, lipophilic lead compounds. Therefore, employing various techniques to reduce issues with the permeability and solubility of lipophilic medications is necessary in the modern era. The researchers have described a number of methods to improve the solubility of APIs, including the use of surfactants, polymorphs, nanoparticles, solid dispersions, size reduction, inclusion complexes with cyclodextrins, salt formation, self-emulsifying formulations, and multicomponent molecular crystals.[4] Each of the aforementioned methods has advantages and disadvantages of its own, but the particular physicochemical characteristics of the polymers and APIs will always determine the success rate. Physical modification is frequently employed to increase the surface area of the particles, enhance the powder's solubility and/or wetting, and boost an API's stability. Especially in the pharmaceutical industry, multi-component crystals such solvates, hydrates, cocrystals, and salts are essential for the design of novel solids. To increase their solubility, weakly water-soluble medications can be produced as crystalline solid formulations, amorphous forms, or lipid formulations. Using co-crystallization in crystal engineering is a potentially effective way to address drug-related issues.[5]

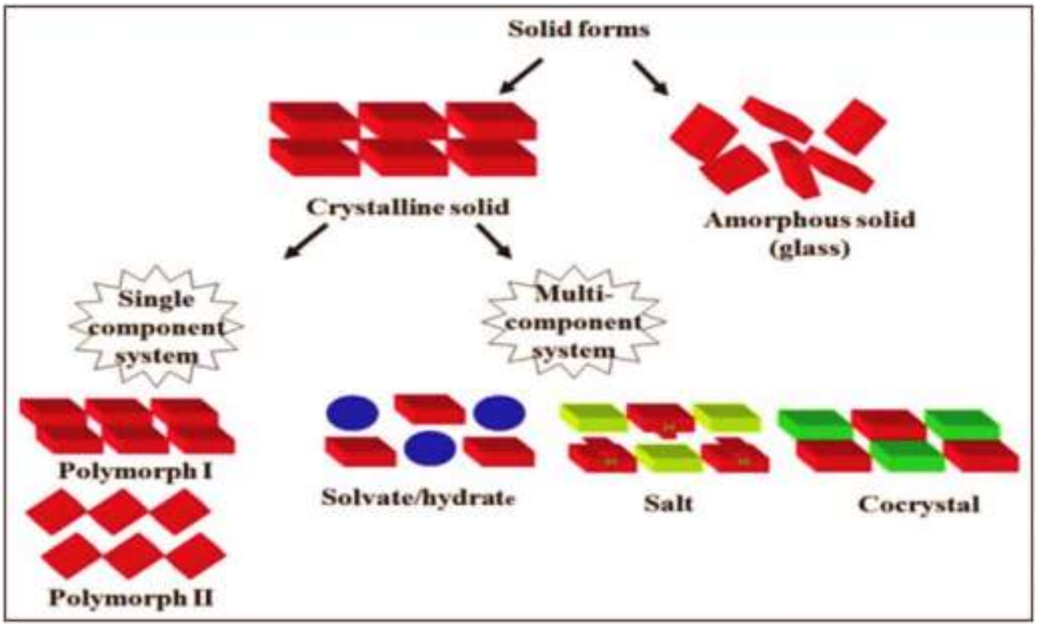

Fig. 1: Different possible solid-state pharmaceutical multicomponent systems.

Cocrystals

Cocrystals are defined by the US Food and Drug Administration (FDA) as crystalline solids made up of two or more distinct molecules in the same crystal lattice, usually drug and cocrystal formers, or "co-formers" for short. Opportunities to construct solid state forms of an active pharmaceutical ingredient (API) beyond traditional solid-state forms, including salts and polymorph, have been made possible by pharmaceutical cocrystals. This includes modifying medications so as to change their solubility or other physical characteristics without changing their pharmacological effects. The FDA further stated that cocrystals can be engineered to improve the stability and bioavailability of pharmaceutical products, hence improving the processability of APIs during the manufacturing process. Quinhydrone, a 1:1 cocrystal between benzoquinone and hydroquinone, was the first cocrystal to be synthesised, according to the literature.[6]

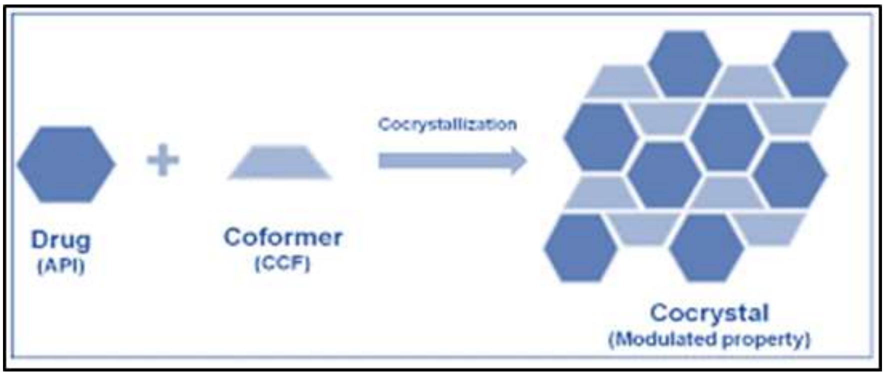

Figure 2: Schematic representation of co-crystal formation.

Pharmaceutical co-crystals can be divided into the following categories based on the components' respective medicinal activities

- Single drug co-crystals: The co-crystal former, also referred to as the coformer, and APIs are present in these co-crystals. The FDA provides lists from which pharmaceutical coformers are chosen. These lists include the names of all materials that are deemed safe for use in the food and medicine industries; these materials are referred to as generally regarded as safe (GRAS).[7]

- Multidrug co-crystals: They often have a stoichiometric ratio and include two or more APIs. A solid single phase multi-component system of this kind may enhance the solubility, dissolution rate, and bioavailability of at least one of the two APIs molecules in addition to providing synergistic effects because the two medicines are present in the same crystal lattice.[8]

Advantage of cocrystals

I. **Increase aqueous solubility:** Cocrystals can make medicines more soluble in aqueous environments, increasing their bioavailability and therapeutic effectiveness.

II. **Tailored drug release:** Cocrystals can be designed to have specific properties that match the needs of a particular drug. This is achieved by selecting a co-former molecule that can form strong intermolecular interactions with the drug molecule, such as hydrogen bonding or π-π stacking. The resulting cocrystal can then have enhanced solubility and bioavailability compared to the original drug molecule.

III. **Improved stability:** Cocrystals can improve the stability of the drug molecule by protecting it from degradation and oxidation. This is because the co-former molecule can act as a protective shell around the drug molecule, preventing it from coming into contact with moisture and other environmental factors that can cause degradation.

IV. **Easy preparation:** Cocrystals can be easily prepared using a variety of techniques, including grinding, solvent evaporation, and spray drying. This makes them a practical and scalable approach for drug development. Additionally, cocrystals can be prepared without the need for specialized equipment or expensive processes, which can help to reduce the cost of drug development.[9]

V. **Better taste:** Cocrystals can improve the taste of bitter drugs by masking their unpleasant taste. This is because the co-former molecule can interact with the drug molecule and reduce the bitterness of the drug. This is particularly important for paediatric and geriatric patients who may have difficulty swallowing tablets or capsules.

VI. **Reduce toxicity:** By reducing the effective dose necessary for therapeutic effectiveness, cocrystals can lessen the toxicity of drugs.[10]

Pharmaceutical cocrystals design strategies

Solid APIs and co-formers come in a variety of forms, but not all of them are suitable for the production of co-crystals. Researchers can estimate the production of co-crystals from chosen or accessible APIs and/or co-formers using a variety of theoretical, experimental, and computational data-based programme approaches.[11] Pharmaceutical cocrystals have emerged as a promising new class of API solids with many advantages. Much effort has been paid to the study of crystal engineering and design strategies that facilitate the formation of cocrystals of APIs and crystal formers. Pharmaceutical crystal creation and design is a multi-step procedure. To create a desirable cocrystal product from an API with limited water solubility, one must first analyse the structure of the target API molecule and determine which functional groups can interact with the appropriate co-formers intermolecularly. Intermolecular interactions include the most common hydrogen bonding, p-p stacking, and van der Waals forces.[12]

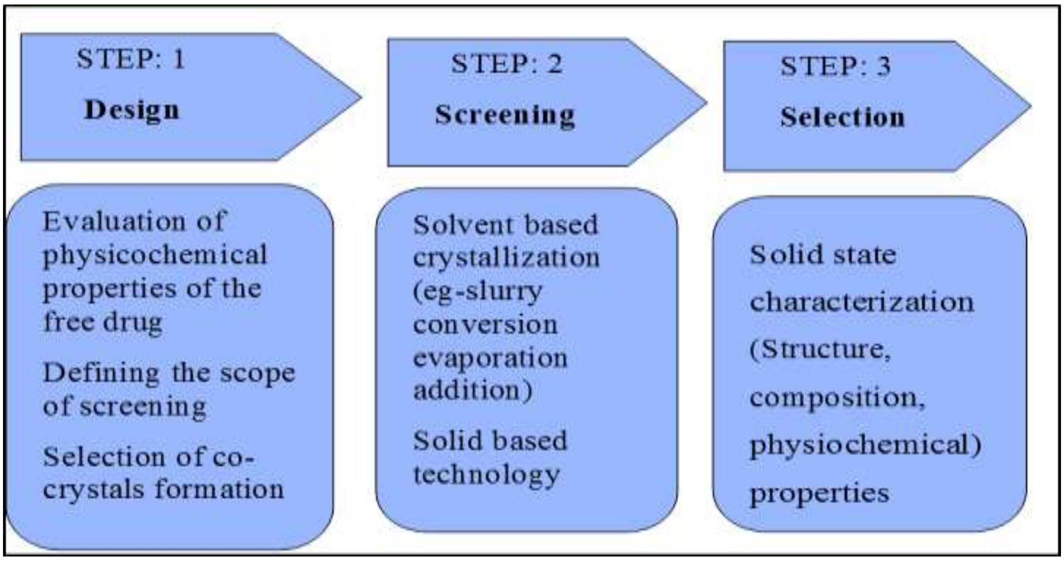

Figure 3: A general guideline for cocrystal Design and Screening.

Co-former selection: One of the main difficulties in creating pharmaceutical crystals is choosing co-formers that work with a certain API.[13] The supramolecular synthon, Hansen solubility parameter, Cambridge Structure Database (CSD), pKa-based models, hydrogen bonds, Fabian's method, and other knowledge-based techniques have all been employed by researchers in the process of choosing suitable co-formers and screening cocrystals.

- **Supramolecular synthon approach:** To improve an API's solid-state properties without altering the API's basic structure, a medicinal cocrystal can be made using crystal engineering. Another aspect of crystal engineering is the principles of synthon production by non-covalent interaction.[14] Supramolecular synthons are divided into other groups

- Super molecular homo synthon: Consisting of self-complementary functions that are identical.
- Super molecular hetero synthons: Composed of different but complementary functionalities

- **Hansen solubility parameter:** The miscibility of a medication and a co-former can be predicted using Hansen Solubility Parameters (HSPs), which can be used to steer cocrystal screening and predict cocrystal formation. Predicting the miscibility of cocrystal components using solubility factors might help guide the selection of potential co formers prior to doing significant cocrystal screening work.[15]

- **Cambridge structural database:** Crystal shapes of small molecules are kept in the Cambridge Structural Database (CSD). To determine a compound's crystal structure, researchers use single-crystal x-ray diffraction. When a structure is solved, its data is saved, but researchers can explore the CSD database to find and retrieve structures. The CSD allows researchers to match existing data with results from crystals grown in their labs.[16]

- **Hydrogen bond:** Hydrogen bonds play a significant part in guiding intermolecular recognition between an API and a co-former molecule for the majority of pharmaceutical cocrystal structures. The following recommendations were made to make designing hydrogen bonded materials easier: All good proton donors and acceptors are used in hydrogen bonding, and if intramolecular six-membered rings can form hydrogen bonds, they typically do so rather than intermolecular ones. After the formation of intramolecular hydrogen bonds, the best proton donors and acceptors that are still present create intermolecular hydrogen bonds with one another.[17]

- **pKa:** For pKa 0, crystallisation is expected, and for pKa 3, salt production. However, a various topics are discovered when using this pKa evaluation technique, and the criteria is pKa in the 0–3 range is less certain because salt or crystallisation could occur. However, not always applicable.[18]

- **Fabian's method:** The molecular descriptors (single atom, bond and group counts, hydrogen bond donor and acceptor count, size and shape, surface area, and molecular electrostatic) were calculated for each molecule. Different sets of reliable cocrystal forming structures were extracted from the CSD. The database listed pairs of molecules that could make cocrystals based on calculated molecular properties.[19] The cocrystal formers' shape and polarity had the greatest descriptor association.

Physiochemical properties of cocrystals

- **Physical stability:** A physical alteration is when the state of a substance changes without the substance's chemical characteristics also changing. Solid-state materials have a variety of physical characteristics, such as a melting point, hygroscopicity, solubility, hardness, plasticity, elasticity, etc.[20] A potent method for enhancing the physical characteristics and preserving the physical stability of drug compounds is co-crystallization. Which during production and storing may undergo unwanted physical changes.

- **Melting point:** The physical characteristic of objects known as the melting point can be used to assess the product's purity due to its sudden melts and narrow ranges. High melting points show that new materials are thermodynamically stable; therefore, choosing a co-former with a higher melting point can improve the thermal stability of an API. When dealing with thermolabile drugs, cocrystals with lower melting points can be helpful. Differential scanning calorimetry (DSC) and thermal gravimetric analysis are the most frequently used methods for determining melting points and performing thermal gravimetric analysis (TGA).[21]

- **Stability study:** Performing a stability study is crucial when creating novel dosage formulations. Several stability studies, including relative humidity stress, chemical stability, thermal stability, solution stability, and photostability study, should be carried out during the creation of pharmaceutical cocrystals. Automated water sorption/desorption experiments are carried out under relative humidity stress to determine the effect of water on the formulation. From few researches it has been found that the cocrystals of glutaric acid and 2- [4-(4-chloro-fluorphenoxy) phenyl] pyrimidine-4-carboxamide revealed moisture at high RH and were found to be steady under various circumstances.[22]

- **Bioavailability:** The rate and volume of pure drug that enters systemic blood is known as bioavailability. Bioavailability refers to the extent and rate at which a drug enters systemic circulation and reaches its intended target in the body. Cocrystals are crystalline materials formed by the combination of two or more different molecular components in a specific stoichiometric ratio. Cocrystals have unique physicochemical properties that can improve the bioavailability and pharmaceutical performance of poorly soluble drugs, such as ketoconazole. The development of new formulations faces a significant hurdle due to the low oral bioavailability of APIs.[23] The primary application of crystal engineering is the creation and synthesis of pharmaceutical cocrystals with improved oral bioavailability and aqueous solubility. Apixaban-oxalic acid cocrystals' oral bioavailability was found to be 2.7 times higher than that of the pure drug in pharmacokinetics research performed on beagle dogs.

- **Permeability:** Drug permeability across the biological membrane is a major factor in drug absorption and diffusion. In few researches it has been found that 5-fluorouracil, a BCS class-III medication, was co-crystallized with a variety of coformers, including 3-hydroxybenzoic acid, 4-aminobenzoic acid, and cinnamic acid, to increase its permeability.[24]

- **Solubility:** To study the formulations of poorly soluble drugs, solubility is a key parameter. Co-crystallization is one method among many that have been used by researchers to increase the solubility of medicines, including salt formation, solid dispersion, particle size reduction, and others.[25,26] The strength of the crystal lattice and the solvation of cocrystal components are two independent variables that affect solubility. Lowering the lattice energy and/or increasing the solvent affinity are two ways to enhance solubility. Both variables can be affected by cocrystals to varying degrees. In order to increase the solubility of the Cocrystal compared to drug, the conformer solubility must be approximately ten times higher than the API. Cocrystal solubility is also linked to coformer solubility.

Method of preparation of cocrystals

The researchers have described a variety of techniques for creating cocrystals. For the synthesis of cocrystals, a few conventional methods based on solution and grinding have been described. Cocrystals are created using the solution method and an appropriate type of solvent. Solvent evaporation, solution crystallization, antisolvent addition, slurry conversion, and reaction crystallisation are a few examples of different kinds of solution methods.[27]

a) Solution based method

The researchers have described a variety of techniques for creating cocrystals. For the synthesis of cocrystals, a few conventional methods based on solution and grinding have been described. Cocrystals are created using the solution method and an appropriate type of solvent. Solvent evaporation, solution crystallization, antisolvent addition, slurry conversion, and reaction crystallisation are a few examples of different kinds of solution methods. In the solution crystallisation process, the medication and coformers are dissolved in a solvent that is heating up while being stirred, and the boiling will continue until the volume of the solution is reduced. When the boiling solution is given about 15 minutes to settle, crystallisation happens quickly. Cocrystals are filtered apart and stored in an oven or the open air to dry.[28]

b) Slurry crystallization method

The process of creating slurry through the addition of various solvents to a mixture of an API and appropriate coformers is known as slurry crystallisation. After the solvent has been decanted, the solid substance is dried and subjected to various evaluation techniques. When the drug and coformer need to be solvent-stable, this technique is chosen for the preparation of cocrystals. In the antisolvent addition technique, API is dispersed in the coformer solution using a dispersion homogenizer after the coformers have been dissolved in various solvents, such as organic solvents. The coformer on the drug is precipitated by adding this solution to distilled water or another appropriate solution.

c) Grinding method

Over the past few years, grinding techniques have been used extensively for the creation of cocrystals and have proven to be more effective than other techniques. There are two different kinds of grinding methods: neat or dry grinding and wet grinding. In dry grinding, the drug and the coformer are combined in a stoichiometric ratio and pulverised in a ball mill or mortar and pestle. By adding a few droplets of solvent to the mixture, wet grinding was accomplished similarly to neat grinding.

d) Spray drying technique

Cocrystals are made by spray drying, which involves evaporating the solvent from a solution or suspension of the medication and the coformer. This technology is the most popular because it uses a quick, continuous, and one-step procedure. In order to prepare and scale up cocrystals, a special environment will be provided by the spray drying procedure.[29]

e) Hot melt extrusion technique

By heating the drug and coformers while vigorously mixing, the hot melt extrusion method produces cocrystals that have improved surface contacts without the use of a solvent. The coformer and API both need to be miscible in molten form for this technique to work, and thermolabile drugs cannot be used.

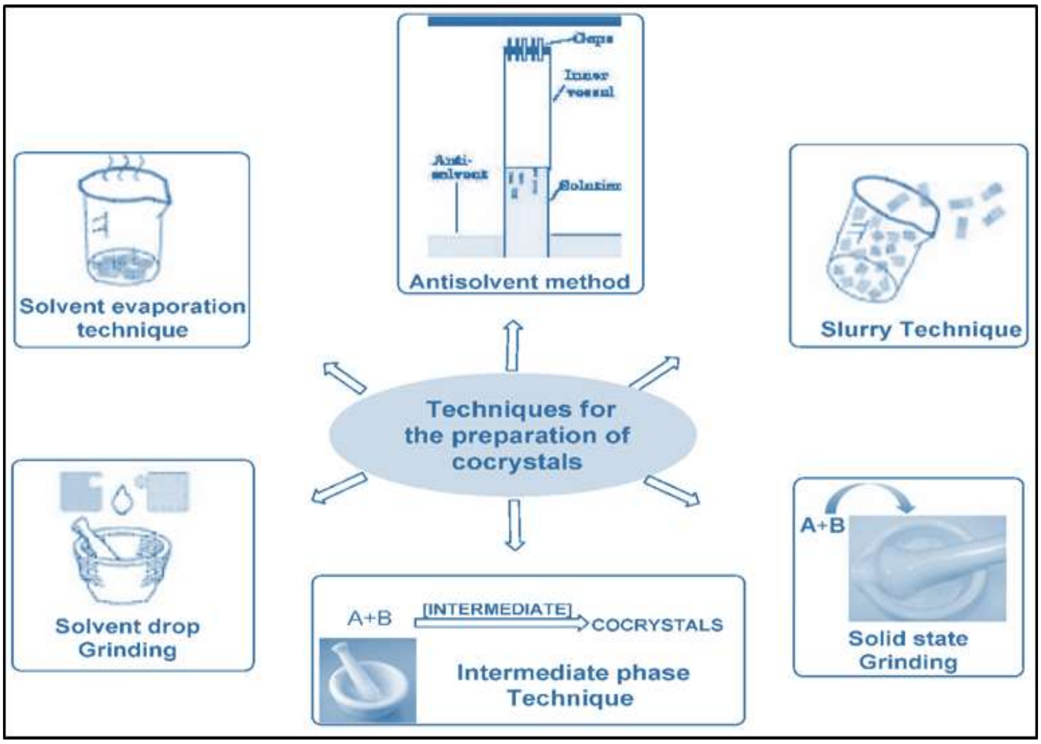

Figure 4: Different method of cocrystals preparation.

Co-crystal characterization methods

Co-crystal structure determination, temperature analysis, and morphological determination are the three classes into which the co-crystal characterization techniques can be divided, as shown in Table 1.

Table 1: Co-crystal characterization methods.

Characterization principle	Diagnosis methods
Structural and Spectroscopy	Single crystal X-ray diffraction (SCXD), Powder X-ray diffraction (PRXD), Fourier-Transform Infrared (FTIR) spectroscopy, Nuclear magnetic resonance (NMR) spectroscopy, Raman spectroscopy.
Thermal	Melting point, Differential scanning calorimetry (DSC), Thermo gravimetric analysis (TGA),
Morphological	Scanning Electron Microscopy (SEM)

Several techniques, including X-ray diffraction, Raman spectroscopy, and Fourier transform infrared (FTIR) spectroscopy, can be used to determine the co-crystal structure. When there are variations in the X-ray pattern from the original material pattern, however, X-ray diffraction (single crystal or powder) provides a definitive diagnostic regarding the development of new crystals. Raman spectroscopy is a helpful method for identifying co-crystals; variations in the material's vibrational mode brought on by light scattering may also point to the production of co-crystals.[30]

In Fourier Transform Infrared Spectroscopy (FTIR), each compound is represented by a fingerprint, with its functional group represented by peaks in a specific range area. Any new band or shift in an existing peak could indicate the formation of a hydrogen bond, and additional research is required to confirm co-crystal formation. In the process of building cocrystals, FTIR is a helpful tool for choosing the right co-former among a variety of chemicals.[31]

The variance in enthalpy and melting temperatures between the co-crystal, its constituents (APIs and coformer), and their physical combination determine the thermal analysis approach. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) are two methods used in thermal analysis.[32]

Co-crystal formation is indicated by the appearance of an endothermic peak in the DSC at a lower melting point or between the raw material melting points. The DSC method depends on measuring phase transitions such melting, polymorphism, and the loss of the volatile cocrystal component.

TGA records the mass loss as a function of temperature, whereas DSC measures changes in power as a function of temperature. TGA is thought to be a useful technique for determining the precise temperature at which a co-crystal begins to break down and lose its volatile component. The stoichiometric ratio of the co-crystal starting materials can be confirmed by the amount of mass loss in TGA.[33,34]

An optical microscope or a scanning electron microscope (SEM) can be used for morphological examination.

A focused electron beam is used in scanning electron microscopy (SEM) to produce a three-dimensional image, highlighting surface features like smoothness or roughness, as well as morphological shapes like cubic, round, or needle.[32,35]

Application of cocrystal

Here are some details on the application of cocrystals in enhancing drug properties

I. Solubility enhancement

Enhancing the solubility of weakly soluble drugs is one of the main uses of cocrystals. The crystal lattice of the drug can be altered to produce a more energetically advantageous structure, leading to greater solubility, by co-crystallizing with a coformer that shares a similar molecular structure. This strategy has been used with numerous medications, such as coffee, ibuprofen, and carbamazepine.[36]

II. Stability enhancement

Drug durability can also be increased by cocrystals by shielding them from environmental deterioration brought on by moisture, light, and heat. The cocrystal can give improved stability by choosing a coformer that is more stable than the drug, resulting in a longer shelf life and better product quality.

III. Bioavailability enhancement

Enhancing the bioavailability of medicines is done using cocrystals. The percentage of a medication that, after administration, enters the systemic circulation and can be used to produce pharmacological effects is known as bioavailability. Drug development faces significant obstacles due to poor drug bioavailability, which effects the drug's therapeutic effectiveness and pharmacokinetics. By increasing a drug's solubility, dissolution rate, permeability, and durability, cocrystals can increase its bioavailability.

By increasing their solubility and rate of breakdown, cocrystals can improve the bioavailability of pharmaceuticals.[37] The increased rate and extent of drug absorption from the gastrointestinal tract as a result of cocrystals' better solubility and dissolution rate can lead to higher plasma concentrations and improved bioavailability.

IV. Taste masking

Specifically for paediatric and geriatric patients who may have trouble swallowing or who may refuse to take their medicine due to its unpleasant taste, taste masking is the process of reducing or eliminating the unpleasant taste of drugs. Several techniques, including microencapsulation, complexation with cyclodextrins, ion-exchange resins, and cocrystallization, can be used to disguise the taste of medications. By creating a complex between the drug and a flavour-masking substance, cocrystals can be used to hide the bitter flavour of medications. Depending on its capacity to create a cocrystal with the drug and compatibility with the formulation, the taste-masking agent may be an excipient or a flavouring agent. The cocrystal can be made to have a low solubility and a slow rate of dissolution, which can lessen the amount of drug released in the mouth and diminish the sense of taste. For example, it has been suggested that saccharin, benzoic acid, or vanillic acid cocrystals of the antibiotic clarithromycin can lessen the bitter flavour of the medication. Due to its lower solubility and slower rate of dissolution, the cocrystal of clarithromycin and saccharin was found to have a superior taste-masking effect than the cocrystals with benzoic acid or vanillic acid.

V. Multidrug co-crystals

When two medications are combined into one formulation, there are many benefits. Aside from the synergistic effect of many medications co-crystalling, at least one drug's physicochemical qualities could also be improved. In the case of a multi-drug regimen system, such as antituberculosis therapies, analgesics, anti-inflammatory, antiviral, and diuretics, drug-drug cocrystal is a crucial formulation factor.[38]

CONCLUSION

Co-crystals, a multicomponent compound created recently using a novel pharmaceutical trend, have proven to be an intriguing technology in the pharmaceutical sector. Co-crystals can be produced using a variety of approaches, including green ones, with great success.

The co-crystal technology will, however, advance much with the recent addition of new techniques like hot melt extrusion and spray drying. Numerous uses of crystal technology in pharmaceutics and drug delivery have proven beneficial. Co-crystals have demonstrated the potential to alter important formulation parameters such powder flowability and compression ability, improving the formulation's accomplishment through physicochemical qualities.

Co-crystallization enhances the pharmacokinetics, stability, and bioavailability performance in addition to the formulation. Co-crystals of multiple medications are a special formulation with two, three, or even more advantages above the individual drugs. When many medications are combined into one crystal, the synergistic effect is enhanced at lower dosages, resulting in fewer side effects, better absorption, and ultimately, better clinical outcomes. Together, these will stimulate further interest in co-crystal research among researchers in the near future, and our review aims to aid in the dissemination of this technology throughout the pharmaceutical sciences community.

REFERENCES

1. Chow K, Tong HHY, Lum S, Chow AHL. Engineering of pharmaceutical materials: An industrial perspective. J Pharm Sci, 2008; 97(8): 2855-77.
2. Paul EL, Tung HH, Midler M. Organic crystallization processes. Powder Technol, 2005; 150: 133-43.
3. Duarte, A.R.C.; Ferreira, A.S.D.; Barreiros, S.; Cabrita, E.; Reis, R.L.; Paiva, A. A comparison between pure active pharmaceutical ingredients and therapeutic deep eutectic solvents: Solubility and permeability studies. Eur. J. Pharm. Biopharm, 2017; 114: 296–304.
4. Butler, J.M.; Dressman, J.B. The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development. J. Pharm. Sci, 2010; 99: 4940–4954.
5. Bagde, S.A.; Upadhye, K.P.; Dixit, G.R.; Bakhle, S.S. Formulation and Evaluation of Cocrystals of Poorly Water Soluble Drug. Int. J. Pharm. Res, 2016; 7: 4988–4997.
6. Jones, W.; Motherwell, W.S.; Trask, A.V. Pharmaceutical cocrystals: An emerging approach to physical property enhancement. MRS Bull, 2006; 31: 875–879.
7. J. B. Ngilirabanga and H. Samsodien, “Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy,” Nano Sel, 2021; 2,3: 512–526.
8. R. Thipparaboina, D. Kumar, R. B. Chavan, and N. R. Shastri, “Multidrug co-crystals: Towards the development of effective therapeutic hybrids,” Drug Discov. Today, 2016; 21,3: 481–490.

9. A. V. Yadav, A. S. Shete, A. P. Dabke, P. V. Kulkarni, and S. S. Sakhare, "Co-Crystals : A Novel Approach to Modify Physicochemical Properties of Active Pharmaceutical Ingredients," Indian J. Pharm. Sci, 2009; 359–370.
10. Emami S, Siahi-Shadbad M, Adibkia K, Barzegar-Jalali M. Recent advances in improving oral drug bioavailability by cocrystals. BioImpacts: BI, 2018; 8(4): 305.
11. Fukte SR, Wagh MP, Rawat S. Coformer selection: An important tool in cocrystal formation. Int. J. Pharm. Pharm. Sci, 2014; 6(7): 9-14.
12. Mohammad MA, Alhalaweh A, Velaga SP. Hansen solubility parameter as a tool to predict cocrystal formation. International journal of pharmaceutics, 2011; 4,407(1-2): 63-71.
13. Ning Qiao, Mingzhong Li, Walkiria Schlindwein, Nazneen Malek, Angela Davies, Gary Trappitt, Pharmaceutical cocrystals: An overview, International Journal of Pharmaceutics, 2011; 419: 1– 11.
14. Lin HL, Hsu PC, Lin SY. Theophylline–citric acid co-crystals easily induced by DSC–FTIR microspectroscopy or different storage conditions. Asian journal of pharmaceutical sciences, 2013; 1,8(1): 19-27.
15. Mohammad MA, Alhalaweh A, Velaga SP. Hansen solubility parameter as a tool to predict cocrystal formation. International journal of pharmaceutics, 2011; 4, 407(1-2): 63-71.
16. Mittapalli S, Mannava MC, Khandavilli UR, Allu S, Nangia A. Soluble salts and cocrystals of clotrimazole. Crystal Growth & Design, 2015; 6, 15(5): 2493-504.
17. Lu E, Rodriguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. CrystEngComm, 2008; 10: 665-68.
18. Vaghela P, Tank HM, Jalpa P. Cocrystals: A novel approach to improve the physicochemical and mechanical properties. Indo Am J Pharm Res, 2014; 4(10): 5055-65.
19. Jiang L, Huang Y, Zhang Q, He H, Xu Y, Mei X. Preparation and solid-state characterization of dapsone drug–drug co-crystals. Crystal Growth & Design, 2014; 3, 14(9): 4562-73.
20. Basavoju S, Boström D, Velaga SP. Indomethacin–saccharin cocrystal: design, synthesis and preliminary pharmaceutical characterization. Pharmaceutical research, 2008; 25: 530-41.
21. Martin FA, Pop MM, Borodi G, Filip X, Kacso I. Ketoconazole salt and co-crystals with enhanced aqueous solubility. Crystal growth & design, 2013; 2.

22. Guo C, Zhang Q, Zhu B, Zhang Z, Mei X. Drugedrug cocrystals provide significant improvements of drug properties in treatment with progesterone. Cryst Growth Des, 2020; 20: 3053-63.
23. Duggirala NK, Smith AJ, Wojtas Ł, Shytle RD, Zaworotko MJ. Physical stability enhancement and pharmacokinetics of a lithium ionic cocrystal with glucose. Crystal growth & design, 2014; 5,14(11): 6135-42.
24. Abourahma H, Cocuzza DS, Melendez J, Urban JM. Pyrazinamide cocrystals and the search for polymorphs. CrystEngComm, 2011; 13(21): 6442-50.
25. Trask AV, Motherwell WS, Jones W. Physical stability enhancement of theophylline via cocrystallization. International journal of pharmaceutics, 2006; 31,320(1-2): 114-23.
26. Bolla G, Nangia A. Pharmaceutical cocrystals: walking the talk. Chemical communications, 2016; 52(54): 8342-60.
27. Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. Crystal Growth & Design, 2018; 10,18(10): 6370-87.
28. Devne SR, Kapse VN, Ingale PL. COCRYSTAL: A REVIEW ON PHARMACEUTICAL CORYSTALS DESIGN AND PREPARATION. World Journal Of Pharmaceutical Research, 2019; 21,8(7): 1936-50.
29. Good DJ, Rodriguez-Hornedo N. Solubility advantage of pharmaceutical cocrystals. Crystal Growth and Design, 2009; 6,9(5): 2252-64.
30. J. Santosh and M. Audumbar, "An Overview on Co-crystallisation," Inventi, 2015; 1: 1–17.
31. S. Ketkar, S. K. Pagire, N. R. Goud, K. Mahadik, A. Nangia, and A. Paradkar, "Tracing the Architecture of Caffeic Acid Phenethyl Ester Cocrystals: Studies on Crystal Structure, Solubility, and Bioavailability Implications," Cryst. Growth Des, 2016; 16,10: 5710–5716.
32. D. W. I. Utami, I. Nugrahani, and S. Ibrahim, "Mefenamic acid-nicotinamide co-crystal synthesized by using melt crystallization method and its solubility study," Asian J. Pharm. Clin. Res, 2017; 10,5: 135–139.
33. S. Ketkar, S. K. Pagire, N. R. Goud, K. Mahadik, A. Nangia, and A. Paradkar, "Tracing the Architecture of Caffeic Acid Phenethyl Ester Cocrystals: Studies on Crystal Structure, Solubility, and Bioavailability Implications," Cryst. Growth Des, 2016; 16,10: 5710–5716.

34. S. K. Nechipadappu, V. Tekuri, and D. R. Trivedi, “Pharmaceutical Co-Crystal of Flufenamic Acid: Synthesis and Characterization of Two Novel Drug-Drug Co-Crystal,” J. Pharm. Sci, 2017; 106,5: 1384–1390.
35. Falsafi SR, Rostamabadi H, Assadpour E, Jafari SM. Morphology and microstructural analysis of bioactive-loaded micro/nanocarriers via microscopy techniques; CLSM/SEM/TEM/AFM. Advances in Colloid and Interface Science, 2020; 1,280: 102166.
36. Vaghela P, Tank HM, Jalpa P. Cocrystals: A novel approach to improve the physicochemical and mechanical properties. Indo Am J Pharm Res, 2014; 4(10): 5055-65.
37. Zhang YX, Wang LY, Dai JK, Liu F, Li YT, Wu ZY, Yan CW. The comparative study of cocrystal/salt in simultaneously improving solubility and permeability of acetazolamide. Journal of Molecular Structure, 2019; 15,1184: 225-32.
38. Wong SN, Chen YC, Xuan B, Sun CC, Chow SF. Cocrystal engineering of pharmaceutical solids: Therapeutic potential and challenges. CrystEngComm, 2021; 23(40): 7005-38.