AN UPDATED REVIEW ON PHARMACEUTICAL CO-CRYSTALLIZATION: CHARACTERISATION AND PREPARATION

***Sunny Antil[1], Garima Verma[2] Rahul Sharma[3]**

Research Scholar, Faculty of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram Delhi-Haridwar Meerut Bypass Road, Nh-58, Meerut-250005

Professor, Faculty of Pharmacy, Swami Vivekanand Subharti University, Subhartipuram Delhi-Haridwar Meerut Bypass Road, Nh-58, Meerut-250005

Professor and Principal, Gateway college of Pharmacy, Sonipat- 131001

Abstract: Background: Co-crystals in the pharmaceutical industry have recently garnered significant attention due to their potential as a sustainable and ecologically friendly method for enhancing the solubility, stability, and bioavailability of poorly water-soluble drugs. They are particularly valuable in drug development research because they require minimal solvent and do not involve lengthy synthetic steps. **Methods**: This review explores various techniques for creating co-crystals, including solvent evaporation, co-grinding, and liquid-assisted grinding. To confirm the formation and structural characteristics of the co-crystals, several characterization techniques were employed, such as SCXRD, PXRD, FTIR, and DSC. **Results**: The study emphasizes the importance of understanding the physicochemical properties of co-crystals and how these properties are influenced by intermolecular interactions. The review also highlights the successful design, synthesis, characterization, and evaluation of medicinal co-crystals. **Conclusion**: Pharmaceutical co-crystals hold promise for enhancing the therapeutic efficacy of drugs by improving their solubility, dissolution rate, and oral bioavailability. This research underscores the potential applications of co-crystals in developing more effective pharmaceutical formulations

***Keywords*:** Co-crystallization, Enhancement, Pharmaceutical, Solubility, Characteristic, Crystallization, Bioavailability.

INTRODUCTION:

In recent years, the pharmaceutical industry has faced a significant challenge: a large proportion of newly developed active pharmaceutical ingredients (APIs) exhibit poor water solubility, which hampers their bioavailability and therapeutic efficacy. This problem is particularly acute for Biopharmaceutics Classification System (BCS) compounds, where approximately 60% to 70% of newly discovered drugs fall into categories with limited solubility [1]. The poor solubility of these compounds makes it difficult to formulate effective oral dosage forms, as their absorption can vary widely in different sections of the gastrointestinal (GI) tract due to fluctuating pH levels. This non-linear absorption complicates the evaluation of drug safety and efficacy, posing a major hurdle for the pharmaceutical development process [2].

A variety of strategies have been employed to enhance the solubility and bioavailability of APIs, such as particle size reduction, salt formation, and the use of solubilizing excipients. However, each of these approaches has its limitations, including stability issues, manufacturing complexities, and unwanted changes to the chemical properties of the drug. To

address these limitations, a growing body of research has focused on an innovative solution: co-crystals [3].

Co-crystals are crystalline materials composed of two or more components, typically an API and a co-former, that are bound together via non-covalent interactions. These structures offer a promising pathway for improving the physicochemical properties of poorly soluble drugs without altering their chemical integrity [4]. The potential of co-crystals lies in their ability to enhance solubility, dissolution rate, and bioavailability, while also improving other properties such as stability, permeability, and tabletability [5].

What sets co-crystals apart from traditional solubility-enhancement techniques is their environmentally friendly nature. Researchers are exploring sustainable methods for synthesizing co-crystals using renewable starting materials and greener solvent systems [6]. This aligns with the growing demand for eco-friendly drug development processes, making co-crystals not only a viable solution for poorly soluble drugs but also a step towards more sustainable pharmaceutical practices.

This review explores the fundamentals of co-crystals, focusing on their design, synthesis, characterization, and evaluation. It also examines the various methods used for co-crystal production, such as liquid-assisted grinding and co-grinding, and highlights the techniques employed for their characterization, including dynamic scanning calorimetry (DSC) [7]. Furthermore, it delves into the impact of co-crystals on improving the bioavailability and therapeutic effectiveness of drugs by enhancing their solubility and dissolution rate.

Co-crystals represent a fast-emerging field in drug development. This review aims to provide a comprehensive understanding of the significance of co-crystals in overcoming solubility challenges, as well as their potential applications in creating more effective and environmentally sustainable pharmaceuticals [8].

Pharmaceutical Co-Crystals:

When referring to a kind of multi-component crystal, the word " ratio that is stoichiometric. Co-crystals include guest molecules that are acceptable in the pharmaceutical business. These molecules are present in addition efficacy of the active pharmaceutical ingredient [API], but it did improve the physical properties of the API, including its solubility, hygroscopicity, and compaction behaviour [9].

Interactions such as hydrogen bonding, pi pi stacking, and van der Waals forces are some examples of the sorts of interactions that may be used in the construction of co-crystals. According to this set of requirements, the solvates and hydrates that make up the API do not meet the criterion for co-crystals. Co-crystals, on the other hand, have the potential to include one or more molecules of a solvent such as water inside their crystal lattice in certain cases. Co-crystals enhance the mechanical behaviour, solubility, dissolving rate, bioavailability, and physical and chemical stability of nonionizable pharmaceuticals, hence improving their medicinal characteristics. This is accomplished without altering the pharmacological behaviour of the medications.

Among the subjects that were discussed in the study were pharmaceutical co-crystals, the expanding area of crystal form selection, and the recent growth of crystal engineering in the pharmaceutical business. It was determined that there were reports on screening techniques, outlining methodology, and common characteristics of the production and operation of co-crystals. Co-crystals have garnered a lot of attention due to the fact that they have the potential to be used in the pharmaceutical industry, as well as in the fields of drug delivery

and design. There are pharmacological co-crystals that have been found for a wide variety of drugs, including acetaminophen, aspirin, ibuprofen, flurbiprofen, and many more [10].

Co-Crystal and Solvates:

When one of the pure components is a liquid at room temperature, we refer to such crystals as solvates. On the other hand, when both of the components are solids at normal temperature, we refer to those crystals as co-crystals. The primary difference between the two is that this is the case.

Salt Versus Co-Crystal and Ionization:

The existence of an ionic centre in an active pharmaceutical ingredient [API] is the most decisive factor in the formation of salt. Because they are not ionizable, active pharmaceutical ingredients [APIs] cannot produce salts. When they are converted into salts, there are only a few non-toxic acids and bases that are appropriate for use in the pharmaceutical industry [11]. An appreciation of the crucial differential between a salt formation and a co-crystal is very beneficial to preformulation duties as well as components of chemical and pharmaceutical research. In the pharmaceutical industry, salts are often favoured over free acids or bases due to the fact that they have the potential to improve the crystallinity, solubility, and stability of medicinal compounds. In the domain of pharmaceuticals, cocrystals represent an innovative alternative technique. Many people have the misconception that a salt will be produced as a consequence of the reaction between an acid and a base. The assumption is that it is a cocrystal and that its value is greater than three. A salt is produced whenever an acidic or basic substance interacts with the active pharmaceutical ingredient [API]. Unlike heterosynthons, which are composed of different molecules, cocrystal homosynthons are composed of the same molecules throughout their whole.[12]

Physicochemical Properties of Co-Crystals:

Physical properties of co-crystals:

When comparing the co-crystal to its mother molecules, the chemical properties of the original compounds will be mostly preserved. The crystal structure of a co-crystal, however, is entirely different from that of the crystals of its mother compounds. As a result, the physical properties of a co-crystal are different from those of its mother crystals.

Melting points:

There is some degree of regularity in the melting temperatures of pyrazine co-crystals with n-alkyl carboxylic acids.5. For acids longer than C7 [heptanoic acid and longer acids], the associated co-crystal shows a change in melting point, which is the opposite of what happens to the n-alkyl carboxylic acids themselves. The odd co-crystals' melting temperatures are consistently higher than the evens' because they have a systematically greater packing efficiency at the methyl-group interface between layers in the structures.

A series of DSC tests were performed on the nonstoichiometric co-crystal of phosphodiesterase-IV inhibitor and L-tartaric acid.Six The co-crystal's melting point is located between that of L-tartaric acid and the inhibitor and rises with the amount of phosphodiesterase-IV inhibitor. The co-crystal in this series with the acid:base ratio of 0.5:1 has the best thermal stability, which indicates that there isn't any phase shift or other transition involving an endothermic or exothermic reaction, while not having the highest melting point.

Hygroscopicity:

Hygroscopicity is the term used to describe a solid medication's capacity to remain stable when exposed to ambient moisture. Hygroscopicity of co-crystals was frequently reported to

be lower than that of the original crystal. When phosphoric acid and an API cocrystallize, the cocrystal is more chemically and physically stable to humidity than the API by itself. 7. A detailed analysis of the co-crystals of caffeine with different carboxylic acids showed that they are generally less hygroscopic than caffeine.8 The cocrystal containing oxalic acid even exhibits complete stability to humidity over a few weeks, out of all of them. Another example is 2-[4-[4-chloro-2-fluorophenoxy]phenyl]pyrimidine-4-carboxamide co-crystallized with glutaric acid. 9. This co-crystal solid is said to be non-hygroscopic.[13]

Solubility and dissolution rate:

The solubility and dissolving rate of an API are highly valued in the pharmaceutical business since they are often associated with its bioavailability.10 The solubility and dissolution rate of the co-crystal may differ from those of the original API.

The aqueous solubility rate of 2-[4-[4-chloro-2-fluorophenoxy]phenyl]pyrimidine-4-carboxamide was eighteen times greater when co-crystallized with glutaric acid than when the homomeric API was crystalline. 9. The co-crystal's quicker rate of breakdown produced plasma concentration levels in dogs that were nearly three times higher than those of the API by itself when administered orally. Another example of a co-crystal exhibiting enhanced solubility is the co-crystal of isonicotinamide and norfloxacin. It has three times more solubility than norfloxacin crystal.[14]

Co-Crystallization Techniques:

Procedures that include crystal engineering have the potential to change the physicochemical properties of a chemical entity. These properties include the chemical entity's solubility, permeability, bioavailability, tabletability, and physical and chemical stability. The process that occurs when two molecules join together by hydrogen bonding without breaking their covalent bonds is referred to as co crystallisation. A study using crystallographic data was conducted, and the findings are shown in Figure 3. The research found that heteromeric molecules are more likely to form hydrogen bonds than homomeric ones. There is a possibility that the two different molecules, rather than the identical molecules stacked in close proximity, are to fault [15].

There are a few different methods that may be used in order to co-crystallize active pharmaceutical ingredients [APIs]. These methods include the grinding process, the inclusion of antisolvents, the evaporation of solvents [solution co-crystallization], and the use of ultrasound to assist in the process. The process of cobalt crystallisation involves the evaporation of the solvent, which results in the formation of solvates or hydrates that are not always desired. In addition to this, it was susceptible to the potential of the creation of homomeric molecules. The addition of extremely little volumes of solvent is required for the solvent drop grinding procedure, which is one of the numerous conventional methods that is considered to be one of the most environmentally friendly [16].

Review Literature:

Sandeep Kumar [2017] The inability of the active pharmaceutical component to dissolve in water and its low oral bioavailability are two factors that impede the development of a recently introduced medication. There are a number of different approaches that have been successful in enhancing the solubility of drugs that are not particularly soluble in water. However, the effectiveness of these approaches is contingent upon the particular physical and This is made possible by the fact that the pharmacological characteristics of the active pharmaceutical ingredient are preserved during the process. [17]

Manjusha Choudhary [2020], As a result of the restricted bioavailability, poor solubility, and compromised physical, chemical, and biological features of active pharmaceutical ingredients [APIs], pharmaceutical researchers are progressively investing a significant amount of time and attention to examining the challenges associated with these qualities. The process of developing a suitable formulation that has improved physicochemical properties is a challenging endeavour for scientific researchers and commercial professionals in the pharmaceutical industry. Although cocrystallization has been around for some time, it has only lately become a highly essential process in the pharmaceutical business. Its purpose is to improve to the pharmaceutical sector. [18]

Minshan Guo [2021] the cocrystals produced by Pharmaceutical include a multitude of constituents, one of which is an active pharmaceutical ingredient, while the other constituents are chemicals that have been granted permission to be used in the pharmaceutical industry. Cocrystallization of a medicinal molecule with a coformer is a contemporary and fascinating technique that has the potential to enhance the performance of pharmaceuticals in a variety of areas, including solubility, dissolving profile, pharmacokinetics, and stability. medicinal cocrystals. As an additional point of interest, we provide a few drug cocrystals in order to illustrate how crystal shapes influence the physical and chemical stability, mechanical and optical characteristics, bioavailability, sustained release, therapeutic efficacy, and mechanical and optical properties of active pharmaceutical components [19].

Kara. Divya Dhatri [2022] The oral route is the one that is recommended for the administration of medicines. There are a number of anticancer drugs that fall into this category; the most common causes for their lack of clinical effectiveness are both their low solubility and their oral bioavailability. The research that is being done to improve the oral absorption of anticancer drugs that have low water solubility and drug impermeability is presently producing successful results. There are a great number of researchers that are interested in the possibility that pharmaceutical cocrystals might improve the physicochemical properties of a number of anticancer drugs. It is possible that pharmaceutical cocrystals have superior solubility, bioavailability, and resistance to phase transitions when compared to other solid forms. [20]

Dutt, Braham [2021] A. One of the end results of an active pharmaceutical ingredient's low solubility is a decrease in its bioavailability. This is particularly true for pharmaceuticals that fall under the biopharmaceutics categorization system [BCS]. In the These approaches include cocrystallization, nanotechnology, and solid dispersions. Additionally, the review will investigate the benefits of cocrystallization in contrast to these other approaches. Techniques A comparison of a number of aspects relating to different techniques of drug administration has been carried out. different aspects include pharmaceutical, pharmacological, and toxicological consequences [21].

Ravi Kumar Bandaru [2021]. In order to develop porosity, thermal properties, and other similar characteristics. There are limitations to the conventional approaches of altering the solid characteristics of pharmaceutical compounds. These approaches include the production of salts, solvates, and polymorphs within the compound.[22]

Rachna Anand [2020], said the solubility and dissolution profile of a medicine are considered to be the two most essential elements that determine the drug's biological activity. These qualities are regulated by the physicochemical properties of the medication. Crystal engineering is a relatively new and promising strategy for changing the physicochemical features of an active without affecting its pharmacological action. This is accomplished via the utilisation of a wide range of crystal formers that are freely accessible for commercial use. Object of the The purpose of this article is to offer a succinct description of the relevance of crystal engineering in the process of improving the physicochemical properties of a prescription medicine [23].

Rahamatullah Shaikh [2018] When it comes to the formulation and administration of active pharmaceutical ingredients [APIs] to patients, the solid state is the most common form. Recently, there has been an increase in the amount of interest that academic institutions and businesses have shown in pharmaceutical cocrystals, which are an alternative solid-state form of active pharmaceutical ingredients [API]. This is due to the fact that the therapeutic product has the potential to possess distinctive physical characteristics. which were made feasible primarily by new and promising criteria given by the FDA in February of 2018. The purpose of this article is to provide an overview of the whole process of producing a pharmaceutical cocrystal medical product, beginning with screening and ending with approval. The study focuses on significant breakthroughs that have occurred over the last 10 years.[24]

Renu Chadha's [2012] It is recommended that medications be administered in solid dosage forms. On the other hand, when they are working on generating new medications, they often run across the problem of high bioavailability that is unexpected. Solid forms, which include things like polymorphs, solvates, salts, and cocrystals, are the ones that are most important for boosting bioavailability and dissolving rate. There are a number of drug delivery formulation strategies that are currently being developed, but the ones that are most important are for enhancing bioavailability. Cocrystallization is a relatively new technique that in recent years has been utilised by the pharmaceutical sector. This makes it possible for the active pharmaceutical ingredient [API] to have a higher level of bioactivity and to be more soluble without compromising its structural integrity [25].

Geetha Bolla [2016] was born. Pharmaceutical cocrystals are a subclass of cocrystals, and the two primary components that make up pharmaceutical cocrystals are known as active pharmaceutical ingredients [APIs] and benign food or drug grade additives [GRAS]. At a stoichiometric ratio that is always the same, the two components of the crystal structure are hydrogen-bonded to one another. In the past ten years, pharmaceutical cocrystals have demonstrated a significant amount of potential for modifying the pharmacokinetic and physicochemical properties of medicinal substances. These properties include bioavailability, physical form, melting point, biochemical and hydration stability, permeability, particle size and shape, tableting and compaction, as well as solubility and dissolution rate.[26]

Diksha J. Patel [2020], The author is. There are significant obstacles that must be overcome in order to produce innovative products, including issues with water solubility, stability, oral bioavailability, and permeability. Because of biopharmaceutical issues, the vast majority of medications that are marketed all over the world are taken orally. Additionally, between forty percent and fifty percent of newly created molecular entities were never brought to market. Therefore, the cocrystallization approach has the potential to provide a solution to issues that arise with APIs that have inadequate physiochemical characteristics. Crystallisation is a technique that has the potential to enhance. [27].

Chauhan, Vishva [2022], The creation and production of cocrystals is now attracting the attention of pharmaceutical companies and research institutions. This is due to the fact that at the manufacturing stage. Developing innovative solid crystalline structures that display modified physicochemical features, including stability, bioavailability, tabletability, melting point, and water solubility. Through the observation of the intermolecular interactions that occur between molecules in a crystal lattice, these characteristics are investigated.[28]

Malaz Yousef [2019] is the year. This is. On the other hand, the molecular entities that are referred to as co-crystals have only recently found their way into practical applications. Over the course of the last decade, these newly developed solids have shown a great deal of potential for modifying the pharmacokinetic and physicochemical properties of pharmaceutical supplements. The characteristics of co-crystals at the molecular level have been investigated in earlier research. These characteristics include their design, growing techniques, and physicochemical characterizations. The inclusion of co-crystals into

acceptable compounds is essential in order to get co-crystals from the laboratory to the bedside, despite the fact that co-crystal formulations receive very little attention [29].
Sandeep Zode [2016], the increasing study in this subject has resulted in a number of effects, including an extension of the production of cocrystals for use in medicines may be challenging, which may delay down the process of their development into medications that are marketable.[30]

Objectives:

1. The Study Enhancement of Pharmaceutical Characteristic.
2. The Study Selected Drug[S] Using Crystallization.

MATERIALS AND METHODS:

Co crystals are created using the following method:

1. The Solvent Method
2. Distillate Evaporation
3. Cooling Technique
4. The Anti-Solvent Method
5. The Solid-state Method
6. Grinding in a solid state
7. The Liquid-Assisted Method
8. Calorimetric Crystallization
9. Slurry method
10. The twin screw method
11. Utilizing the Freeze-Drying Method
12. Fluid at supercritical temperature
13. Radiation using lasers
14. Reaction-based crystallization
15. Crystallization helped by ultrasonography
16. The Spray Drying Method

Solvent method:

The super saturation process was the main factor behind the crystallization that occurred in this approach. In order to achieve this goal, it is necessary to identify the eutectic point that corresponds to the concentration of the medication, the conformer, and the solvents. This technique is comprised of three phases that are contained inside a mixed solvent. The optimal condition for this approach is when the drug and the co-former are regarded to be under saturation or unsaturated mean, while the co crystals are thought to be at super saturation. It is feasible for the co crystal to be stable if the active pharmaceutical ingredient [API] or the co-former will be less soluble. This is because the co-former reflects all of the concentrations that are located in the eutectic points. The ratio of the medication to the co-former is one to one, and the eutectic is the solution that is at its lowest possible concentration. According to the solubility value, the lowest solvent content represents the greatest value. [31]

Solvent evaporation:

In pharmaceutical research facilities, this method is the one that is utilized the most commonly and is regarded as being extremely dependable. It is also the one that is utilized to create the co crystal. When using this technique, the active pharmaceutical ingredient [API] and the co-former are both dissolved in the same solvent. Following the determination of the amount of the solvent based on the stoichiometric ratio, the solvent is then evaporated at a temperature that is controlled in order to prevent any degradation from taking place. This

particular sort of evaporation results in the production of hydrogen bonds between the different functional groups, in addition to the nucleation of co-former inside the co crystals that have been created. Within the context of the X-ray diffraction research, this method was a strategy that was frequently utilised throughout the analytical phase of the inquiry. [32]

Cooling method:

However, it was most extensively used in the bulk manufacture of pure crystals. It is less popular and utilized in the pharmaceutical preparation of limited quantity of crystals because to the time-consuming method that it entails. However, it was employed in the preparation of purified crystals in bulk. Crystallization of the active pharmaceutical ingredient [API] was accomplished by the use of this technique by bringing the temperature of the solution down to a level that was lower than room temperature or even lower. This was accomplished through the process of supersaturating the solution. At a temperature of 40.0 ± 0.5 degrees Celsius, a particular quantity of the drug was properly dissolved in a particular volume of the solvent. Under continuous stirring, the solution was brought down to a temperature of 10.0 ± 0.5 degrees Celsius in a water bath at a rate of roughly 0.25 degrees Celsius per minute. This was accomplished while the solution was being churned constantly. After that, the crystals that had been produced were recovered by means of vacuum filtration, rinsed many times with distilled water, kept at a temperature ranging from 25 to 30 degrees Celsius in order to get rid of the solvent that was present in them, and finally, they were placed in a desiccators for storage. [33, 34]

Anti-solvent technique:

This technique, which is also known as vapour diffusion, was successful in producing co crystals of a pure grade. The precipitation of the medicine was achieved by the use of this method by adding an anti-solvent to the solution in which the active pharmaceutical ingredient [API] was either insoluble or low solubility. When the second solution was introduced to the first antisolvent, a supersaturation was seen in the mixture. An antisolvent was chosen for this method, and within it, the active pharmaceutical ingredient [API] was dissolved in a ratio of 2:1 [Antisolvent: API]. Subsequently, another antisolvent or a solvent was chosen to dissolve the coformer. Following this, the two solvents were mixed together at a temperature of 40.0 ± 0.5 degrees Celsius, which resulted in the precipitation of the drug in the form of co crystals. Finally, the crystals were vacuum-filtered, washed with distilled water three times, and dried at room temperature. [35]

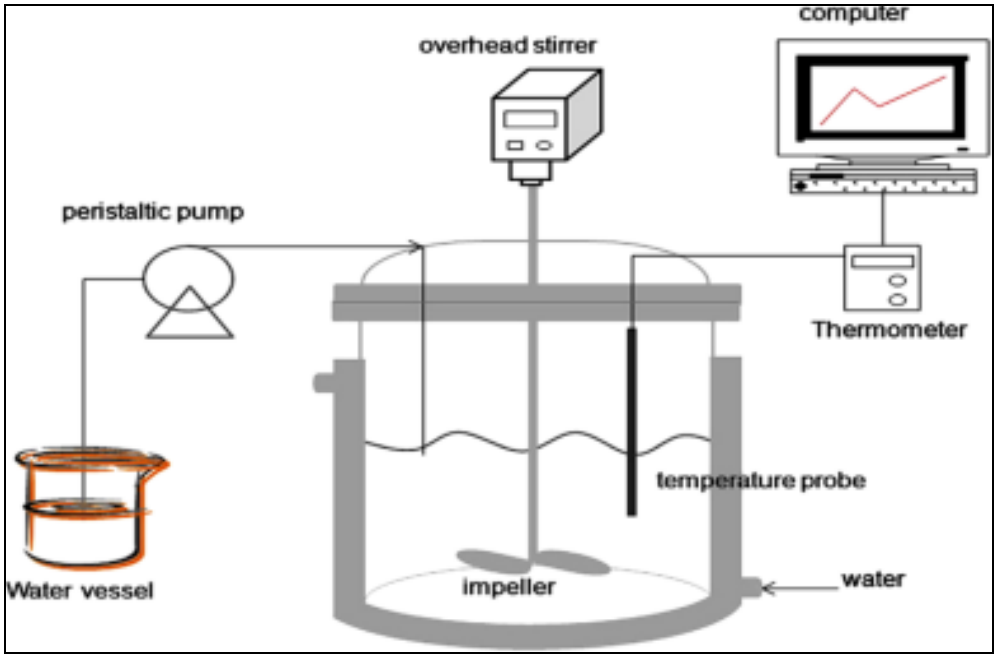

Figure 1: Utilization of anti-solvent apparatus in the procedure

Solid-state technique:

In this method, the drug and the coformer are allowed to come into physical contact with one another, which results in the formation of a liquisolid mass or a eutectic mixture. The co crystals are obtained by evaporating the solvent, and this method follows a mechanism that includes vapour diffusion of the two solids, absorption of moisture, formation of a eutectic mixture, amorphization, and other similar processes. This technique was maintained under a fixed temperature and humidity in order to obtain high-quality co crystals. There was no use of mixing or grinding method involved in the making of the co crystals; however, in some cases it was seen to be used. It produced fewer organic co crystals; however, in recent times, it has gained some popularity due to its speed and the fact that it requires a minimum amount of solvent or none at all, which has attracted its useability. In this method, it appeared that polymer alters the eutectic point of normal API and improves its physical stability. [36]

Solid state grinding:

A considerable quantity of the medication and the coformer was taken in accordance with the stochiometric ratio, and then they were combined with the assistance of a grinding instrument that assists in the reduction of size, which in turn assists in the formation of a covalent link between the active pharmaceutical ingredient [API] and the coformer. Rebuilding phase, transformation phase, and crystal disintegration phase are the three phases that make up this method's procedure. Despite the fact that this approach has various drawbacks, such as polymeric transition throughout the process and incomplete crystal formation, among other things, this method comes with three stages. [37,38]

Liquid-assisted technique:

Kneading, solvent drop, and wet grinding are some of the other names for this process. The incorporation of a smaller quantity of solvent into the combination of the active pharmaceutical ingredient [API] and coformer, which helps to speed up the formation of co crystals, was a very helpful strategy that allowed for the production of the majority of pure co crystals with a greater yield value. Grinding the instruments that are employed, such as a mortar and pestle, a ball mill, or a vibratory mill, might result in a rapid crystallisation of poor quality and quantity if the grinding speed and duration are not taken into consideration. This can also be the case while grinding the instruments. In the process of liquid aided

grinding or kneading, a tiny amount of liquid [solvent] is added to the grinding mixture in a manner that is almost stoichiometric. The active pharmaceutical ingredient [API] and the polymer should be compatible with one another for this procedure; otherwise, there would be no production of crystals. [39]

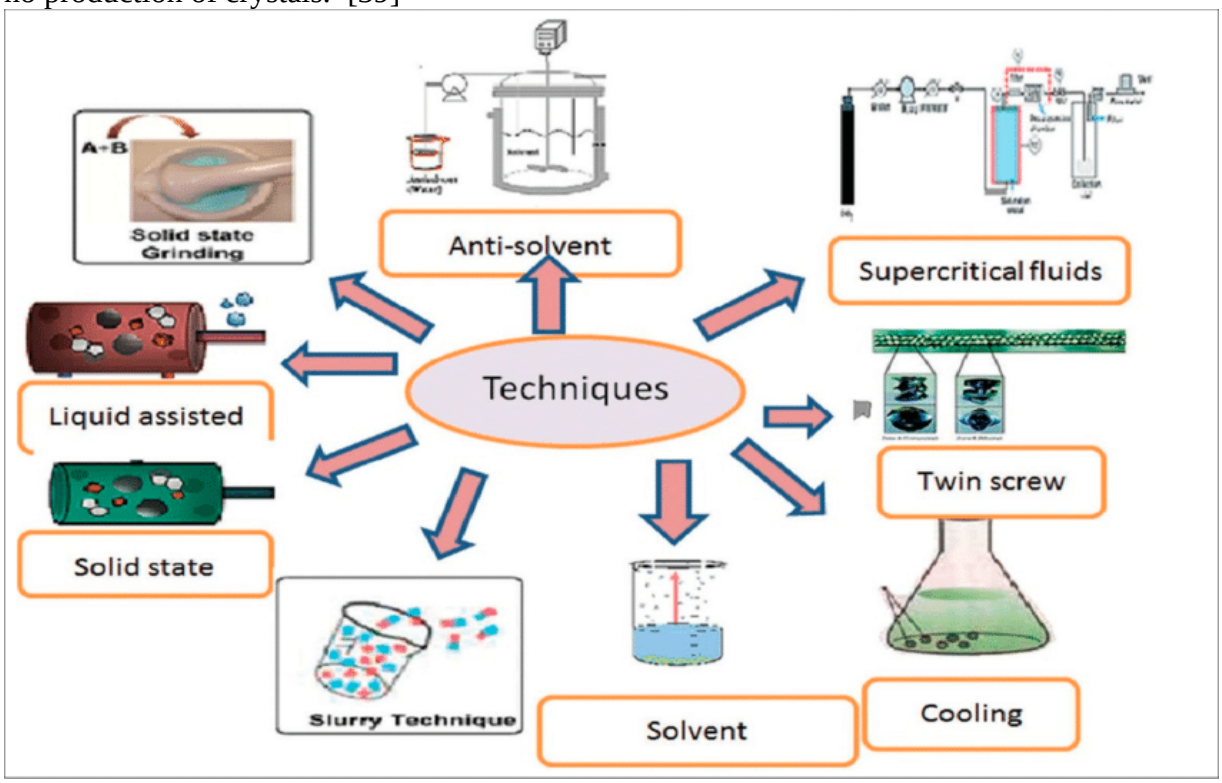

Figure 2: Techniques of co crystal formation

Heat-induced crystallization:

In this method, the drug and the coformer were brought together, and heat was applied, which resulted in the melting of the drug and the coformer, which assisted in the formation of crystals. The temperature was kept at 160 degrees Celsius with continuous stirring until the mixing phase, and then the mixture was cooled to obtain co crystal. This method was also known as the hot melt extrusion method or the solvent drop method. This strategy contributes to the enhancement of surface contact, as well as the selection of the medication that a coformer ought to have by virtue of its thermostable character. [40]

Slurry technique:

In this approach, the solvent is added to the combination of co-crystal materials that dissolves, and then the mixture is mixed with the assistance of an appropriate mixer. After that, the solvent is evaporated at room temperature, and the quantity of the drug and co-former ratio is determined based on the stoichiometric ratio. To use this approach, the substance that is selected must be stable in the solvent, and the method's restriction is that it requires a greater amount of time and solvent. [41]

Twin screw method:

2009 was the year that the author Medina et al. presented this approach for the very first time. In this method, the drug and polymer were chosen according to a stoichiometric ratio, and then they were placed in an extruder with heat applied and continuous stirring. This method helps in the formation of crystals through eutectic mixtures or through a variety of other means. Since this method does not involve any kind of solvent, it is more environmentally friendly than other methods that involve solvents. [42,43]

Freeze drying method:

Using this technique, a drug and coformer solution was created by using a common solvent (Figure 2). After that, the solution was frozen for a short period of time, and it reached temperatures below 0 degrees Celsius. After that, a very high vacuum pressure is applied to the solution, which causes the frozen solution to sublimate into gas. The solid powder that is left over has a low density and amorphous properties, and it is the product of this process. In addition to being known as lyophilization, this procedure is mostly utilised for the purpose of protecting food products from deterioration.

Supercritical fluid method:

The supercritical fluids that are used in this method are responsible for dissolving the active pharmaceutical ingredient [API] and the coformer in a high-pressure chamber. After allowing the mixture to sit for some time, the pressure is then released, which ultimately leads to the formation of crystals. In this particular approach, the supercritical fluid that was utilised was a high-density liquid. CO2 This method has been gaining popularity for the manufacture of nanocrystals over the last few years. The most common supercritical fluids that are used to create co-crystals are carbon dioxide and water. This method adheres to the atomization process, which assists in the development of nuclei for the growth of crystals. [44]

Laser irradiation:

In this method, a high-frequency CO_2 laser was used to irradiate the powder mixture of the co crystal ingredients and begin the recrystallization of the co crystals. The author made an interesting discovery, which is that the polymer that was used must go through a sublimation phase in order to initiate the crystallisation process. This discovery enables us to comprehend that the rearrangements between the molecules of the API and the polymer, as well as the formation of the nuclei for the crystallisation process, take place in the vapour phase. The procedure is carried out in such a way that the high-frequency laser contributes to the elevation of temperature, which initiates the melting of the polymer, and the quick cooling contributes to the production of crystals.[45]

Crystallization by reaction:

In this method, the author has reported the rapid generation of crystals within minutes to an hour by following the method on microscopic and macroscopic scales under certain fixed conditions such as temperature and pressure. The nucleation and crystallisation process begins with the effect of the co-crystal components on reducing the solubility of the molecular complex that the crystallisation process is intended to produce. In comparison to previous approaches, this one is more significant and less harmful to the environment. [46, 47]

Ultrasound-aided crystallization:

Following the application of the active pharmaceutical ingredient [API], the polymer was combined and dissolved in a solvent at a certain temperature. After that, the solution was stored in a sonicator, and then the solution was treated with ultrasonic waves in a sonicator. This method is extremely widely used for the creation of nanocrystals. It was necessary to keep the water at a constant temperature during this process in order to avoid it from breaking. After that, the solution was kept in order to evaporate the solvent, which led to the production of co-crystals. [48,49]

Spray drying process:

In this approach, a slurry combination, emulsions, suspension, organic solvent mixes, and aqueous mixtures are utilized. It is the method that is utilized the most frequently in order to obtain a wide range of goods, ranging from food items to medicinal medications. Due to the fact that it involves atomization and spraying the substance into a heated chamber during quick drying with hot air or at a higher temperature, this method is not appropriate for the production of thermolabile pharmaceuticals. [50]

For the purpose of obtaining the crystals, a few preparations of co-crystals that are now on the market and their respective methods are utilized.

Table 1: reported co-crystals of API along with their preparation technique and conformer.

Sl. No.	Active compound	Coformer	Method	Reference
1	Ibuprofen	Nicotinamide	Solvent evaporation	[42]
2	Ibuprofen	Citric acid	Grinding	[43]
3	Simvastatin	Nicotinamide	Solvent evaporation	[44]
4	Ketoconazole	Ascorbic acid	Slurring method	[45]
5	Fluoxetine	Succinic acid	Solvent evaporation	[46]
6	Acyclovir	Nicotinamide	Solvent evaporation	[47]
7	Acyclovir	Theophylline	Solvent evaporation	[48]
8	Quercetin	Isonicotinamide	Solvent evaporation	[49]
9	Quercetin	Malonic acid	Grinding method	[50]

DISCUSSION:

In order to achieve this goal, it is necessary to identify the eutectic point that corresponds to the concentration of the medication, the conformer, and the solvents. This technique is comprised of three phases that are contained inside a mixed solvent. The optimal condition for this approach is when the drug and the co-former are regarded to be under saturation or unsaturated mean, while the co crystals are thought to be at super saturation. It is feasible for the co crystal to be stable if the active pharmaceutical ingredient [API] or the co-former will be less soluble. use of renewable starting materials and solvent systems, researchers are working to create environmentally friendly synthesis processes for the production of co-crystals. These sustainable processes, which also lessen the effect on the environment, have the potential to be used in the development of more environmentally friendly pharmaceuticals that have improved bioavailability and solubility. Over the course of the last several years, a significant number of active pharmaceutical ingredients [APIs] have been shown to have a poor solubility in water. BCS compounds make up around sixty percent to seventy percent of the chemicals that were found in these newly developed medications. The author made an interesting discovery, which is that the polymer that was used must go through a sublimation phase in order to initiate the crystallisation process. This discovery enables us to comprehend that the rearrangements between the molecules of the API and the polymer, as well as the formation of the nuclei for the crystallisation process, take place in the vapour phase.

REGULATORY GUIDELINES AND APPROVALS FOR PHARMACEUTICAL CO-CRYSTALS

The regulatory landscape for pharmaceutical co-crystals has evolved significantly in recent years, as they have become recognized as a distinct solid-state form with unique properties and advantages over other forms such as polymorphs, salts, and hydrates. Regulatory bodies,

including the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other international agencies, have established specific guidelines for the approval of co-crystals to ensure their safety, efficacy, and quality.

FDA Guidance on Co-Crystals

In 2013, the FDA released a draft guidance titled *"Regulatory Classification of Pharmaceutical Co-Crystals"*, followed by the final guidance in 2018, which provides a clear framework for how co-crystals are classified, evaluated, and approved. According to the FDA, co-crystals are treated as distinct from other solid-state forms such as salts and polymorphs, primarily because of the nature of the interactions between the API and the co-former. While salts involve ionic interactions, co-crystals rely on non-covalent interactions, such as hydrogen bonding.

Key highlights from the FDA guidance on co-crystals include:

1. Classification: Co-crystals are classified as "pharmaceutical co-crystals" when they involve an API and a co-former that are held together by non-covalent bonds, without altering the chemical structure of the API. Importantly, co-crystals are not considered "new molecular entities" (NMEs), which simplifies the regulatory approval process compared to new drugs**.**

2. Co-Former Selection: The FDA requires that the co-former used in the co-crystal be pharmacologically inert and generally recognized as safe (GRAS). The safety of the co-former must be supported by toxicological data, especially when it is not a commonly used excipient in pharmaceutical formulations.

3. Solubility and Dissolution Testing: The FDA emphasizes that co-crystals should demonstrate enhanced solubility and dissolution rate compared to the non-crystallized form of the API. The agency requires robust data to show that the improved solubility leads to increased bioavailability and therapeutic efficacy. Comparative studies between the co-crystal form and the pure API are often necessary to support this claim.

4. Pharmaceutical Equivalence: According to the FDA, co-crystals must exhibit pharmaceutical equivalence to the original API in terms of pharmacokinetic properties, such as absorption and bioavailability. However, co-crystals are not considered polymorphs, and the changes in their solid-state properties must be thoroughly characterized.

5. Regulatory Filing: When submitting a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA), co-crystals must be identified and characterized as part of the drug product's formulation. The FDA requires detailed information on the structure, synthesis, and stability of the co-crystal, along with any potential for phase transformation during manufacturing or storage. Stability testing data is crucial to demonstrate that the co-crystal form remains stable throughout the drug's shelf life.

6. Patent Considerations: Co-crystals can offer a strategic advantage in extending patent protection for a drug product. The new crystalline form can be patented, provided it demonstrates novel properties such as improved solubility, stability, or bioavailability compared to the existing form of the drug. However, this patent strategy must be approached cautiously, as regulators expect robust data to justify claims of improved performance.

EMA Guidelines on Co-Crystals

The European Medicines Agency (EMA) has also issued guidance on co-crystals, focusing on their evaluation in terms of quality, safety, and efficacy. Like the FDA, the EMA recognizes co-crystals as a separate solid-state form that can offer enhanced properties without changing the API's chemical identity.

Key aspects of the EMA's regulatory stance include:

1. Quality by Design (QbD): The EMA encourages the application of Quality by Design (QbD) principles to the development of co-crystals. This involves a systematic approach to understanding the critical material attributes (CMAs) and critical process parameters (CPPs) that influence the performance of the co-crystal. This approach ensures that the manufacturing process consistently produces co-crystals with the desired properties.

2. Toxicological Assessment: Similar to the FDA, the EMA requires a comprehensive toxicological assessment of the co-former used in the co-crystal. The co-former should either have prior approval for use in pharmaceuticals or be supported by safety data from preclinical and clinical studies.

3. Regulatory Submission: Co-crystals must be fully characterized in regulatory submissions, including details of their structure, solid-state properties, and dissolution behavior. The EMA also emphasizes the need for in vivo bioequivalence studies to demonstrate that the co-crystal form has comparable or superior bioavailability to the non-crystallized API.

Other International Regulatory Guidelines

Regulatory bodies in countries such as Japan, Canada, and Australia have also begun to issue guidelines specific to co-crystals. These guidelines align closely with those of the FDA and EMA, focusing on the need for comprehensive characterization, safety evaluation of co-formers, and demonstration of enhanced solubility and bioavailability.

Challenges in Regulatory Approval

Despite the clear benefits of co-crystals, obtaining regulatory approval can still pose challenges. For instance, regulators often require extensive stability testing to ensure that the co-crystal does not undergo undesirable phase transformations during manufacturing or storage, which could affect its performance. Additionally, the requirement for in vivo bioequivalence studies can add complexity to the approval process, particularly if the co-crystal demonstrates significantly altered pharmacokinetics.

The regulatory pathway for co-crystals is well-established, with agencies like the FDA and EMA offering specific guidance to facilitate their approval. Co-crystals present an attractive option for improving the solubility and bioavailability of APIs while adhering to stringent regulatory standards. By ensuring that co-formers are safe and that the co-crystal form enhances drug performance, pharmaceutical companies can take advantage of co-crystals to create more effective and sustainable drug products.

CONCLUSION:

Pharmaceutical co-crystals offer a promising approach to overcoming the challenge of poor water solubility in drug development. By modifying the physicochemical properties of active pharmaceutical ingredients (APIs) without altering their chemical structure, co-crystals have the potential to significantly enhance solubility and, subsequently, oral bioavailability. Co-crystals are particularly beneficial in cases where polymorphism complicates drug formulation, salts cannot be formed due to the neutrality of the compound, or poor solubility impairs efficacy. However, despite the growing interest and ongoing research in this area, the body of evidence supporting the widespread application of co-crystals in pharmaceutical formulation remains relatively limited.

Limitations and Future Directions

While co-crystals show clear potential, there are still several limitations and gaps that need to be addressed in future research. First, the current studies on co-crystals are often confined to solubility and dissolution data, with fewer investigations into the long-term stability and scalability of co-crystal production. Stability studies over time and under various environmental conditions (such as humidity and temperature variations) are crucial to ensure that co-crystals remain stable throughout their shelf life and do not undergo undesirable phase transformations.

Additionally, although co-crystals can improve bioavailability, the mechanisms through which they affect pharmacokinetics need to be better understood. More in-depth studies, including in vivo pharmacokinetic studies and clinical trials, are essential to fully characterize the performance of co-crystals in a real-world therapeutic context. This will help establish whether the enhanced solubility translates into meaningful improvements in drug efficacy and safety in patients.

Future research should also focus on developing a more comprehensive framework for co-former selection. Although the FDA and other regulatory bodies provide guidelines for co-former safety, there is still a need for high-throughput screening methods to identify optimal co-formers that improve solubility and bioavailability while maintaining safety and regulatory compliance.

Practical Applications in Pharmaceutical Formulation

The findings of this research can inform the development of new strategies in pharmaceutical formulation, particularly for drugs with poor solubility that have limited therapeutic efficacy. For example, co-crystals can be used in the formulation of generic drugs, where patent expiration may lead to increased competition and the need for novel formulations that enhance drug performance. Co-crystal technology can also be applied in developing pediatric and geriatric formulations, where bioavailability and patient compliance are often challenging.

Furthermore, co-crystals could play a key role in personalized medicine, where drug solubility and bioavailability may vary depending on individual patient profiles, such as differences in gastrointestinal pH or enzyme activity. By tailoring co-crystal formulations to specific patient needs, pharmaceutical companies could offer more precise and effective treatments.

Pharmaceutical co-crystals present a novel and effective solution for improving the solubility and bioavailability of poorly soluble APIs, addressing a critical limitation in oral drug delivery. However, to fully realize their potential, further research is needed to explore their long-term stability, scalability, and in vivo performance. By addressing these gaps, co-crystal technology can pave the way for more sustainable and effective pharmaceutical formulations, potentially revolutionizing the field of drug development and offering new opportunities for the treatment of conditions requiring enhanced oral bioavailability.

REFERENCES:

1) Kumar S, Nanda, A. Pharmaceutical Cocrystals: An Overview. *Indian J. Pharm. Sci.* **79**. (2017)10.4172/pharmaceutical sciences.1000302).
2) Kara, Dhatri D,Rathnanand, Mahalaxmi. Cocrystals and Drug–Drug Cocrystals of Anticancer Drugs: A Perception towards Screening Techniques, Preparation, and Enhancement of Drug Properties. *Crystals*. **12**. 1337(2022).10.3390/cryst12101337
3) Bandaru, Ravi, Rout, Smruti, Rekha, Kenguva, Gowtham Gorain B , Alhakamy N, Kesharwani P Dandela R. Recent Advances in Pharmaceutical Cocrystals: From Bench to Market. *Front. pharmaco.***12.**10.3389/fphar.2021.780582.(2021)
4) Anand, Kumar R, Nanda A, Pharmaceutical Co-Crystals - Design, Development and Applications. *Drug Deliv. Lett.* **10**. 169-184. 10.2174/2210303109666191211145144.(2020)
5) Shaikh, Singh R, Walker, Croker G, Denise. Pharmaceutical Cocrystal Drug Products: An Outlook on Product Development. *Trends Pharmacol Sci*. **39**. 10.1016/j.tips.2018.10.006 (2018).
6) Chadha R, Saini A, Arora P, Bhandari S, Pharmaceutical Cocrystals: A Novel Approach for Oral Bioavailability Enhancement of Drugs. *Crit Rev Ther Drug Carrier Syst.* **29**.183-218. 10.1615/CritRevTherDrugCarrierSyst.v29.i3.10. (2012).
7) Bolla G, Pharmaceutical Cocrystals: Walking the Talk. *Chem. Commun.***52**.8342-8360(2016).
8) Patel D, Puranik, Prashant, Pharmaceutical Co-crystal: An Emerging Technique to enhance Physicochemical properties of drugs. *Int. J. Chemtech Res.*. 13. 283-290(2020).
9) Chauhan V, Mardia R, Patel M Suhagia B, Parmar K. Technical and Formulation Aspects of Pharmaceutical Co-Crystallization: A Systematic Review. ChemistrySelect.**7**.(2022) 10.1002/slct.202202588.
10) Yousef M, Vangala V. Pharmaceutical Co-crystals: Molecules, Crystals, Formulations, Medicines. *Cryst. Growth Des.* 2019, 19, 12, 7420–7438 (2019)10.1021/acs.cgd.8b01898.
11) Karimi-Jafari M, Padrela L, Walker GM et al. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. Cryst Growth Des **18(**10)6370–87(2018).https://doi.org/10.1021/acs.cgd.8b00933
12) Guo M, Sun X, Chen J et al. Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. *Acta Pharm Sin B* **11**:2537-64.(2021)https://doi.org/10.1016/j. apsb.2021.03.030
13) Dhondale MR, Thakor P, Nambiar AG *et al.* Co-crystallization approach to enhance the stability of moisture-sensitive drugs. *Pharmaceutics* **15**:189. (2023) https://doi.org/10.3390/pharmaceutics15010189
14) Ngilirabanga JB, Samsodien H. Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy. *Nano Sel* 2:512–26. (2021) https://doi.org/10.1002/ nano.202000201

15) Jagadeesh Babu N, Nangia A. Solubility advantage of amorphous drugs and pharmaceutical cocrystals. *Cryst Growth Des;* 11(7) 2662–79 (2011). https://doi.org/10.1021/cg200492w
16) Fong SYK, Ibisogly A, Bauer-Brandl A. Solubility enhancement of BCS Class II drug by solid phospholipid dispersions: Spray drying versus freeze-drying. *Int J Pharm* **496**,382–91(2015). https://doi.org/10.1016/j.ijpharm.2015.10.029
17) Yuvaraja K, Khanam J. Enhancement of carvedilol solubility by solid dispersion technique using cyclodextrins, water soluble polymers and hydroxyl acid. *J Pharm Biomed Anal* **96**,10–20(2014). https://doi.org/10.1016/j.jpba.2014.03.019
18) Hisada N, Takano R, Takata N *et al*. Characterizing the dissolution profiles of supersaturable salts, cocrystals, and solvates to enhance in vivo oral absorption. *Eur J Pharm Biopharm* **103**, 192–9 (2016). https://doi.org/10.1016/j.ejpb.2016.04.004
19) Savjani KT, Gajjar AK, Savjani JK. Drug solubility: Importance and enhancement techniques. ISRN Pharm 195727(2012). https:// doi.org/10.5402/2012/195727
20) Etter MC. Hydrogen bonds as design elements in organic chemistry. *J Phys Chem* **95**, 4601-10.(1991)https://doi.org/10.1021/ j100165a007
21) Etter MC. Encoding and decoding hydrogen-bond patterns of organic compounds. *Acc Chem Res* **23**,120–6(1990).https://doi. org/10.1021/ar00172a005
22) Reddy DS, Craig DC, Desiraju GR. Supramolecular synthons in crystal engineering. 4. Structure simplification and synthon interchangeability in some organic diamondoid solids. *J Am Chem Soc* **118**,4090-93(1996) https://doi.org/10.1021/ja953373m
23) Almarsson O, Zaworotko MJ. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem Commun*, **17**, 1889–96 (2004). https://doi.org/10.1039/b402150a
24) Duggirala NK, Perry ML, Almarsson O et al. Pharmaceutical cocrystals: Along the path to improved medicines. *Chem Comm* **52**,640–55(2016). https://doi.org/10.1039/ c5cc08216a
25) Singha S, Jana R, Mondal R et al. Photo-responsive Schottky diode behavior of a donor–acceptor co-crystal with violet blue light emission. *Cryst Eng Comm* **23**, 3510–23(2021). https://doi.org/10.1039/d1ce00020a
26) Singha S, Goswami S, Dey SK et al. Synergistic effect of various intermolecular interactions on self-assembly and optoelectronic behaviour in co-crystals/salts of tetrabromoterephthalic acid: A report on their structure, theoretical study and Hirshfeld surface analysis. *Cryst Eng Comm,* **22,** 8197–207(2020). https://doi.org/10.1039/d0ce01102a
27) Braga D, Grepioni F, Maini L et al. From unexpected reactions to a new family of ionic co-crystals: The case of barbituric acid with alkali bromides and caesium iodide. *Chem Comm* **46**,7715–7(2010).https://doi.org/10.1039/c0cc02701d
28) Qiao N, Li M, Schlindwein W et al. Pharmaceutical cocrystals: An overview. *Int J Pharm* **419**, 1–11(2011). https://doi.org/10.1016/j. ijpharm.2011.07.037
29) Kale D, Zode S, Bansal A. Challenges in Translational Development of Pharmaceutical Cocrystals. *J Pharm Sci.* **106**(2), 457-470(2017). 10.1016/j.xphs.2016.10.021.
30) Dutt B, Choudhary M, Budhwar V. Cocrystallization: An innovative route toward better medication. *J Rep Pharma Sci*, **9**,256-70(2020).
31) Guo M, Sun X, Jiahui C , Cai T, Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. *Acta Pharmaceutica Sinica B*.**11**(8), 2537-2564(2021). 10.1016/j.apsb.2021.03.030.

32) Kara DD, Rathnanand M, Cocrystals and Drug–Drug Cocrystals of Anticancer Drugs: A Perception towards Screening Techniques, Preparation, and Enhancement of Drug Properties. *Crystals*. **12**, 1337(2022). 10.3390/cryst12101337.
33) Dutt B, Choudhary M, Budhwar V, A Comparative Study of Selected Drug Delivery Systems: Key Emphasis on Cocrystallization. *Drug Deli Let.***11**(2),136-155(2021), 10.2174/2210303111666210111142458.
34) Dutt B,Correlation among crystal structure, mechanical behavior, and tabletability in the co-crystals of vanillin isomers. *Cryst Growth Des* 15,1827–32(2021). https://doi. org/10.1021/cg5018642
35) Kumar RB, Hydrogen bonds as design elements in organic chemistry. J Phys Chem, **95**, 4601-10(1991) https://doi.org/10.1021/ j100165a007
36) Rachna A, Encoding and decoding hydrogen-bond patterns of organic compounds. *Acc Chem Res*, **23,** 120–6(1990). https://doi. org/10.1021/ar00172a005
37) Rahamatullah S, Supramolecular synthons in crystal engineering. 4. Structure simplification and synthon interchangeability in some organic diamondoid solids. *J Am Chem Soc*, **118**:4090–3(1996). https://doi.org/10.1021/ja953373m
38) Chadha R, Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem Commun* 12, 1889–96(2004). https://doi.org/10.1039/b402150a
39) Geetha B, Pharmaceutical cocrystals: Along the path to improved medicines. *Chem Comm*, 52, 640–55(2016). https://doi.org/10.1039/ c5cc08216a
40) Patel JD, Photo-responsive Schottky diode behavior of a donor–acceptor co-crystal with violet blue light emission. *Cryst Eng Comm* **23**, 3510–23(2021). https://doi.org/10.1039/ d1ce00020a
41) Chauhan V, Synergistic effect of various intermolecular interactions on self-assembly and optoelectronic behaviour in co-crystals/salts of tetrabromoterephthalic acid: A report on their structure, theoretical study and Hirshfeld surface analysis. *Cryst Eng Comm* **22**, 8197–207(2020). https://doi.org/10.1039/ d0ce01102a
42) Malaz Y, From unexpected reactions to a new family of ionic co-crystals: The case of barbituric acid with alkali bromides and caesium iodide. *Chem Comm* 46, 7715–7(2010). https://doi.org/10.1039/c0cc02701d
43) Zode S, Pharmaceutical cocrystals: An overview. *Int J Pharm* , 419, 1–11(2011). https://doi.org/10.1016/j. ijpharm.2011.07.037
44) Yadav B, Khusrsheed A, Sinh R, Cocrystals: A Complete Review on Conventional and Novel Methods of its Formation and its Evaluation. *Asian J. Pharm. Clin. Res.* 12, 68–74(2019).
45) Moradiya HG, Islam MT, Scoutaris N, Halsey SA, Chowdhry BZ, Douroumis D. Continuous manufacturing of high quality pharmaceutical cocrystals integrated with process analytical tools for in-line process control. *Cryst Growth Des* 16, 3425-34. 2564 (2016)
46) Zhao L, Hanrahan MP, Chakravarty P, DiPasquale AG, Sirois LE, Nagapudi K, Lubach JW, Rossini AJ. Characterization of pharmaceutical cocrystals and salts by dynamic nuclear polarization-enhanced solid-state NMR spectroscopy. *Cryst. Growth Des.*, **18**(4), 2588-601(2018).
47) Chaudhari S, Nikam SA, Khatri N, Wakde S. Co-crystals: a review. *J. Drug Deliv.* Ther., 8(6), 350-8(2018).
48) Thayyil AR, Juturu T, Nayak S, Kamath S. Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications. *Adv. Pharm. Bull*, 10(2), 203(2020).

49) Gnanamoorthy P, Karthikeyan V, Prabu VA. Field Emission Scanning Electron Microscopy [FESEM] characterisation of the porous silica nanoparticulate structure of marine diatoms. *J. Porous Mater* **21**(2), 225-33(2014).
50) Rekdal M, Pai A, Choudhari R, Sathyanarayana MB. Applications of co-crystals in pharmaceutical drugs. *Syst. Rev. Pharm* 9(1), 55-7(2018).