Advances in Bioresearch
Adv. Biores., Vol 15 (5) September 2024: 432-442

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.15.5.432442

Advances in Bioresearch

REVIEW ARTICLE

A Comprehensive Review on Cocrystal

Sanchi Kamble, Revan Karodi
DR. D Y Patil college of Pharmacy Akurdi, Pune
Corresponding Author: Kamble Sanchi
Email: sanchikamble67@gmail.com

ABSTRACT

Low oral bioavailability and poor water solubility present serious problems for medication developers. According to the Biopharmaceutics Classification System, classes II and IV include a large number of medications that have solubility problems. One method that has shown promise co-crystallization is an approach used to boost lubricity of drugs that are not highly soluble in water. To develop a new crystalline solid that maintains the active pharmaceutical ingredient's (API) pharmacologic properties while having improved physicochemical characteristics such soluble content, equilibrium, the drug's bio and permeability, it entails mixing the API with an appropriate co-former. Selecting the proper co-former is crucial in cocrystal design. Researchers employ a variety of techniques to screen potential co-forms, including the, electron-like screening model for real solvents (COSMO-RS), hydrogen bond theories, syntonic engineering, The Cambridge Structural Database (CSD), Fabian's method, lattice energy calculation, online cocrystal imaging method, thermal analysis, measuring saturation temperatures, and empirical observations.

Received 24.05.2024 Revised 01.06.20234 Accepted 11.07.2024

How to cite this article:
Sanchi Ke, Revan K . Comprehensive Review on Cocrystal. Adv. Biores., Vol 15 (5) September 2024: 432-442.

INTRODUCTION

Since solid dosage forms are simple to make and accepted by patients, they account for more than 80% of marketed formulations. The solubility and dissolution rate of medicines have a major impact on gastrointestinal absorption in oral drug delivery systems. In pharmaceutical clinical trials, 80–90% of active pharmaceutical ingredients (APIs) are poorly soluble. BCS classes 2 (low solubility/low permeability) and 4 (poor solubility/high permeability) are the two categories into which the plenty of the API are divided [1]. Improving BCS II medication solubility and dissolution rates is a significant challenge. It is challenging to generate solid dosage forms for most APIs due to their unfavourable physical-chemical characteristics, which include poor flowability, compatibility, and poor water solubility [2]. During processing and storage, heat, light, and moisture can produce physical-chemical changes (degradation) and instability due to polymorphic transformations, which can have a substantial effect on the quality and performance of a medicinal product [3]. In the pharmaceutical industry, in order to create novel solid dosage forms, multi-component systems such as solvents, dries out, different forms, and co-crystals are essential [4].

What are co-crystals?

co-crystals are a precisely engineered combination of two or more compounds that form a new solid crystalline structure with unique properties. The components, which can be organic, inorganic, or a combination of both, are combined in specific stoichiometric ratios, meaning they are carefully balanced to ensure the formation of a uniform structure. This process results in the generation of a dynamic and homogeneous crystalline structure with enhanced properties and potential applications. Co-crystals were described in a variety of ways, including as organic chemicals and addition compounds. Drug processing, delivery, and efficacy were all directly impacted by the physiochemical and technical improvements made to pharmaceutical products. A substance's essential components are directly impacted by the crystal structure of the API. About 40% of the 90% of novel chemical entities (NCE) that have been thoroughly examined have solubility limitations, meaning that they cannot be absorbed by the body through standard methods [5][6].

Making API in salt forms—despite the ionisable groups that cause the production of the corresponding salts—was one of the greatest ways to achieve the increased bioavailability of API. A novel solid-state formulation of molecules and complexes had to be created in light of all the information, hetero molecular crystals [7].

Different solid forms

Substances in their solid state are described by chemists as there are essentially two types of solid matter depending on how its structures are arranged: crystalline and amorphous forms, which have different characteristics. Crystal materials are further divided into two groups: substances with several crystal components and compounds with a single crystal component. Hydrates, salts, solvates, polymorphs, and co-crystals are among the solid forms that result from the assembly of several molecules in these multicomponent crystalline substances in various patterns [8].

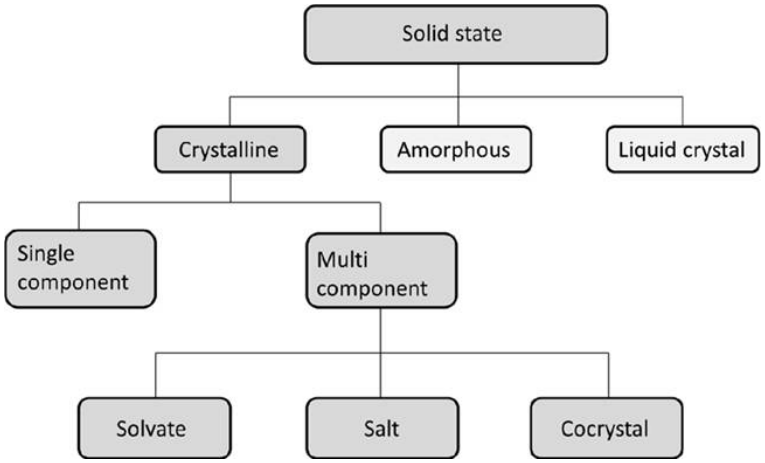

Fig 1: Classification of different solid forms

Comparison of cocrystal and other solid form:

Cocrystal Versus Salts, Solvates, Hydrates: The compounds known as polymorphs can exist as hydrates and solvates, as well as other crystalline forms. (sometimes referred to as pseudo-polymorphs), and amorphous forms Because of the differences in their Compared to typical crystal configurations, polymorphs show distinct physical and chemical traits. The compounds that arise when a whole proton is transferred from one material to another are known as salts. [9]. Cocrystals and Salts can be viewed as either side of multicomponent structures. Salts can also use to solubility improvement, crystallinity and pharmaceutical compound stability.

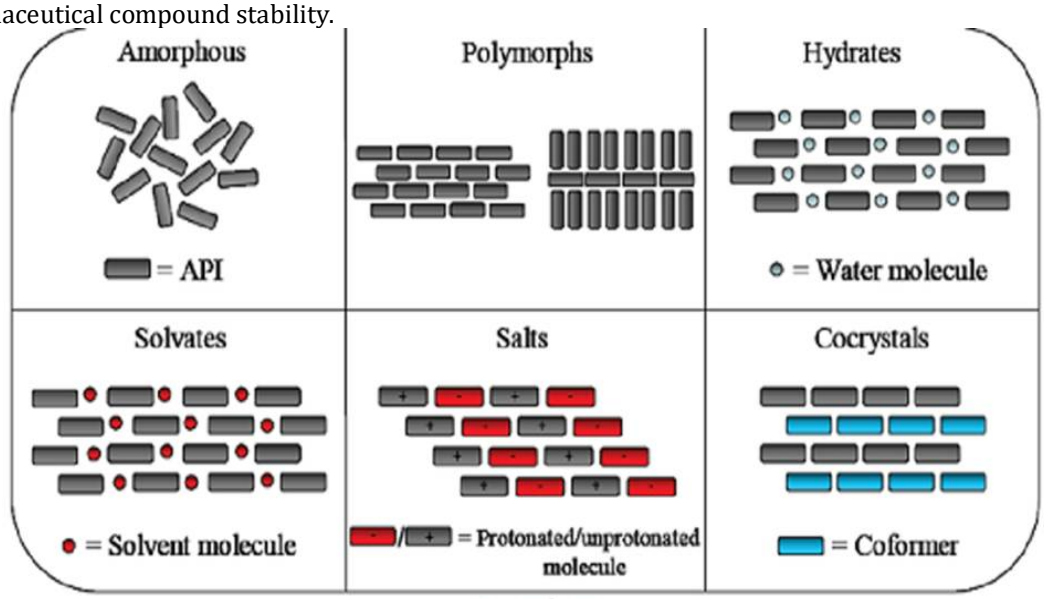

Fig No:2 Comparison of different solid forms

Different types of parameters are used to define co-crystals using different definitions. The shared parameter is less the less Cocrystals, sometimes referred to as multi-component crystals, are crystalline

solids consisting of two or more distinct components held together by freely reversible non-covalent interactions. The different elements that, depending on the environment, can become solid, gas, liquid or ionic or neutral species. A co-former is a molecule that is deemed pharmaceutically acceptable (GRAS), does not alter the intrinsic activity, and does not alter the structural composition of the API. Depending on the co-former component's makeup, these variations in the various pharmacological qualities occur.[10]

GRASS APPROVED CO-FORMER:

Substances that, in the opinion of the classified as widely acknowledged as prudent (GRAS) for use as food additives by America to get Department of Health and Human Services.

- ✓ Saccharin
- ✓ Nicotinamide
- ✓ Hippuric acid
- ✓ 4-amino benzoic acid
- ✓ 4-Hydoxy benzoic acid
- ✓ Succinic acid
- ✓ Cinnamic acid
- ✓ Citric acid
- ✓ Glutaric acid
- ✓ Mannose
- ✓ Lactose
- ✓ Vinylic acid
- ✓ Sucrose
- ✓ Maltose

Steps involved in Cocrystal Engineering:

1. Selection of API
2. Selection of conformer
3. Selection of suitable approach
4. Screening of co-crystal
5. Co-crystal characterization
6. Evaluation of Co-crystal

Selection of co former with API by different screening methods

A primary problem in co-crystal development is co-former selection. Pharmaceutical co crystal creation and design is a multi-step, intricate process. A co-former and an active ingredient in a drug (API) are the minimum number of components that make up a co-crystal. An excipient, an additional API, or any substance on the GRAS list can function as the co-former. Co-formers are chosen by experimental or knowledge-based techniques. All kinds of coformers for an API mostly used experimenting as a traditional approach, and the structure of the co-crystal was subsequently clarified by appropriately described approaches. The procedure of using this kind of method is costly and time-consuming. In order to choose the best co-former for an API, research implemented additional knowledge-based methodologies that were created and put into practice. following are the screening methods.[10]

1. Hydrogen Bond rules:

The hydrogen-bonded supra molecular synthons are the key to the success of co-crystal invention. It is unequivocally demonstrated that in crystal engineering, bonding constituted the strongest interactions. In crystal engineering, hydrogen bonds are known as "key-interactions" due to their strength, directionality, and abundance in organic molecules. Apart from offering valuable insights such as favoured connection patterns, hydrogen-bond selectivity, and the stereotypical electrical characteristics of bonds made of hydrogen, illustrate the connections between graph sets that analyse bond patterns of one or more patterns.

General guidelines for Etters Hydrogen bond rules

1) Every eligible donor and acceptor were utilized.

2) Inter molecular hydrogen bonds are typically not preferred over intra-hydrogen bonds in six-membered rings when they are able to produce them.

3) Following the establishment of the intramolecular hydrogen bonds, the optimal donor and acceptor of protons will proceed to create intermolecular hydrogen bonds. with one another molecule.[11]. Selective hydrogen bonding is contingent upon the functional group. [12][13].

2.Synthonic engineering

By using crystal engineering, a pharmaceutical cocrystal can be created with the intention of improving an API's solid-state properties without altering its basic core. Understanding the fundamentals of synthon creation through non-covalent contact is also a part of crystal engineering. [14]. It is usual for the carboxylic acid homosynthon in Fig. to develop through a C O· · ·H–O hydrogen bond. The amide homodimer in Figure 1(c), which forms a cocrystal by a C O· · ·H–N hydrogen link, is another extensively researched homosynthon. In addition to homosynthons,[15] other advantageous heterosynthons include furthermore depicted in Figure 3, including alcohol-ether in Figure 3 (e), carboxylic acid-pyridine in Figure 1(a), and carboxylic amide in Figure 1(b).

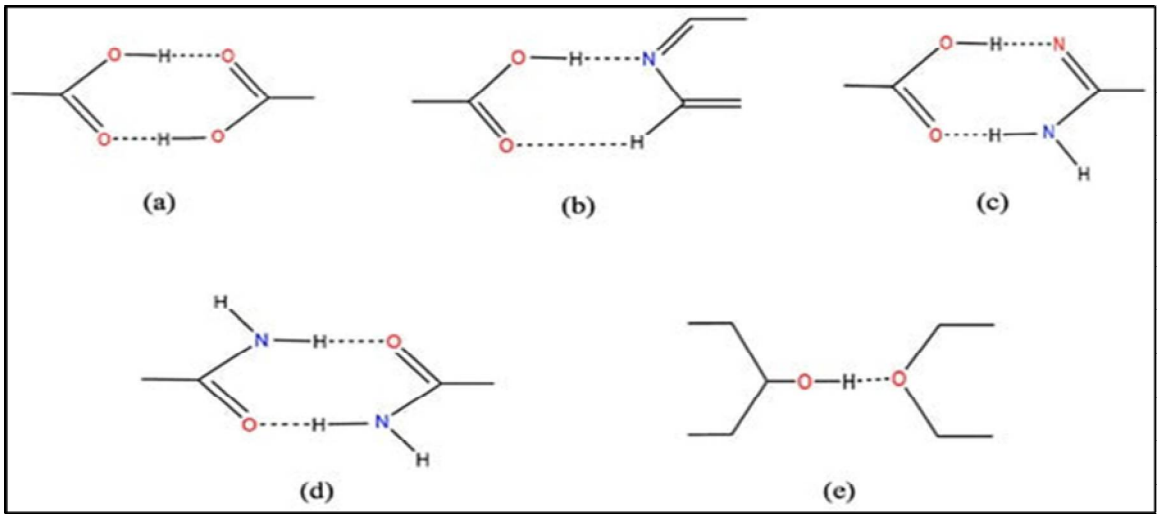

Figure No 3: Typical supramolecular synthon,(a) Homosynthon (b) Heterosynthon

3.Cambridge structural database:

The most popular methods for choosing a coformer and creating cocrystals are hydrogen-bond rules, pKa rules, and screening based on the Cambridge Structural Database (CSD), which are covered in detail below. 2.1. CSD Supramolecular retrosynthesis analysis, which comprises between-molecular unit locking to obtain the necessary cocrystal structure, can be performed with the use of the CSD. [16]. There are currently more than 1.2 million crystal structures in the CSD library.

4.Pka Value :

One way to show how strong an acid is to use its pka value. When the solution's dissociation constant is acidic, PKA is a negative logarithm. The most simple and efficient way to determine if the obtained product is salt or co-crystal is to use the ΔpKa determination method. The ΔpKa rule has been modified by Cruz-Cabeza et al. to be utilized as a tool for measuring and predicting co-crystal formation. Ka (base) – pKa (acid) = ΔpKa If the value of ΔpKa falls -1 to 4, co-crystal formation is indicated [17] It is highly probable that salt production has taken place if the difference in pKa (ΔpKa) is larger than 4. [18].

Using the ΔpKa rule, it was expected that the corresponding GRAS compounds will form salts or co-crystals. Theophylline (1:1) ratio pyrimethamine produced cocrystals with a pKa of 1.66, and 2-oxoglutarate (1:1) pyrimethamine generated a salt with a pKa of 4.47[19][20]

5.Fabian's method

Through the use of the Cambridge Structural Database (CSD), several sets of confirmed co-crystals that comprise a structure were isolated, and molecular properties like size and shape, surface area, molecular electrostatics, and the counts of individual atoms, bonds, and groups were calculated for each molecule. A database describing molecule pairings able to produce co-crystals was constructed using computed molecular properties. Coformer shape and polarity showed the strongest descriptive correlations [21].

6.Hansen Solubility Parameter (HSP)

Hildebrand and Scott established the notion of solubility parameters and advanced the idea of miscibility with comparable values [22]. Three distinct components made up a molecule's total cohesive energy, such as: Dipole-dipole forces (Dispersion Polar) bonding with hydrogen.

The cohesive energy parameters can be utilized to ascertain a material's physicochemical characteristics, such as its melting point and solubility. The cohesive energy is the addition of the forces that hold a material together, including ionic, covalent, hydrogen, and Vander Waals bonds [22]. To compute the

solubility parameters (δ), CED is utilized. υ= [CED] 0.5 = [ΔEV/VM] 0.5 -------- (1) in where VM stands for molar volume and EV for energy of vaporization. The units used to measure δ were [J/cm3 0.5][23][24].

7.Virtual Co-crystal Screening:

A computational method for finding new drugs is called virtual screening. The use of computer programs to "an automatically evaluate very large libraries of compounds" The software used to conduct the virtual screening was created by Professor Christopher Hunter and his colleagues. The hierarchical ordering of interactions between functional groups, which establishes the structure of a crystalline solid, formed the basis for the virtual screening of co-crystals. To forecast the intermolecular interactions, this method made use of Hunter's hydrogen bond characteristics, such as α and β. E is the energy of solid forms; it is equal to -∑ijαiβj. As per Hunter's approach, co-crystals are thought to have exclusively attractive electrostatic interactions [25].

Physiochemical properties of cocrystals

Physical and chemical characteristics, including: stability, dissolution, solubility, melting point, and crystallinity These characteristics are crucial for advancing a novel compound—like a cocrystal—through its early stages of development.

1.Melting Point :

The melting point can be found by dividing the fusion's change in entropy by its change in enthalpy because the melting process is thermodynamic and there is no change in free energy connected with the transition. Because it provides more accurate thermal information, such as the enthalpy of fusion, differential scanning calorimetry, or DSC, is generally chosen when obtaining data on melting points above traditional melting point apparatus. To categorize polymorphic pairs of chemicals as enantiotropic or monotropic.[26]

2.Stability:

A parameter that is carefully considered when developing a novel chemical entity is stability. Measurements of both chemical and physical consistency are collected frequently under accelerated equilibrium settings [27]. The absorption of water is taken into account during handling and packaging. The presence of water can also cause form alterations, degeneration, and worse if the result of consuming water is not looked into early on in the process. Additional research on heat stress is included [28].

3.Solubility:

Increasing a poorly soluble material's solubility is one of the primary objectives of cocrystal research. There is little doubt that cocrystals expand the range of solid shapes that are conceivable for neutral chemicals. The solubility of a free acid or free base can be increased by either salt or cocrystal, but it's not always clear if one has formed, and comprehending the system may require a number of approaches. There are a few considerations to consider when referring to solubility data. The first connects equilibrium with data of kinetic (or perceived) solubility. Kinetic solubility estimates are usually obtained from a single measurement taken at a single time. If any preliminary trials have been conducted, it remains unknown.

4.Intrinsic dissolution:

By pressing a disc or pellet in a dissolving tank—typically with the use of a Woods device—this is accomplished [29]. The dissolving rate (in mg/cm2·min) is calculated by measuring the concentration of the solution over time. For powders that are not easily compressed, compression pressures may be crucial since the disk must stay unbroken during the experiment. Additionally, it's critical that the pellet's form remain unchanged both during the dissolution study and after pressing. After the experiment is over, XRPD data on the initial disc and the remaining disk can be acquired to identify any significant form changes that might have an impact on the dissolving results.

5.Bioavailability

It gauges how quickly and how much a medicine releases into the bloodstream. [42] The bioavailability of new medications in animals is a major consideration. There are numerous approaches to set up studies in order to collect accurate data for advancement. Among the species that can be utilized in animal research are rats, rabbits, dogs, pigs, and monkeys. Small-scale studies (4-6 animals) may be used in these investigations, which are usually carried out in the early phases of research, in order to quickly determine pharmacokinetic data on a novel form. All forms/formulations are typically administered to the animals, with a one-week washout interval between each treatment. This allows all the research materials to be directly compared inside the same animals. Studies on the bioavailability of crystals in animals are scarce [30].

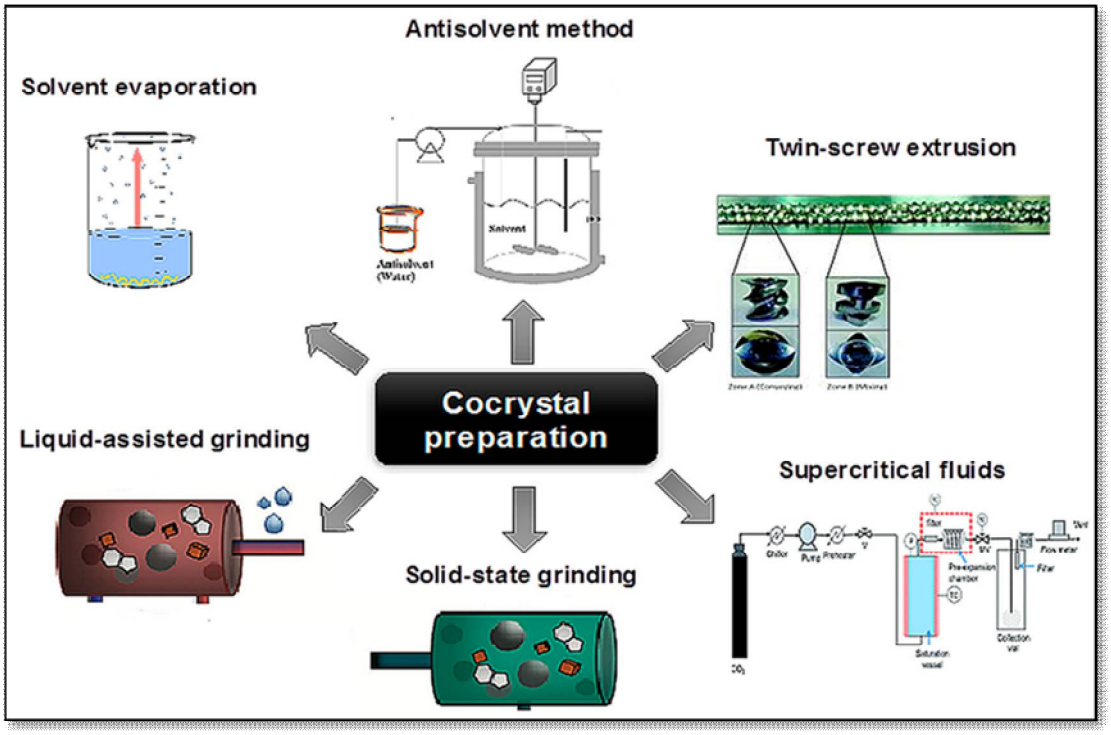

Fig No:4 Preparation method of Co-crystals

Preparation of co-crystal:

Co-crystal can be synthesized using various techniques, including solution-based methods, soli-state grinding technique, and other reported approaches. Solution-based crystallization is effective when the two components have comparable solubility, although it does not guarantee co-crystal formation. Ensuring the appropriate solubility of both components is crucial to prevent undesired precipitation. Solid-state grinding technique yields outcomes akin to solution methods and involved dry grinding often produces superior results due to enhanced reaction kinetics and improved interaction between the components, thereby promoting the formation of co-crystal

1. **Grinding**

A. solid Assisted grinding

1. **Manual**
2. **Mechanochemical (ball mill)**

B. Liquid assisted grinding

2. **Solvent evaporation**
3. **Slurring**
4. **Antisolvent co-crystallization**
5. **Supercritical fluid processing**
6. **Sonocrystallization**
7. **Spray drying**
8. **Hot melt extrusion**

1.Grinding

A.Solid assisted grinding

Solid-state grinding technique have proven effective in producing co-crystal powder samples. There are two main approaches:

a. **Manual:**

it is also called as net grinding where the dry mix of powder is done under the pressure with the help of motor pestle and. for definite period of time and at definite temperature

When creating co-crystals, the end result is frequently the same regardless of the grinding or solution procedure utilised. This homogeneity could imply that patterns of hydrogen-bond connectivity are innate properties of the molecules and not influenced by outside variables like as crystallisation conditions or solvent influences. There are certain exceptions to the general rule, though. While growth in solution and solid-state grinding can yield some co-crystal materials, grinding alone can yield others. It is possible that the difficulty of obtaining suitable molecular configurations, rather than The explanation is the steadiness

of the initial stages for the failure to produce co-crystals through grinding. Solvent addition as a stabilizer may have a role in co-crystal formation situations where it is successful in solution but fails to gel in grinding. There have long been references to the use of solid-state pounding for co-crystal preparation[31].

b. Mechanochemical:

In this technique, the conformer and API should undergo size reduction under the pressure in ball mill. whereas, the temperature should be monitored to avoid degradation of API or conformer solid-state griding offers in efficiency advantages compared to solution-based methods because there's no less of yield due to solubility in a solvent. challenges associated with dry grinding encompass difficulties in co-crystal formation, partial conversion to the desired co-crystal product, and the potential occurrence crystalline imperfections that,might lead to the emergence of amorphous components. Obtaining a mixture of co-crystal and excess starting material due to incomplete conversion is undesirable, as it necessitates additional purification steps to obtain pure co-crystal product [32][33][34].

B. liquid assisted grinding:

A tiny quantity of solvent is introduced to solid particles prior to milling in order to achieve liquid assisted grinding. The solvent should stay during the grinding process since it aids in the formation of cocrystals. When it comes to cocrystal formation, liquid assisted techniques might be more effective than neat techniques. The kinetics of cocrystal formation might even get faster as the amount of solvent in the grinding media increases. Still unclear, though, is this. Because it wets the solid surface, the liquid component probably accelerates reaction kinetics. It has been stated that liquid assisted grinding comes in several forms. utilizing neat and liquid assisted grinding (LAG) techniques [35].

Using the solvent drop grinding crystallization process, extremely water-soluble cocrystals of the weakly soluble nutraceutical Hesperetin (HESP) were produced. In the end, their research improved bioavailability to optimise pharmacokinetic features. Furthermore, the produced cocrystals' dissolution in an aqueous buffer revealed around four to five times higher concentration of hesperetin than that of the pure [36].

2.Solution co-crystallization:

Yet success cannot be guaranteed by similar solubility on its own. Consider co-crystallizing components as polymorphic compounds, which are substances that can take on many crystalline forms. This is one way to look at them. Chemical molecules are structurally flexible because they can exist in various polymorphic forms, showing that they are not limited to an only one kind of packing mode. When a molecule coexists with another, there is a greater chance of transferring it into a different packing arrangement [37]. It is evident that polymorphism by itself does not ensure that a chemical will operate as a co-crystallizing agent, but a molecule's capacity to engage in intermolecular interactions undoubtedly plays a crucial part. Preparation on a small scale has been explained. A 500 ml glass crystallization vessel with a water jacket was used for scale-up crystallization. A water bath with circulation was used to regulate the temperature. Attached to different vessel ports were an overhead stirrer with a Teflon blade and glass shaft, a digital thermometer, and a reflux column. A reaction vessel was filled with the medication and co-crystal former [38].

3.Slurry conversion:

We investigated water and several organic solvents to look into slurry conversion. We mixed the solvent (50 or 100 ml) with the co-crystal (10 mg) and let the combination sit at room temperature for a few days. Following this time, we decanted the solvent and used nitrogen for five minutes to dry the residual solid material. Lastly, we examined the residual solids using PXRD [39].

4.Spray drying:

One helpful instrument for creating co-crystals is a spray drier. After the components are dissolved in an easily evaporated solvent, they are sprayed into a heated air stream. As a result, the solvent rapidly evaporates, leaving the co-crystals behind. Following their creation, the co-crystals must undergo testing to ensure that they are pure and possess the required qualities [40].

5.Supercritical fluid processing:

The most often utilised supercritical fluid in the fabrication of co-crystals is carbon dioxide (CO_2) because of its remarkable solid-state permeability. After dissolving the medication and coformer in CO_2, they are added to a stainless-steel tank [41]. Co-crystal formation is facilitated by the rapid expansion of CO_2 brought about by progressive depressurization. Nevertheless, the technique is hindered by the drug's and coformer's restricted solubility in the supercritical fluid, which lowers the co-crystals' purity.

6.Solvent evaporation technique:

The method most frequently employed to produce co-crystals is solvent evaporation. After dissolving the medicine and coformer in a solvent is subsequently evaporated to yield crystals. How solubility the drug

and coformer are will affect the solvent selection. The drug's and the coformer's functional groups engage through intermolecular bonds to produce the co-crystal. This method's requirement for a lot of solvent is one of its drawbacks[42]. When Mounika et al. tested various methods for creating fexofenadine-tartaric acid co-crystals, they discovered that solvent evaporation was the simplest and enhanced the stability and solubility of the medication. Utilizing this technique, co-crystals containing several medications, such as sulfadimidine-aspirin, can also be created. Savjani and Pathak used solvent evaporation, wet grinding, and the addition of an antisolvent to create acyclovir co-crystals. They came to the conclusion that the co-crystals produced by solvent evaporation were superior to those produced using the other two techniques [43][44].

7.Antisolvent crystallization:

Supersaturation is another technique used to make co-crystals of high quality. This procedure involves adding a different liquid—a buffer for example—to the solution containing the drug and coformer once they have reached supersaturation. The extra liquid should be able to dissolve in the solvent so that the co-crystal can be made.9 The negative side of this method is that it takes a lot of solvent to do it[45][46][47].

8.Sonocrystallization:

Co-crystals can be created via sonocrystallization by dissolving the medication and coformer in a shared solvent and then sonicating the mixture at a fixed temperature [48]. To keep the temperature of the sonicator constant, cold water is delivered[49].

Preformulation of co-crystal:[50,51]

Repose Angle(Θ)

By the funnel method, the powder's angle of repose was calculated. The precisely weighed 10 grams of powder were taken in a funnel. Once the height was adjusted, the powder was allowed to freely flow through the funnel and onto the surface.

The following formula was used to measure the powder cone's diameter and determine the angle of repose.

$$\text{Tan} = r / h,$$

where

θ is the angle of repose

h is the cone's height

r is the cone base's radius

Bulk density:

Equivalent to 10 grams of powder from each formulation, which has been gently shaken prior to break up any agglomerates that may have formed was added to a measuring cylinder holding 50 ml. The powder's mass and bulk volume were calculated. The following formula was utilized to get the bulk density.

$$\text{Bulk density} = \frac{\text{Weight of co-crystal granules}}{\text{Volume of co-crystal granules}}$$

Tapped density:

A predetermined amount of time was put into tapping the measuring cylinder which held a known mass of blend. The smallest amount of space used in the cylinder, and the blend's mass was determined. The following formula was used to get the tapped density.

$$\text{Tapped density} = \frac{\text{Weight of granules of co-crystal}}{\text{Volumes of granules after 100 tapping}}$$

Carr's Index:

The simplest technique for determining the free flow of powder is compressibility, which is a measure of how easily A Carr's index, which is calculated as follows, indicates the amount of material that can be converted to flow.

$$\text{Carr's index (\%)} = \frac{\text{Tapped volume of powder-volume of powder}}{\text{Tapped volume of powder}} \times 100$$

Hausner's ratio:
Less than 1.25 for Hausner's ratio indicates good flow, and more than 1.5 for poor flow properties. This was computed by using the following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Co-crystals possess distinct characteristics

1.Melting point

They have certain qualities that set them apart from other crystalline forms, including a melting point that denotes the temperature at which the liquid and solid phases dwell in balance.55 The melting points of the pure API, along with co-formers and co-crystals, were determined using capillary methods and liquid paraffin as the liquid medium.[52]

2.Differential scanning calorimetry (DSC)

A method for determining the melting point of an object and thermal characteristics is differential scanning calorimetry, or DSC. Recently, cocrystals have been quickly examined using it as a technique [53].

3.Scanning electron microscopy

Using an electron beam with a lot of energy to scan a material is known as scanning electron microscopy. The atoms in the sample interacts with the electrons to produce signals that provide details about the sample's surface topography. Using this method, one can acquire cocrystal micrographs and ascertain the particle size[52][53][54].

4.Single X-ray diffraction (SXRD)

Atomic-level determination of the solid structure of cocrystals is possible through the use of SXRD. For SXRD testing, it isn't always possible to obtain a competent pharmaceutical cocrystal. As a result, to verify the production of cocrystals, scientists increasingly employ powder X-ray diffraction (PXRD) [52][53][54].

5. Raman spectroscopy

An effective method for researching rotations, vibrations, and Raman spectroscopy is one of the system's additional low-frequency modes. It can be used in a variety of ways to distinguish the distinctive peaks of cocrystal products[52][53].

6.Fourier infrared spectroscopy (FT-IR) :

Infrared (IR) spectroscopy is a widely used method for figuring out a compound's chemical structure. It is an extremely effective technique for separating salts and cocrystals when the creation of hydrogen bonds involves a carboxylic acid. When deprotonation has taken place, a carboxylate anion (COO-) has a single C-O stretch in the fingerprint area of 1000–1400 cm-1. A neutral carboxylic group (COOH) has a strong carbonyl (C–O) stretching peak of 1700 cm−1 and a weak C–O stretch of 1200 cm−1.

The components will exhibit two broad stretches at approximately 2450 and 1950 cm-1 if a neutral intermolecular O-H· · ·N hydrogen bond has formed between them. Concerns regarding the condition of the[54].

To ascertain the drug-conformer interaction, the samples were combined with potassium bromide in a 1:1 molar ratio, compacted onto a disc, and then scanned between 4000 and 400 cm−1 at a resolution of 4 cm−1.[55]

Advantages of co-crystal:

1. Compared to amorphous solids, co-crystals have a number of advantages, such as the capacity to create stable crystalline forms without breaking covalent bonds.
2. Additionally, it is theoretically possible to produce co-crystals with any kind of medicinal molecule, even ones that are non-ionizable or only slightly ionisable food preservatives, pharmaceutical excipients, additives, and other APIs are just a few examples of the many potential counter molecules that exist.
3. Cocrystal creation seems to offer a benefit over other solid-state modification methods used by the pharmaceutical industry in drug delivery, chiral resolution, and novel molecule synthesis (e.g., nutraceutical co-crystals) [56]
4. Pharma experts believe that co-crystallization could improve the pharmaceutical intellectual property situation [57][58].

REFERENCES

1. Jagadeesh Babu N, Nangia A. (2011): Solubility advantage of amorphous drugs and pharmaceutical cocrystals. Cryst Growth Des ;11:2662–79. https://doi.org/10.1021/cg200492w
2. Fong SYK, Ibisogly A, Bauer-Brandl A. (2015): Solubility enhancement of BCS Class II drug by solid phospholipid dispersions: Spray drying versus freeze-drying. Int J Pharm 2015; 496:382–91. https://doi.org/ 10.1016/ j.ijpharm.2015.10.029
3. Krishna GR, Shi L, Bag PP et al. (2015): Correlation among crystal structure, mechanical behavior, and tablet ability in the co-crystals of vanillin isomers. Cryst Growth Des; 15:1827–32. https://doi.org/10.1021/cg5018642
4. Jones W, Motherwell WDS, Trask AV. (2006): Pharmaceutical co-crystals: An Emerging approach to physical property enhancement. MRS Bull; 31:875-879
5. Ranjit T and Bipul S. (2018): Drug-Drug and Drug-Nutraceutical cocrystal/salt as alternative medicine for combination therapy: A crystal engineering approach. Crystals. ; 8(2): 101. Available online: http://apps. Who.int/iris/bitstream/10665/43443/1/WHO-TRS-937-eng.pdf
6. Mukherjee S. (2011): Crystal Engineering of pharmaceutical co-crystals. Graduate school theses and dissertation. University of South Florida; 1-24.
7. Jung MS, Kim JS, Kim MS, Alhalaweh A, Cho W, Hwang SJ, Velaga SP. (2010): Bioavailability of indomethacin-saccharin co-crystals. J Pharm pharmacol ;62(11):1560-1568.
8. Aakeroy C B, Fasulo M E, and Desper J. (2007): Co-crystal or salt: Does it really matter? Molecular Pharmaceutics. ; 4(3):
9. Abida Rehman, Amit Delori, David S Hughes and William Jones. (2018): Structural studies of crystalline forms of triamterene with carboxylic acid, GRAS and API molecules. IUCrJ,; 5: 309-324
10. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. (2006): Pharmaceutical co-crystals J Pharm Sci; 95:499-516.
11. Etter MC. (1991): Hydrogen bonds as design elements in organic chemistry. J Phys Chem:95;4601-10
12. Martínez-Alejo, J.M.; Domínguez-Chávez, J.G.; Rivera-Islas, J.; Herrera-Ruiz, D.; Höpfl, H.; Morales-Rojas, H.; Senosiain, J.P. (2014): A twist in cocrystals of salts: Changes in packing and chloride coordination lead to opposite trends in the biopharmaceutical performance of fluoroquinolone hydrochloride cocrystals. Cryst. Growth Des. 14, 3078–3095.
13. Anna Karagianni, Maria Malamatari and Kyriakos Kachrimanis. (2018): Pharmaceutical Cocrystals: New solid phase modification approaches for the formulation of APIs. Pharmaceutics; 10(18).
14. Sulbha R. Fukte, Milind P. Wagh, Shilpa Rawat, Coformer Selection (2014): An Important Tool in Cocrystal Formation, International Journal of Pharmacy and Pharmaceutical science; 6(7).
15. Bis J A, Vishweshwar P, Weyna D, Zaworotko M J. (2007): Hierarchy of supramolecular synthons: Persistent Hydroxyl Pyridine Hydrogen bonds in cocrystals that contain a cyano acceptor. Molecular pharmaceutics.; 4: 401-416.
16. Laszlo F. (2009): Cambridge structural database analysis of molecular complementarity in cocrystals. Cryst Growth Des ;9(3):1436-43.
17. B. Sarma, (2009):"Structural and Thermal Analysis of Organic Solids," PhD thesis, University of Hyderabad, India, investigated co-crystals and clarified that 0<ΔpKa3.75 were regarded as fully salt forms, and ΔpKa as a neutral synthon
18. Abida Rehman, Amit Delori, David S Hughes and William Jones. (2018): Structural studies of crystalline forms of triamterene with carboxylic acid, GRAS and API molecules. IUCrJ, ; 5: 309-324.
19. Cruz-Cabeza A J. (2012): Acid – base crystalline complexes and the pKa rule. Crystal Engineering communications. ; 14: 6362-6365.
20. Whitesider G M, Wong A P. (2006): The intersection of biology and materials science. MRS Bull 2006; 31: 19-27.
21. Laszlo F. Cambridge structural database analysis of molecular complementarity in cocrystals. Cryst Growth Des 2009;9(3):1436-43.
22. Mohammad AM, Amjad A, Velaga SP. (2011): Hansen solubility parameter as a tool to predict the cocrystal formation. Int J Pharm ;407:63-71.
23. Greenhalgh DJ, Williams AC, Timmins P, York P. (2001): Solubility parameters as predictors of miscibility in solid dispersions. J Pharm Sci :88;1182-90
24. Van Krevelen DW, Hoftyzer P. (1976): Properties of polymers, their estimation and correlation with chemical structure. 2nd ed. Amsterdam: Elsevier Science
25. Shete A, Murthy S, Korpale S, Yadav A, Sajane S, Sakhare S, et al. (2015): Cocrystals of itraconazole with amino acids: screening, synthesis, solid state characterization, *In vitro* release and antifungal activity. J Drug Delivery SciTechnol ;28:46-5.
26. Musumeci D, Hunter CA, Prohens R, Scuderi S, McCabe JF. (2011): Virtual cocrystal screening. ChemSci ;2:883-90.
27. Jain, A.; Yang, G.; Yalkowsky, S. H. Ind. Eng. Chem. Res.2004,43, 7618–7621. (b) Jain, A.; Yalkowsky, S. H.J. Pharm. Sci.2006,95, 2562–2618.
28. International Conference on Harmonization (ICH) Q1A, Stability testing of new drug substances and products. http://www.ich.org/LOB/media/MEDIA419.pdf.(44)
29. Reutzel-Edens, S. M. and Newman, A. W. (2006): The Physical Characterization of Hygroscopicity in Pharmaceutical Solids, InPolymorphism; Hilfiker, R. Ed.; Wiley-VCH: Weinheim, ; pp 235-258.
30. Intrinsic dissolution and Woods apparatus. Pharmacopeia, 2008; Vol. 1, p 526.

31. Bermajo, M.; Gonzalez-Alvarez, I. (2008): How and where are drugs absorbed? in Preclinical Development Handbook; John Wiley and Sons: Hobo-ken, pp 249-280.
32. Blagden N, de Matas M, Gavan PT, York P. (2007): Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev. ;59:617–30.
33. Aitipamula,S., Banerjee,R. Bansal,A.K. Biradha,K. Cheney,M. L.Choudhary,A. R.Desiraju,G. R.Dikundwar, A.G. Dubey, R, Duggirala N.and Ghogale, P.P.(2012): Polymorphs, salts, and co-crystal: what's in a name? crystal growth & design 12(5) ,pp2147-2152
34. Muresan-Pop,M.Vulpoi,A.Simmon,V Todia M.Magyare,K.Pap,Z Simmon A Fillip,C. And Simmon, (2022): Co-crystal of etraverine by mechanochemical activation. Journal of pharmaceutical science
35. Friscic, t. and johns , w.(2009): recent advanced in understanding the mechanism of crystal formation via grinding. Crystal growth and 9(3),pp.1621-1637
36. Padrela, L.; de Azevedo, E. G.; Velaga, S. P. (2012): Powder X-ray diffraction method for the quantification of cocrystals in the crystallization mixture. Drug Dev. Ind. Pharm. 38 (8), 923–929.
37. Chadha, K.; Karan, M.; Bhalla, Y.; Chadha, R.; Khullar, S.; Mandal, S.; Vasisht, K. (2017): Cocrystals of Hesperetin: Structural, Pharmacokinetic, and Pharmacodynamic Evaluation. Cryst. Growth Des. 17 (5), 2386–2405
38. Blagden N, de Matas M, Gavan PT, York P. (2007): Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev.;59:617–30
39. Magali BH, Matthew LP, Lisa AS, Sherry LM, Vetter A, Hector G, et al. (2007): Performance comparison of a co-crystal of carbamazepine with marketed product. Eur J Pharm Biopharm. ;67:112–9.
40. Kumar S, Nanda A. (2017): Pharmaceutical cocrystals: an overview. Indian J Pharm Sci.;79(6):858–71. doi: 10.4172/pharmaceutical-sciences.1000302.
41. Chandramouli Y, Gandhimathi R, Yasmeen BR, Vikram A, Mahitha B, Imroz SM. (2012): Review on cocrystal as an approach with newer implications in pharmaceutical field. Int J Med Chem Anal. 2(2):91–100
42. Karagianni A, Malamatari M, Kachrimanis K. (2018): Pharmaceutical cocrystals: new solid phase modification approaches for the formulation of APIs. Pharmaceutics. ;10(1) doi: 10.3390/pharmaceutics10010018. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list]
43. Kotak U, Prajapati VD, Solanki HK, Jani GK, Jha P. (2015): Co-crystallization technique its rationale and recent progress. World J Pharm Pharm Sci. ;4(4):1484–508
44. Thipparaboina R, Kumar D, Chavan RB, Shastri NR. (2016): Multidrug co-crystals: towards the development of effective therapeutic hybrids. Drug Discov Today. 21(3):481–90. doi: 10.1016/j.drudis.2016.02.001
45. Savjani JK, Pathak C. (2016): Improvement of physicochemical parameters of acyclovir using cocrystallization approach. Braz J Pharm Sci. ;52(4):727–4. doi: 10.1590/S1984-82502016000400017.
46. Raza SA, Schacht U, Svoboda V, Edwards DP, Florence AJ, Pulham CR. et al. (2018): Rapid Continuous Antisolvent Crystallization of Multicomponent Systems. Cryst Growth Des. 18(1):210–8. doi: 10.1021/acs.cgd.7b01105
47. Douroumis D, Ross SA, Nokhodchi A. (2017): Advanced methodologies for cocrystal synthesis. Adv Drug Deliv Rev. ;117:178–95. doi: 10.1016/j.addr.2017.07.008.
48. Savjani JK. (2015): Co-crystallization: an approach to improve the performance characteristics of active pharmaceutical ingredients. Asian J Pharm. ;9(3):147–51. doi: 10.4103/0973-8398.160309.
49. Nanjwade V, Manvi F. (2011): Characterization of Prulifloxacin Salicylic acid complex by IR, DSC and PXRD. Journal of Pharmaceutical and Biomedical Sciences; 5(15):1-6.
50. Mullaicharam ARB, Kuppuswamy S, Hurmathunissa S, Umamaheswari R. (2006): Evaluation of nanoparticals containing Clarithromycin and its tissue distribution study. The Indian Pharmacist ; 5:85-88
51. Chaudhari S, Nikam S, Khatri N, Wakde S. (2018): Co-crystals: a review. J Drug Deliv Ther. 8(6S):350–8. doi: 10.22270/jddt.v8i6-s.2194.
52. Karagianni A, Malamatari M, Kachrimanis K. (2018): Pharmaceutical cocrystals: new solid phase modification approaches for the formulation of APIs. Pharmaceutics. ;10(1) doi: 10.3390/pharmaceutics10010018.
53. School, D. G. & Mukherjee, S. (2011): Scholar Commons Crystal Engineering of Pharmaceutical Cocrystals.
54. Panzade P, Shendarkar G. (2019): Design and preparation of zaltoprofen-nicotinamide pharmaceutical co-crystal via liquid assisted grinding method. Indian J Pharm Educ ; 53: S563-70
55. Prasad RV, Rakesh MG, Jyotsna RM, Mangesh ST, Sapkale P, Mayur PK. (2012): Pharmaceutical Cocrystallization : A Review. Int J Pharm Chem Sci. ;1(3):725–36.
56. Shah k, borhade S, londhe v. (2014): Utilization of cocrystallization for solubility enhancement of a poorly soluble antiretroviral drug – ritonavir. Int j pharm pharm sci. ;6(2):2–4.
57. Asija R, Mangukia D, Asija S. (2011): Pharmaceutical cocrystals: an overview. Int J Pharm [Internet]. 31;419(1-2):1–11.