Co-crystallization an alternative modified technique for solubility enhancement

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Abstract - **Solubility refers to the process of a solid dissolving in a liquid phase to produce a homogeneous molecular dispersion, which is critical for therapeutic success. Despite their potential pharmacokinetic action, poor water solubility of medicines is a crucial factor in their successful commercial introduction. API and a stoichiometric amount of pharmaceutically approved co-crystal former make up co-crystals. The article provides a brief overview of co-crystallization, including how it differs from other states and why it is important as a substitute for salt production. The study also discusses the current FDA notice on co-crystallization guidance, as well as the various procedures for creating co-crystals. Which have been improved, emphasising their significance in the current trend of increasing solubility. Various examples of the co crystals which increases the properties of drugs.ie solubility, stability, bioavailability.**

keywords - **co-crystal, solvent evaporation, solvent drop grinding, hot melt extrusion, high throughput co-crystallization, sonocrystallization**

INTRODUCTION

1.1 Solubility: Solubility refers to a substance's ability to dissolve in a specific solvent. It is a concentration of dissolved solute in a saturated solution at a certain temperature in quantitative terms. In qualitative terms, it refers to the continuous interaction of two or more compounds to form a single phase, which is characterised by clear homogeneous molecular dispersion. The maximum amount of solute dissolved in a solvent at equilibrium is measured. Saturated solution is the name given to the resulting solution. Dissolution-related absorption issues occur when a drug has a low water solubility. [1, 2]

1.2 solubility expression: [2, 4]

Table 1 Solubility expression

Definition	Parts of solvent required for one part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From 100-1000
Very slightly soluble	From 1000-10,000
Insoluble	Greater than 10,000

1.3 Possible causes for poor oral absorption:

1. When a drug's aqueous solubility is less than 100 micrograms per millilitre, it is considered to be weakly soluble.
2. Intrinsic dissolving rate of 0.1 mg/cm2/min is poor.
3. (>500) molecular weight
4. Crystals with a lot of energy[2]

1.4 Biopharmaceutical Classification System (BCS):

BCS brought us to the FDA, which divides drugs into four categories based on permeability and solubility. [2,4]

Table 2 BCS classification of drug:

Class	Permeability	Solubility
I	High	High
II	High	Low
III	Low	High
IV	Low	Low

1.5 Factors affecting solubility: [1,2]

The number of factors that influence solubility.

1. Particle size
2. Temperature
3. Molecular size
4. Nature of solute and solvent

5. Pressure
6. Polarity
7. Polymorphs

2. Co-Crystallisation

Solid dosage forms, such as tablets and capsules, are the most prevalent type of dosage delivery. The API cannot be created in its pure form due to multiple issues of instability. Polymorphs, salts, solvates, hydrates, amorphous, and cocrystal are solid forms. [3] Co-crystallisation refers to the process of two distinct molecules forming a covalent link by hydrogen bonding. [5] A more precise description of co crystal is "a multicomponent (solvates, hydrates, co crystals, and salts) crystal produced between two solid compounds in the presence of an appropriate ion or molecule under atmospheric or environmental circumstances." [2] Co crystallisation occurs when the formulation's overall physicochemical qualities (hygroscopicity, solubility, and compaction behaviour) are improved. The API and the former are the two components that make up Cocrystal. [3, 15]

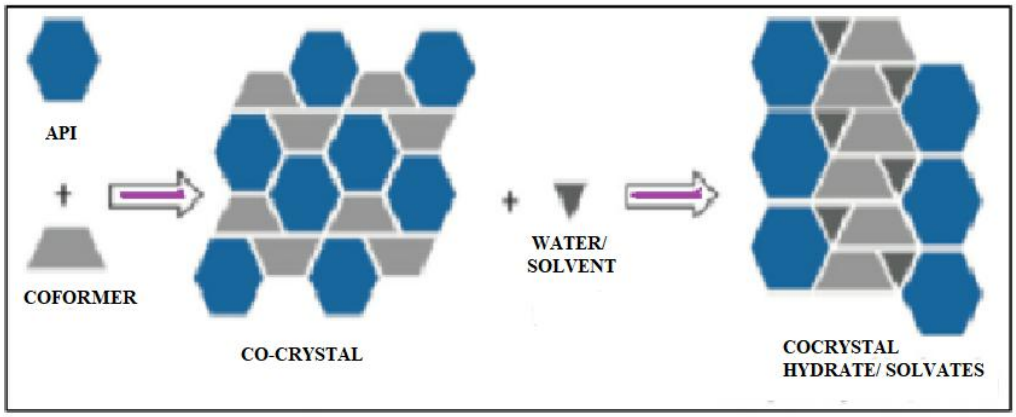

Fig. 1- Possible multicomponent co crystals

Co-crystal anhydrases, crystal hydrates, (solvates), anhydrases of co-crystals of salts, and hydrates (solvates) of crystals of salts are the most dynamically evolving group of solid medicines substances. [3, 15]

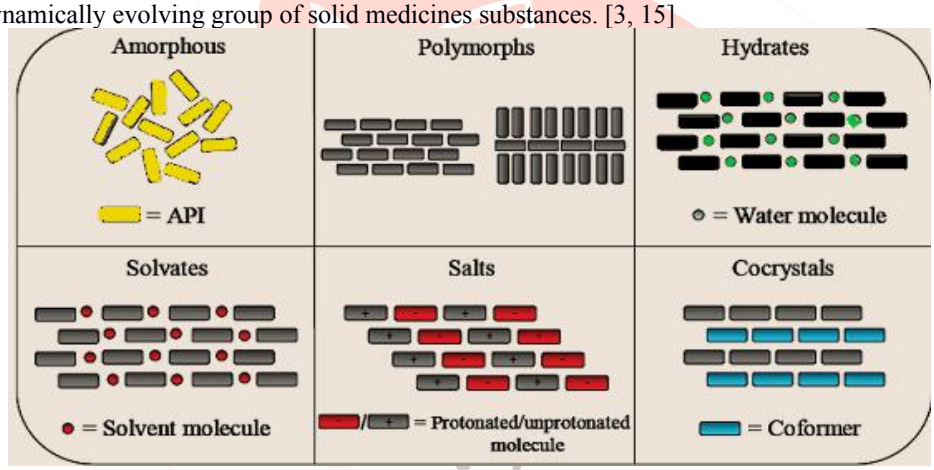

Fig. 2 – The different solid forms

At room temperature, Co Crystals are more stable. Saccharin, nicotinamide, and acetic acid are three co-crystallizing agents that are classed as generally regarded as safe (GRAS), which restricts their use in pharmaceuticals. [4] In terms of BCS categorization, APIs in classes II and IV have traditionally struggled with increasing solubility. As a result, co-crystallization is applied in this problem. The cocrystals are chosen for their superior solubility and stability. Aspirin co-crystals, rac-ibuprofen, and flurbiprofen, for example. It is made by employing 4, 4-bipyridine to disrupt the carboxylic acid dimmers. Because there is no production of covalent bonds or charge transfer, high throughput (HT) crystallization methods have recently been created to better comprehend this. [3, 15]

2.1 Mechanism

A hydrophobic drug molecule and a hydrophilic coformer molecule are used to make pharmaceutical cocrystals. Three primary processes are involved in the process of cocrystals entering solution:

1. The cocrystal's intermolecular linkages are broken.
2. In the solvent, breaking intermolecular bonds
3. Intermolecular bonds between cocrystal and solvent molecules are formed.

Solvation, not breaking away from the crystal lattice, has been shown to be the limiting step in dissolving cocrystals of hydrophobic medicinal compounds in aqueous conditions. Coformers appear to lower the solvation barrier of hydrophobic drug cocrystals to a degree proportional to the pure coformer. As a result, coformer aqueous solubility and cocrystal solubility are linked. Melting values, on the other hand, are not reliable predictors of cocrystal aqueous solubilities because solubility is limited by drug hydrophobicity rather than cocrystal lattice strength. [19]

2.2 Role of hydrogen bonding in co crystallization:

All good hydrogen bond donners and acceptors would be utilised in hydrogen bonding in co crystalline investigations. The best hydrogen bond donners in the crystal structure tend to interact with the best hydrogen bond acceptors, according to the design of co crystals. In the design of specific hydrogen bonding interactions, the "best donners, best acceptors" guideline can be quite useful. In the creation of co crystals, hydrogen bonding is crucial. A hydrogen bond formation can be studied by anticipating the surroundings of proton donners and acceptors in a crystal structure using the Cambridge structures database. [6]

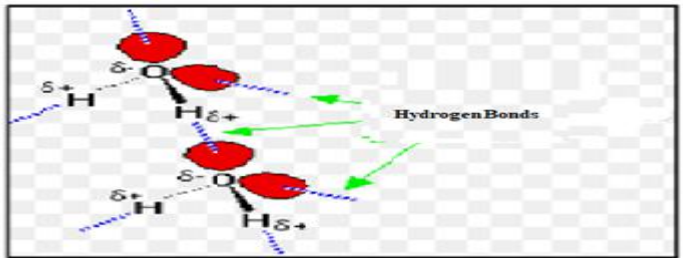

Fig. 3- hydrogen bonding framework between two different molecules.

2.3 Co crystallization against ionization: The situation is different in the co crystallization process. The conversion of a molecule to a neutral form in co-crystallization, regardless of whether the API is ionic, non-ionic, acidic, or basic, may be regarded non-toxic in co crystallization, thereby expanding the scope of co crystallization over salt creation. Excipients, food additives and preservatives, vitamins, amino acids, and other biomolecules, as well as another API, are examples of the former or counter molecules. [3]

2.4 Co crystals versus solvates: The distinction between solvates and co crystals is the physical condition of the components. Solvates are formed when one of the components is liquid and the other is solid; on the other hand, co crystals are formed when both of the components are solid [14, 3].

2.5 Co crystals versus salt formation: For formation, salt formation is used, and co crystallization is used to improve solubility and stability [14]. Co crystallization does not require an API charge to create its salt form, whereas salt formation requires [3].The reaction can be used to explain salt production.

A – H ⟶ (A-) (B+ - H)

3. Different preparation techniques of co crystallization:

Co crystallization can be done in a variety of ways.

i) Co-crystallization from solution
Solvent evaporation
Solvent reduced slurring
ii) Solid state grinding
Solvent free grinding
Solvent drop grinding
iii) High throughput co crystallization
iv) Hot melt extrusion
v) Sono crystallization method

3.1 Co crystallization from solution:

a) Solvent evaporation:

This is the most common method of co crystallization, which entails supersaturating the solution through evaporation, chilling, and adding a solubility-altering solvent or substance [9]. This method is based on the development of a hydrogen bond between a favourable pharmacological component and a complimentary conformer [6]. It will precipitate out if the two have differing solubilities. The thermodynamic stability of molecules should always be considered before evaporating for optimum outcomes. The main disadvantage of the evaporation technique is that it does not work well in large-scale preparation and requires a lot of solvents [10, 3].

b) Solvent reducing slurring/slurry crystallization:

The method of preparing a suspension by adding various solvents to a mixture of API and co-former is known as solvent reducing slurry [13]. The physical stability of the crystallization solution to co crystals and its solid co former [3] is a major factor in the method selection. With 16 co formers, co crystals were synthesized through slurry crystallization. Slurry crystallization could be done with a variety of solvents [11]. 100 to 200 mL of solvent was added, and the resulting suspension was stirred at room temperature for a few days. The solvent was then decanted, and the solid product was dried for a few minutes under nitrogen flow before being characterized using PXRD analysis [9]. For example, utilizing distilled water to make co crystals for trimethoprim and sulfamethoxazole [11].

Disadvantage – it requires a large number of solvents [9].

3.2 Solvent state grinding:

a) Solvent free grinding:

The solid-state grinding technique of solvent free grinding involves mixing, pressing, and crushing the material in a mortar and pestle or mill [3]. It reduces particle size while increasing the covalent reactivity of the mixture. The preparation of molecular assemblies can be done in two ways: neat or dry grinding (DG) method and LAG approach. The solid form of API and co

former are manually mashed together using a mortar and pestle or mechanically using a ball mill in the DG method. In order to obtain the desired co crystal products, the LAG technique necessitates the addition of a little amount of solvent. [12]

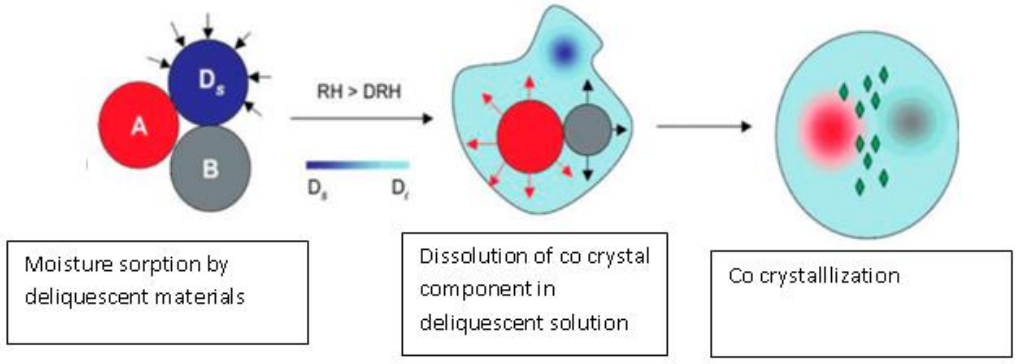

Fig. 4- illustration of the moisture uptake process

Failure to create a co crystal, incomplete conversion to the co crystal, resulting in a combination of cocrystals and some amorphous material are all issues with dry grinding [13].

b) Solvent drop grinding:

Solvent drop grinding is an emerging phase in the improvement of polymorphic selectivity in several co crystal models [9]. Materials can be ground with this approach by adding a little amount of solvent [3]. The additional solvent has an effect on the catalyst. The method of solution crystal growth is used to create co crystals. This approach has an advantage over solid state grinding. This approach, for example, can be used to make co crystals of caffeine and glutaric acid [11].

3.3 High Throughput co crystallization:

High throughput co crystallization is currently used in the pharmaceutical business. High T.C.S. was formerly a popular method for finding new crystals. It is costly to obtain [16]. Three steps are involved in high-throughput crystallization:

1. Planning the experiment
2. Carrying out the protocol
3. Data analysis

It consists of both hardware and software. This technique is enabled to analyze data, draw conclusions, save and retrieve data as needed. The first goal of HTS is to produce a modest number of successful results. The second HTS is usually carried out under controlled conditions [3]. Hit rates for HT Crystallization experiments range from 10% to 100% depending on the type of experiment and modes employed. This system consists of hardware for experimental design and handling, robotic dispensing and execution software, an automated high-speed microanalytical equipment, end-to-end sample tracking, and integrated Cheminformatics analysis software for data visualisation, modelling, and mining [15].

3.4 Hot melt extrusion method:

The process of hot melt extrusion is fundamental for the synthesis of co crystals [7]. This approach is chosen based on the thermodynamic stability of the compounds [9]. The API and co-former are mixed simultaneously using heat and pressure above their melting point in the hot melt extrusion method [12]. Because of the great efficiency of the mixing, there is better surface contact. Co crystals can be made without the need of a solvent [7]. In the hot melt extrusion procedure, good extruder selection is critical [12]. Solvent drop extrusion technique can be used to optimize hot melt extrusion, which has the advantage of allowing hot melt to be carried out at a lower temperature. The temperature of the barrel rises as the mixture is continuously added [11]. Twin screw estruses could be employed in the manufacture of pharmaceutical crystals for proper homogenous mixing of the compound [12]. The carbamazepine nicotinamide co crystal was synthesized using a hot melt extrusion process with polymer as a former [9].

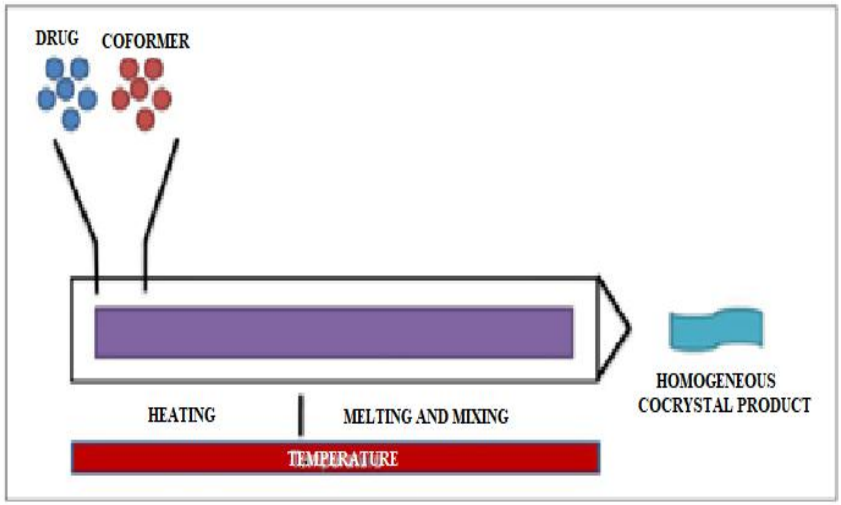

Fig. 5- schematic diagram of hot melt extrusion process

Procedure for HME compaction

1. Extruder feeding through a hopper;
2. Mixing, grinding, and particle size reduction, as well as venting and kneading;
3. Flow through the die.
4. Extrusion from the die and subsequently downstream processing [17].

3.5 Sonocrystallization:

The development of a sonochemical process for the manufacture of very small organic crystals has been completed. This approach was designed particularly for the production of monocrystals. The manufacture of caffeine maleic acid co crystals began with the use of ultrasonic techniques. The investigation of the solvent drop grinding method and the sonochemical approach for preparing caffeine and theophylline as API and L-tartaric acid as conformer has begun. Sonocrystallization appears to be a significant approach since the method's result was consistent [3][9][15][11].

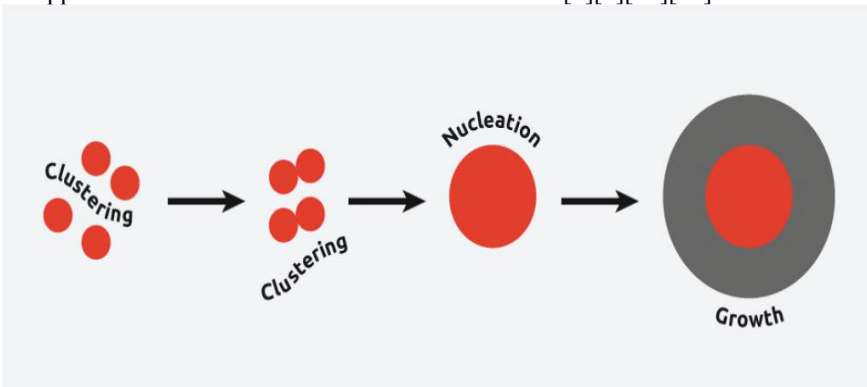

Fig. 6- Sonocrystallization process

4. Examples

A handful of the many research papers for API co-crystals that have been published in the literature according to the BCS classification have been highlighted in this overview.

4.1 BCS I Class

i) Co-crystals of Fluoxetine Hydrochloride (Prozac): Three co-crystals of the antidepressant Fluoxetine hydrochloride exist, each containing coformers such as Benzoic acid, Fumaric acid, and Succinic acid. The drug's water solubility can be varied thanks to co-crystal formation.

ii) Co-crystals of Caffeine: Caffeine co-crystals can provide hygroscopicity resistance and better physical characteristics in pharmaceutically viable drugs. For a period of 7 weeks, one of the cocrystals containing Oxalic acid showed relative humidity stability of up to 98 percent.

iii) Co-crystals of Theophylline: Theophylline, in combination with several aliphatic dicarboxyllic acids, improved the relative humidity stability of co-crystals. For a duration of seven weeks, co-crystals were stable at 75 percent relative humidity.

4.2 BCS II Class

i) Co-crystals of Ibuprofen and Flurbiprofen: Cocrystallizing with nicotinamide increased the low dissolution rates and poor water solubility of the two anti-inflammatory Profens, Ibuprofen and Flurbiprofen. Other physicochemical parameters, including as moisture sorption and mechanical qualities, were also improved via co-crystallization.

ii) Co-crystals of AMG-517: By co-crystallizing with various aliphatic and aromatic carboxylic acids, AMG-517, an antagonist of transient receptor potential vanilliod 1 (TRPV1), was solved. Within 1–2 hours, co-crystals with six coformers reach their maximal solubility.

iii) Co-crystal of Carbamazepine (Tegretol): In the instance of the antiepileptic medicine Carbamazepine (Tegretol), the issues of low water solubility, dissolution limited bioavailability, and the requirement of large dosage were solved in its co-crystal with Saccharin. Co-crystals have better physicochemical features, such as a faster dissolving rate and more stable suspension.

iv) Co-crystals of Itraconazole (Sporanox): Itraconazole has been co-crystallized with Succinic acid, L-Malic acid, and L-Tartaric acid, all of which are 1, 4-Dicarboxylic acids. The profile of dissolution is almost identical to that of the commercially available Sporanox. In terms of solubility and bioavailability, co-crystal appears to be a step forward.

v) Co-crystal of Griseofulvin: Using the solution crystallization approach, antifungal, low solubility medication Griseofulvin was co-crystalized with coformer Acesulfame. As a result, novel formulations for co-crystal hydrate may be possible. It has exceptional stability up to 150°C, with a three-fold increase in solubility and a dissolving rate as fast as 20 minutes.

vi) Co-crystals of Ethenzamide: Solid state grinding and solvent vaporisation crystallization procedures were used to generate pharmaceutically imp Ethenzamide. When compared to pure Ethenzeamide crystals, all of the co-crystals showed improvements in physical attributes such as solubility and intrinsic dissolution rate.

4.3 BCS Class III

i) Co-crystal of Adefovir Dipivoxil: When compared to the pure API, Adefovir Dipivoxil, an anti-hepatitis B medication, had a higher dissolving rate and stability. The co-dissolving crystal's profile was discovered to be pH independent, with a two-fold improvement in dissolution efficiency.
ii) Co-crystals of Pyrazinamide: In comparison to the pure API, co-crystals of the anti-tuberculosis medication Pyrazinamide with co-crystal coformers such Malonic acid, Succinic acid, and Glutaric acid had increased solubility. The dissolving rate of Co crystals was likewise higher than that of pure crystals.

4.4 BCS Class IV
i) Co-crystal of Furosemide: The physicochemical properties of a co-crystal of Furosemide, a low soluble and low permeability antihypertensive medication, with Caffeine were found to be improved in a study. Co-crystals outperformed pure compounds in terms of solubility, stability, and dissolution rates.
ii) Co-crystal of Norfloxacin: The antibacterial medicine Norfloxacin is co-crystal solvated with the coformer Isonicotinamide. The resulting cocrystal has three times the solubility of a pure crystal of Norflxacinm, according to reports.

4.5 Drug-Drug Co-Crystals: The usage of a pharmaceutically approved GRAS (generally recognised as safe) chemical as a coformer is substituted by another API in a drug-drug co-crystal (combination medications). Co-crystals have better physicochemical qualities including solubility, dissolution rate, and hygroscopicity than monocrystals.
i) Co-crystal of Meloxicam: Aspirin Meloxicam, a non-steroidal anti-inflammatory medication, was co-crystallized with Aspirin, an analgesic API that serves as a coformer, to solve it. Meloxicam's solubility was reduced to 0.22 mg/ml, and the time it took to reach maximum concentration was cut in half.
ii) Co-crystal of Pyrazinamide: Diflunisal Pyrazinamide, an anti-tuberculosis medication, was cocrystallized with Diflunisal, a nonsteroidal anti-inflammatory medicine. Grinding, annealing, and solution crystallization procedures were used to create a 1:1 co-crystal. This can reduce pyrazinamide's adverse effects while also improving Diflunisal's water solubility.
iii) Co-crystal of Lamivudine : Zidovudine Lamivudine and Zidovudine, two anti-HIV medicines with limited permeability, are given orally as a physical mixture of 150 mg and 300 mg, respectively, under the name Combivir. A 1:1 co-crystal hydrate was created using a slow evaporation procedure to test the two medicines' potential to form co-crystals.

4.6 Nutraceuticals
Nutraceuticals with low water solubility and thus low bioavailability are frequently employed as possible APIs. Many scientific investigations have resulted in nutraceutical co-crystals with pharmaceutically acceptable substances that have better physicochemical qualities.
i) Co-crystals of Quercetin: Caffeine, Isonicotinamide, and Theobromine were used to co-crystallize Quercetin, which has a low water solubility and bioavailability. Tmax (minimum time to attain peak concentration) is 10 and 5 minutes, respectively, whereas Quercetin dehydrate takes 30 minutes.
ii) Co-crystals of Curcumin: The anticancer nutraceutical Curcumin was co-crystallized with Resorcinol and Pyrogallol, resulting in co-crystals with increased water solubility and intrinsic dissolution rates. The solubility of curcumin cocrystals was found to be roughly 2 times and 5 times that of pure Curcumins, respectively.
iii) Co-crystals of Pterostilbene
Piperazine with Glutaric acid with Pterostilbene (a stilbenoid found in blueberries and grapes). For eight weeks, co-crystals were physically stable at room temperature to 65°C and relative humidities ranging from ambient to 98 percent. [18]
4.7 Polymorphism in Pharmaceutical Co-crystals: Polymorphs have diverse crystal structures, resulting in differences in physical and chemical properties such as solubility, stability, and hygroscopicity. It was previously thought that just a few co-crystals could be polymorphic, however recent research has showed that a large number of co-crystals can be polymorphic. The number of polymorphs associated with a pharmaceutical co-crystal varies, with the highest number reported to date for Furosemide being five: Nicotinamide 1:1 cocrystal, Barbituric acid–Urea 1:1 cocrystal, Pimelic acid–4,4′-Bipyridine co-crystal, and Ethenzamide–Gentisic acid 1:1 co-crystal all have three. [18]

5. Physicochemical Properties and Characterization:
i) Solubility: Co-crystallization is a process that is frequently utilised when the primary goal is to improve solubility. As a result, co-crystals frequently improve solubility, which is impossible to do with a single molecule. Telmisartan, for example, is a class II medication, meaning it has a low solubility. As a result, it must be formulated to overcome the issue of its low solubility. Co-crystals are a preferable option in these situations. Consider another example, where two unique cocrystals of exemestane/maleic acids (EX/MAL) and megestrol acetate/saccharin (MA/SA) were created using a solution approach with varied particle sizes to improve the solubility of two APIs, exemestane (EX) and megestrol acetate (MA) (MA). In comparison to solo API, cocrystallization of EX and MA improved solubility.Even at large particle sizes, EX/MAL demonstrated a high dissolving rate. In fine particles, MA/SA cocrystals displayed supersaturation. However, when compared to pure MA, the supersaturation of cocrystals increased eight times in 15 minutes and two times in four hours.
ii) Maximum wavelength: When the co-crystal solution is permitted for UV scanning, the scan yields a peak indicating the API's maximum wavelength. If the conformer is also an API, the scan will reveal two lambda max peaks for both APIs. As a result, it can be concluded that the co-crystals have formed and are both present in the solution.
iii) Stability: Stability is a crucial feature to consider when developing a formula. As a result, chemical stability, solution stability, thermal stability, and relative humidity stability are all significant in the case of cocrystals. Water absorption/desorption assays can be used to determine the relative humidity stability of cocrystals. Cocrystals of 2-[4-(4-chloro-2-fluorphenoxy) phenyl] pyrimidine-4-carboxamide and glutaric acid, for example, revealed less than 0.08 percent water

content up to 95 percent relative humidity when exposed to this absorption/desorption cycle. Cocrystals are stable in terms of relative humidity, according to the results of such research. Chemical and thermal stability have received little research.
iv) Intrinsic Dissolution: Co-crystallization is a new technology for increasing solubility that is mostly utilised with BCS class II pharmaceuticals. 2-[4-(4-chloro-2 fluorophenoxy) phenyl] pyrimidine-4-carboxamide, a low solubility API, was cocrystallized with glutaric acid to generate an 18-fold increase in intrinsic dissolution rate.
v) Bioavailability: Bioavailability refers to the extent to which a medicine penetrates the systemic circulation. The bioavailability increase of glutaric acid and 2-[4-(4-chloro-2 fluorphenoxy) phenyl]-pyrimidine-4-carboxamide (PPPA) cocrystals was investigated in dogs. When the API was formulated in cocrystal form, the AUC was found to be three times higher.
vi) Melting Point: One of the physicochemical aspects of co-crystals is their melting point. It is the temperature at which the solid and liquid phases of matter are in balance. The melting point of co-crystals changes as they form, coming in between the melting points of two distinct molecules. If such data are obtained, the formation of co-crystals can be confirmed. Consider the optically active form of 2-phenyl butyric acid and 2-phenyl propionic acid, and the racemic form of 2-phenyl butyric acid and 2-phenyl propionic acid, respectively. These two crystallise together with isonicotinamide. When the melting point of the racemic group was compared to the optically active form, it was discovered that the racemic group had a greater melting point.This conclusion can be explained by the fact that centrosymmetric space groups have a denser packing pattern.
vii) Melt (Hot stage microscopy): Melt (Hot stage microscopy) is an analytical method for determining the properties of cocrystals. Cocrystal characteristics are described as a function of time and temperature. As the name implies, this analytical approach combines the qualities of microscopy with heat analysis. Additional characteristics that allow for more material characterisation include image editing tools, high-resolution colour cameras, and video-enhanced microscopy. Other characterization techniques, like as hot stage microscopy, are used in a variety of ways to validate transitions. Hot-stage microscopy is used in the pharmaceutical industry to validate transitions discovered using other techniques in a variety of ways. Hot stage microscopy can be used to examine crystal forms and hydrates, solid-state characterisation of bulk medications, and other physiochemical properties.Because hot melt is a visual approach, when paired with other characterization techniques like DSC, it has boosted the visual collection capability. This visual technique must be checked during transitions such as melts and recrystallization.
viii) Scanning Calorimetry (DSC): This method of characterisation entails heating or cooling two specimens to the same temperature and in the same environment, one of which is the sample and the other of which is the reference. The energy required to establish a temperature difference of zero between the two specimens is plotted, and the results are examined. There are two sorts of DSCs that are used on a regular basis. The first is the power compensation DSC, which requires the two specimens to be kept in separate identical furnaces. The temperature of each can be made same by altering the power input. As a result, heat capacity or enthalpy is used to express energy. Another type of DSC involves keeping both sample containers in the same furnace and connecting them via a low-resistance heat flow path. The rest of the interpretation is identical to the previous one.
ix) XRD: XRD Is a type of analytical technique that uses phase identification to offer information on unit cell dimensions. This result is obtained through constructive diffraction of the monochromatic Xray and the crystalline substance. A cathode ray tube that has been filtered and collimated to produce monochromatic radiation before being directed towards the sample produces the monochromatic beam. The sample is finely pulverised to create a homogeneous sample and assess the average bulk composition when it comes to sample preparation. The sample's dspacing is investigated. When the sample is presented in a random orientation, it generates a set of d-spacing. Because each mineral has its own set of d-spacing, the sample is analysed in this way.The most important requirement for all of this to happen is that the sample follows Bragg's equation (n=2d sin), which ties electromagnetic radiation wavelength to diffraction angle 2.
X) Vibrational spectroscopy (IR and Raman): Electromagnetic radiation, which has frequencies ranging from 4000 to 400 cm-1, has proven to be one of the most powerful ways for detecting organic structure. This electromagnetic radiation is referred to as infrared (IR) radiation in inorganic chemistry, and it is studied using IR spectroscopy. The radiations that are bombarded are absorbed by the interatomic bonds. As a result, a specific chemical bond will absorb different radiations and at different frequencies depending on the environment. As a result, their absorption data, which is given as a spectrum, assists in the derivation of some structural inferences. [3]

6. Advantages

i) For any APIs, pharmaceutical cocrystallization can be employed instead of salt production. Among the many counter molecules available are food additives, preservatives, pharmaceutical excipients, vitamins, minerals, amino acids, and other biomolecules, as well as other APIs for cocrystallization.
ii) Cocrystal formation from polymorphic compounds is easier than co-crystal formation from non-polymorphic compounds. In a range of well-defined and robust intermolecular interactions, polymorphic molecules have the ability to create hydrogen bonds.
iii) The only distinction between cocrystallization and recrystallization is that they both involve heteromeric and homomeric molecules. As a result, API purification in the form of cocrystals may be possible.
iv) According to the industrial application, the solvent drop grinding method used to make cocrystals used less solvent. The solvent drop grinding method, also known as kneading, does not require a large amount of solvent to evaporate. As a result, it is both cost-effective and illustrates the use of green chemistry.
v) Furthermore, no filtration or filtering is required while using the grinding process. [5]

7. LIMITATIONS

i) Although co-crystal production is straightforward, the precise relationship between cocrystal structure and physical attributes is unknown.
ii) A temperature range that is ideal should be determined. The use of a solid-state grinding process is required due to excessive heating. Unintentional phase change, clumping polymorphism, or crystallization may occur.
iii) The solid state grinding method produces extremely small particles. As a result, X-ray structural identification is difficult in Crystallography.
iv) Separation of the co-crystal phase into separate components, as well as storage at a certain relative humidity level, with reservations regarding its applicability. [20]
v) Another disadvantage is phase shifts throughout the formulation process. The API is still being developed. Cocrystals may also be vulnerable. During the production process, excipients are employed to combat ion displacement. [5]

8. CONCLUSION: Pharmaceuticals are the pillar of the healthcare industry. Hence it poses a great challenge in formulating a new type of delivery system or altering the API form to enhance or improve the characteristics which hinder its acceptability. Hence in case, of co-crystallization, it is a new method which can be used to overcome various physical, chemical, or physiological drawbacks ion an API. In the case of formulation aspect, the co-crystallization offers a new area to develop a new method of preparation, characterization of API. Hence it can act as opportunities for industries who want to claim for an Intellectual property. Another challenging area is the new techniques for screening these API. According to the various papers reviewed the liquid-assisted grinding and neat grinding a method of choice as compared to solvent-based approaches. Cocrystals are the best alternative for APIs which cannot be converted into its salt form. This is because of the absence of any ionic charge. Hence, in the case of co-crystallization, which consists of simply an API and conformers, can be used to enhance various properties of the API. Whether it is enhancing solubility, pharmacokinetic properties, or improving the stability co-crystallization has established its presence.

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