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APPLICATION OF CO-CRYSTALS TECHNOLOGY IN PHARMACEUTICALS

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ABSTRACT

Weak aqueous solubility and poor oral bioavailability are main constraints in the production of new products. One technique used to increase the solubility of poorly aqueous soluble drugs is crystallization, which also helps to enhance physicochemical properties such as melting point, tablet power, solubility, stability, bioavailability and permeability with the preservation of pharmacological properties of the active pharmaceutical ingredient. In the medical and pharmaceutical industries, co crystals can be used to improve various properties, such as dissolution rate, melting point, solubility, chemical stability, etc. To increase the solubility of weak aqueous compounds, crystals are used to increase the solubility of aqueous compounds that are weakly soluble. It has the capacity to alter solid-state materials' physical properties. It is also used in taste masking, enhancement of mechanical property, and development and extension of intellectual property.

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INTRODUCTION

One of the most challenging aspects of the drug development process, especially for the oral-drug delivery system, remains to improve the oral bioavailability of drug solubility. Numerous methods are available and reported in the literature to increase the solubility of drugs that are poorly water-soluble. Techniques are chosen on the basis of certain factors, such as the properties of the medicinal substance under consideration, the nature of the excipients to be selected, and the nature of the dosage type intended. The Biopharmaceutical Classification System (BCS) is an experimental model that tests permeability and solubility under prescribed conditions. The poor solubility and low dissolution rate of poorly water-soluble drugs in aqueous gastrointestinal fluids also cause inadequate bioavailability. The original aim of the system was to help control post-approval changes and generics by providing, where necessary, approvals based solely on in vitro results. Importantly, because the majority of drugs are and remain orally dosed, the device was built around oral drug delivery. Waivers Permission to skip in vivo bioequivalence studies is reserved for drug products which meet certain solubility and permeability criteria and which dissolve rapidly as well. However, the industry is using the BCS more and more as a tool in the production of drug products. BCS can be used, as a simple example, to flag drugs that should not be clinically tested unless suitable formulation techniques are used. Through the use of improved formulation techniques aimed at increasing solubility or dissolution rate, a BCS Class II compound, permeable yet relatively insoluble, will likely not be a good clinical candidate. There are various schemes that try to funnel a given API, depending on the BCS type of the API, into unique drug distribution techniques. Today, in their methods, most approaches remain fragmented, ignoring economically and biologically relevant variables. However, the BCS can provide a tremendous tool for successful drug development when combined with other data [1-5].

Methods for Solubility Enhancement [6,7]

In order to increase the rate of dissolution and thus the oral absorption and bioavailability of such products, enhancing the oral bioavailability of poorly water-soluble drugs continues to be one of the most challenging aspects of drug development. There are several techniques to enhance the aqueous sbilities of poorly water-soluble drugs. Current approaches for improving the water-solubility of poorly soluble drugs are given below;

1. Reductions of particle size
2. Use of co-solvents
3. Complexation of approach
4. Solid dispersion technology
5. Synthesis of prodrugs and analogues
6. Emulsions, micelles and liposomes
7. Use of carriers (natural, synthetic)
8. Use of liquid-solid techniques
9. Use of hydrotropic agents (hydrotropes)
10. Cocrystallization

Co-crystallization

"Co-crystals are solids which are monophonic crystalline materials that typically have a stoichiometric ratio of two or more distinct molecular and/or ionic compounds. Since co-crystals are formed in a stoichiometric ratio with their molecular components, through non-covalent interactions, such as ionic interactions, hydrogen bonds, and van der waals interactions, intermolecular reactions between API and coformer interact. Pharmaceutical cocrystals can improve some of the physicochemical properties of APIs, such as the solubility, dissolution rate, bioavailability, and stability, without altering their inherent chemical structures. By crystallizing active pharmaceutical ingredients with precisely selected coformers, crystals are obtained to design drugs that demonstrate improved stability, high solubility, and thus high bioavailability and optimized drug uptake.

Cocrystals are divided into two categories –

i) Cocrystals are made of inorganic-organic components,

ii)Cocrystals are made only of organic components.

Organic molecules co-crystallized with alkali and alkaline earth salts, mineral acids, and halogens, as in the case of halogenated quinones, are inorganic-organic cocrystals. Aromatic compounds were present in the majority of organic-organic cocrystals, with a large fraction containing di- or tri-nitro aromatic compounds. Cocrystals are used for such drugs having BCS Class II (low solubility/high permeability) and BCS Class IV (low solubility/ low permeability) and cause difficulty related to dissolution, solubility, stability, therapeutic effectiveness etc [8,9,10].

Definitions:

Crystallization is defined as alteration of physical properties of by modifying drug at molecular level. Process of Cocrystallization requires drug and coformer for formation of cocrystal.

Cocrystallization is also characterized as altering the physical properties of drugs by altering them at the molecular level by means of means that, with the aid of different methods, one can tailor the physicochemical properties of drugs to improve them, so there is no need for any other additives to improve the physicochemical properties of substances.

Pharmaceutical cocrystals can be defined as a multi-component system containing a specific stoichiometric ratio of an active pharmaceutical ingredient (API) and cocrystal coformer (CCF) linked through intermolecular interactions, such as hydrogen bonds, π-π binding, and van der Waals forces drug modification to alter the physical properties of a drug, especially the solubility of a drug without altering pharmacological properties [1,11,12].

Different method of cocrystallization is given in figure 1.

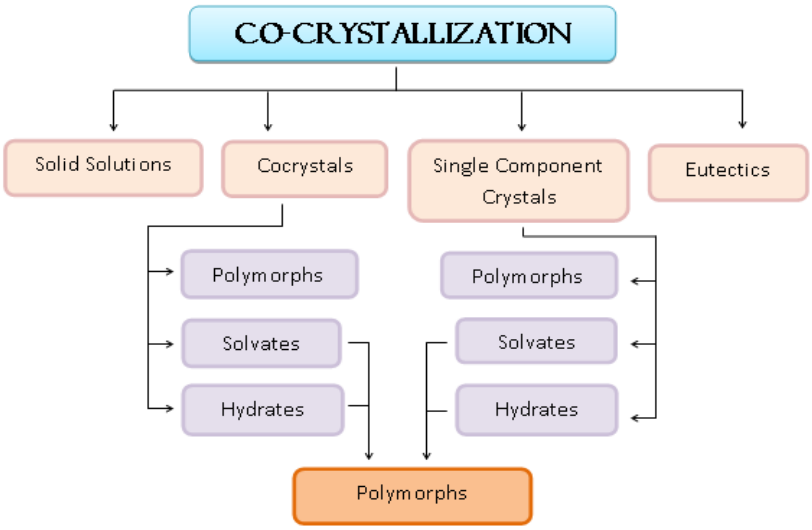


Figure 1: Method of Cocrystallization.

Cocrystallization - Mechanism

Many variables influence the synthesis of new cocrystals, which are often influenced by the existence of the solvent and the reactants. For example, the presence of functional groups and the solubility of reactants in the solvent are just a few of the effective parameters, in addition to several experimental conditions such as the stoichiometric ratio of the coformer and API, temperature, stirring, pH, and type of glassware, several methods are capable of cocrystal synthesis. However, the lack of control over the cocrystals' nucleation, crystallization, and phase evolution is still a major scientific challenge. Mechano-chemical techniques are promising green chemistry and inexpensive synthetic pathway techniques for cocrystal processing. Cocrystallization is not a single process mechanism, but rather a sequence of processes which include;

i. Molecular diffusion,
ii. Eutectic formation, and
iii. Cocrystallization through an amorphous phase.

In these three processes above, the presence of an intermediate bulk phase (gas, liquid or amorphous solid) with increased mobility and/or higher energy of reactant molecules with regard to the starting crystalline forms is the common point. The formation of solid cocrystals is aided by an intermediate liquid phase in liquid phase assisted cocrystallization, e.g., when one of the reactants is liquid under atmospheric conditions. Cocrystallization may take place via the formation of amorphous intermediates in cases where there is no special mass transfer pathway (i.e., liquid or gas phase). This is possible in cocrystallization of molecular solids with strong intermolecular interactions (e.g., hydrogen bonds). In addition, it has been stated that grinding at temperatures below the reactants' glass transition temperature results in the formation of amorphous phases. Grinding higher than that, however, would result in metastable polymorphic forms. It has been proposed that liquid simply plays the role of lubricant in liquid assisted grinding by providing a medium to promote molecular diffusion. Since the cocrystals produced after liquid assisted grinding are usually thermodynamically stable, the low solvent fraction during liquid assisted grinding is of little importance in regulating the process outcome [12, 13, 14, 15].

Properties that alter with Cocrystallization:

Figure 2 gives the physicochemical properties of drug substances or APIs that could substantially alter and enhance their characteristics [16, 17, 18, 19, 20].

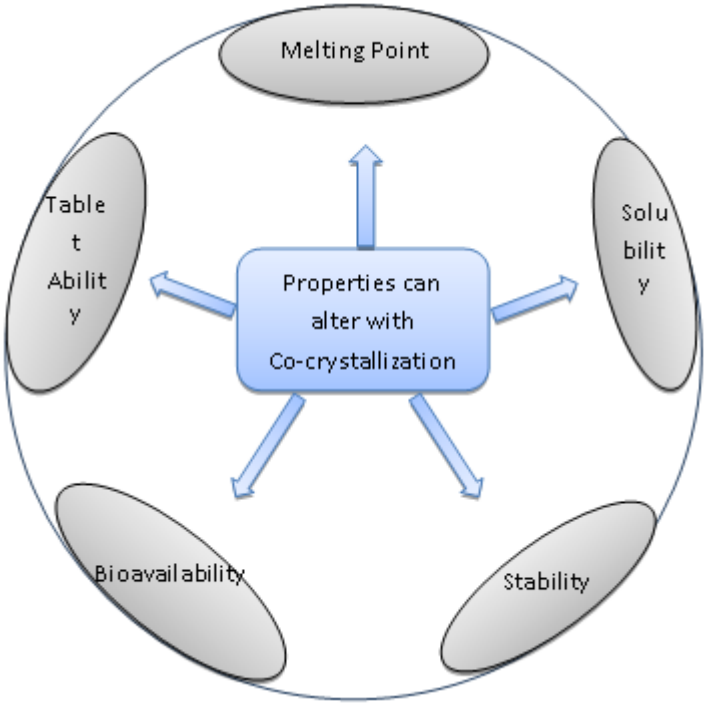


Figure 2: Properties Alter with Co-crystallization.

Melting Point:

It is one of the physical features of solids and is used to determine purity. At a sharp melting point with a small range, pure substances or solid melt. The thermodynamic stability of any API can be regulated by its meting point, so the usefulness of the high melting point conformer for its better stability and also useful in the case of thermolabile drugs is very significant in the case of cocrystal synthesis. The most popular techniques used to calculate the melting point are differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA).

Tablet-ability:

Cocrystal formation strengthens the drug's tablet capability. Tablet-ability implies the substance's ability to transform into tablet form. Important parameters of preformulation research are crystal packaging, tablet-ability and compaction. We can alter these properties with the aid of cocrystallization by using suitable conformers.

Solubility:

Approximately 60 to 70 percent of drugs are included in BCS Class II (low solubility/high permeability) and IV (low solubility/low permeability). It is therefore essential to improve the solubility of these drugs in order to develop new formulations. With the processing of cocrystals, it is possible to increase the solubility of low soluble drugs. With the cocrystal method, some researchers have improved drug solubility. With the Cocrystallization process, there is a substantial improvement in aqueous solubility, finding a 1.92-fold increase in solubility of Class II drug saturation with low solubility. Cocrystals were produced via the cooling crystallization process using succinic acid as a conformer. Using the shake flask technique, the solubility study of cocrystals was performed and found a 3.6-fold increase in cocrystal solubility over pure drug solubility.

Stability:

It is also imperative for study to be carried out during the development of new dosage formulations. Various stability tests, such as chemical stability, thermal stability, solution stability and photo stability, should be performed during the production of pharmaceutical cocrystals. The stability of cocrystals is found to be greater than that of other types of drugs.

Bioavailability:

The rate and extent of pure drugs that enter systemic circulation is defined as bioavailability. One of the major obstacles in the production of formulations is the poor oral bioavailability of APIs. The bioavailability of drugs can be increased or improved with the aid of cocrystallization. The bioavailability of different drugs with cocrystal type conversion has been improved by several researchers. E.g. Clarithromycin is a class II BCS compound, prepared by using urea as a conformer by the process of solvent evaporation for cocrystals. The formulation of the produced tablet is assessed. It is concluded that, compared with the Advertised Tablet, the formulated tablets of Clarithromycin co-crystals displayed improved solubility and in-vitro drug release profile. Increases oral bioavailability and therapeutic effects [1, 21, 22, 23].

Selection of Coformers and Screening of Cocrystals

A co-crystal is a single crystalline solid that contains two neutral molecules, one being an API and the other being a former co-crystal. An excipients or another drug could be the Co-crystal former. The USFDA has maintained a catalog of thousands of substances that can be used as possible coformers for pharmaceutical cocrystals with no harmful side effects, the non API portion used as coformer should be non-toxic. The option of Coformer for an API is the most important aspect of the design and screening of cocrystals. The selection of Coformer is carried out mainly by different approaches, such as experience-based methods and experimental methods. The Hit and Trial technique is mainly used for all types of coformers for an API and these are described by sufficient techniques to validate the structure of the cocrystal. This approach is costly and time consuming. Researchers have used many different knowledge-based methods to pick appropriate coformers and screening cocrystals, including the following approaches: Hydrogen-bonding tendency, synthonic engineering, Cambridge Structure Database (CSD) supramolecular compatibility, pKa-based models, Fabian's process, Lattice energy calculation, real solvent conductor-like screening model (COSMO-RS), Hansen solubility parameter, virtual cocrystal screening (MEPS-based on molecular electrostatic potential surfaces), thermal analysis, saturation measurement [3, 4, 24, 25, 26, 52, 53, 54, 55, 56, 57, 58, 59].

Hydrogen bonding propensity

In cocrystals, by non-covalent bonding such as hydrogen bonding and van der Waal forces, API and coformers interact with one another. Among all of these, the bonding of hydrogen between API and coformer plays an important role in cocrystal formation. Better defined a graph-set notation method that was often used as a hydrogen bonding labeling motif and suggested 3 guidelines for preferable hydrogen bond formation: All hydrogen molecules that are acidic in nature will be present in the formation of bonds, all hydrogen bond acceptors will be used when hydrogen bond acceptors are available, and hydrogen bonds will be formed when there will be best donors of hydrogen bonds and acceptors of hydrogen bonds. The quantitative measurement of the formation of hydrogen bonds between the donor and the acceptor feature groups present in the indomethacin and isonicotinamide groups was analyzed by assigning a value between 0 and 1 and higher, indicating the formation of hydrogen bonds [24, 27, 28, 51].

Synthonic engineering

Desiraju identified the "synthon approach" for the selection of coformers that formed a supermolecule to create "supramolecular synthons" by using unique molecular fragments within the cocrystal. According to this approach, the functional groups present in API and coformer will play a major role in the creation of cocrystals, and individual APIs will use coformer with an acceptable functional group. Synthons are present as basic structural units in supermolecules that are associated with noncovalent bonding. There are two types of Supramolecular Synthon approaches: supramolecular homosynthons and supramolecular heterosynthons. Supramolecular homosynthons consist of the same functional groups present in APIs and coformers, such as amide-amide homosynthons, carboxylic acid-acid homosynthons, while supramolecular heterosynthons consist of various functional groups, such as acid-pyridine heterosynthons, carboxylic acid-amide homosynthons. In general, supermolecular heterosynthons are more preferred than homosynthone [53].

Cambridge Structure Database (CSD)

CSD is a validated method for facilitating the statistical analysis of the motifs of packaging and thus providing information on common functional groups. CSD is used to provide information dependent on the functional group involved in supramolecular synthons regarding the molecular interaction of drugs and coformers. CSD will prepare the library of suitable coformers for an API. This is a computer-based technique that is used to find suitable cocrystal forming pairs and decreases the time and experimental expense of testing [4,5,29, 30, 53].

pKa-based models

It is possible to forecast the formation of crystals or salts by proton transfer between acid and base. It is possible to predict the formation of salts or cocrystals by evaluating pKa= [pKa (base)-pKa (acid)]. It is widely agreed that if the difference in the pKa values is greater than 2 or 3, proton transfer will happen from acid to base. A lower value of pKa (less than 0) indicates cocrystal formation, while a higher value (more than 2 or 3) indicates salt formation. By observing 6465 cocrystals from CSD, the pKa rule was validated and quantified and clarified a linear relationship between the pKa value and the probability of proton transfer between acid-base pairs. It was analyzed that when the value of pKa<-1, an ionized complex is formed, a non-ionized complex should be created when the value of pKa<4 and the probability of ionized complex formation increase by 17 percent by increasing pKa by one unit from 10 percent at pKa=-1 to 95 percent at pKa=4. The probability of the formation of cocrystals and salts can be determined by calculating the pKa value. For the preparation of cocrystals, this is an easy and less time consuming process [4,5, 29,30,31].

Fabian's method

The CSD extracted various sets of reliable cocrystal forming structures and measured the molecular descriptors (single atom, bond and group counts, donor and acceptor counts of hydrogen bond, size and shape, surface area and molecular electrostatic) for each molecule. The database identified pairs of molecules which were able to form cocrystals on the basis of measured molecular properties. The shape and polarity of cocrystal formers were linked to the strongest descriptor correlation [32,33].

COSMO-RS

COSMO-therm software based on the COSMO-RS fluid phase thermodynamic method was used to define the miscibility of coformers in the super cooled liquid (melt) phase for the screening of acceptable coformers for an API. Compared to pure materials, excess enthalpy, Hex (a major factor for H-bonding interactions) between API and coformer mixture reflects the propensity of these two compounds to co crystallize. This was shown to enable a fair ranking of coformers for an API by COSMO-RS theory and the experiments should concentrate on those coformers that have an increased likelihood of cocrystallization, leading to the greatest improvement in the solubility of the API. Solvents with the highest value of Hex with an API were selected in a similar way as possible coformers for cocrystallization were found, which had the least likelihood of forming solid solvents. This approach was used to choose different itraconazole coformers and Axitinib solvents (tyrosine kinase inhibitor) to prevent the formation of hydrates and solvents [34, 35].

Hansen solubility parameter

Another important approach used to calculate the mixability of drugs and coformers used for cocrystal systems is the Hansen solubility parameter. The miscibility of the components could predict the solid state formation of cocrystals. The success rate of the synthesis of cocrystals was increased by using components with similar miscibility. The two components have been shown to be miscible if the cumulative difference in HSPs is $<7MPa^{0.55}$, otherwise immiscible. Another method estimates the miscibility of two components if the difference is $\leq 5\ MP^{0.5}$ between two substances which are supposed to be cocrystal formation [36, 37, 55].

Virtual cocrystal screening

Musumeci et al. predicted that the creation of cocrystals was the responsibility of all potential intermolecular contact sites present on the surface of molecules. The strength of the hydrogen bond depends on the donors of the H-bond and the acceptors of the H-bond; the best donor of the H-bond and the best H-bond form the strongest H-bond, and the next best H-bond accepter interacts with the next donor of the H-bond, and so on, until all sites are fulfilled. This approach assumed that the energy difference, ΔE, between the two pure solids and cocrystals in different stoichiometries give an idea about the cocrystal formation. The results showed that the probability of cocrystal formation was 50% more, when ΔE difference of cocrystals and two pure solids should be more than 11 kJ/mol. This approach was validated by using about 1000 compounds from literature for APIs (caffeine and carbamazepine) and ΔE parameter was found to be favourable and fast screening tool [2, 38, 39, 57] .

Cocktail cocrystal method

For screening of cocrystal formation, a modern "co crystal cocktail method" was developed in which four coformers were ground in ball mill simultaneously with API, this method reduced the workload by 50 percent and thus compared to traditional single time-consuming methods it was convenient and less time consuming. The chemical moieties present in interactions between coformers and drugs and synthons were generated between drugs and coformers, i.e. homosynthons or heterosynthons. Itraconazole crystals were prepared using this process with succinic acid and serine, and the results showed the highest rate of solubility and dissolution in vitro relative to all other formulations[38, 39, 40, 58].

Thermal analysis

A rapid thermal phase, i.e. For the scanning of the cocrystals, the DSC was used. By heating the physical mixture (1:1) in DSC, the probability of cocrystal formation can be determined. A hypothesis was suggested that three endotherms and two exotherms represented the formation of cocrystals with stoichiometric diversity, two endotherms and one exotherm represented one cocrystal formation with a certain molar ratio, and no cocrystal formation was represented by one endotherm. DSC studied the physical mixture of 20 identified drug-coformer systems and found that an exothermic peak was often correlated with the formation of cocrystal formation. For cocrystal screening and compatibility analysis of API and coformer, DSC was used. This is a very simple cocrystal formation screening method and a small amount of sample is used for analysis. In this phase, no solvent is needed, so it is also known as the "green technique." But, for those compounds which are thermally unstable and volatile in nature, this technique is not sufficient. Some physical transformations take place during scanning, making it difficult to understand correctly[41, 42].

Synthon matching

Synthon matching is the computational theory used to analyze the crystal structure's intermolecular interactions and is an effective cocrystal screening method. The main drawback of this method is that it is not possible to precisely establish the in vivo properties of cocrystals. To estimate the probability of hydrogen bond formation between API and coformer, this synthon approach is used. Different methods have been developed over the past few years to qualitatively and quantitatively evaluate the intermolecular interactions in crystal structures, such as the protein conformational similarity index, hydrogen bond graph analysis, Voronoi-Dirichlet polyhedral for crystal packing, continuous symmetry tests, and the Hirshfeld surface using computer programs such as ESCET, COMPACK, TOPOS, Xpac, Crystal Explorer, and dSNAP, respectively [41, 42, 43].

Methods of Preparation of Cocrystals:

There are mainly 4 methods of preparation of cocrystals [1, 27, 28, 29, 30]:

i) Solid State Method
ii) Solution Based Method
iii) Supercritical fluid Method
iv) Miscellaneous Method

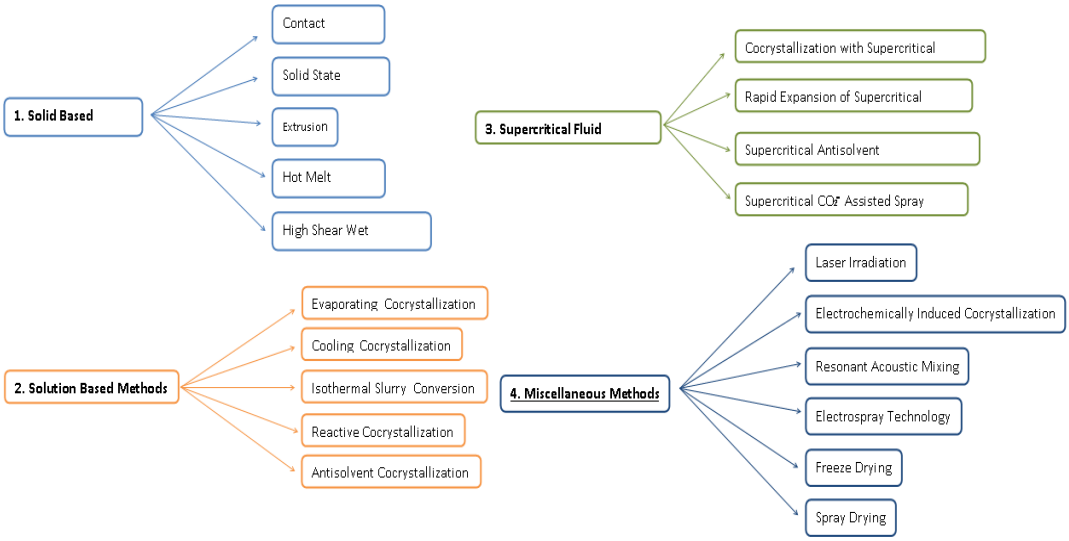


Figure 3: Different method of Co crystals preparation.

Contact Formation:

Spontaneous formation of cocrystals under a regulated atmospheric condition through the mixing of pure API and coformer. In this process, during cocrystallization, no mechanical forces are applied. However, short grinding of pure components individually until mixing has been performed in some instances [1, 39, 40].

Solid State Grinding:

To produce cocrystal powder samples, solid state grinding methods have been used successfully. Two modes of grinding occur—

i) Dry Grinding
ii) Wet Grinding.

The combination of the target molecule and the coformer in its dry solid forms requires neat grinding with the application of pressure by manual or mechanical means [1].

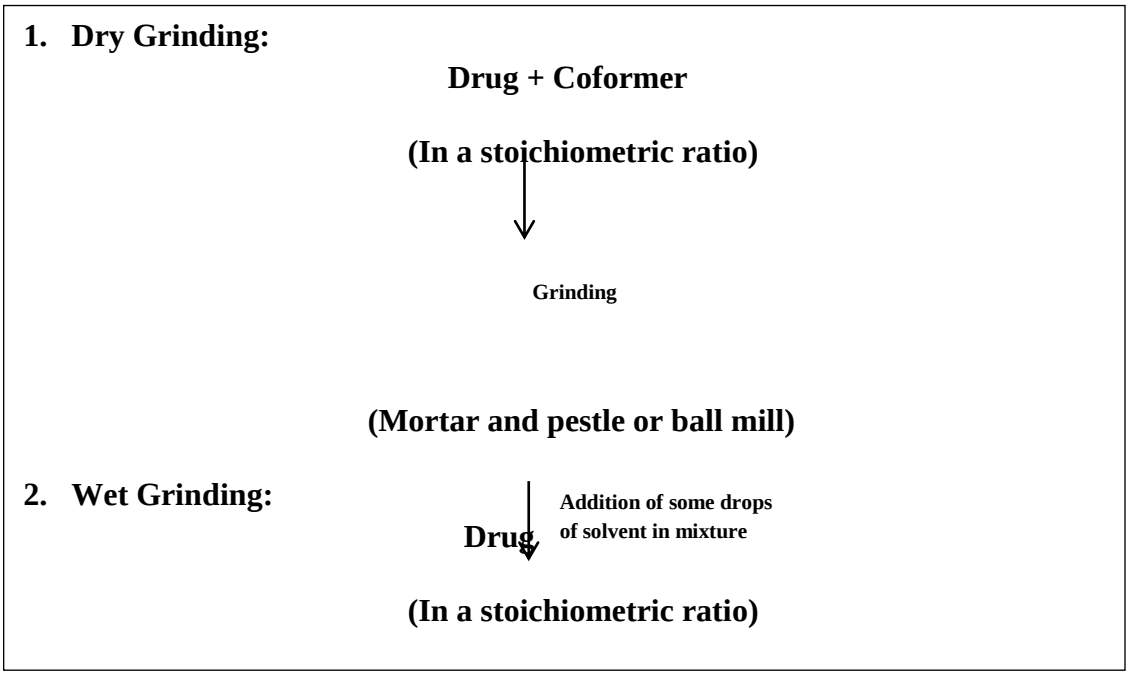


Figure 4: Schematic representation of solid state griding method

Extrusion:

Twin Screw Extrusion (TSE) works at temperatures below the melting point of either the starting material or a correctly called twin screw extruder happens in a separate piece of equipment. Two co-/counter-rotating screws in a single barrel make up this device. Screw action offers the simultaneous mixing and movement of content along the barrel length [1, 40, 41, 42].

Hot Melt Extrusion:

A relatively recent addition to cocrystal preparation options is hot melt extrusion (HME). Via the use of a heated screw extruder, this specialist technique integrates simultaneous melting and blending of the target molecule and the coformer.
In a molar ratio, the starting materials are usually mixed and fed to the heated extruder. Melting occurs, facilitating the starting materials to be combined intimately. In the melt, the cocrystal nucleates first, and the pure cocrystal extrudate is constantly separated from the extruder. The benefits of the technique are the removal of the use of organic solvents, rapid running times, and improved conversion compared to solution-based processes, decreased waste, and the technology is well adapted to continuous pharmaceutical manufacturing [1, 41, 42].

High Shear Wet Granulation:

In the presence of a binder, this technique requires the agglomeration of powder particles through a liquid medium. Technically, the procedure is performed in a high shear granulator which, by means of impellers and choppers, imparts shear on the powder mixture [41, 42].

Evaporative Cocrystallization:

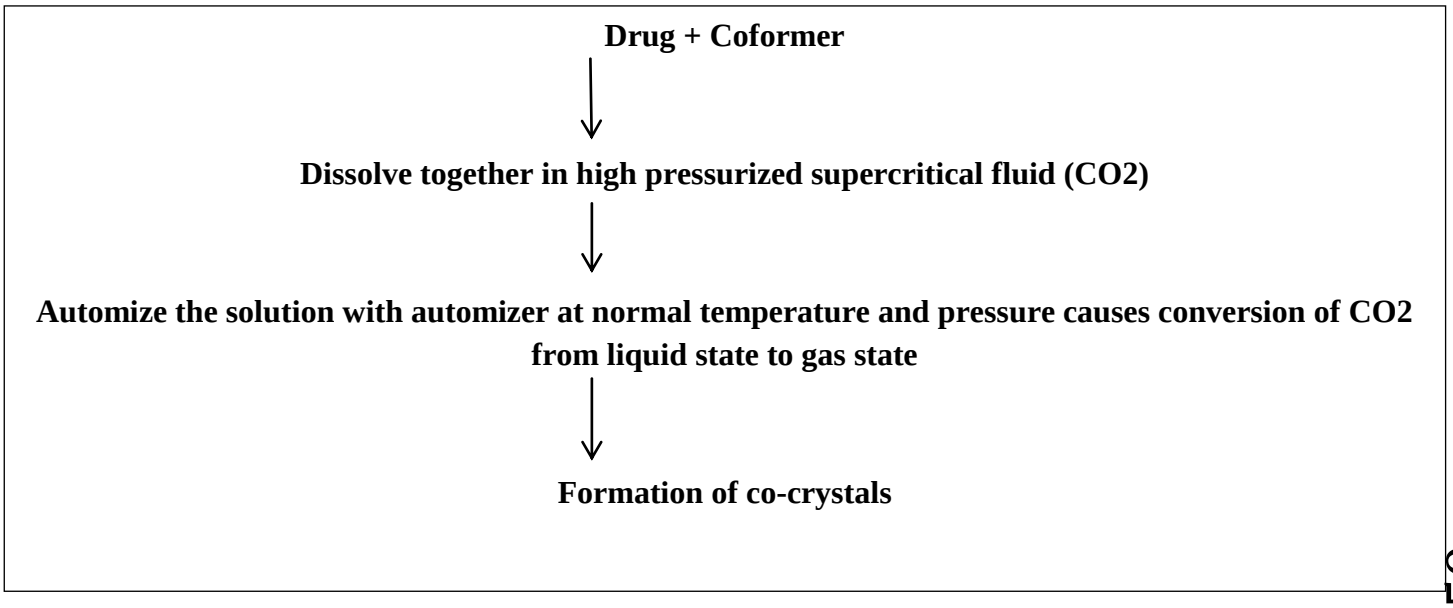
It is a popular cocrystal generation tool, usually used to generate single crystal cocrystals suitable for diffraction studies to elucidate the structure of cocrystals. The technique involves the nucleation and growth of a cocrystal in a solvent from a solution of both coformers, with super saturation given by evaporation by removal of the solvent from the solution. To ensure the recovery of clean crystals, individual cocrystals, or the bulk crystal sample, should be collected until the solution evaporates into dryness [2, 41, 42].

Isothermal Slurry Conversion:

This technique requires the suspension of the target molecule and the coformer in a solvent with the solid fraction still remaining in excess, typically in a fixed molar ratio. The technique may also work in practical terms by adding the target molecule to the solvent solution or suspension of the coformer. Although this is a solution-based process, it does not require a clear (fully dissolved) starting solution to be produced. The rate at which slurry conversion takes place can vary depending on the driving force of solubility, the relative concentrations of the target molecule and coformer, and the system's nucleation and growth kinetics [41, 42].

Supercritical Antisolvent additions:

This is one of the methods of precipitation or recrystallization of the former and active pharmaceutical component of the co-crystal. The buffers (pH) and organic solvents contain solvents [1].



Spray drying technique:

Spray drying is a single-step, continuous process of turning liquids into solid powders (solutions, suspensions, slurries). Due to its continuous, highly controllable, and fast process, it is advantageous. Although spray drying is commonly used in the formulation of amorphous solid dispersions. Owing to the rapid solvent evaporation, presence of the coformer, or contact between the drug and the coformer in liquid form, crystallization has been observed in highly supersaturated regions of the drug [1, 2].

Drug + Coformer

↓

Prepare solution or suspension with evaporating solvent

↓

Spray solution in hot air steam to evaporate solvent

↓

Formation of cocrystals

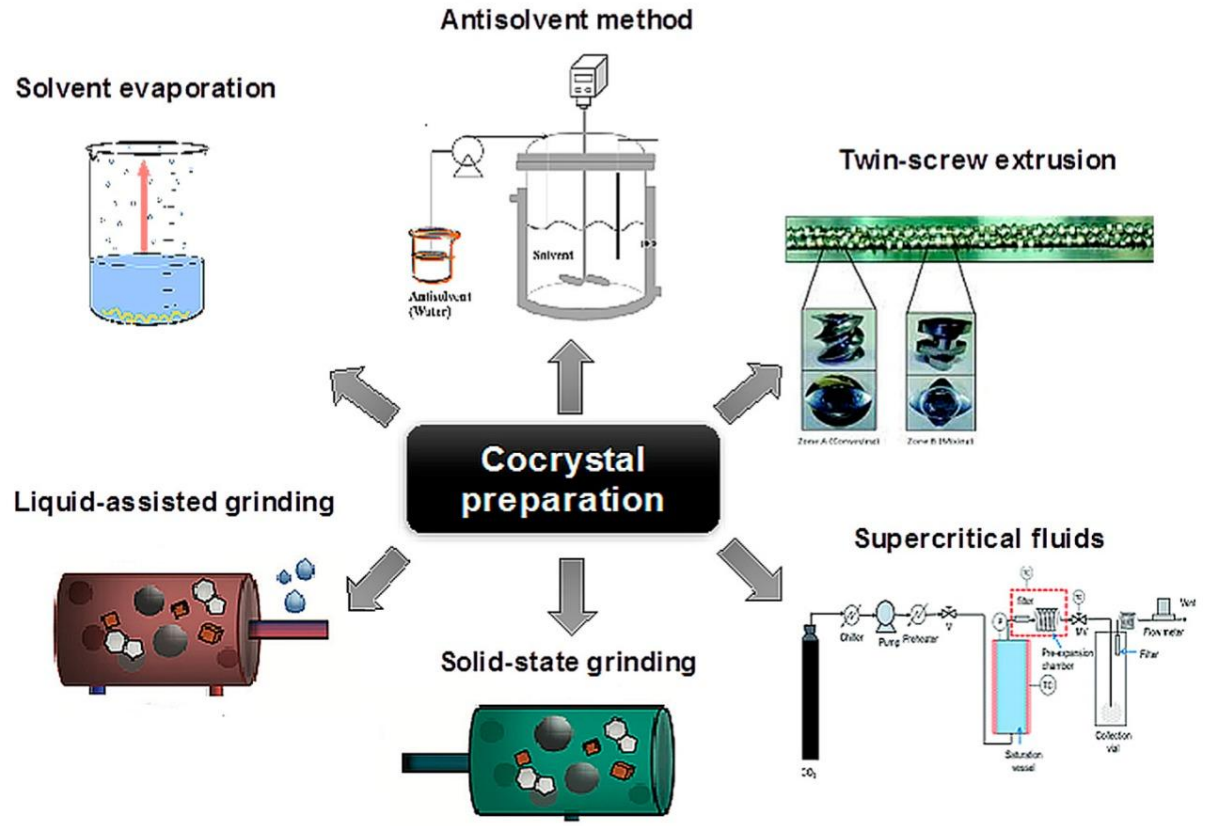


Figure 5: Diagrammatic representation of different method of cocrystals preparation.

Mechanism of Cocrystallization:

Many variables influence the synthesis of new cocrystals, which are often influenced by the existence of the solvent and the reactants. For example, the presence of functional groups and the solubility of reactants in the solvent are just a few of the effective conditions, in addition to several experimental conditions such as the stoichiometric ratio of the coformer and API, temperature, stirring, pH, and type of glassware are just a few of the effective parameters.

Several methods are capable of cocrystal synthesis. Nevertheless, the lack of control over the cocrystals' nucleation, crystallization, and phase evolution is still a major scientific challenge. Mechanochemical techniques are promising techniques focused on green chemistry and inexpensive synthetic pathways for cocrystal processing. Grinding was used as one of the primary techniques for cocrystal formation for the first time in 1893.

Cocrystallization is not a process of a single mechanism, but rather a series of mechanisms that involve

i) Molecular diffusion,
ii) Eutectic formation, and
iii) Cocrystallization through an amorphous phase.

The existence of an intermediate bulk phase (gas, liquid, or amorphous solid) with increased mobility and/or higher energy of reactant molecules with respect to the starting crystalline forms is the common point in these three mechanisms. The formation of solid cocrystals is aided by an intermediate liquid phase in liquid phase assisted cocrystallization, e.g., when one of the reactants is liquid under atmospheric conditions. Cocrystallization may take place via the formation of amorphous intermediates in cases where there is no special mass transfer pathway (i.e., liquid or gas phase). This is possible when molecular solids with strong intermolecular interactions are cocrystallized (e.g., hydrogen bonds). In addition, grinding at temperatures below the glass transition temperature of the reactants has been reported to result in the formation of amorphous phases; but grinding at higher than that will lead to metastable polymorphic forms.

It has been proposed that liquid simply plays the role of lubricant in liquid assisted grinding by providing a medium to promote molecular diffusion. The low solvent fraction during liquid-assisted grinding is of little significance in controlling the outcome of the process, since the cocrystals formed after neat and liquid-assisted grinding are usually thermodynamically stable[44, 45, 46].

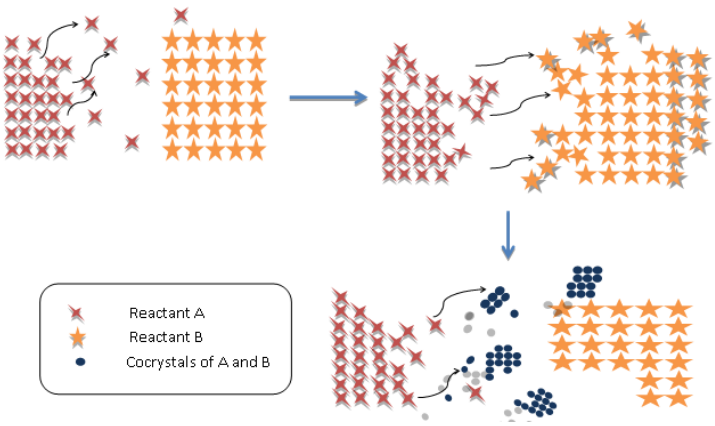


Figure 6: Mechanism of Cocrystal Formation.

Characterization of Cocrystals:

It includes the study of structural and physical properties of cocrystals.

Structural: i) Infrared spectroscopy
ii) Single crystal x-ray crystallography
iii) Powder x-ray diffraction

Physical: i) Melting point apparatus
ii) Differential scanning calorimetry
iii)Thermogravimetric analysis

In general, the XD approach is used for evaluating the structure of cocryatals. Single crystal evaluation and powder XRD are included in the XRD analysis. This technique for cocrystal characterization is commonly used. Thermal analysis is also one of the methods used for cocrystal characterization. Thermal techniques such as thermogravimetric analysis and differential thermal analysis and colorimetry for differential scanning are commonly used for cocrystals. Methods of spectroscopy are also used to classify cocrystals, such as vibrational spectroscopy and magnetic nuclear resonance. NMR is a powerful characterization tool that can provide detailed information on the structure of organic pharmaceutical cocrystals and complexes. Raman spectroscopy is also one of the instruments used for crystallization phase observation. It is used to separate polymorphs, salts, cocrystals, solid solutions and hydrated salts from each other. For the detection and quantitative study of cocrystals, the Fourier-transform Raman is also used [47, 48, 49, 50,].

Applications:

Crystallization is useful in order to enhance the physicochemical properties of drugs without changing the molecular structure of drugs. Whenever the drug dissolution rate is important rather than the equilibrium solubility, cocrystals may be better than the salt form of the drug. Crystallization is an alternative way of improving the solubility and bioavailability of drugs that are poorly soluble in water, especially in the case of neutral or weakly ionized compounds. The opportunity to change the melting point, tabletability, solubility, resilience, bioavailability and permeability improvements is also given by Cocrystallization for the development of energy products, pharmaceuticals and other compounds, the engineering of crystals is essential. This approach is most widely studied and used in drug discovery and, more specifically, the development, development and implementation of active pharmaceutical ingredients (API). By altering the structure and composition of the API, the bioavailability of a drug may be dramatically impacted. The engineering of cocrystals takes advantage of the specific properties of each product to establish the most favorable conditions of solubility that could theoretically improve the bioavailability of the drug. The underlying purpose is to enhance the superior physico-chemical properties of the API while keeping the properties of the drug molecule itself stable.

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