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COCRYSTALLIZATION TECHNIQUES FOR ENHANCEMENT OF SOLUBILITY

Rani M. Umate*, Gouri R. Dixit, Kanchan P. Upadhye, Suparna S. Bakhale, Chetna S. Dakhate and Anup R. Thakre

Department of Pharmaceutics, Priyadarshini J. L. College Pharmacy, Electronic Zone MIDC, Hingna Road, Nagpur-16, Maharastra, India.

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***Corresponding Author'**
Rani M. Umate
Department of Pharmaceutics, Priyadarshini J. L. College Pharmacy, Electronic Zone MIDC, Hingna Road, Nagpur-16, Maharastra, India.

ABSTRACT

The aim of this review is focused on the improvement of the solubility and bioavailability of poorly soluble drugs by using Crystal engineering approaches. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules especially in oral formulation. So many times it becomes challenging to formulate poorly water soluble drugs. Therefore it is necessary to improve solubility of drug by methods like co-solvency, salt formation, addition of solubilizing agent, micronization complexation, solid dispersion etc. A pharmaceutical co-crystal is a novel approach where single crystalline solid incorporates two neutral molecules, one being an active pharmaceutical ingredient (API) and the other a co-crystal former. Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, taste masking. This review cover the co-crystallization, techniques, properties and application in pharmaceutics.

KEYWORDS: Bioavailability, BCS-II Cocrystal, Conformer, Solubility, Salt formation.

INTRODUCTION

The oral route of drug administration is the most important method for administering drugs for systemic effects. Almost more than 90% drugs are orally administered. Drug absorption, sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium

Common problems that challenge the successful drug delivery and manufacture include deficiencies in their properties, such as solubility, stability, bioavailability, organoleptic properties and mechanical properties. It's easy to solve solubility problem of amorphous form, But difficult for crystalline drug. The *in-vivo* performance of orally administered drugs depends upon their solubility and tissue permeability characteristics limited. Poorly soluble drugs have reduced systemic circulation and hence less bioavailability. Different techniques have been applied and studied to improve solubility and bioavailability of such drugs. The techniques include use of surfactants, solid dispersion, drug Micronization, polymorphism etc.[1]

Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophillic membranes being the important ones. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micelle solubilization, hydrotropy etc. Actually, only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action (vascular system for instance). As solubility and permeability is the deciding factor for the *in-vivo* absorption of the drug, these can be altered or modified by enhancement techniques. The bioavailability of drug depends on several factors; drug solubility in an aqueous environment and drug permeability through lipophillic membranes. Due to this major reason, solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility.[2]

Poor aqueous solubility is caused by two main factors.

1. Strong intermolecular interactions which make the solubilization of the solid energetically costly.
2. High lipophilicity.

The biopharmaceutical classification system (BCS) is used in the field of pharmaceutical science and technology. This is a valuable tool for the formulation scientists, for the selection and design of the formulation of any drug substance. The BCS has also got a place in various guidance documents of regulatory importance.

Table 1

BCS Class	Solubility	Permeability	Oral Dosage Form Approach	Chances of Non-oral Dosage Form being Required
1	High	High	Simple solid oral dosage form	
2	Low	High	• Techniques to increase surface area like particle size reduction, solid solution, solid dispersion • Solutions using solvents and/or surfactants	
3	High	Low	Incorporate permeability enhancers, maximize local lumenal concentration	
4	Low	Low	Combine 2 and 3	

Fig 1: BCS classification.

BCS divides active pharmaceutical ingredients (API) into four classes based on drug dissolution rate and gastrointestinal permeability as BCS class I, II, III and IV. BCS class I drugs are highly soluble, highly permeable, BCS class II drugs are poorly soluble, highly permeable, BCS class III drugs are highly soluble, poorly permeable and BCS class IV drugs are poorly soluble, poorly permeable. Out of all these the BCS class II drugs defined by high permeability and low solubility, high permeability is a positive trait of these drugs but low solubility poses a big challenge to the scientists to formulate them.

Process of solubilization

The process of solubilization involves the breaking of intermolecular or inter-ionic bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. Solubilization process occurs into three steps.[3]

Step I: Holes open in the solvent

Step II: Molecule of solid break away from bulk

Step III : The freed solid molecule is integrated into hole in the solvent

Fig.2: Process of solubilization

Factors affecting solubilization

A. Solubility

Solubility is an important parameter for evaluating the properties of a pharmaceutical cocrystal. Traditional methods for improving solubility of poorly water soluble drugs include salt formation, solid dispersion (emulsification), and particle size reduction (micronisation). There are practical limitations with these techniques. A pharmaceutical cocrystal is a novel approach to improve the physicochemical properties such as solubility of compounds.

B. Molecular size

Molecular size will affect the solubility of drug. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

C. Nature of the solute and solvent

While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their natures.

D. Temperature

Temperature will affect solubility. If the solution process absorbs energy then the temperature is increased as the solubility will be increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are

less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

E. Pressure

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

F. Polymorphs

A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropy. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be converted from one another without undergoing a phase transition.

Techniques to improve solubility

The technology as ‘solubility improve’ can be misleading, since although the phenomenon of super-saturation is real, the techniques used do not increase the solubility of insoluble compounds. It is also important to be aware that water solubility also requires the specification of temperature and pH. many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be met at the site of absorption. This article focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds and the ways in which these technologies have made a difference. The techniques that are used to overcome poor drug solubility are discussed under following major headings.[4]

I. Physical Modifications

1. Particle size reduction:- (Micronization, Nanosuspension)
2. Modification of the crystal habit:- (Polymorphs, Pseudopolymorphs)
3. Drug dispersion in carriers:- (Eutectic mixtures, Solid dispersions, Solid solutions)
4. Complexation:- (Use of Complexing agents)

5. Solubilization by surfactants:- (Microemulsions, Self microemulsifying drug delivery systems)

II. Chemical Modifications

A. Salt Formation

B. Co-crystallization.

C. Co-solvent

D. Hydrotropy

A. Particle size reduction

Particle size reduction can be achieved by Micronization and Nanosuspension. Each technique utilizes different equipments for reduction of the particle size.

- **Micronization**

The solubility of drug is often intrinsically related to drug particle size. By reducing the particle size, the increased surface area improves the dissolution properties of the drug. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The is used to increased surface area for dissolution.[22] Micronisation increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

- **Nanosuspension**

Nanosuspensions are sub-micron colloidal dispersion of pure particles of drug, which are stabilised by surfactants. The advantages offered by Nanosuspension is increased dissolution rate is due to larger surface area exposed, while absence of Ostwald ripening is due to the uniform and narrow particle size range obtained, which eliminates the concentration gradient factor.

B. Modification of the crystal habit

Polymorphism is the ability of an element or compound to crystallize in more than one crystalline form. Different polymorphs of drugs are chemically identical, but they exhibit different physicochemical properties including solubility, melting point, density, texture,

stability etc. Broadly polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties. In the case of an enantiotropic system, further study involves the detection of metastable form of crystal. Metastable forms are associated with higher energy and thus higher solubility. Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area.

C. Solid dispersion in carrier

The solid dispersion approach to reduce particle size and therefore increase the dissolution rate and absorption of drugs was first recognised in 1961. The term "solid dispersions" refers to the dispersion of one or more active ingredients in an inert carrier in a solid state, frequently prepared by the melting (fusion) method, solvent method, or fusion solvent-method. Novel additional preparation techniques have included rapid by freeze drying and using supercritical fluids and spray drying, often in the presence of amorphous hydrophilic polymers and also using methods such as melt extrusion. The most commonly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone polyethylene glycols, Plasdone-S6. Many times surfactants may also used in the formation of solid dispersion. Surfactants like Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used. The solubility of etoposide, glyburide, itraconazole, ampelopsin, valdecoxib, can be improved by solid dispersion using suitable hydrophilic carriers. The eutectic combination of chloramphenicol/urea and sulphathiazole/ urea served as examples for the preparation of a poorly soluble drug in a highly water soluble carrier.

D. Complexation

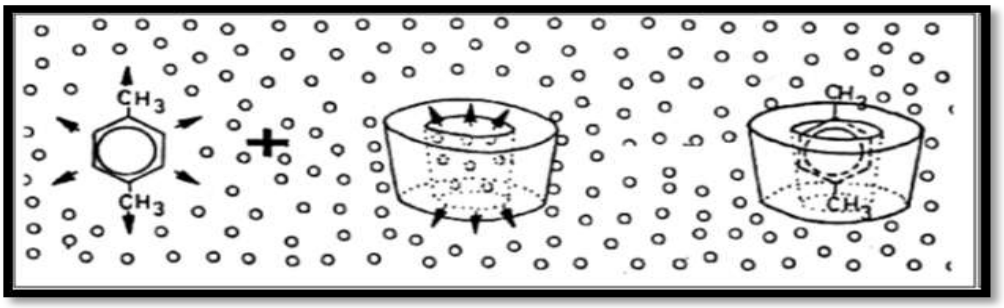
Complexation is the association between two or more molecules to form a non bonded entity with a well-defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interaction .Ex. of complexing agents are; chelates- EDTA, EGTA, molecular complexes- polymers, inclusion complexes cyclodextrins.

1. Stacking complexes

It is driven by association of non-polar area of drug and complexes agent this results in exclusion of the non-polar area from contact with water, thereby reducing total energy of the system. Stacking can be homogeneous or mixed, but results in clear solution.

2. Inclusion complexes

They are formed due to the ability of a compound to enclose in another complex. There are no forces involved between them and therefore there are no bond is also called as no-bond complexes.



Drug Cyclodextrin Drug/ Cyclodextrincomplex

Fig 3: complex formation by Cyclodextrin.

E. Solubilization by surfactants

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a Hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitterionic or nonionic. When small a polar molecule are added they can accumulate in the hydrophobic core of the micelles. This process of solubilization is very important in industrial and biological processes. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent.

II. Chemical modifications

1. Salt Formation

The most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex.Aspirin**,** Theophylline, Barbiturates.

2. Co-crystallization

New approach available for the enhancement of drug solubility is through the application of the co-crystals, it is also referred as molecular complexes. A Co-crystals may be defined as crystalline material that consist of two or more molecular (electrical neutral) species held together by non-covalent forces. It can be prepared by evaporation of a heteromeric solution or by grinding the components together or by sublimation, growth from the melt & slurry

preparation. It is increasingly important as an alternative to salt formation, particularly for neutral compounds.

3. Co-solvent

It is well-known that the addition of an organic cosolvent to water can dramatically change the solubility of drugs. Weak electrolytes and nonpolar molecules have poor water solubility and it can be improved by altering polarity of the solvent. Solvent used to increase solubility known as cosolvent. It is also commonly referred to as solvent blending. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water.

4. Hydrotropy

It designates to increase in solubility in water due to presence of large amount of additives. It improves solubility by complexation involving weak interaction between hydrophobic agents (Sodium benzoate, sodium alginate, urea) and solute. Ex. sublimation of theophylline with sodium acetate and sodium alginate.

Method of cocrystallization

In case of discovery focused pharmaceutical companies enhancement of solubility in case of API with limited aqueous solubility are becoming increasingly prevalent in the research and development portfolios.[5] To date many methods are adopted for the formulation of cocrystals. The most common method are based on solution method and grinding method . Such molecules pose a great challenge in the pharmaceutical development.

A. Grinding Method

There are two different techniques for cocrystal formation via grinding. The first method is neat grinding, which is also called dry grinding, consisting of mixing the stoichiometric cocrystal components together and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill. The second technique for cocrystal synthesis via grinding is that of liquid-assisted grinding (also referred to as solvent-drop, wet co-grinding), in which minor amounts of an appropriate solvent is added in. Significant improvements in kinetics of cocrystal formation by grinding can be achieved by the addition of minor amounts of an appropriate solvent.

B. Hot Melt Extrusion

Extrusion is useful method for synthesis of cocrystals, It involves highly efficient mixing and improved surface contacts, Co crystals are prepared without use of solvent. Cooling leads to super saturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix. A molecular dispersion can be achieved or not, depends on the degree of supersaturation and rate of cooling used in the process. An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed. Another important requisite is the thermostability of the drug and carrier.

C. Solvent Evaporation

Solvent evaporation is the most conventional method in case of crystallization. In this technique the material is mixed with the common solvent and evaporated completely. In evaporation stage the solution of molecules are expected to undergo various hydrogen bonding reactions. But in case of co-crystallization which consists of API and conformers solubility of both in the selected solvent plays a great role. If the solubility of the two is not similar, then the one with low solubility than the other will precipitate out. This does not mean that solubility alone is the criteria for success.

D. Cooling Crystallization Method

In almost all cases solubility decreases with temperature. One can take advantage of this by dissolving your solute in a solvent system to give a near saturated solution at one temperature and then letting the system cool to a lower temperature. If one is blessed with access to a water bath or crystal growing cabinet that has temperature ramp capabilities, cooling times of a day to a week or more are typically chosen. Surprisingly, the cooling times of only a few hours or overnight which are all that one can normally get using “natural” thermal gradients are also often successful.

E. Sonocrystallization Method

The development of sonochemical method for preparation of organic cocrystals of very finite size has been done. This method was primarily developed for preparation of nanocrystals. Caffeine- maleic acid cocrystal preparation commenced with use of ultrasound method. The comparative study of method of preparation of caffeine and theophylline as API and L-tartaric acid as coformer by Solvent drop grinding method and sonochemical method has

been commenced. The results of methods were consistent hence Sonocrystallization proves to be a significant approach.

Crystal engineering

Crystal engineering is defined as 'the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design and new solids with desired physical and chemical properties. A principal tool is the hydrogen bond, which is responsible for the majority of directed intermolecular interactions in molecular solids. It is concerned with the construction of crystal structures of organic and metal organic species, using design principles that are derived from an understanding of the intermolecular interactions that prevail in molecular solids.[6] The formation of a pharmaceutical cocrystal involves incorporation of an API with a pharmaceutically acceptable molecule in the crystal lattice. The resulting multicomponent crystalline phase maintains the intrinsic activity of the parent API. Representative examples of pharmaceutically acceptable cocrystal formers that are able to cocrystallise with APIs include carboxylic acids, amides, carbohydrates, alcohols, and amino acids. The most common supramolecular synthons utilised in pharmaceutical cocrystals are shown in Fig.4. through C=O· · ·H–O hydrogen bond is very common Another widely studied homosynthon is amide homodimer in forming a cocrystal through C O· · ·H–N hydrogen bond. A part from homosynthons, some favorable heterosynthons. Such as carboxylic acid-pyridine in carboxylic–amide in Fig. 4 and alcohol-ether in Recently, studies of hydrogen bonds competition have attracted increasing interest from a number of researcher.

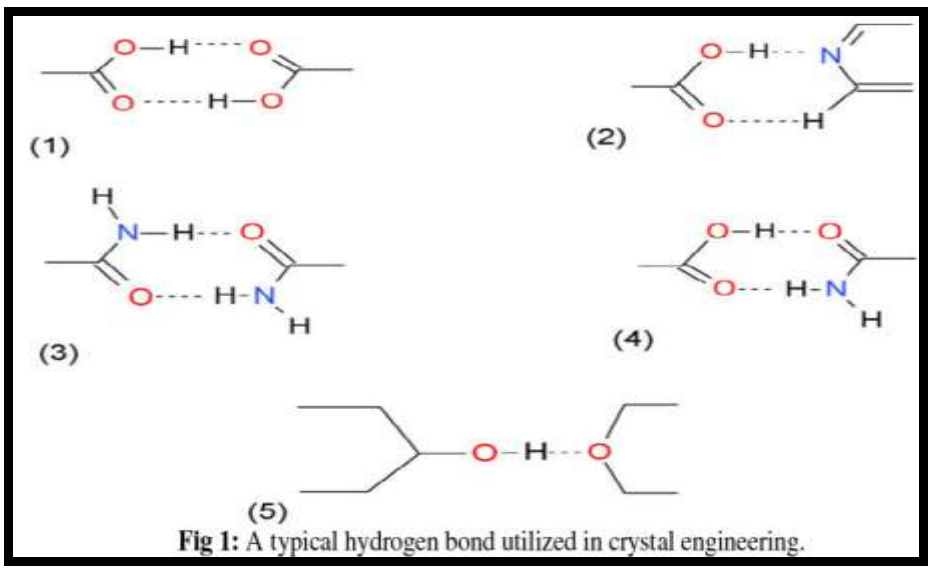


Fig 1: A typical hydrogen bond utilized in crystal engineering.

Fig .4: Typical hydrogen bond in crystal engineering

Cocrystallization

As pharmaceutical cocrystals have rapidly emerged as a new class of API solid. Pharmaceutical cocrystal design is a multistage process. Co-crystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions (primarily hydrogen bonding. The ability of an API to form a co-crystal is dependent on a range of variables, including the types of co-former, the API co-former ratio the solvent.[7]

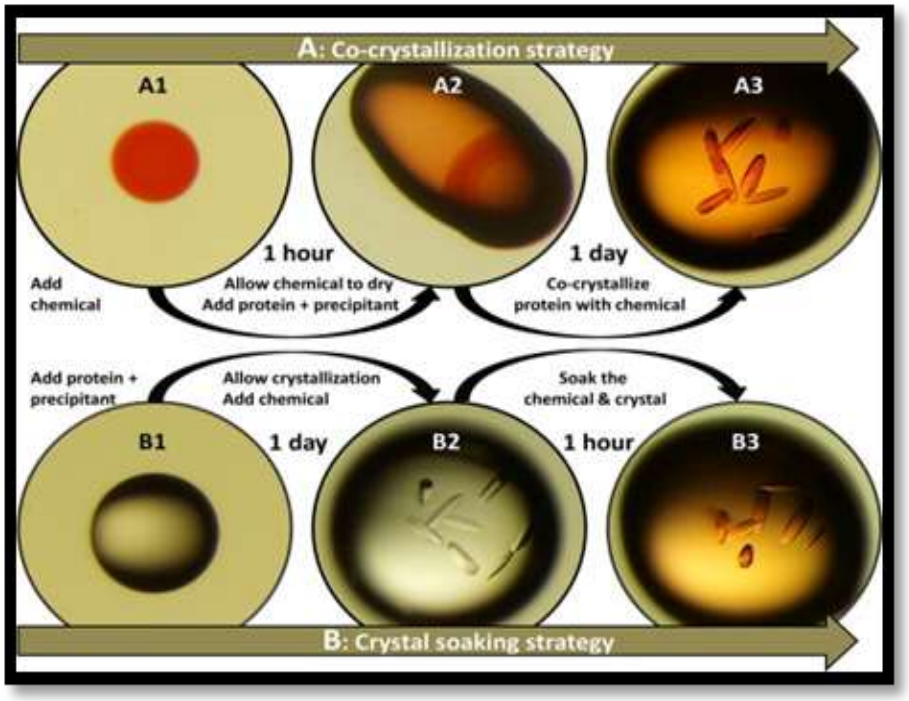


Fig. 5: Formation of cocrystallization strategy and crystal soaking strategy.

Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of co-crystal co-former forms of an API. Co-crystal formation improved the performance of a drug known to have poor solubility. . In most pharmaceutical cocrystal structure hydrogen bond plays an important role in identifying intermolecular interactions between an API and a coformer molecule. The following guide lines were proposed to facilitate the design of hydrogen bonded solids method for modifying physicochemical properties of drugs. Such as bioavailability, dissolution rate, stability, solubility, hygroscopicity, and compressibility without altering their pharmacological action. Other techniques for improving dissolution rate include micronization to produce an increased surface area for dissolution.[8]

❖ **Advantages**

- Selection of co-crystals can enhance the solubility, to a similar extent as that seen with different polymorphs i.e. upto 5 fold
- It can be utilized for non-ionisable API's.
- In chemical processing co-crystal formation may be used as a purification step.
- It is simple technique.
- Lower cost involved.
- Applicable for wide range of drugs.
- Reduce chemical degradation when expose to light.
- They are emerging as an attractive option to polymorphs, salts, solvates and crystal habit manipulation in dosage form design.

❖ **Disadvantages**

- Selection of the suitable solvent is tedious process.
- Maintenance of processing parameters (temperature, agitation) is difficult.
- For parentral and product line extension products, there is a risk of in situ formation of a less soluble form.

❖ **Application of Cocrystal**

- Compared to other solid-state modification techniques employed by pharmaceutical industry.
- Cocrystal formation appears to be an advantageous alternative for drug discovery. (eg. new molecule synthesis, neutraceutical cocrystal)
- Expert are of the opinion that pharmaceutical intellectual property landscape benefit through cocrystallization.

❖ **Pharmaceutical Approaches**

- The physiochemical properties of active pharmaceutical ingredients can be modified while the pharmacological activities of these drug molecules remain the same.
- The shelf life of APIs can be extended by using cocrystals in pharmaceutical product [As well as the formation of solid dispersions and inclusion complexes with Cyclodextrin.
- cocrystal formation can also increase the solubility and dissolution rate of an API.

Design of cocrystal

In order to get a desirable cocrystal product of an API with limited aqueous solubility, the first step is to study the structure of the target API molecule and find out the functional groups which can form intermolecular interaction with suitable coformers. As explained before, these intermolecular interactions include Vander Waals contacts, π-π stacking interactions, and the most common interaction in cocrystal structure of the hydrogen bonding. The next step is to choose a cocrystal former. The primary request for a coformer is to be pharmaceutically acceptable, for ex pharmaceutical excipients and compounds classified as generally as safe (GRAS) for use as food additives. Coformer selection is the crucial step for designing a cocrystal. During the design process, there are lots of worthwhile reference resources, including both empirical and theoretical resources, such as Cambridge Structural Database (CSD), hydrogen bond theories, and many empirical conclusions. CSD is valuable tool to study intermolecular interactions in crystal.[9]

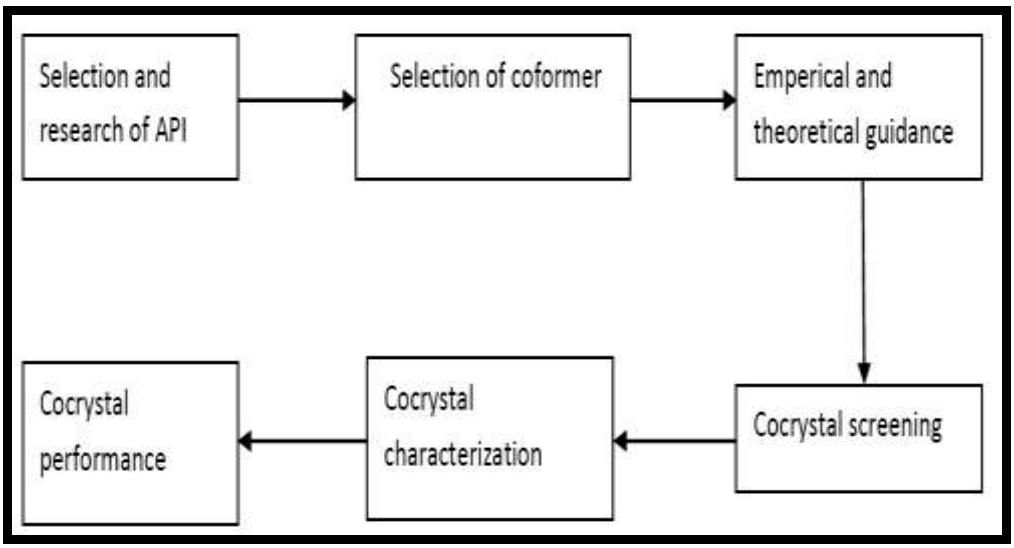


Fig. 6: Steps for cocrystal design and preparation.

It can be utilised to identify stable hydrogen bonding motifs, through referring to structural property. Various screening methods of cocrystals are solution method, hot stage thermal microscopy and computed crystal energy landscape method Cocrystals consist of a single crystalline phase of multiple components in a given stoichiometric ratio, where the different molecular species interact by hydrogen bonding or by other non-covalent bonds. Because of its strength and directionality, the hydrogen bond has been the most important interaction in cocrystal formation supramolecular arrangements in pharmaceutical crystals are often based on synthons of strong and weak hydrogen bonds.

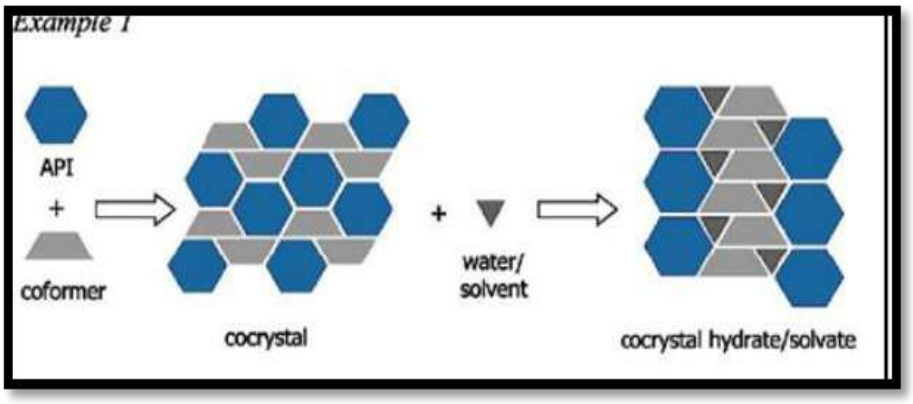


Fig. 7: Steps for cocrystal preparation.

Physicochemical properties for cocrystallization

Physicochemical properties of cocrystals are most important for the development of APIs. The pharmaceutical cocrystal as an alternative approach during drug development is the adjustment of the physicochemical properties to improve the stability and efficacy of dosage form. Physicochemical properties such as crystallinity, melting point, solubility, dissolution, bioavailability, and stability have been extensively studied. Some key physicochemical properties of pharmaceutical cocrystals are summarized as follows.

1. Solubility

Solubility is an important parameter for evaluating the properties of a pharmaceutical cocrystal. Traditional methods for improving solubility of poorly water soluble drugs include salt formation, solid dispersion (emulsification), and particle size reduction (micronisation). There are practical limitations with these techniques4. A pharmaceutical cocrystal is a novel approach to improve the physicochemical properties such as solubility of compounds. Solubility is a great interest from researchers.

2. Melting point

The melting point of cocrystals, in general, differs from those of the individual components due to changes in molecular interactions, composition and structure.compares the melting points of some drugs, coformers and the corresponding pharmaceutical cocrystals. Cocrystals with lower melting points can be advantageous during pharmaceutical processing; for example when a melted state of a thermally labile API is desired during some processes such as hot melt extrusion, a cocrystal with a melting point lower than that of the pure crystalline API will allow for melting at lower temperatures to avoid chemical degradation.

3. Intrinsic dissolution

Intrinsic dissolution measures the rate of dissolution of a pure drug substance from a constant surface area, which is independent of formulation effects and measures the intrinsic properties of the drug as a function of dissolution media, ex. pH, ionic strength and counter-ions. The sample used in the intrinsic dissolution test is pressed into a disk or pellet, which should be no form change upon pressing and the disk needs to remain intact during the experiment. Most of the APIs studied for cocrystallisation are classified as BCS (Biopharmaceutics Classification System) class II drugs, which have high permeability and low solubility.

Screening of Cocrystal

The ultimate goal of co-crystal screens is to discover a solid form of an API with improved physical properties. From this perspective, an efficient co-crystal screening protocol can be split into three phase:

- Co-crystal design.
- Co-crystal screening.
- Co-crystal selection.

A general guideline for co-crystal screening is schematically presented in figure

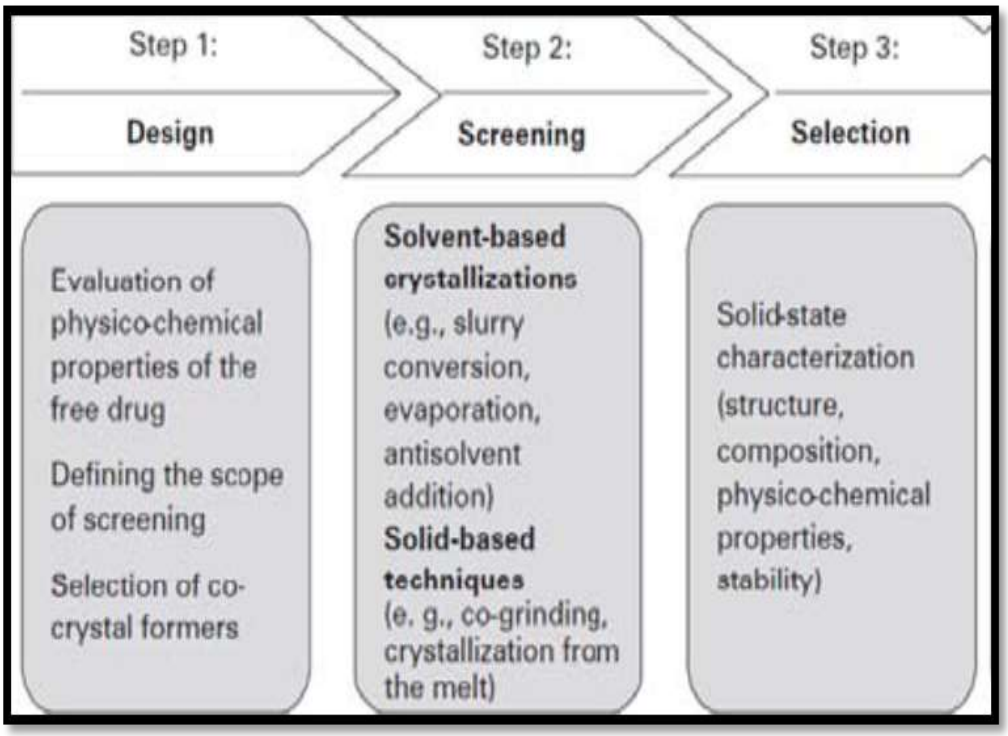


Fig. 8: Steps for screening of cocrystal preparation.

Cocrystal characterization techniques

Cocrystal characterization is an important constituent part within cocrystal research. The basic physicochemical properties of cocrystals can usually be characterized by Powder X-ray Diffraction (PXRD), Single Crystal X-ray Diffraction (SXRD), Infrared spectroscopy (IR), Raman spectroscopy, Differential Scanning Calorimetry (DSC), Solid State Nuclear Magnetic Resonance Spectroscopy (SSNMR), Scanning Electron Microscopy (SEM), and Terahertz spectroscopy.[10]

- **PXRD** is a characterization technique for the determination of solid-state structure of cocrystals at an atomic level. However, the problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, PXRD are utilised more frequently to verify the formation of cocrystals. While, PXRD cannot distinguish solvates, hydrates or polymorphs from cocrystals, to make things worse, pharmaceutical cocrystals are prone to forming isostructural phases. Raman spectroscopy is a spectroscopic technique used to study vibrational, rotational, and other low-frequency modes in a system, which has been demonstrated to be a powerful tool for distinguishing isostructural phase. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products.

- **IR** is a very common spectroscopic technique in determining the chemical conformation of compounds. It can be very powerful tool in distinguishing cocrystals from salts when carboxylic acid is involved in hydrogen bond formation. A neutral carboxylic group (–COOH) has a strong carbonyl (C=O) stretching peak around 1700 cm−1 and a weak C–O stretch around1200 cm−1; however, if deprotonation has occurred, a carboxyl anion (–COO−) has only a single C–O stretch in the finger print region of 1000–1400 cm−1.

- **DSC** is the most widely used technique for the thermal property testing of cocrystals. DSC is preferred technique for obtaining comprehensive melting point data and additional thermal data, such as enthalpy of melting, can also be simultaneously obtained. In addition to being a characterization technique, DSC has recently been used as a screening tool for rapid crystal cocrystal screening.

- **SEM** is a type of electron microscope that images a sample by scanning it with a high energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that

make up the sample producing signals which provide information about the sample's surface topography. It is applied to determine the cocrystal micrograph and particle size.

CONCLUSION

Application of pharmaceutical cocrystals is very important alternative way to improve the bioavailability of poorly water-soluble drugs, especially for these neutral compounds or those having weakly ionisable groups. Another way for cocrystals application is modification of drug pharmacological action. for ex insulin.

Cocrystals investigation and production are very interesting for researchers and very useful for medics and Pharmacologists conversion of crystalline form to amorphous form of drug results in improvement of solubility. This can be achieved by implementation of solid based techniques need grinding and liquid assisted grinding. A key advantage of co-crystal as a solid form of API is possibility of achieving the high dissolution rate comparable to that of amorphous form. Cocrystals which were prepared by solvent evaporation method gives a lower energy and is more homogeneous in terms of crystal composition.

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