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# PHARMACEUTICAL CO-CRYSTALS: A NOVEL APPROACH AND TECHNIQUES FOR SOLUBILITY ENHANCEMENT

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## ABSTRACT

Majority of drugs marketed worldwide are administered by oral route. About 40% of the new molecular entities coming from discovery were never brought to the market because of biopharmaceutical issues like low solubility, low dissolution rate, low permeability and first-pass metabolism. There are various methods to improve the dissolution/bioavailability of poorly soluble drugs including Pro-drug approach, Salt synthesis, Particle size reduction, Complexation, Change in physical form, Solid dispersions & Spray drying. Amongst them Salt formation is one of the most frequently used approaches to improve physiochemical properties of moieties which involve formation of ionic bonds. Co-crystallization is a method of formation of mainly hydrogen bond between the drug molecule and co-former so API regardless of acidic, basic, or ionisable groups could potentially be co-crystallized. Co crystallization can improve physiochemical properties like solubility, dissolution rate, chemical stability and melting point. Interactions which are responsible for the formation of co-crystals include hydrogen bonding, π-stacking, and Vander Waals forces. The article gives a brief review on the co-crystallization, their method of synthesis, its importance as an alternative over salt formation, Characterization and applications.

**KEYWORD:** Co crystal, Solubility and Bioavailability Aspects, Drug Solubility, Novel Approach.

## ➢ INTRODUCTION

Many a times an API cannot be formulated in its pure form due to various issues of instability. Thus they are converted to solid forms such as polymorphs, salts, solvates, hydrates, amorphous and co-crystals. Each of them imparts a different physiochemical property and affects other performance. Now a day there is most challenging situation is to enhance solubility of certain drugs. 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. This review presents the improvement in dissolution profile of drug, bioavailability & solubility by co-crystallization technique. Co-crystals basically consists of two components that are the API and the former. Co crystallization is an effective crystal engineering approach various properties of the drug as well as modifying crystal structure. A definition of a co-crystal can be "multicomponent crystal that is formed between two compounds that are solids under ambient conditions, where at least one component is an acceptable molecule or ion". Some drugs marketed in the form of racemic co crystals include: atenolol, atropine, certirazine, disopyramide, fluoxetine, ketoprofen, loratadine, modafinil, omeprazole, warfare, zopiclone etc. Co-crystals differ from salts in such way as, in salts a proton is transferred from the acidic to the basic functionality of the crystallization partner, as the pka difference between the partners is sufficiently large. In co-crystals, no such transfer takes place The relationships between various solid forms are shown in (Fig.1).[1]

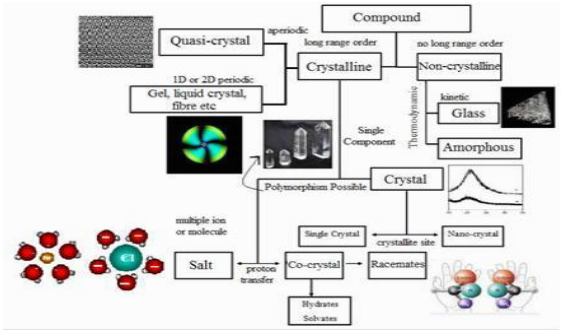


**Fig.1: The relationship between various solid dosage forms.**

## CO CRYSTALS

The APIs can be incorporated into crystalline lattice with the help of co crystal formers for the development of new solid moiety known as co crystals. As an alternative to the solid dosage forms, co crystals are emphasized prominently for the development of dosage forms. With the help of such kind of modifications to the APIs, the physicochemical properties of the drug molecules can be improved significantly. However the modification of drug molecules in co crystal form does not affect their pharmacological response, rather there will be an increment in physical properties of drug molecules such as compaction behavior, hygroscopicity and aqueous solubility.[2]

Co-crystals are considered advantageous in the following situations -

1. Drug molecules lacking easily ionisable functional groups (such as those containing Carboxamide, phenol, weakly basic N-heterocyclic, etc.) can be intermolecular manipulate
2. Via co-crystals to tune their physicochemical properties, Compound having particular sensitive groups to treatment of acid and base,
3. Availability of larger number of neutral GRAS compounds to make co-crystals as Compared to counter ions to make pharmaceutical salts,
4. Overcoming problems in filterability through co-crystallizing a compound.[3]

Co crystals are known as crystalline complexes of two or more neutral molecular constituents, bound together in crystal lattice through non covalent interaction. The pharmaceutical co crystal are prepared by combination of API and coformer i.e. pharmaceutically acceptable molecule inside a crystal lattice. As a matter of fact co crystals increase the diversity of API form. Co crystallization is molecular association of similar or different molecules, the network of hydrogen bonds results in generation of families in the molecular network.[4]

### Designing of co crystals

Crystal design involves the construction of solid crystals with acceptable physical properties with respect to supra molecular structure assemblies. The molecular interactions in the crystalline solids are a result of non covalent bonds such as hydrogen bonds between functional atoms. Due to interaction between compatible molecular assemblies' changes in physicochemical properties occurs such as Solubility, dissolution rates stability and melting point. Co crystallization with pharmaceutically acceptable (GRAS) compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior. Co crystals have regained attention as attractive solid forms for drug development. (Fig.2).[4]

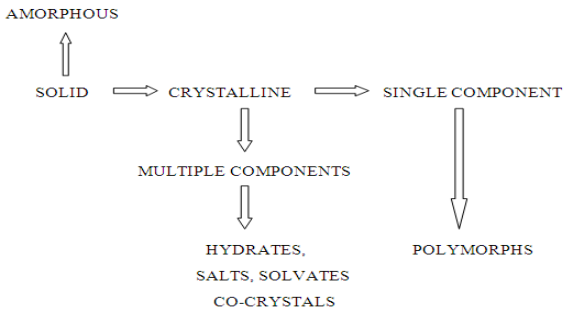


**Fig. 2: API solid form classification based on structure and composition.[5]**

## PHARMACEUTICAL CO-CRYSTALS

The development of pharmaceutical co crystals is considered to be an important approach for optimization of physical properties of the drug molecules. Two or more neutral components are held together in a crystalline geometry by the help of hydrogen bonding, resulting in the development of co crystals. The development of pharmaceutical co crystals possess several benefits in comparison to the conventional salt forms of the drug moiety which includes

1) Both the components i.e. weekly non ionizable as well as weakly ionizable drug components are preferable for development of co crystals, where as such kind of flexibility is not applicable for development of salts of the same,
2) Only 10-12 acidic or basic counter ions are there which are normally useful in the development of salts of API, but the development of co crystals includes a huge number of potential counter molecule.[1]

### Development of crystals

The active pharmaceutical ingredients (APIs) in crystalline forms are more promising towards the stability, reproducibility and purification of the same in comparison to other types of solid forms, hence having the most priority in comparison to other forms. The properties like dissolution rate and intrinsic solubility of several crystalline forms are different and thus are playing an important role in enhancing the bioavailability. The stability with respect to temperature and humidity are more significantly depending on packaging of crystals. The conditions in which there will

be legal issues and challenges towards the protection of patents of APIs in relation to unpredictable crystalline structures and physicochemical properties, that can be resolved by the development of pharmaceutical co-crystals.[1,2]

## ➢ SCREENING OF COCRYSTALS

Co-crystals can be prepared from two molecules of any shape or size having complementary hydrogen bond functionalities. 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 solvents, the temperature, the pressure, the crystallization technique, etc. Experimental screening for co-crystal formers is not trivial. Synthesis of co-crystals can be accomplished via a number of methods, including slow solvent evaporation crystallization from solution, solvent-reduced (e.g. slurring, solvent-drop grinding) and solvent-free [e.g. grinding, melt [(hot stage microscopy)], **h**igh **t**hroughput **c**rystallization and co-sublimation techniques. Typically co-crystals are prepared by slow solvent evaporation that is only viable if compatible solubility in a given solvent exists between the components comprising the potential co-crystal. Solvent drop grinding has been reported to be a cost-effective, green, and reliable method for discovery of new co-crystals as well as for preparation of existing co-crystals. A slurry crystallization technique was used in co-crystal screening of two nonionizable pharmaceutical host compounds, stanolone and mestanolone, with 11 pharmaceutically acceptable guest acids and results demonstrated the importance not only of hydrogen bonding but also of geometric fit in co-crystal formation.[5] Screening of co crystals such includes near infrared spectroscopy which was evaluated for co crystal screening in comparison with Raman spectroscopy. In this study Indomethacin was used as parent drug with L-aspartic acid and saccharin as coformer. The molar ratio of 1:1 with each coformer was selected. For the preparation co crystals two methods are used, in case of saccharin the solvent drop technique is used. While for L-aspartic acid the method solvent evaporation was used. Raman spectroscopy showed straight peaks and shows satisfactory data but near infrared does not showed proper results. NIR shows good result in combination with multivariate modeling by principle component analysis. The development of thermal method for rapid co crystal screening was done. The compound sparing most efficient and highly automated differential scanning colorimetry method developed. Co crystal screening through hot melt microscopy was studied. In this method nicotinamide coformer with seven active pharmaceutical ingredients were used. The synthon stability of each combination was checked. This method allowed identification of thermodynamic landscape within the binary phase and make the screening more efficient. Screening of cocrystals with similar structure was carried out. Piracetam and Levitiracetam are structurally similar. The synthesis of Piracetam cocrystals with 10 different acids had been studied. For the experimental work these ten acids were used to form co crystals of Levitiracetam. The profound result obtained with 40% success rate.

The co crystal hydrates were screened with solvent drop grinding method. The study on all the preparation method was carried out by considering variables along with combination of these techniques and its effect on co crystal formation. Recently for co crystal of caffeine and adipic acid newer screening methods are used. The capability of co crystal formation for antiviral drugs like lamivudine and zidovudine were analyzed. The application of newer synthetic approaches for designing of co crystals was studied. Co crystals of itroconazole-succinic acid characterization are done by single crystal x-ray. The comparative study on two structurally identical solids was carried out. Trimethoprim and pyrimethamine with carboxylic acid salts used as coformer. The co crystals were prepared by various methods and evaluated by different techniques. Among all these methods the solid grinding and solvent-drop grinding was found to be efficient screening tool.[4]

## ➢ MOLECULAR MECHANISM OF CO CRYSTAL FORMATION

The co crystal formation studies mainly aimed at understanding the design of co crystal. In early study approach based on hydrogen bond rules includes certain assumption that all good proton donors are used in hydrogen bonding and every good donor finds a suitable acceptor in crystalline structure. The numerous studies based on method of preparation such as during the co grinding and storage the generation of amorphous phase led to co crystal formation. There are several examples of co crystal formation by moisture uptake such as Caffeine, carbamazepine-nicotinamide, carboxylic acid. The mechanochemical co-crystallization mechanism involves the competitive behavior of intermolecular halogen bonds. The further formation of finite molecular arrangement of competing strong halogen bonds which progresses to polymerization of infinite chain cross linking through strong intermolecular halogen bonds.[4,5]

## ➢ TECHNIQUES OF PREPARATION OF COCRYSTALS

There are several methods through which solution is supersaturated such as evaporation, cooling and incorporation of solubility lowering solvent or substance. The most common technique used for preparation of co crystals is the evaporation. Co crystallization through solution evaporation based crystal growth technique did not offer optimal result. Some of the established techniques that are currently used for co crystal formation such as mechanical co crystal synthesis and Solvothermal co crystal synthesis. In mechanochemical co crystallization the suitable ratios of reactants are grinded to produce phase transformation in to crystalline form. Solvothermal method involves the dissolution of suitable ratios of reactants in solvent undergoing super saturation. The coformer used during development of co

crystal is GRAS chemical i.e. generally recognized as safe.

There are two ways of producing co-crystals mainly they are, solution based and grinding methods. The solution based method is important one because of its nature of producing most of the co-crystals which can qualify for the single X-ray diffraction (SXRD) testing. It includes evaporation of a heterometric solution method, reaction crystallization and cooling crystallization methods. The grinding methods include neat grinding and solvent drop grinding. Apart from theses convictional methods of co-crystallization methods, today there are many other new emerging methods, such as co-crystallization using supercritical fluid, hot-stage microscopy, and ultrasound assisted. Co-crystals can be prepared by solid and solvent based techniques. The solvent-based techniques involve solvent evaporation, slurry conversion, cooling crystallization and precipitation. The solid based techniques involve net grinding, solvent assisted grinding and sonication (applied to both to dry or wet solid mixtures) 80 to 85$^{o}$ C.[6]

**1. Grinding method**

The product acquired when preparing co-crystals from grinding is usually consistent with that obtained from solution. This may specify that patterns of hydrogen-bond connectivity are not idiosyncratic or determined by non-specific and uncontrollable effects of solvent or crystallization conditions. Disappointment in co-crystals formation by grinding co-crystallization possibly due to an incapability to generate suitable co-crystal arrangements rather than due to the stability of the initial phases. The current technique of liquid assistant grinding (solvent drop grinding) has been shown to improve the kinetics and facilitate co- crystal formation and as lead to increased attention of solid-state grinding as a method for co -crystallization.

Two methods of co-crystals has been developed which are –

- Neat grinding (dry grinding, solid state grinding) and
- Solvent drop grinding (SDG).

**Neat grinding** can be done in different methods such as, mechanical grinding using ball mill mixture, vibratory mail or by manual grinding using motor and pestle, thus developing the co-crystals by grinding method.

**Solvent drop grinding** was performed by the regular addition of solvent the choice of solvent is important and should be able to dissolve the compound.[6]

**a) Solid state grinding**

Solid state grinding is alternative synthetic method for solution based co crystallization process. This method offers increase in selectivity and simplicity over solution crystallization technique.[6] Solid state grinding is basically associated with pressing, crushing and mixing of materials either manually through using the mortar and pestle or mechanically with the help of a mill. As per the development of co crystals are concerned, solid state grinding is considered as an innovative approach, a suitable alternative of the synthetic technique like solution based co crystallization. However in some cases the solid state grinding has proved its effectiveness more intensely in comparison to the synthetic methods. The simplicity in developing co crystals with solid state grinding makes it the most important as well as convenient technique for screening of the same. Etter and coworkers investigated co crystals and found that the lattice design is a beauty of hydrogen bonding between the molecules thus agreed with the concept that the co crystals can be generated by suitable modifications in the lattice arrangement of the parent crystalline moiety through solid state grinding.[1]

**b) Solvent drop grinding**

This technique is considered to be a very good alternative to solid state grinding in the development of pharmaceutical co crystals. The technique involves the grinding of two different materials as that of solid state grinding along with a little quantity of solvent which is acting as a catalyst for the development of co crystals. The technique was first demonstrated through co crystallization of nitrogenous bases with cyclohexane tricarboxylic acid derivatives.[1]

Solvent drop grinding is emerging step in advancement of polymorphic selectivity in various models of co crystals. Solvent drop grinding includes grinding of two materials together like solid state grinding with incorporation of small quantity of solvent. The solvent added act as catalyst. It is anticipated that this approach will open new opportunities in both the synthesis and characterization of co-crystals, regardless of the inabilities to characterize materials synthesized using this method by single-crystal X-ray diffraction. Initially their synthesis is carried out by solution crystal growth method. Some crystals were readily prepared with solid grinding method but some did not successfully preceded further. For them solvent drop grinding technique found to be efficient. Solvent drop grinding is useful in synthesis of crystalline salt with pharmaceutical substances.[6] However there are several other examples of solvent drop grinding mediated co crystal development which are mainly based on stoichiometric selectivity. Solvent drop grinding is not only associated with co crystals synthesis but also in the synthesis of crystalline salts. The high throughput robotics technique is extremely associated with the screening of salts optimized with their altered physical properties.[1]

**2. Co-crystallization from Solution**

The two components must have similar solubility for solution co crystallization; otherwise the component which has least soluble will precipitate out entirely. On the other hand similar solubility of two components alone will not promise success. It has been recommended that it possibly useful to believe polymorphic

compounds, which exist in more than one crystalline form as co-crystallizing components. Scale-up crystallization was carried out in a water-jacketed glass crystallization vessel and temperature was controlled by a circulating water bath. Teflon blade and overhead stirrer with a glass shaft were attached to vessel ports and also a reflux column, digital thermometer were attached. The API and co-crystal former were added to this vessel and were dissolved in ethanol/methanol mixture and heated to 70o C under reflux for 1 hour. To induce precipitation of co-crystal, temperature was decreased at a rate of $10^{o}$ C in a stirred, unseeded system. Literate to improve solids recovery decrease the additional temperature.[6]

**a) Solvent Evaporation**

This method works best for water insoluble drugs. The solvent evaporation method provides good encapsulation efficiency and produces amorphous form of compound, which gave better solubility and dissolution than its crystalline form.[7] Solvent evaporation is the most conventional method in case of crystallization. In this technique the all material is mixed with the common solvent serially and evaporated completely. During evaporation stage the solution of molecules are expected to undergo various hydrogen bonding reactions. But in case of Co crystallization which consists of coformer and active ingredient, solubility of both in the selected solvent plays a great role. If the solubility of both is not similar, then the one with low solubility than the other will precipitate out. Molecule has ability to participate in the intermolecular interaction to form a co-crystal. The major disadvantage of this method is that it requires large amount of solvent.[2] These Method used for increase intrinsic solubility of Fluoxetine hydrochloride by using multiple coformers like succinic acid, fumaric acid and benzoic acid. Norfloxacincocrystals were synthesized with Isonicotinamide, Malonic acid and maleic acid as conformers.[6]

**b) Slurry Crystallization**

Slurry crystallization is simple process which includes the addition of crystallization solvent in the components i.e. API along with its acceptable former. The selection of this process is mainly depends upon the physical stability of the crystallization solution to co crystals and its solid former. Experimentations in slurry conversion were carried out in different organic solvents and water. 100 to 200 ml of Solvent was added and the resulting suspension was stirred at room temperature for few days. After few days, the solvent was decanted and the solid product was dried under a flow of nitrogen for few minutes. The remaining solids were then characterized using PXRD analysis.[6] Preparation of co crystals for Trimethoprim and sulfamethoxazole through slurry technique simple distilled water is used as solvent. The major disadvantage of this method is that the yield obtained was not sufficient as compared with solvent drop grinding method. The major disadvantage of this method is that the yield obtained was not sufficient as compared with solvent drop grinding method.[2]

**3. Hot melt extrusion**

In extrusion process of forming a new material, the extrudate, by forcing a material through a die under controlled conditions. The raw materials are pumped through the die by a rotating screw under elevated temperatures (see Fig.3). Extruders provide extensive mixing and agitation that causes de-aggregation of the suspended particles in the molten polymer resulting in a uniform dispersion. Hot-melt extrusion (HME) is used for mixing, melting, and reacting of materials, thereby combining several separate batch operations into one unit and increasing manufacturing efficiency. Most extruders consist of three parts: a conveying system for material transport and mixing, a die system that forms the extrudate and down-stream supplementary equipment such as cooling, cutting or collecting the products.[8]

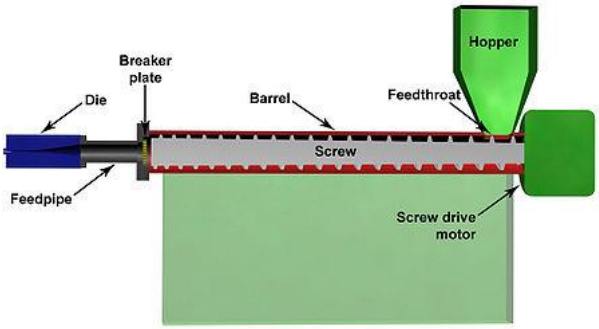


**Fig.3: Extrusion process**

Extrusion is useful method for synthesis of co crystals, it involves highly efficient mixing and improved surface contacts, Co crystals are prepared without use of solvent. The selection of this method is primarily depends on thermodynamic stability of compound. This method was studied with the use of four models for co crystal formation. Solvent drop extrusion technique used to optimize and make the process more flexible. Solvent drop extrusion technique gives an advantage to carry out process at lower temperature. Hot melt extrusion method was used in synthesis of Carbamazepine nicotinamide co crystals with polymer as former. Continuous co crystallization, API and coformer poured in the twin extruder. As a result of continuous addition of mixture the barrel temperature also increases.[6]

***Example-*** Patent on Co crystals of sorbitol and mannitol by hot melt extrusion.[2]

**4. Sonocrystallization Method**

The development of sonochemical method for preparation of organic co crystals of very finite size has been done. This method was primarily developed for preparation of nanocrystals. Caffeine- maleic acid co crystal preparation commenced with use of ultrasound method. The comparative study of method of preparation of caffeine and theophylline as API and Ltartaric 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.

**Example-** Patent on Co-crustal of fluoxetine HCL & benzoic acid in acetonitrile by Sonication. [2]

**5. Antisolvent addition**

Anti-solvent crystallization is the separation and purification method which is used as an effective way to prepare micro to nano-size drug particles. This technique produces crystals from solutions and controls the crystalline properties such as particle size and their morphology. The use of the antisolvent in crystallization reduces the solubility of a solute in the solution and to induce rapid crystallization. The physical and chemical properties of the antisolvent can alter the rate of mixing with the solutions and thereby affect the rate of nucleation and crystal growth of the crystallizing compounds. Additionally, parameters of crystallization experiments strongly influence the mechanism of particle formation and govern the form of crystal size and its distribution.[9] Generally, the antisolvent contains hydrophilic stabilizer (i.e. Surfactants) which is absorbed on the crystal surface to inhibit crystal growth. Hydroxypropyl methylcellulose (HPMC) is a non-toxic in nature and has good hydrophilic property which is widely used as thickening, emulsifying and stabilizing agent in food and pharmaceutical formulations. However, this technique involves some basic problems, i.e. Difficulty in maintaining the size of the particles produced after precipitation, usually with a rapid growth rate which leads to a broad particle size distribution (PSD). The technique involves dissolution, followed by precipitation and then drying. Thus, the mechanical energy input is minimized but the resulting nanoparticles might be crystalline or amorphous and also depending on the process conditions. Even if the particles are crystalline, the crystal growth rate must be controlled to limit the particle size. Also, Poor micromixing during anti-solvent process leads to accidental zones of local supersaturation and, therefore, aggregation of particles. In contrast, ultrasound proves to be a feasible mixing method to provide uniform conditions throughout the vessel during antisolvent process.[8] This is one of the methods for precipitation or recrystalization of the co-crystal former and active pharmaceutical ingredient. Solvents include buffers (pH) and organic solvents. Example preparation of co-crystals of aceclofenac using chitosan, here coformer solution i.e. chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. The prepared dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.

**Example-** Patent on Preparation of VX-950 and 4-hydroxybenzoic acid co-crystal by crystallization from dichloromethane, tetrahydrofuran and n-heptane solution using an antisolvent addition process.[2]

**6. Supercritical fluid atomization process**

Supercritical fluid technology, a recently emerging technology in pharmaceutical industry, utilizes supercritical fluids. Supercritical fluids use offers additional advantages compared to the other co-crystal production methods. Co-crystallization by supercritical solvent is a method where an API and a co-crystal former are mixed together by magnetic stirring after being pressurized by supercritical CO2 in a high-pressure vessel. The Supercritical Anti-Solvent (SAS) technique explores the anti-solvent effect of supercritical CO2 to precipitate particles from solutions; the supercritical fluid enhanced atomization SEA technique explores essentially the CO2 atomization enhancement in a spray drying process. Theophylline saccharin Co-crystal new form with a 1:2 stoichiometry was obtained by the supercritical fluid enhanced atomization process method that has not been previously reported by traditional screening methods. Pure co-crystals of itraconazole: malic acid was produced using either supercritical CO2 or a traditional liquid solvent, such as n-heptane and were Confirmed by both XRD and DSC. Phase transformation during processing affect the mechanism of conversion of crystalline drugs to co-crystal.[2]

**Advantages of supercritical fluid technology**

Supercritical fluid technology is a highly versatile technology and has been extensively used, since the last two decades, in various processes including solubilization, surface modification, nanocrystal formation to obtain the requisite particle size and size distribution. SFT has overcome the limitations of conventional coating techniques like thermal and solvent based methods because most of the pharmaceuticals are thermolabile advantages such as,

1. Rapid one step processing;
2. Moderate operating temperature, has made supercritical fluids a fascinating technology specially for heat sensitive materials;
3. It has enabled the particle size to be reduced to such a great extent, that it can be used for aerosol drug delivery system.
4. The solubility of poorly water soluble drugs can be enhanced, without heating the substance, simply with the help of micronization induced by scCO2;
5. SFT has proved to be an effective alternative for the preparation of solid dispersions and microspheres. Such solid dispersions and microspheres exhibit good flow properties, small
6. particle size, and the residual organic solvent level is quite low as compared to the conventional techniques;
7. It minimizes the use of hazardous and toxic organic solvent e.g. dichloromethane, as reported by Hassan et al. for the preparation of poorly soluble antifungal agent, Itraconazole. In other words, SFT has the

potential to replace the use of organic solvents that have been commonly used in the production of solid composite lipid/drug nanoparticles;

8. A significant research has been carried out to study the enzymatic activity in supercritical medium. As per the conventional techniques, it is believed that the enzymes show activity only in aqueous media, but the supercritical fluids have proved that their activity in such mediums is higher when compared to that in the aqueous medium which has been explored for various biotechnological applications.[9]

**Limitations of supercritical fluid technology (SFT)**

The elevated pressure required, high maintenance cost and requirement of the accessories/auxiliary equipments limits the use of SFT for most of the pharmaceuticals. Therefore, it seems that this technique can not completely substitute the conventional techniques as it is not applicable for processing of all pharmaceuticals.[9]

**7. Cavitation & Melt Sono-Crystallization**

In cavitation process is the generation, subsequent growth and collapse of cavities resulting in very high energy densities of the order of 1 to 1018kW/m3. Cavitation can occur at millions of locations in a reactor simultaneously and generate conditions of very high temperatures and pressures (few thousand atmospheres pressure and few thousand Kelvin temperature) locally, with the overall environment being that of ambient conditions. Thus, chemical reactions requiring stringent conditions can be effectively carried out using cavitation at ambient conditions. Moreover, free radicals are generated in the process due to the dissociation of vapours trapped in the cavitating bubbles, which results in either intensification of the chemical reactions or in the propagation of certain unexpected reactions.

Cavitation also results in the generation of local turbulence and liquid micro-circulation (acoustic streaming) in the reactor, enhancing the rates of transport processes.[10]

**8. Melt Sono-Crystallization (MSC)**

Sonocrystallization can be used to impart a variety of desirable characteristics to high-value products. Dow Chemical, USA is already using sonocrystallization for adipic acid crystallization, but it is a closely guarded secret. Impurities have been reduced from 800 to less than 50 ppm. Ultrasound can be used beneficially in several key areas of crystallization such as:

a) Initiation of primary nucleation, narrowing the metastable zone width.
b) Secondary nucleation.
c) Crystal habit and perfection.
d) Reduced agglomeration.
e) A non-invasive alternative to the addition of seed crystal (seeding) in sterile environment.
f) Manipulation of crystal distribution by controlled nucleation.

The formation of primary nuclei is a function of ultrasonic parameters such as frequency of oscillations, intensity of irradiation and physical properties of the liquid such as degree of Super-saturation and operating parameters such as temperature.[7,9]

## CHARACTERIZATION OF CO-CRYSTALS

Characterization of co crystal is of almost importance and there are different analytical methods ranging from simple melting point determination to complete structural determination through single crystal X-ray crystallography method. Other methods like studying the morphology of crystals by microscopic methods, observing changes in crystal forms with temperature, interpreting molecular motion, phase transition by thermal methods, and chemical environment by the use of vibrational spectroscopy and solid state NMR are used.[2]

❖ **Solubility**

Co-crystallization is a technique most frequently used when the main aim is to enhance the Solubility. Thus the co-crystals usually increase the solubility which is not possible in case if single molecule.

❖ **Maximum wavelength**

When the co-crystal solution is allowed for UV scan the scan gives the peak showing maximum wavelength of the API. If the coformer is also an API the scan will show two peaks of lambda max of both the API.

❖ **Stability**

Stability is an important parameter to be considered for any formulation. Hence in case of Co crystals it is also important to ensure the chemical stability, solution stability, thermal stability and relative humidity. The relative humidity of the co crystals can be analyzed by water absorption/desorption experiments.[2]

**Melting point**

Is the temperature at which the solid phase is at equilibrium with the liquid phase. Melting point of pure API, co-formers and co crystals are obtained by capillary method using liquid paraffin.[6]

**Differential Scanning Calorimetry (DSC)**

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC). In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.[11]

❖ **Thermal analysis**

The third important method, which is widely used in pharmaceutical industries for characterization of polymorphism, purity, salvation, degradation and drug compatibility, is thermal analysis, which includes Thermogravimetry, Differential Thermal Analysis (DTA).[2]

❖ **Infrared spectroscopy**

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material.[11] The study of molecular motions by use of vibrational spectroscopy is also sometimes employed in the characterization of polymorphs.

❖ **Nuclear magnetic resonance**

Nowadays solid state NMR is also used for characterization. NMR studies give the chemical environment of the nuclei which is different in polymorphs because of magnetic nonequivalence. NMR peaks for the magnetically non-equivalent nuclei will differ in different polymorphs and can yield very useful information.[2]

❖ **Scanning electron microscopy**

SEM is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is used to determine the co crystal micrograph and particle size.[6]

❖ **Single X-ray diffraction (SXRD)**

Is a technique for determination of the solid-state structure of co crystals at an atomic level. The problem is that a single pharmaceutical co crystal which is qualified for SXRD testing cannot always be produced. Therefore, powder X-ray diffraction (PXRD) are utilised more frequently to verify the formation of co crystals.[6]

➢ **APPLICATIONS OF CO-CRYSTALS**

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization.[3]

➢ **CONCLUSION**

To achieve the desired therapeutic activity of drug, a research scientist go through several approaches that can enhance solubility, stability, bioavailability and other parameters. Cocrystallization is a new approach to pharmaceutical industry and co-crystal provide a new direction to deal with problems of poorly soluble drugs. Co-crystal have more potential than hydrates, solvates and amorphous forms to improve physicochemical properties. Co-crystal research will go through co-crystal polymorphism, salt co-crystal, glassy co-crystal and higher order co-crystal in future.

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