International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 6 Nov-Dec 2022, pp: 2139-2152 www.ijprajournal.com ISSN: 2456-4494

A Review on Co-Crystal

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Submitted: 17-12-2022 Accepted: 31-12-2022

ABSTRACT
Co-crystal formation is one of the methods to improve the physic-chemical properties of the active pharmaceutical ingredient. Co-crystallization with pharmaceutically acceptable compounds do not affect the pharmacological activity of the API but can improve physical properties such as solubility, dissolution rate, moisture stability and compaction behavior. Co-crystal are most dynamically developing group of multicomponent solid pharmaceutical substances. Co-crystal can be divided into co-crystal anhydrates, co-crystal hydrates (solvates0, co-crystal of salts (unsolvated, unhydrates, solvates or hydrated). Techniques for preparation of co-crystal are solvent evaporation, anti-solvent method. Hot melt extrusion and solvent evaporation, anti-solvent method, hot melt extrusion and solvent free grinding. Co-crystals are characterized by hot stage microscopy, differecial scanning calorometry, X-ray diffraction, IR and Raman spectroscopy.
Keywords : Co-crystals, physic-chemical properties, bioavailability, anionic co-crystal, solubility.

I. INTRODUCTION

Co-crystals are the preparation which helps to improve Physicochemical properties of many pharmaceuticals. Physicochemical properties involves dissolution rate, solubility, chemical stability, and moisture uptakes influence therapeutic efficacy values.

Poor dissolution rate, solubility, chemical stability and moisture uptakes influence therapeutic efficacy of many pharmaceuticals and significantly lower the market values of a drug multi compound crystals. E.g solvates, hydrateds, co crystals, salts play important role in the designs of new solid particularly in pharmaceutical area.

1.2Background

Co-crystals are crystalline materials composed of two or more different molecules, typically active pharmaceuticals ingredient (API) and co crystals forms (co formers), in the same crystal lattice. Pharmaceuticals co crystals have provided opportunities for engineering solidarity state forms beyond conventional solid state forms of an API such as salts and polymorphs.

Co-crystals can be tailored to enhance drugs product bioavailability and stability and to enhance the Procesaability of APIs during drug product manufacture. Another advantage of co crystal is that they generate a diverse array of solid state forms for APIs that lack ionizable functional group, which is prerequisite for salt formation.

1.2 History

- Co-crystals history begins in 1844 with "FRIEDRICH WOHLER" and the discovery of the first co crystals, quinhydrone during the study of quinine.
- Co crystals are not identified at the time due to the late discovery of X-ray analytics. After that in 1958 complete structure and intermolecular interaction were published.
- This co crystals consist of quinine and Hydroquinone in a ration of 1:1
- In fact, many of the first co crystals were hidden under different names, such as adducts, molecular complexes, organic molecular compounds and solid state complexes. Many were discovered in the early 1900s.
- According to "Paul pfieffer" in his book "OrganischeMolekulverbindungen". Co crystals are divided to those consisting of both inorganic and organic components and to those composed of organic components only.
- Although the first co crystal patent date back to 1937 (reference), the term co crystals used since 1967, when it was suggested to descried a complex of hydrogen bonds that is formed between 9 methyl adenine and l-methyl thymine.
- The term was subsequently spread in the 1990s by Margret Etter.
- The debate on co crystals began in 2003 began in 2003 with a controversial letter by

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Desirajuexplaning his performance for it to be known as "a multicomponent system that held together by the non-covalent interaction".

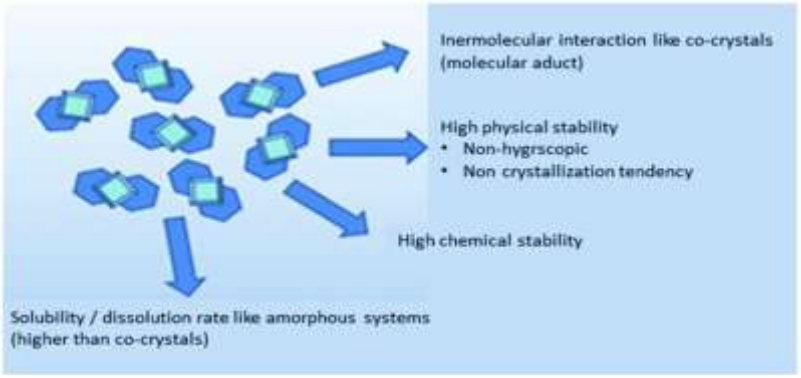
- The European medicines agency (EMA) defines variant as a variant of solid forms of API, association them with salts, polymorphs, hydrates and cosolvates.
- In 2015, the EMA released document specifically related to the use of co crystals in pharmaceutical research, in addition to the one released in 2014.
- Nevertheless, co-crystals are expected to consist of two neural components held together by non-covalent bonds, pointing out that there may be intermediate states between salts and co crystals.
- Polymorphism suggests that a compound which may exist in other crystalline forms will have great degree of flexibility. Thus, the surface energy describing its thermodynamics and allowing it to grow into crystals offers in a higher probability of forming crystals.
- To date, it has not been possible to fully predict whether a co crystalizing reaction will be successful or not and thus the reaction are carried out.

II. DEFINITION

Co-crystals are solids that are crystalline single phases materials composed of two or more different molecular or ionic compounds generally in the stoichiometric ration which are neither solvate or simple salts.

A broader definition is that Co-crystals "consist of two or more components that form a unique crystalline structure having unique properties several sub classification of co-crystals exist.

Co-crystals can encompasses many type of compound, inducing hydrates, solvates, and clathrate, which represent the basic principle of host guest chemistry. Hundreds of examples of co-crystallization are the reported annually.



2.1 Co former

A co former is an isomer of a molecular that differ from another isomer by the rotation of a single bond in the molecule. A conformer is also known as a conformational isomer thus in simple words "The isomers that are formed are known as conformer"

2.2 Advantages

- Co-crystals are the stable crystalline form as compared to amorphous dosage form.
- Co-crystals increased solubility thus increased bioavailability.
- Co-crystalization technique can be used for purification.
- Co-crystals improve the product quality by improving stability.

2.3Disadvantages

- It is difficult to scale up co-crystals
- Co-crystal formation is not appropriate in thermo-labile drug.
- There is a chances of impurities if polymer use are not biocompatible.
- A large number of experiment are necessary to measure the ternary phase diagram.
- In some methods of co-crystals formation there is chances of formation of large amount of environmental pollution.

2.4 The solubility of co crystals follows:

- Lipinski rule of five
- Biopharmaceutical classification system

a. Lipinski rule of five:

- A lipinskli in 1997, based on the observation that most orally administered drugs are relatively small and moderately lipophilic molecules.

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- It is also known as pfizer's rule of five, The rule describes molecular properties important for the drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion (ADME). However the rule does not predict if a compound is pharmacologically active.
- The rule plays important role in drug discovery when there is need of increase the activity and selectivity of API.

b. Biopharmaceutical classification system

- Guidance provided by the U.S. Food and drug administration for predicting the intestinal drug absorption.
- The fundamental bases established by Dr.Gordon Amidon. They proposed that the drug development tool that allows estimation of the contributions of 3 major factors, that affect oral drug absorption from immediate released solid oral dosage forms.
- BCS works on the properties like dissolution, solubility, and intentional permeability of the pharmaceuticals.

III. DIFFERENT SHAPES OF CO CRYSTALS

- **Co crystals anhydrates**

The formation of co crystal hydrates represents a potential route to achieve molecular materials with improved properties, particularly stability stability under conditions of high relative humidity. We describe the use of neat and liquid-assisted grinding for screening for hydrated forms of pharmaceutical co crystals.

- **Co crystals hydrates (Solvates)**

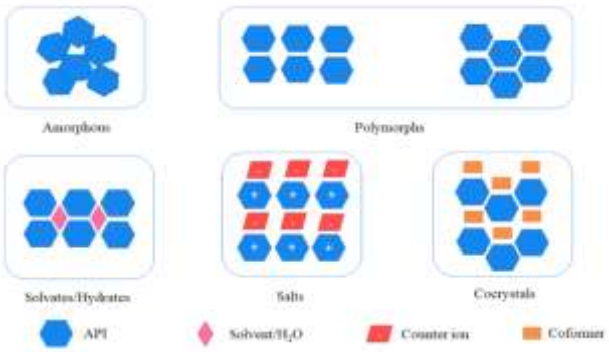
Co-crystals can be constructed through several types of interaction, including hydrogen bonding, p stacking, and vander walls forces. Solvates and hydrates of the API are not considered to be co-crystals by this definition. However, co-crystals may include one or more solvent/water molecules in the crystal lattice.

- **Anhydrates of co crystals of salts**

Co-crystals are multi-component crystals based on hydrogen bonding interactions without the transfer of hydrogen ions to form salts; this is an important feature, since Bronsted acid-base chemistry is not a requirement for the formation of a co-crystal.

- **Hydrates (solvates) of co crystals of solid**

Co-crystals can be constructed through several types of interaction, including hydrogen bonding, p stacking, and vander walls forces. Solvates and hydrates of the API are not considered to be co-crystals by this definition. However, co-crystals may include one or more solvent/water molecules in the crystal lattice.



Shapes of Co crystals

IV. PHYSICO-CHEMICAL PROPERTIES OF CO CRYSTALS

a. Melting point

Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase. It is a fundamental physical property and and important consideration during solid drug development. There are complex correlations between the melting point of pharmaceutical product and its process ability. Solubility and stability and stability. Much research work has been carried out to investigate if the melting point of a co crystal changes with respect to the individual components and if the melting points can be estimated and modulated within a series of co crystals. For example, the melting points of co-crystals to the API AMG517 (an insoluble small molecule VRI vanilloid receptor 1) antagonist and their respective co-formers were compared by stantoa and Bajm showing that all these co-crystals

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have a melting point that fell between the melting point of the API and their corresponding conformers.

b. Stability

Stability is a very important parameters when evaluating the properties of a pharmaceutical co crystal, Usually, the stability testing of a newly developed co crystal includes four aspects relative humidity stress, thermal stress, chemical stability and solution stability. The relative humidity stress test is used to identify the best storage conditions for the product because the amount of water present in the co crystal can lead to quality deterioration.

In was found that better performance of the co-crystals was displayed during water sorption/desorption experiments. For examples, negligible amount of water was sorbed by indomethacin-saccharine co-crystals indynamic vapor sorption and desorption experiments. Co crystals of glutaric acid and 2-[4-{4-chloro-2-fluorphenoxy}phenyl] pyramidine-4-carboxamide sorbed less than 0.08% water up to 95% relative humidity over repeated sorption/desorption cycles. Results showed that these co-crystals are stable with respect to moisture under normal processing and storage conditions.

Thermal stress and chemical stability are relatively less studied areas about co-crystal properties. Very few reports were found and these limited studies showed that thermal stress studies can provide valuable information about physicochemical stability.

c. Solubility

Solubility is another important parameter for evaluating the properties of pharmaceutical co-crystal. Traditional methods for improving solubility of poorly water soluble drugs include salt formation solid dispersion (emulsification) and particle size reduction (micron-isation). However, there are practical limitations with these techniques. Pharmaceutical co crystallization as a novel way to improve the physicochemical properties of a drug such as solubility, which has attracted great interests from researchers tried to improve the solubilities of two APIs exemestane and megestrolacetate, in which two novel co crystals, exemestane/maleic acis and megestrolacetate/saccharin, were prepared from organic solutions with different particle sizes.

d. 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, eg. Ph, ionic strength and counter-ions. The sample used in the intrinsic dissolution test expressed 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 co-crystallization are classified BCS (Bio-pharmaceutics Classification system) class II drugs, which have high permeability and low solubility. Thus, intrinsic dissolution rate is a good indicator for in vivo performance of APIs.

One co-crystal example, a low solubility API, 2-[4-{4-chloro-2-fluorphenoxy}phenyl] pyramidine-4-carboxamide, was co-crystallized with glutaric acid to achieve 18 times higher intrinsic dissolution rates.

e. Bioavailability

In pharmacology, bioavailability is a measurement of the extentto which a drug reaches the systemic circulation. The ultimate goal for co-crystal investigation is to improvethe bioavailability of an API. Animal bioavailability is an important parameter to consider when preparing new forms of a compound. There are limited numbers of animal bioavailability studies on crystals. The co-crystal of glutaric acid and 2-[4-{4-chloro-2-fluorphenoxy}phenyl] pyramidine-4-carboxamide was used to demonstrate an improvement in the oral bioavailability of the API in dogs single dose dog exposure studies confirmed that the co-crystal increased plasma AUC values by three timesattwo different dose levels, the mean pharmacokinetic metrics calculated from the dog study data are summarized in another pharmacokinetic study on the indomethacin-saccharine co-crystal also shows an improved bioavailability of the co-crystal over the API indomethacine.

V. PHARMACEUTICAL CO CRYSTALS DESIGNS STRATEGIES

Pharmaceutical co-crystals have rapidly emerged as a new class of API solids demonstrating great promise and numerous advantages. Much work has focused on exploring the crystal engineering and design strategies that facilitate formation of co-crystals of APIs and co-crystal formers. Pharmaceutical co-crystal design and preparation is a multi-stage process, In order to get a desirable co-crystal product of an API molecule and find out the functional groups which can form intermolecular interaction with suitable conformers.

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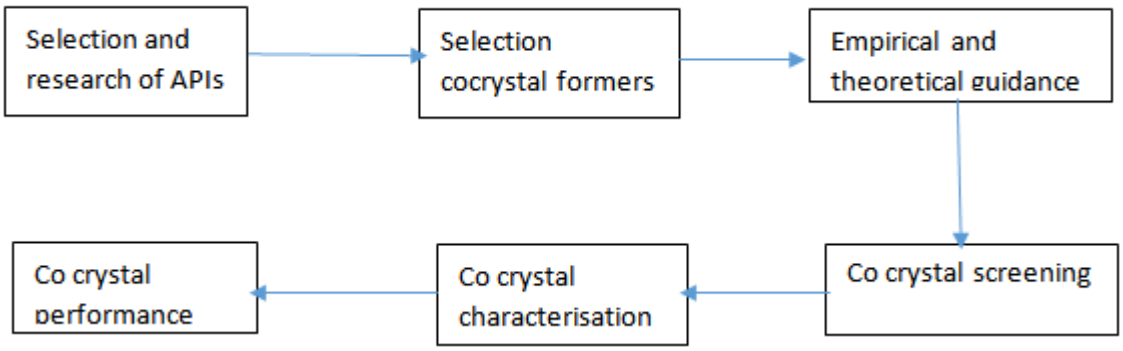
As explained before, these intermolecular interactions include van-der-waals contacts, stacking interactions, and the most common interaction in co-crystal structure of the hudrwgen bonding. The next step is to choose a co-crystal former. The primary request for a conformer is to be pharmaceutically acceptable, for example, pharmaceutical excipients and compounds classified as generally as safe for use as food additives. Co-former selection is the crucial step for designing a co-crystal.

During the design process, there are lots of worthwhile reference resources, including both empirical and theoretical resources, such as Cambridge structural database, hydrogen bond theories and many empirical conclusions. CSD is valuable tool to study intermolecular interactions in crystals. It can be utilized to identify stable hydrogen bonding motifs, through referring to structural property relationships present in classes of known crystal structures contained in the CSD.



Pharmaceutical co crystals designs strategies

A supramolecular library of co-crystal formers has been developed based on the information of CSD, within this library a hierarchy of guest functional groups is classified according to a specific contribution to a crystal packing arrangement, which is dependent on the functionalities contained on the host molecule.

As a general guideline, the hierarchy of the supramolecular synthons within a range of common functional groups can be utilized. According to these studies, certain functional groups, such as carboxylic acid, amides, and alcohols are particularly amenable to the formation of supramolecular heterosynthons. For most pharmaceutical co-crystal structures, hydrogen bonds takes an important role in directing intermolecular recognition between an API and a co-former molecule. A graph-set notation system introduced by Etter was used widely to describe and label hydrogen bond motifs. In the graph-set system four principal motifs are used : chains, dimers, rings, and intramolecular hydrogen bonds as descriptors of hydrogen-bonded molecular solids. Additionally, the following guidelines were proposed to facilitate the design of hydrogen bonded solids:

- All good proton donors and acceptors are used in hydrogen bonding.
- If six-membered ring intramolecular hydrogen bonds can form. They will usually do so in preference to forming intermolecular hydrogen bonds.
- The best proton donors and acceptors remaining after intramolecular hydrogen bond formation, form intermolecular hydrogen bonds to one another. Recently pKa has been used to predict the possibility of co-crystal formation between two co-crystal components.

In the pharmaceutical industry the pKa difference between two reactants is used as, typically –pKa>3, a criterion for selecting counter ions for salt formation. The same criterion has been used for selection of a co-crystal former. However many problems using this pKa evaluation method are found and the criterion is not always applicable. In the meantime, there are many exceptions, such as Johnson and Rumon reported that pKa< 3.75 can produce neutral COOH. An interactions and therefore further study is needed. In a newly published research work, miscibility of a drug and co-former should be miscible for co-crystal formation, The results show that the drug and co-crystal components using solubility parameters can guide the selection of potential co-formers prior to exclusive co-crystals screening work.

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Steps involved in co crystals formation

- Selection of API
- Selection of co former
- Empirical and therapeutic guidance
- Co crystals screening
- Co crystals characterization
- Co crystals performance
- Slurry technique

VI. METHOD OF CO CRYSTALS PREPARATION

1. Solution Method
- Evaporation Co crystallization
- Cooling crystallization
- Reaction crystallization

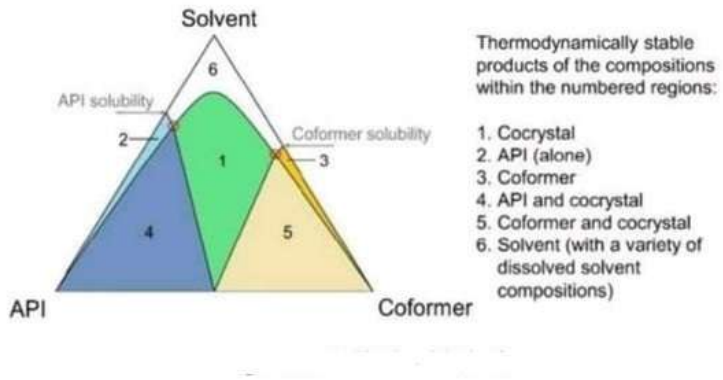
2. Grinding Method
- Neat/Dry grinding method
- Liquid assisted grinding method

3. Antisolvent Method
4. Slurry conversation method
5. Supercritical fluid technology

1. Solution method

In practice, solution co-crystallization is based on the following two strategies use of solvents or solvent mixtures where the co-crystal congruently saturates and thus the components have similar solubility, or

Use of non-equivalent reactant concentrations in order to reach the co-crystal stability region in non-congruently saturating solvents, which can be illustrated by iso-thermal ternary phase diagrams.



Solution Method

Two crystal components components A and B have similar solubilities in solvent and solution co-crystallization with equimolar components A and B have non-equivalent solubilities shown in fig solution co-crystallization through evaporation of an equimolar solution may result in the formulation of single component system.

a. Evaporation co crystallization method

Co-crystallization by evaporation of stoichiometric solutions is based on strategy 1 and it is the most important tool for co-crystal screening. In order to design successful co-crystal screening experiments, it is very important to consider reactant solubilities. In which two co-crystal components A and B have similar solubilities in solvent S and the 1:1 pure crysal can be formed when equimolar components are dissolved in the solvent by evaporation. To date, many successful co-crystal ezamples were obtained by this method.

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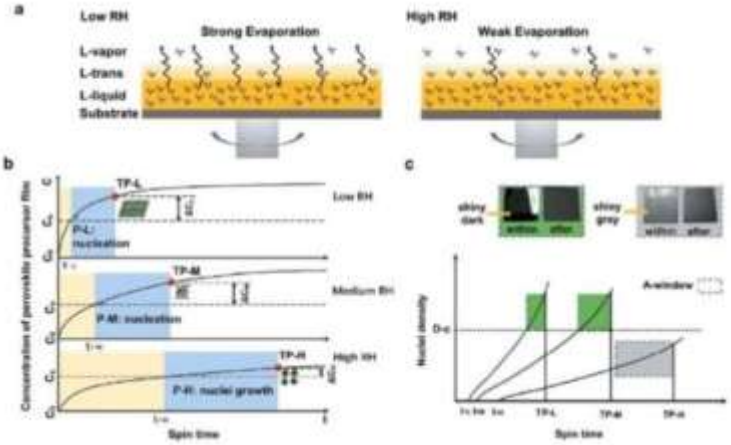
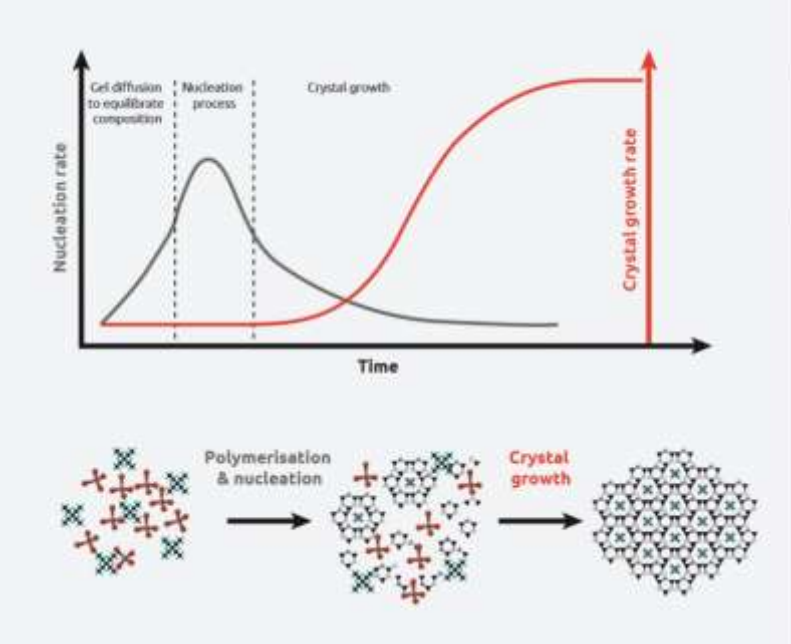


Evaporation co crystallization Method

b. Reaction crystallization

If co crystal components A and B have non equivalent solubilities as sjpwomg sp;itopm co-crystallization through evaporation of an equipmolar solution may result in the formation of single component crystals because super saturation is generated with respect to less soluble reactant or both less soluble reactant and co-crystal.

There is a risk of crystallising a single reactant or a mixture of individual reactant and co-crystal. The reaction co-crystallizatoin approach has been adopted for this situation RC experiments are performed by adding reactant B to a saturated or close to saturated solution of reactant A and then the solution becomes supersaturated with respect to co crystal AB, where co crystallization proceeds along the route Ras showing fig.



Reaction crystallization

c. Cooling crystallization

Another solution method called cooling crystallization involves varying the temperature of the crystallization system, which has recently attracted much more attention for potential of a large scale of co-crystal production. First, large amounts of reactants and solvent are mixed in a reactor typically a jacketed vessel, and then the

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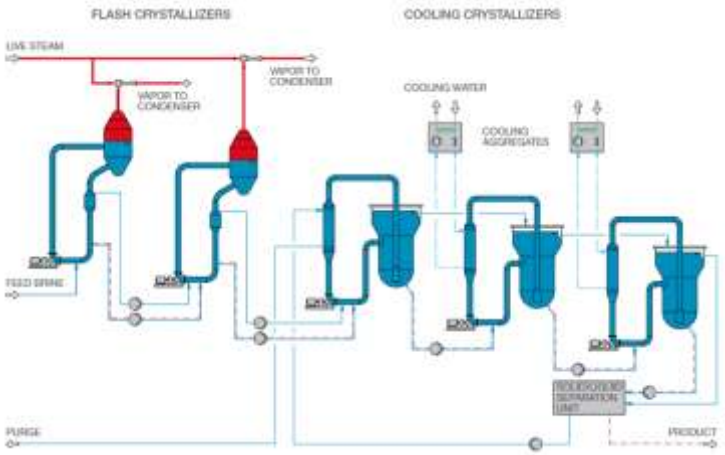
system is heated to a higher temperature to make sure all solutes are totally dissolved in the solvent and is followed by a cooling down step. Co-crystals will precipitate when solution becomes supersaturated with respect to co-crystal as the temperature dropdown.

Co-crystals of caffeine and p-hydroxy-benzoic acid were obtained through cooling crystallization experiments. Their intermolecular interactions of caffeine and p-hydroxy benzoic acid at different concentration ratios in a methanol solvent have be investigated by cooling crystallization, showing that by understanding the details of the intermolecular interactions it not only enhances the effectiveness on co-crystal screening but also servesas a qualitative and predictive indicator for the final crystalline products.



Cooling crystallization

2. Grinding Method

It has been witnessed great progress in co-crystal formation via grinding method over the past few years. There are two different techniques for co-crystal formation via grinding.

The first method is neat grinding, which is also called dry grinding, consisting of mixing the stoichiometric co-crystal components together and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill.

The choice of solvent used in grinding is important and one basic requirement is that it should be able to dissolve at least part of the original components. Comparing this method to the slow evaporation co-crystallization method, little solvent is used in SDG, which therefore appears to be a cost-effective, environmentally friendly, and reliable method for the discovery of new co-crystals as well as for the preparation of existing co-crystals.

Grinding method

This method requires one or both reactants exhibiting significant vapour pressures in the solid state. To date many kinds of pharmaceutical co-crystals have been successfully synthesized by neat

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grinding. Various mechanisms have been utilized to describe the process of neat grinding, involving a different types of intermediate phases, such as molecular diffusion, eutectic formation, and amorphous phase, in which one of the three distinct intermediate bulk phases should exhibit enhanced mobility and higher energy of reactant molecules with respect to their starting crystalline forms.

3. Other Method

Recently several novel methods have appeared in the area of pharmaceutical co-crystallization. The application of a supercritical fluid technology into co-crystal formation has been carried out by Padrela. The feasibility of SCF technologies in the screening and design of co-crystals was studied. The utilization of SCF is based on its three fundamental properties solventpower, miscibility with organic liquids, atomization enhanncement. In Padrela's work, indomethacin-saccharin co-crystals with different morphologies and sizes were produced using supercritical fluid techniques, demonstrating the potential of SCF technologies as screening method for co-crystals

Ultrasound has been used to prepare co-crystals from solution or suspension Ultrasound assisted solution co-crystallization (USSC) has been studied using a non-congruently soluble pair of caffeine and maleic acid in methanol, in which pure caffeine/maleic acid 2:1 co-crystal was obtained. It is suggested that ultrasound applications in USSC must have altered super saturation conditions of caffeine and maleic acid in solution favouring generation of caffeine/maleic acid 2:1 co-crystal nuclei. Further investigations need to be carried out for understanding the nucleation mechanisms during USSC.

- slurry technique

Slurry of drug and conformer was prepard in different organic solvents and water. The resulting suspension was stirred at room temperature and solvent was decanted. The resulting solid material was dried and characterized. Acyclovir-succinic acid co-crystals were prepared by slurry technique.

VII. Mechanism for co-crystals

Amorphous phases generated by pharmaceutical processes lead to co-crystal formation during co-grinding and storage. The mechanisms underlying moisture uptake generated co-crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with dicarboxylic acid ligands, (maleic acid, glutaric acid, and malonic acid) when solid mixtures with co-crystal reactants were exposed to deliquescent conditions involve.

a. Moisture uptake
b. Co-crystal aqueous solubility
c. Solubility and dissolution of co-crystal reactants
d. Transition concentration

For carbamazepine nicotinamide co-crystal synthesis, nucleation and growth of co-crystals were directed by the effect of the co-crystal components on reducing the solubility of molecular complex to be crystallized.

A molecular-level mechanism for cases of mechano-chemical co-crystallization via halogen bonds was reported and was based on the observation and structural characterization of intermediates that appeared in early stages of reaction. The mechanism arises from the competition of strong and weak intermolecular halogen bonds of the N…I and S…I type and involves the initial formation of finite molecular assemblies, held together via N…I bonds that subsequently polymerize into infinite chains by cross-linking through S…I bonds co-crystallization of exemestane and crystals. The mechanism of dissolution enhancement varied. With exemestane/maleic acid co-crystal, fine particle formation resulted in enhancement, whereas with megestrol acetate / saccharin co-crystal, enhancement was due to the maintenance of the co-crystal form and rapid dissolution before transformation to the original crystals.

The mechanisms of conversion of crystalline drugs to co-crystals and factors affecting co-crystal stability were reported. Co-former solution concentration controlled the formation and stability of different stoichiometry co-crystals. Studies with 1:1 and 2:1 carbamazepine-4aminobenzoic acid co-crystals indicated that the co-crystal richer in co-former was found more stable at higher conformer concentration co-crystallization also occurred in solid mixture of co-crystal reactants. Cp-crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or sorption and deliquescence in reactant mixture. In the solid-state, co-grinding carbamazepine with saccharin or nicotinamide formed co-crystals.

7.1 Some other evaluation method

- IR – spectroscopy

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- Differential scanning calorimetry
- Evaluation of pre- compression parameter
- Evaluation of post compression parameter
- Scanning electron microscopy
- Percentage yield
- Determination of melting point
- Solubility analysis
- In vivo drug release studies.

a. IR – Spectroscopy

IR spectroscopy was employed to determine the probably interaction between drug and conformer. The samples were dispersed in KBr paller and scanned using Shimadzu IR spectrophotometer between 4000-4000cm^{-1} with resolution of 4cm^{-1}

b. Differential scanning calorimetry

The thermal behavior of drug alone and co-crystal was determined by Differential scanning calorimetric studies by mattlet Toledo DSC 8229 Module.Weighed samples were heated in aluminum pans at rate of 5^0 C/min from 0 to 300^{0}C temperature range, under a nitrogen stream. The instrument was calibrated using medium and empty aluminum pan was used as a reference.

c. Power X-ray diffraction

The silicon sample holders were utilized to get diffraction patterns of pure piroxicam and co-crystal. The instrument was equipped with a fine focus X-ray tube and each sample was placed on to a goniometer head that was motorized to permit spinning of the sample during data acquisition.

d. Evaluation of pre compression parameters.

Prior to compression powder blends were evaluated for tapped density bulk density and flow and compressibility parameters. Flow properties of powder were determined by angle of repose and compressibility by carr's index and Hauser ratio.

e. Evaluation of Post Compression parameters

1. Thickness and weight variation

The thickness of the tablets was measured using digital vernier caliper.

2. Hardness and friability

Five tablets were randomly selected from each batch and hardness to tablets was determined by using Monsanto hardness Tester.

f. In vitro disintegration time

The digital tablet disintegration test apparatus was used to determine in vitro d9isintegration time using distilled water at 37_+2^0 The time in second taken by tablet for complete disintegration with no residue remaining apparatus was recorded as mean _+ SD.

g. In vivo drug release study

The drug release studies were performed using USP dissolution test apparatus employing paddle method. The dissolution test was performed using 900 ml of 0.1 n hydrochloric acid at 37_+0.5^0 and paddle speed of 50 rom samples were collected at predetermined time intervals and replaced with equals volume of fresh medium. The study was continued for 60 min sample were then filtered though 0.45 nm membrane filter and analysed at 353 nm using UV spectrophotometer.

VIII. APPLICATIONS OF CO CRYSTALS

Co crystallization has a bonus to optimize the chemistry properties of medicine while not sterilization the molecular structure of medicine.

The chew over whether co-crystals or salts will have the desired properties depends upon the API and specific project

Co crystals with negative pKa value will give non-ionised drug when dissolved whereas salt will give ionized API, which is more soluble in water.

Whenever dissolution rate of drug should be important rather than equilibrium solubility, co-crystals can be better than salt form of drug.

Co crystallization is an alternative way to enhance the solubility and bioavailability of poorly water soluble drugs, especially for those compounds which are neutral or weakly ionized in nature.

Further, co-crystallization also offers possibility of altering improving the melting point, tablet ability, solubility, stability, bioavailability and permeability.

Marketing preparation

BRAND NAMES	API	USES	MANUFACTURER
ENTRESTO	Sacubritil+ valsartan	Heart failure treatment	Novartis
DEPAKOTE	Sodium valproate + valproic acid	In treating seizures disorder, depression	Abbott

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VIAGRA	Slidenafil	Erectile dysfunction, CHF	Pfizer
LEXAPRO	Escitalopram oxalate	Anti-anxiety	Forest Laboratories
TEGRETOL	Carbamazepine	Anti-epileptic	Novartis
SPORANOX	Itraconazole	Anti-fungal	Janssen pharma
PROZAC	Fluoxetine	Anti-depressant	Lily
EZETIMIDE	Methyl paraben	Anti-fungal	Reddy's Laboratory
DASATINIB	Propyl gallate	Anti-oxidant	Reddy's Laboratory
ZANAZOL	Vanilline	Flavouring agent	Lannett
NAPROXEN	Urea	-	Reddy's Laboratory
NAPROXEN	Thiourea	-	Reddy's Laboratory
LAMOTRIGINE	Salicylic acid	Skin Disorders	GVK Biosciences
LAMOTRIGINE	Cinnamic acid	Laxative	GVK Biosciences
LAMOTRIGINE	Ferulic acid	Laxative	GVK Biosciences

IX. CONCLUSION

Co-crystal of drugs and drug candidates represents a new type of material for pharmaceutical development co-crystal are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs. Co-crystals have the potential to be much more useful in pharmaceutical products than Solvates or hydrates. The relevance of co-crystals in API formulation include the ability to fine-tune physical properties. Characterization of API, identify and develop new proprietary forms of prescribed drugs and the opportunity to generate intellectual property.

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Volume 7, Issue 6 Nov-Dec 2022, pp: 2139-2152 www.ijprajournal.com ISSN: 2456-4494

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