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Review Article

Co-Crystals: A Review

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ABSTRACT

In development of new product major constraints are poor aqueous solubility and low oral bioavailability. Crystallization is one the approach has been used for enhancement of solubility of poorly aqueous soluble drugs also helps to improve physicochemical properties such as melting point, tabletability, solubility, stability, bioavailability and permeability with preserving the pharmacological properties of the active pharmaceutical ingredient. Different methods have been used for the synthesis of cocrystal such as grinding, slurry, antisolvent, hot melt extrusion, sonocrystallization, supercritical fluid, spray drying etc. The article highlights the co-crystallization, its methods and significance.

Keywords: Pharmaceutical Co-crystals, Co-crystallization, solubility, stability, bioavailability, Grinding, Slurry conversion, Solvent evaporation.

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INTRODUCTION

From recently discovered large numbers of drugs around 60-70% are related to the BCS Class II (low solubility/high permeability) and IV (low solubility/ low permeability)¹ and cause difficulty related to dissolution, solubility, stability, therapeutic efficacy etc.² Need of today's era is to decrease problems regarding solubility and permeability of available drugs with different methods. Multi-component crystals like solvates, hydrates, co-crystals, salts contribute key role in the design of new solids mainly in the pharmaceutical area.

Cocrystals:

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

Cocrystals are multicomponent molecular crystals where all components are at a stoichiometric ratio and comprise of two or more chemically different molecules includes modification of drugs to alter physical properties of a drug, especially a drug's solubility without altering its pharmacology effect.^{3,4,5}

Implications of cocrystals:

Cocrystallization is defined as alteration of physical properties of by modifying drug at molecular level means one can tailored physicochemical properties of drugs to improve it by mans of various methods enlisted blow, so there is no need to any other additives to improve physicochemical property of substances¹¹. APIs and

conformers properties, nature of molecular interaction between them and synthetic procedures are important factors in altering only physicochemical properties but not alter pharmacological properties. The effect on the physicochemical properties of the API is dependent on the available coformer^{12,13}.

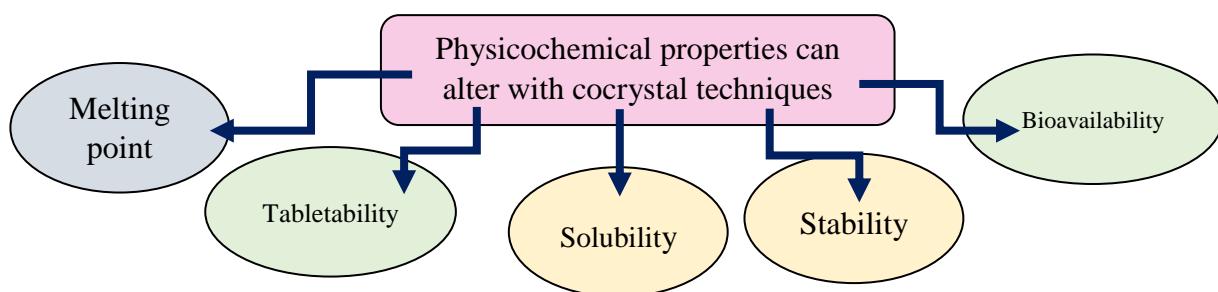
Pharmaceutical cocrystals can enhance the physicochemical properties of drugs like melting point, tabletability, solubility, stability, bioavailability, permeability and these properties are highlighted here with suitable examples.

Melting point:

It is one of the physical properties of solid and used for determination of purity. Pure substances or solid melt at sharp meting point with narrow range¹⁵. Thermodynamic stability of any API can be govern by its meting point so utility of high melting point conformer for its better stability and also useful in case of thermolabile drugs, so selection of conformer is very important in case of synthesis of cocrystals¹⁶. Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) are most common techniques used to determine melting point. Zhang et al studied synthesis of Carbamazepine Cocrystal by using Nicotinamide and saccharin as conformer in two different solvents like ethanol-water solvent mixture and polyvinyl pyrrolidone (PVP) solution. Author studied melting point of cocrystal with the help of differential scanning colorimetry and observed that in case of DSC curve of starting material that is carbamazepin and nicotinamide in ethanol water mixture showed melting around 195°C and 132°C, respectively. And cocrystals

formed showed single endothermal peak is around 162°C, which was located between the melting point of carbamazepin and nicotinamide, while carbamazepine and saccharin in ethanol water mixture showed melting around 176 and 181°C and cocrystals formed showed melting point at 173°C¹⁷. Jadhav et al (also studied melting point study of fenofibrate cocrystals formed with different conformers like para amino benzoic acid, benzoic acid and salicylic acid and observed that melting point of pure fenofibrate was at 78-82°C and melting points of conformers like para amino benzoic acid, benzoic acid and salicylic acid was 184-186°C, 158-160°C, 122-124°C

respectively, while conformers formed showed melting point at 76-78°C, 74-76°C, 70-72°C respectively. Author concluded that melting point of fenofibrate was decreased than pure one and individual conformers¹⁸. Author synthesized Cocrystal of Piroxicam using sodium acetate, saccharine sodium Urea, Nicotinamide, resorcinol conformer and studied difference in melting point of drug and cocrystals. Melting point of sodium acetate, saccharine sodium conformers were high previously but after forming cocrystal with Piroxicam it get decreased, while melting point of cocrystal of Urea, Nicotinamide, resorcinol was increased¹⁹.



Tabletability:

Tabletability means ability of substance to get covert in tablet form. Crystal packing, tabletability and compaction are important parameters of preformulation study; with help of cocrystallization we can alter these properties by using suitable conformers. Zheng zheng et al synthesized cocrystals of Resveratrol with conformers 4-aminobenzamide and isoniazid and studied its enhanced solubility and tabletability. Author observed that tabletability of RES is poor and because of this even at high pressure that is 0.6 MPa and lamination of tablets, while tablets prepared with cocrystals of Resveratrol-4-aminobenzamide, tensile strength more than 3 MPa is attained at 250 MPa compaction pressure. Author concluded that cocrystal formation improved tabletability of drug. Compaction behavior of cocrystals of paracetamol with trimethylglycine and oxalic acid was found to be better than pure drug. Tabletability of resveratrol was enhanced by formation of cocrystals with 4-aminobenzamide and isoniazid. Cocrystals showed higher tabletability than either pure drug or conformers. Mechanical properties of APIs could be altered by varying crystal packing by cocrystallization and cocrystals of vanillin isomers with same coformer showed higher tabletability than isomers and coformer²⁰. Paracetamol have poor compression property, to overcome this problem normally we use wet granulation method for preparation of paracetamol tablet and this is very tedious job, so to resolve this problem Latif et al. synthesized paracetamol cocrystals to improve compaction or tabletability of paracetamol. Author prepared cocrystal of paracetamol by using caffeine as conformer by methods like dry grinding; liquid assisted grinding, solvent evaporation, anti-solvent addition and observed that the compaction power and mechanical property of paracetamol has been increased²¹.

Solubility:

As discussed in introduction about 60 to 70 % drugs are belongs to BCS Class II (low solubility/high permeability) and IV (low solubility/ low permeability)¹, so its need to improve solubility of these drugs to develop the various formulations. With development of cocrystal one can increase the solubility of lo soluble drug many researchers

have been improved solubility of drug with this technique. For eg. Mounika et al. developed cocrystals of Fexofenadine by using Tartaric acid as conformer by solvent evaporation technique and studied cocrystals for saturation solubility according to the method of Higuchi and Connors. Author performed drug solubility study with water as well as 0.01 N HCl and observed that solubility of Co-crystals in water is increase with 11 folds more than the pure drug and solubility of Co-crystals in 0.01 N HCl is 2.47 folds more than the pure drug²². Iyan et al developed Simvastatin-nicotinamide co-crystals by solvent evaporation to improve the solubility of simvastatin by co-crystallization using nicotinamide as co-crystal agent or co-former and evaluated for solubility. Observation was saturated solubility of co-crystal show a threefold increase compared to raw simvastatin²³. Chadha et al also improved solubility of efavirenz by cocrystal technique. Author synthesized cocrystals of efavirenz by using oxalic acid dihydrate and citric acid monohydrate as conformers to improve a physicochemical property that is solubility and dissolution rate. As both conformers have high water solubility that is 14.3g/100 ml and 64.7g/100 ml respectively and contain hydrogen bond donor and acceptor groups, which can be used for designing cocrystals of efavirenz leading to improvement in solubility²⁴. Shubhangi et al synthesized cocrystals of poorly water soluble drug Darunavir. It is BCS Class II drug having low solubility. Co crystals were developed by cooling crystallization method using succinic acid as conformer. Author determined aqueous solubility of darunavir by saturation solubility by dissolving excess amount of cocrystals in water for 24 hrs on the rotary shaker, analyzed with spectrophotometer and observed that with Cocrystallization technique there is significant improvement in the aqueous solubility, found 1.92 fold increases in saturation solubility²⁵. Author Rajurkar also developed Co Crystals of Ezogabine to improve Aqueous Solubility using carboxylic acids as conformer by grinding; ultrasound assisted co-crystallization and solvent evaporation techniques and found that 10-11 fold improvement in solubility of co crystals than pure drug²⁶. Muddukrishna et al studied synthesis of paclitaxel and naringen cocrystal to improve solubility by solvent assisted grinding method. Paclitaxel (PTX) is a class-4 drug; this drug has low aqueous solubility. Solubility study

of paclitaxel and naringen cocrystal was done at room temperature for 72 hours by shake flask method, analyzed samples with HPLC method and found 2.4 fold increases in the saturation solubility²⁷. Prabhakar et al also prepared Cocrystal of Piroxicam and studied for solubility. Author used various conformers like adipic acid, benzoic acid, cinnamic acid, citric acid, glutaric acid, hydroxybenzoic acid, hippuric acid, malonic acid, resorcinol, saccharine sodium, 1-hydroxy-2-napthoic acid, sodium acetate, urea, catechol, ferulic acid, aerosil-200, nicotinamide, para amino benzoic acid, anthranilic acid and succinic acid for synthesis of cocrystals and performed saturated aqueous solubility of cocrystal and found significant increase in solubility of drug after formulating as cocrystals [28]. Muddukrishna Co-Crystals of Etravirine to improve Solubility by using Tartaric Acid as conformer with slow evaporation technique. Etravirine is a BCS Class IV drug having low solubility and low permeability. Solubility study of cocrystals was done by shake flask method and found 3.6 fold increase in solubility of cocrystals than pure drug²⁹.

Stability:

It is also imperative study has to be done during the development of new dosage formulation. Different stability studied like chemical stability, thermal stability, solution stability and photostability should be performed during development of pharmaceutical cocrystals. Iyan 23 et al developed Simvastatin-nicotinamide co-crystals by solvent evaporation to improve the solubility of simvastatin by co-crystallization using nicotinamide as co-crystal agent or co-former and evaluated for stability study at 40°C and relative humidity (RH) 75% in one month found it stable.

Bioavailability:

Bioavailability is defined as the rate and extent of pure drug that reaches into systemic circulation. Low oral bioavailability of APIs is one of the major challenges in development of formulations, with help of cocrystallization one can enhance or improve the bioavailability of drug. Many researchers have enhanced the bioavailability of

different drugs with conversion in cocrystal form. For eg. Mounika et al prepared cocrystals of Fexofenadine. Fexofenadine is class II drug according to the BCS classification with low solubility and high permeability, the rate limiting steps in attaining desired bioavailability. Hence Author prepared cocrystals of Fexofenadine using Tartaric acid as a co-former by solvent evaporation and observed that with cocrystallisation technique drug had maximum release as compared to the formulation²². Pinky et al formulated cocrystals tablets dosage form of clarithromycin to enhance the bioavailability. As Clarithromycin is BCS Class II drug author prepared cocrystals by using urea as conformer by solvent evaporation method. Developed tablet formulation and evaluated. Author concluded that the formulated tablets of Clarithromycin co-crystals showed improved solubility and in-vitro drug release profile as compared to Marketed Tablet. And thereby increases oral bioavailability and therapeutic effect³⁵. Zhang et al studied synthesis of Carbamazepine Cocrystal by using Nicotinamide and saccharin as conformer by solvent evaporation technique³⁶.

Methods of Preparation:

Co-crystal formation described in the literature indicates the notoriously difficult situation these systems present with regard to preparation it has been known to take 6 months to prepare a single co-crystal of suitable quality for single X-ray diffraction analysis. This is partly because such a heteromeric system will only form if the non-covalent forces between two (or more) molecules are stronger than between the molecules in the corresponding homomeric crystals. Design strategies for co-crystal formation are still being researched and the mechanism of formation is far from being understood.

Co-crystals can be prepared by solvent and solid based methods. The solvent-based methods involve slurry conversion solvent evaporation, cooling crystallization and precipitation. The solid based methods involve wet grinding; solvent-assisted grinding and sonication (applied to either to wet or dry solid mixtures) 80 to 85°C.

Methods for Preparation of Co-crystals

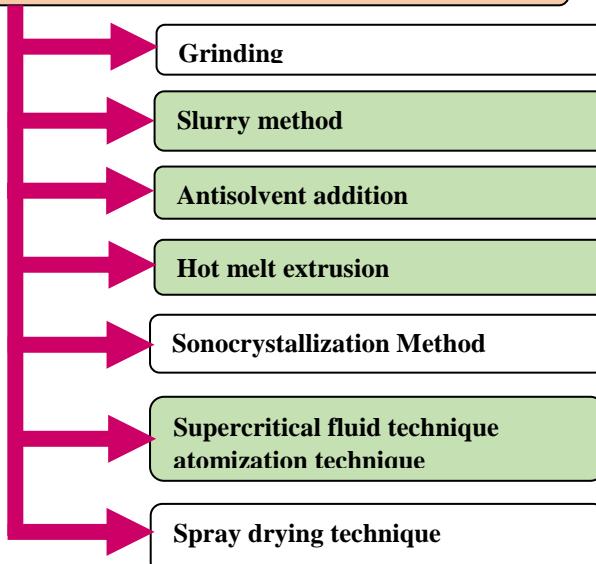
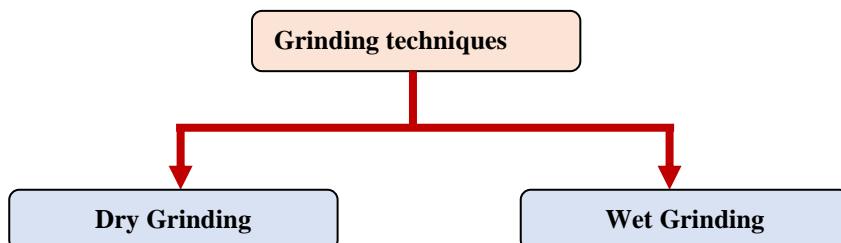


Figure 1: Methods of preparation of cocrystals

Grinding:**Figure 2: Grinding techniques for preparation of cocrystals****1. Dry Grinding: (Pharmaceutical Cocrystals: An Overview)**

Drug + Coformer
(In a stoichiometric ratio)
↓
Grind
(Mortar and pestle or ball mill)

2. Wet Grinding:

Drug + Coformer
(In a stoichiometric ratio)
↓
Grind
Addition of some drops of solvent in mixture
(Mortar and pestle or ball mill)

Cocrystals have been synthesized by grinding method. Sungyup et al prepared Adefovir dipivoxil Co-crystals by using glutaric acid and suberic acid as coformer by liquid-assisted grinding³⁷, Prabhakar et al synthesized Cocrystal of Piroxicam by dry grinding method, sodium acetate used as coformer. Author reported modified properties of piroxicam cocrystal and formulated orodispersible tablets having faster disintegration and greater dissolution rate. Ibuprofen-amino acids co-crystal screening via co-grinding methods²⁸. Muhamad et al synthesized Ibuprofen-amino acids cocrystals by dry grinding as well as liquid assisted grinding method³⁸. Gaikwad et al studied synthesis of cocrystals of Fenofibrate by grinding method³⁹.

Slurry conversion:

Drug + Coformer
(In a stoichiometric ratio)
↓
Addition of solvent to form slurry

Slurry conversion experiments were conducted in different organic solvents and water. Solvent (100 or 200 ml) was added to the co-crystal (20 mg) and the resulting suspension was stirred at room temperature for some days. After some days, the solvent was decanted and the solid material was dried under a flow of nitrogen for 5 min. The remaining solids were then characterized using PXRD. For eg DWI et al reported synthesis of nicotinamide cocrystal by slurry method. Author mixed both powders of Artesunate and nicotinamide homogeneously in mortar and added water to the mixture to form slurry⁴⁰. Noriyuki et al studied synthesis of cocrystals of stanolone and mestanolone using slurry crystallization⁴¹. Prafulla et al synthesized caffeine/maleic acid co-crystal by ultrasound-assisted slurry co-crystallization techniques⁴². Erizal et al prepared cocrystals of trimethoprim and sulfamethoxazole by slurry technique. Cocrystallization was formed by simply adding water as solvent to mixture of trimethoprim and sulfamethoxazole and developed cocrystals was characterized by thermomicroscopy, scanning electron microscope, powder X-ray diffraction, differential scanning calorimetry. Author also studied effect of temperature on formation of cocrystal and observed that transformation to cocrystalline phase was accelerated by increasing the temperature of storage⁴³.

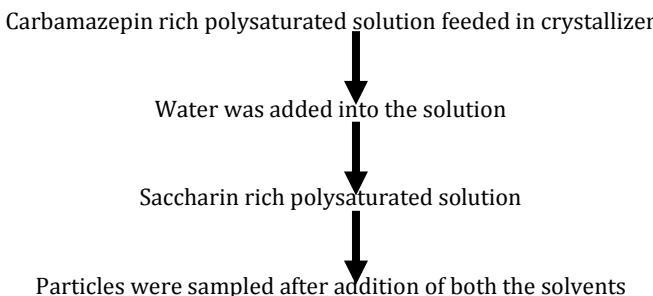
Antisolvent addition:

This is one of the methods for precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient. Solvents include buffers (pH) and organic solvents. For example preparation of cocrystals of aceclofenac using chitosan, in which 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. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug. Momoko et al studied synthesis of co-crystals by Antisolvent addition method by two sequences⁴⁴.

First sequence was:

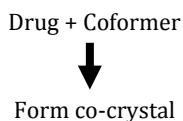
Carbamazepin rich polysaturated solution feeded in crystallizer
↓
Saccharin rich polysaturated solution
↓
Water was added into the solution
↓
Particles were sampled after addition of both the solvents

Second sequence was:



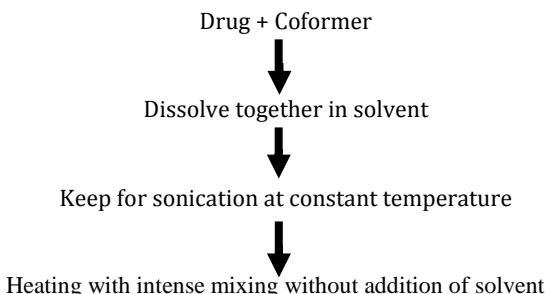
And characterized sample by X-ray diffraction (XRD) analysis. While Jeong et al and Nan-Hee et al prepared indomethacin-saccharin co-crystals by an anti-solvent crystallization process and compared with co-crystals by evaporation method^{45,46}.

Hot melt extrusion



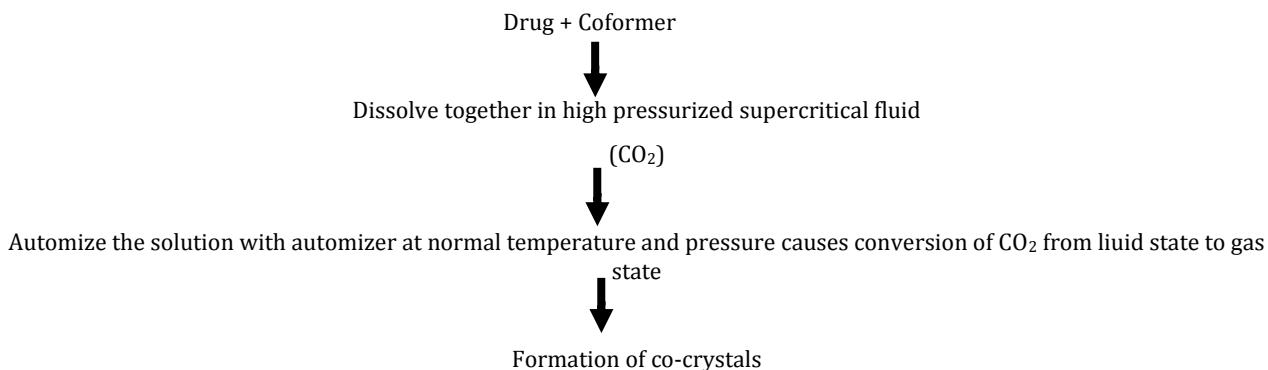
Hot melt extrusion drug and coformers are heated with intense mixing without addition of solvent, for eg Li et al, synthesized ibuprofen/isonicotinamide cocrystal suspensions single-step hot-melt extrusion process⁴⁷. Kevin et al studied synthesis of Carbamazepine Cocrystals by Hot-Melt Extrusion author used Carbamazepine as the drug and nicotinamide used as conformer and characterized cocrystal matrix by differential scanning calorimetry, Fourier transform infrared spectroscopy, and powder X-ray diffraction⁴⁸.

Sonocrystallization Method⁴⁹:



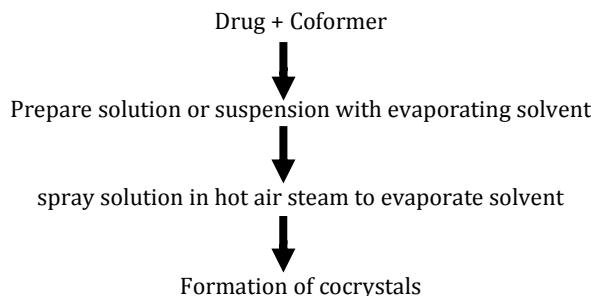
Several researchers studied preparation of cocrystals by sonocrystallization method Prafulla et al studied synthesis of cocrystals of Caffeine/Maleic Acid by Ultrasound-assisted Slurry Co-crystallization. Author constructed two phase diagram that is one in the absence of and one in the presence of ultrasound, prepared slurry by varying quantity of amounts of caffeine, maleic acid, and water and other one was subjected to 12 ultrasound pulses of 5 s each separated by a gap of 1 s, using a 20-kHz high-power ultrasound set at 50% amplitude at 25°C⁵⁰.

Supercritical fluid atomization technique [Supercritical Antisolvent (SAS) Method]:



Abhijat et al prepared and characterized Carbamazepine and Nicotinamide co-crystals by supercritical fluid process (SCF) method and characterized developed cocrystals by dissolution studies, differential scanning calorimetry, hot stage microscopy, scanning electron microscopy, H NMR and X-ray powder diffraction⁵¹. Courtney et al studied synthesis of Cocrystals of itraconazole and succinic acid by gas antisolvent (GAS) cocrystallization using pressurized

CO₂. Author dissolved itraconazole and succinic acid in a liquid solvent (tetrahydrofuran) at ambient conditions and pressurized solution with CO₂, which decreased the solvating power of tetrahydrofuran and caused crystallization of itraconazole-succinic acid cocrystals. Characterized cocrystals by Powder X-ray diffraction, Fourier transform infrared spectroscopy, differential scanning calorimetry, and scanning electron microscopy⁵².

Spray drying technique:

Ning et al synthesized cocrystals of 2,4,6,8,10,12 hexanitrohexaazaisowurtzitane (CL-20) and 2,4-dinitro-2,4-diazapentane (DNDAP) in a 2:1 molar ratio by a rapid and continuous spray drying method spray drying method⁵³. Amjad et al synthesized Theophylline Cocrystals by Spray Drying technique. Author prepared Cocrystals of Theophylline with urea and saccharin with nicotinamide by spray drying by using various solvents and solution concentrations while dying was done with nitrogen gas⁵⁴.

CHARACTERIZATION OF CO-CRYSTALS:

Characterization of co-crystals includes study of structural and physical properties^{55,56,57,58}.

Following are the techniques for the characterization of cocrystals used by different authors for characterization.

Structural:

Infrared spectroscopy,

Single crystal x-ray crystallography and
powder x-ray diffraction

Physical: ^{55,56}

Melting point apparatus,
Differential scanning calorimetry,
Thermogravimetric analysis

XD method is generally used for to determine structure of cocrystal. XRD study includes single crystal evaluation as well as powder XRD. No. of researchers have used this technique for characterization of cocrystals. Thermal analysis also one of the technique used for the characterization of cocrystals. For cocrystal Thermal techniques like characterization thermogravimetric analysis and differential thermal analysis and differential scanning colorimetry are generally used. Spectroscopy methods are also used to characterize cocrystals like vibrational spectroscopy and nuclear magnetic resonance. NMR is a powerful characterization tool that can provide detailed information on the structure of organic pharmaceutical cocrystals and complexes^{59,60}. Raman spectroscopy also one of the tool used for observation of crystallization process. It is used to differentiate between polymorphs, salts, cocrystals, solid solutions and hydrated salts⁶¹. Fourier-transform Raman is also used to for the identification and quantitative analysis of cocrystals⁶². Zhang et al prepared cocrystals of carbamazepine and characterized same with Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), and Powder X-ray Diffraction (PXRD) techniques⁶³. shahram et al synthesized piroxicam cocrystals and evaluated them using powder X-ray diffraction, Fourier-transform infrared spectroscopy, DSC etc⁶⁴ Desai et al also prepared Carbamazepine Cocrystals by Solvent Evaporation Technique and evaluated them for Visual morphology, differential scanning calorimetry, infrared spectroscopy, x-ray diffractometry etc⁶⁵. crystals of piracetam and gentisic acid prepared by slow evaporation were characterized by IR, melting point, DSC, PXRD and single crystal X-ray diffraction⁶⁶.

Table 1: Reported Methods of Co-Crystals

Drug	Co-former	Method used to prepare	Ref.
Piroxicam	Adipic Acid, Benzoic Acid, Cinnamic Acid, Citric Acid, Glutaric Acid, P-Hydroxybenzoic Acid, Hippuric Acid, Malonicacid,Resorcinol, Saccharine Sodium, 1-Hydroxy-2-Napthoic Acid, Sodium Acetate, Urea, Catechol, Ferulic Acid, Aerosil-200, Nicotinamide, Para Amino Benzoic Acid, Anthranilic Acid and Succinic Acid	Dry grinding method.	67
Darunavir	Succinic acid	Cooling crystallization	68
Aceclofenac	Sodium Saccharin	Solvent-drop grinding method	69
Clarithromycin	Urea	Solvent evaporation	70
Paracetamol	Caffeine	Dry grinding, liquid assisted grinding (lag), solvent evaporation (se), and anti-solvent addition	71
Myricetin	Proline	Solution crystallization based on the ternary phase diagram principle	72
Efavirenz	Lactic acid and Adipic acid	Solvent evaporation	73
Fenofibrate	Nicotinamide	Kneading, solution crystallization, antisolvent addition and solvent drop grinding methods	74
Carbamazepine	Glucomannan	Solution mediated phase transformation	75
danazol	vanillin	Solution crystallization	76
Felodipine	Xylitol	Wet co-grinding	77

Fexofenadine	Tartaric acid	Solvent evaporation	78
Fenofibrate	Nicotinamide	Solution cocrystallization technique	79
Fenofibrate	Saccharin, succinic acid, and sucrose	Solution evaporation, slow evaporation, antisolvent addition, net grinding method, and solvent-drop grinding methods	80
Simvastatin-	Nicotinamide	Solvent evaporation	81
Prulifloxacin	Salicylic acid	Solution crystallization technique	82
Carbamazepine	Succinic acid	Solvent-drop grinding method	83
Lornoxicam	Saccharin, salicylic acid, tartaric acid and pyrogallol	Liquid assisted grinding, reaction co-crystallization and cooling crystallization	84
Simvastatin	Aspartame	Slurry	85
Mesalamine	Glutamine	Liquid assisted grinding	86
Dipfluzine-	Benzoic acid	Solvent-assisted co-grinding and the solvent ultrasonic methods	87
Simvastatin	Malic acid	Liquid assisted grinding	88
Gliclazid	Succinic acid, Malic acid	Liquid assisted grinding	89
Efavirenz	Fumaric acid	Neat grinding method	90
Acyclovir	Tartaric acid, succinic acid, malonic acid, glutaric acid, adipic acid, citric acid, 4-amino benzamide, 4-hydroxy benzamide, 4-amino benzoic acid, malic acid, oxalic acid, fumaric acid	Solvent evaporation, wet grinding, and an anti-solvent addition	91
Diacerein	Urea and tartaric acid	Solvent drop grinding method	92
Hesperetin	Picolinic acid, nicotinamide, and caffeine	Solvent drop grinding technique	93
Ketoprofen	Cinnamic acid, glutaric acid, maleic acid, malonic acid, nicotinamide, oxalic acid, p-amino-benzoic acid, p-amino salicylic acid, saccharin and urea	Fusion method	94
Theophylline	Acesulfame, saccharin	Solvent drop grinding method	95
Mefloquine hydrochloride	Benzoic acid citric acid, oxalic acid, saccharin, salicylic acid, succinic acid, pure mefloquine tablets	Solution cocrystallization method	96

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