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.

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) and cause difficulty related to dissolution, solubility, stability, therapeutic efficacy etc. 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:

Cocrystallization 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.

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 means of various methods enlisted below, so there is no need to any other additives to improve physicochemical property of substances. 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.

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 melting point with narrow range. Thermodynamic stability of any API can be govern by its melting 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 cocrystals. 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 calorimetry 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°C. Chaudhary 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 conformers. Author synthesized cocrystal of Piroxicam using sodium acetate, saccharine sodium Urea, Nicotinamide, resorcinola conformer and studied difference in melting point of drug and cocrystals. Melting point of sodium acetate, saccharine sodium coformers were high previously but after forming cocrystal with Piroxicam it get decreased, while melting point of cocrystal of Urea, Nicotinamide, resorcinol was increased.

**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-amino benzenamide 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-amino benzenamide, 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-amino benzenamide and isoniazid. Cocrystals showed higher tabletability than either pure drug or coformers. 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 coformer. 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 increased.

**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], 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 drug. Iyan et al developed Simvastatin-nicotinamide co-crystals by solvent evaporation to improve the solubility of simvastatin by co-crystalization 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 simvastatin. Chaudhary et al also improved solubility of efavirenz by cocrystal technique. Author synthesized cocrystals of efavirenz by using oxalic acid dihydrate and citric acid monohydrates 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 solubility. 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 aequous 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 aequous solubility, found 1.92 fold increases in saturation solubility. Author Rajurkar also developed Co Crystals of Ezogabine to improve Aequous 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 drug. Muddukrishna et al studied synthesis of paclitaxel and naringenin cocrystal to improve solubility by solvent assisted grinding method. Paclitaxel (PTX) is a class-4 drug; this drug has low aequous 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 solubility. 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, phthalic acid, hippuric acid, malonic acid, resorcinol, sucrose, tartric acid, 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-Cryystals 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 drug [29].

Stability:
Stability 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 has been 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 Tartaricacid as a co-former by solvent evaporation and observed that with cocrystallisation technique drug hoed maximum release as compared to the formulation [30]. 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 effect [31]. Zhang et al studied synthesis of Carbamazepine Cocrystal by using Nicotinamide and saccharin as conformer by solvent evaporation technique [32].

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 net grinding; solvent-assisted grinding and sonication (applied to either to wet or dry solid mixtures) 80 to 85° C.
Grinding:

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 conformer by liquid-assisted grinding. Prabhakar et al synthesized Cocrystal of Piroxicam by dry grinding method, sodium acetate used as conformer. 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 methods. Muhammad et al synthesized Ibuprofen-amino acids cocrystals by dry grinding as well as liquid assisted grinding method. Gailowad et al studied synthesis of cocrystals of Fenofibrate by grinding method.

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 slurry. Noriyuki et al studied synthesis of cocrystals of stanolone and mestanolone using slurry crystallization. Prafulla et al synthesized caffeine/maleic acid co-crystal by ultrasound-assisted slurry co-crystallization techniques. 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 storage.

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 sequences.

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:

Carbamazepine rich polysaturated solution fed in crystallizer

Water was added into the solution

Saccharin rich polysaturated solution

Particles were sampled after addition of both the solvents

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.\textsuperscript{45,46}

**Hot melt extrusion**

Drug + Coformer

Form co-crystal

Hot melt extrusion drug and coformers are heated with intense mixing without addition of solvent, for eg Li et al, synthesized ibuprofen/isonicotinamide co-crystal suspensions single-step hot-melt extrusion process.\textsuperscript{47} Kevin et al studied synthesis of Carbamazepine Cocrystals by Hot-Melt Extrusion author used Carbamazepine as the drug and nicotinamide used as coformer and characterized cocrystal matrix by differential scanning calorimetry, Fourier transform infrared spectroscopy, and powder X-ray diffraction.\textsuperscript{48}

**Sonocrystallization Method**\textsuperscript{49}

Drug + Coformer

Dissolve together in solvent

Keep for sonication at constant temperature

Heating with intense mixing without addition of solvent

Several researchers studied preparation of cocrystals by sonocrystallization method Prafulla et al studied synthesis of corystals 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 25ºC.\textsuperscript{50}

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

Drug + Coformer

Dissolve together in high pressurized supercritical fluid

(CO\textsubscript{2})

Automize the solution with automizer at normal temperature and pressure causes conversion of CO\textsubscript{2} from liquid state to gas state

Formation of co-crystals

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 diffraction.\textsuperscript{51} Courtney et al studied synthesis of Cocrystals of itraconazole and succinic acid by gas antisolvent (GAS) cocrystallization using pressurized CO\textsubscript{2}. Author dissolved itraconazole and succinic acid in a liquid solvent (tetrahydrofuran) at ambient conditions and pressurized solution with CO\textsubscript{2}, 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 microscopy.\textsuperscript{52}
Spray drying technique:

Drug + Coformer

Prepare solution or suspension with evaporating solvent

spray solution in hot air steam to evaporate solvent

Formation of cocrystals

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 method. 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 drying was done with nitrogen gas.

CHARACTERIZATION OF CO-CRYSTALS:

Characterization of co-crystals includes study of structural and physical properties. 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:

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. 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 salts. Fourier-transform Raman is also used to for the identification and quantitative analysis of cocrystals. 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) techniques. Shahram et al synthesized piroxicam cocrystals and evaluated them using powder X-ray diffraction, Fourier-transform infrared spectroscopy, DSC et al also prepared Carbamazepine Cocrystals by Solvent Evaporation Technique and evaluated them for Visual morphology, differential scanning calorimetry, infrared spectroscopy, x-ray diffractometry et al crystals of piracetam and gentisic acid prepared by slow evaporation were characterized by IR, melting point, DSC, PXRD and single crystal X-ray diffraction.

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, Malonic acid, Resorcinol, Saccharine Sodium, 1-Hydroxy-2-Naphthoic Acid, Sodium Acetate, Urea, Catechol, Ferulic Acid, Aerosil-200, Nicotinamide, Para Amino Benzoic Acid, Anthranilic Acid and Succinic Acid | Dry grinding method.                         | 67   |
| Darunavir          | Succinoyl 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  Solution cocrystallization technique  78
Fenofibrate  Nicotinamide  Solution evaporation  79
Fenofibrate  Saccharin, succinic acid, and sucrose  Solution evaporation, slow evaporation, antisolvent addition, solvent-dropping methods  80
Simvastatin  Nicotinamide  Solution evaporation  81
Prulifloxacin  Salicylic acid  Solution cocrystallization technique  82
Carbamazepine  Succinic acid  Solution-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 solubility 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
Ayclovir  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  Solution evaporation, wet grinding, and an anti-solvent addition  91
Diacerein  Urea and tartaric acid  Solution grinding method  92
Hesperetin  Picolinic acid, nicotinamide, and caffeine  Solution grinding technique  93
Ketoprofen  Cinnamic acid, glutaric acid, maleic acid, malonic acid, nicotinamide, oxalic acid, p-amino benzoic acid, paminosalicylic acid, saccharin and urea  Fusion method  94
Theophylline  Acesulfame, saccharin  Solution grinding method  95
Melloquine hydrochloride  Benzoic acid, citric acid, oxalic acid, saccharin, salicylic acid, succinic acid, pure melloquine tablets  Solution cocrystallization method  96

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