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AN OVERVIEW: SOLUBILITY ENHANCEMENT OF POORLY SOLUBLE DRUGS BY CO-CRYSTALLIZATION TECHNIQUE

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Abstract:

Recent studies has found that discovering and developing of new medication attaining a inefficiency in their therapeutic action, so main reason for low therapeutic action is that poor solubility, permeability and low oral bioavailability of API. To overcome these problem Co-crystallization method is adopted to enhance solubility, dissolution rate and bioavailability of API. Co-crystallization is a novel approach to improve physicochemical properties of API, Co-crystals which formed with API and Coformer does not alter the physicochemical as well as pharmacological activity of API, though this approach will enhance solubility, dissolution rate, bioavailability as well as stability of API. In this particular review we focused on properties of Co-crystal, selection of Co-former which plays a major role in formation of Co-crystals, various methods of preparation of Co-crystal like Solid based and Liquid based technique, Characterization of prepared Co-crystals include Melting point, FTIR, DSC etc, Co-crystal which are available as Marketed product and patent works on Co-crystals were reviewed to understand in depth about Co-crystallization technique.

Key words: Co-crystallization, Solubility, Dissolution rate, Bioavailability, Co-former.

I. INTRODUCTION

The Important Phenomenon and as a most of time discussed but a still or not a completely resolved issue, "Solubility or dissolution enhancement technique remains a most challengeable field for the researchers in the formulation design and developmental process. Solubility and dissolution these are the core concepts of any physical as well as chemical science including their biopharmaceutical and pharmacokinetic considerations in the treatment with any medicine.[1] As a result, recently more than 40% of new chemical compounds are fails before entering into the drug developmental process because of their non-optimal biopharmaceutical properties.

These properties such as rate and extent of absorption, rate of distribution etc. Solubility of a poorly water soluble drug is a frequently encountered challenge in screening studies of New Chemical Entities (NCE) as well as in formulation design and development.[1] Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction and mole fraction.[2]

Detailed View on Co-Crystallization Method:

Cocrystallization is a reliable approach to alter physical and chemical properties of active pharmaceutical ingredients (APIs) such as solubility, dissolution rate, hygroscopicity, melting point, stability, and compressibility without modifying their biological activity and empirical structure. Nowadays, cocrystallization has received increasing attention in the pharmaceutical field and has been broadly reported in scientific papers.[3]

Co-crystals:

Etter was the first person to coin the term "co-crystal" concept and design guidelines for bonding in a cocrystal. Desiraju was also first person to introduce the idea of hydrogen bond. This made the start of an era in crystal engineering and cocrystal formation. In 2004, pharmaceutical cocrystals were described as a unique class of novel, crystalline materials which could alter the physicochemical properties of APIs.[4] The definition of pharmaceutical co-crystal is given as: 'Co-crystals are crystalline single phase solids made up of two or more distinct molecular and/or ionic compounds generally in a stoichiometric ratio that are neither solvates nor simple salts. A pharmaceutically approved co-crystal is made up from the active pharmaceutical ingredient (API) combination with a benign material termed as co-former.[5]

The co-former can be any other excipient or API that, when combined, minimises the dose as well as the negative effects.[6]

Advantages of cocrystals:

i. No need to make or break the covalent bonds;
ii. Theoretical capability of all type API molecules (weakly ionizable or non-ionizable) to form cocrystals;
iii. Stable crystalline form;
iv. Presence of numerous potential counter-molecules i.e., co-formers like food additives, preservatives, pharmaceutical excipients and or APIs; and
v. Improvement in physicochemical properties as well as pharmacokinetic properties of an API without compromising its pharmacological activity.[7]

Disadvantages of cocrystals:

i. Co-crystal formation requires more solvents
ii. Environmental hazardous
iii. Difficult to scale-up
iv. Not suitable for thermal labile drugs.[8]

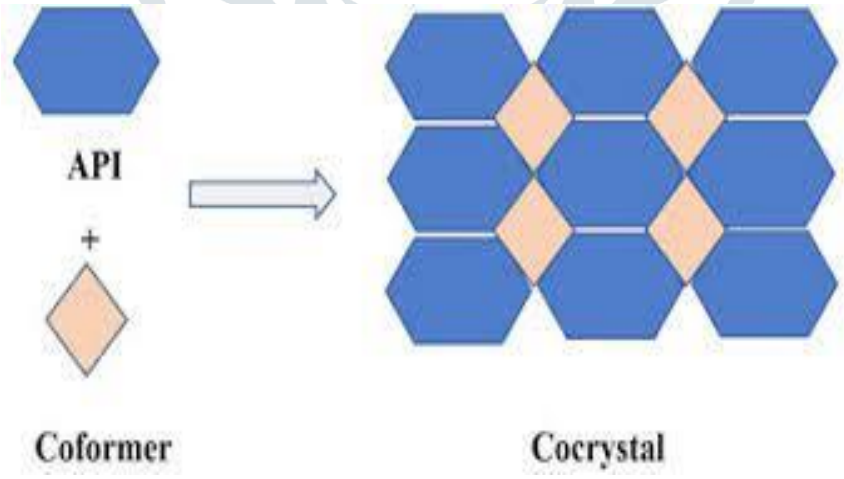


Fig No. 01 Formation of Co-crystal

Properties of co-crystal:

Cocrystals consist of an API and a generally regarded as safe (GRAS) molecule, with specific stoichiometric compositions.[8] The Co-formers must contain functional groups that form complementary hydrogen bonds with the drug. Hydrogen bonds often profoundly affect molecular recognition owing to their specific interactions.[9] Cocrystals are multicomponent crystals comprising salts, solvates, inclusion crystals and hydrates. In solvates, one component is liquid at room temperature, whereas in cocrystals, both components are solid at room temperature.[10] 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.[11]

Various co-formers used in pharmaceutical cocrystallization: 4-Aminobenzoic acid, Acetamide, Adipic acid, Benzoic acid, Caffeine, Cinnamic acid, Citric acid, Fumaric acid, Glutaric acid, Isonicotinamide, L-Prolin, Malonic Acid, Nicotinamide, oxalic acid, Saccharin, Succinic Acid, Tartaric acid, Urea, Vanillin [12]

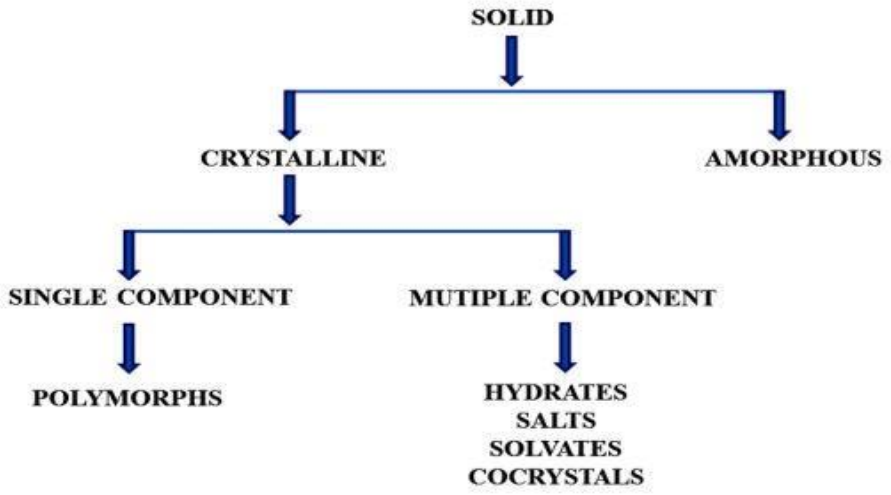


Fig No. 02 API Solid form classification based on structure and composition

Cocrystal versus Salts, Solvates, Solid dispersions, Hydrates

Salt formation is generally directed at a single acidic and basic functional group and cocrystal can simultaneously address multiple functional groups in a single reaction, including acidic, basic and non-ionizable molecules. In the formation of salts transfer of hydrogen atom occurs and it does not occur in the formation of cocrystals. If one component is liquid at room temperature then the crystals are designated as solvates and if both components are present in solid form then crystals are designated as cocrystals. In solvates one component is present in a liquid form so they are less stable as compared to cocrystal. When solvent present in solvates is water then it is termed as hydrates.[13]

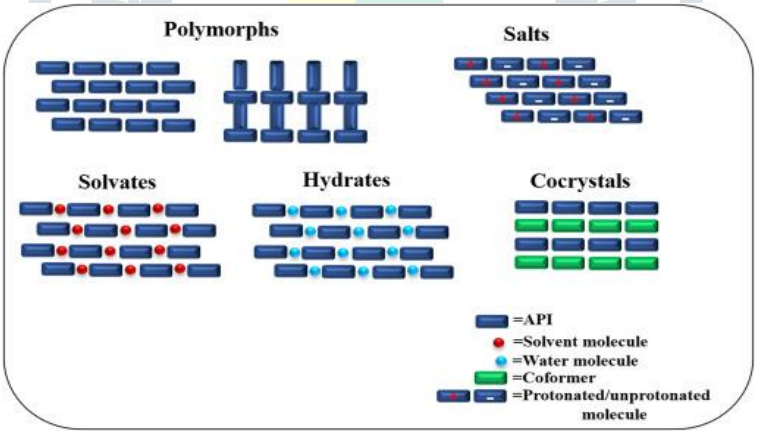


Fig No.03 comparison of different solid forms of API

Criteria for co-crystal former selection:

In crystal engineering approach, the pharmaceutical properties of drugs can be changed without disturbing their inherent structures, the presence of various chemical groups such as carboxylic acid, Amides, Alcohol and carbohydrates conformer leads to formation of cocrystals with different drugs. Due to strength, directionality hydrogen bonds are used often for designing of cocrystal.

Different screening methods include:

Δ pKa rule:

The value of Δ pKa is widely being used for cocrystal screening by using the following equation:

$$\Delta \text{ pKa} = [\text{pKa (base)} - \text{pKa (acid)}]$$

When the difference in pKa values is greater than 2–3 between the API and Co-former indicates transfer of proton will take place between acids and bases. The value of pKa lesser than 1 exhibits the formation of cocrystals, whereas the values greater than 2–3 revealed the formation of salts.[14]

Hydrogen bonding:

The researcher can design cocrystals based on empirical understanding hydrogen-bonds patterns can be determined using guidelines provided by Etter M.C and Donohue J.

Rules provided by them are:

a. All acidic hydrogen present in a molecule will be utilized in hydrogen bonding in the crystal structure of that compound
b. All good acceptors will be used in hydrogen-bonding when there hydrogen-bond donors are available,
c. Preferentially hydrogen bonds are formed between the best hydrogen-bond donor and the best hydrogen-bond acceptor. The important systems which can form hydrogen bonds are N-H…N, N-H…C1, N-H…O, O-H…N, O-H…O, where dash indicates covalent and dots indicates non-covalent contacts with acceptor atom.[15]

Cambridge structural database:

Cambridge structural database (CSD) can incorporate to assess the intermolecular hydrogen bonding possibility between different molecules. CSD single crystal x-ray crystallography can be employed for characterizing the crystal structure of a compound. The resolved structure can be saved in CSD and information can be searched, retrieved and utilized from the database at any time. ‘Atoms’ and ‘powder cell’ are two examples of the software which can be used to visualize the structure by the information obtained from the CSD.[16]

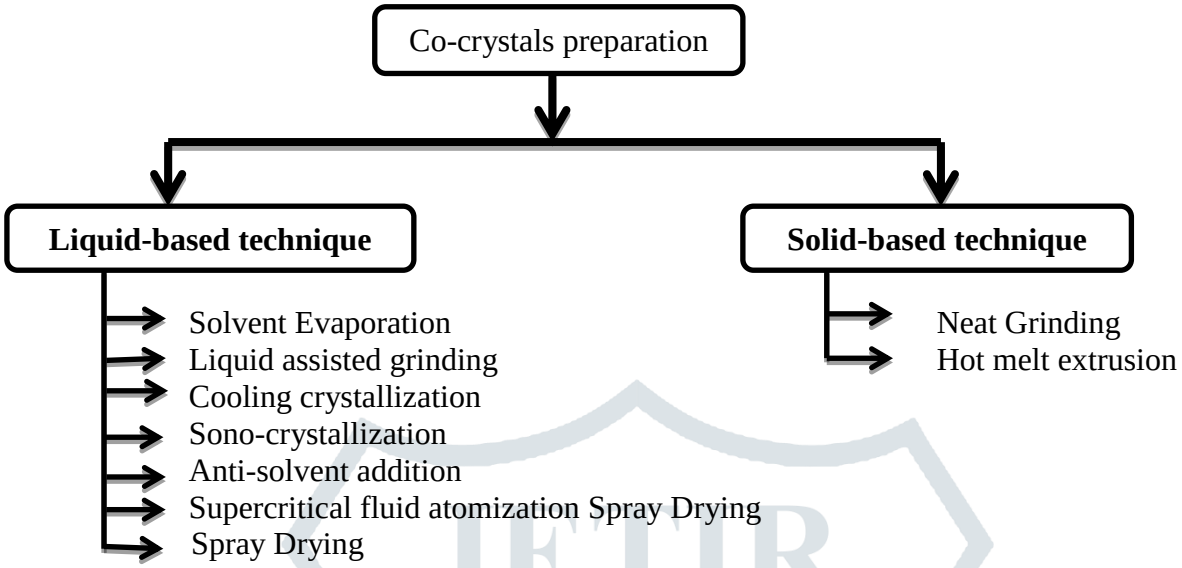
Hansen solubility parameter:

Hansen solubility parameters (HSPs), is one of a screening method that can specify cocrystal formation. HSPs have been widely used to predict liquid–liquid miscibility, miscibility of polymer blends, surface wettability and the adsorption of pigments to surfaces. They may also reveal the compatibility between conformer and API by simple mathematical approaches.[17]

Various methods preparation of co-crystal:

Mainly techniques of preparation of co-crystal are divided into Two i.e (listed in below flow chart)[18]

a. Solid-based technique
b. Liquid-based technique



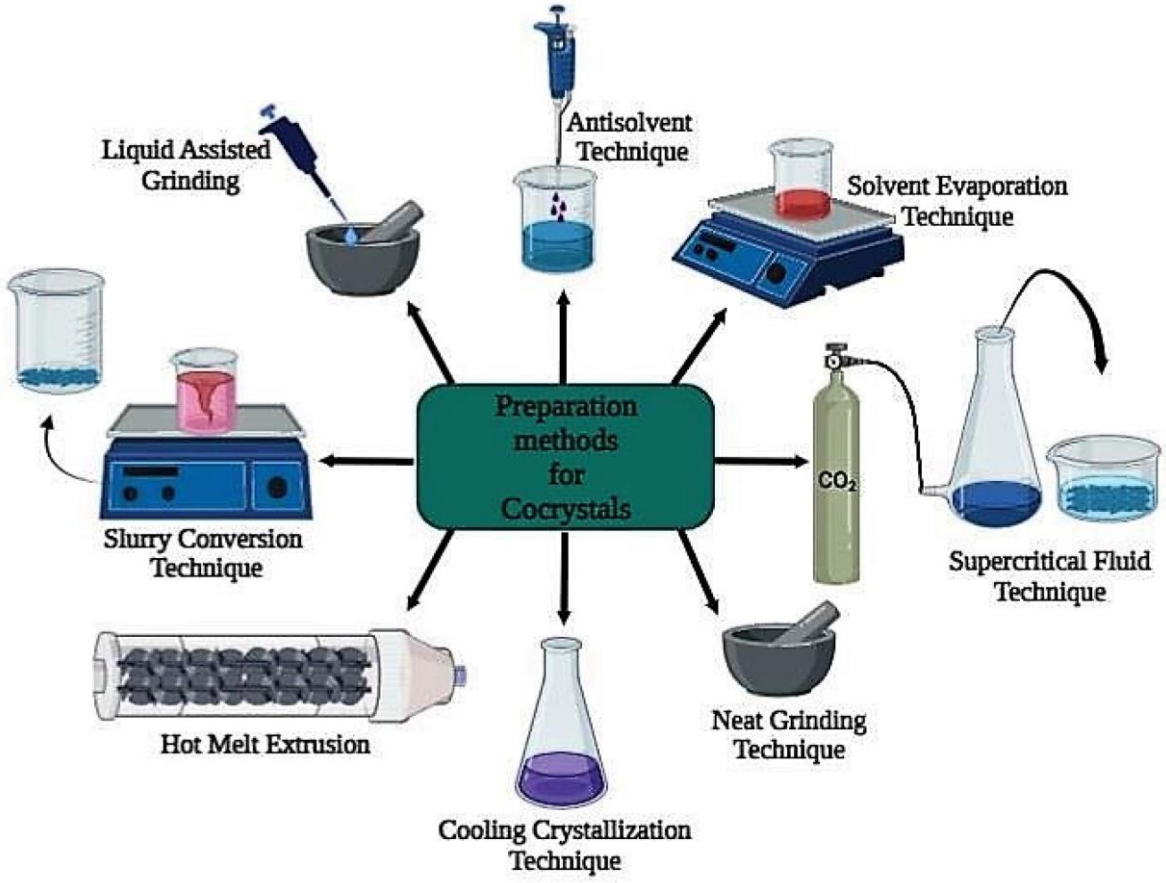


Fig No.04 Various methods of Co-crystal preparation

a. Solid based technique:

Dry Grinding:

This method is also known as Neat Grinding, In this technique API and co-formers are mixed in stoichoimetric proportion using manual method by mortar and pestle, Grinding can also achieved by mechanical grinding using ball mill, vibratory mill, planetary milling, these Grinding process helps in size reduction which helps in the covalent bonding of API and co-former and that results in formation of co-crystals. Incomplete crystal formation is due to improper set-up in instruments.[19,20]

Hot melt extrusion method:

It has a very effective mixing and stronger surface contact, extruding is a technique that aids in the formation of a mutual crystal. The cocrystal is not created using a solvent. The major criterion for choosing this method is the compound's thermodynamic stability. The technique has been improved and its versatility has increased by using a solvent droplet extruding technology. This method has the benefit of allowing the procedure to be carried out at lower temperatures. Hot-melt extrusion was used to create Carbamazepine and Nicotinamide co-crystals utilising the polymer as the former. In a double extruder, the API and co-former are constantly crystallised together.[21,22]

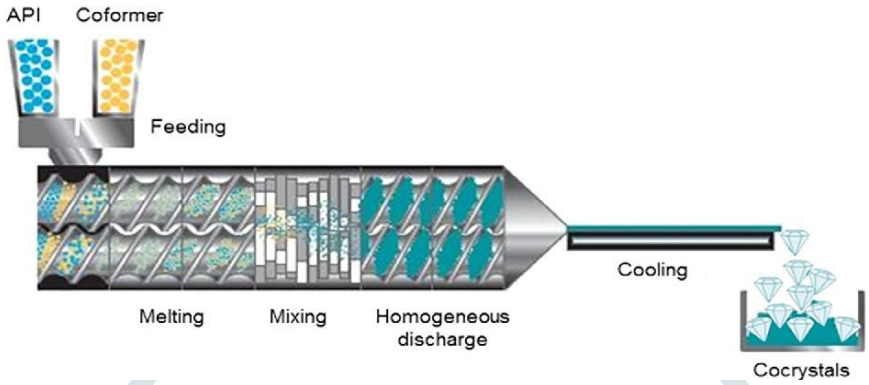


Fig No.05 Hot Melt Extrusion Method

a. Liquid based techniques:

Solvent evaporation technique:

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 co-former 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.[23]

Liquid Assisted Grinding:

This method is a modification of the conventional grinding method. This involves mixing the two components and adding a very small amount of solvent during the milling process, which is a highly co-crystallizing reaction. Bring speed. In this process, the solvent functions as a medium that promotes molecular diffusion is an important factor in the formation of a multicomponent composite framework, and as a catalyst has been used to improve the supra-molecular selectivity of the crystal system. Its advantages are improved efficiency, the ability to control polymorphism formation, and increased crystallinity of the product, making various isomers suitable for co-crystallization. With this method, after suitable grinding for a considerable time, some crystals have insufficient crystal-forming efficiency, resulting in an increase in the co-crystal ratio. Using this method, it is possible to produce co-crystals of high purity with greatly reduced production times.[24]

Cooling crystallization:

This method of cocrystallization is less popular and used in the pharmaceutical preparation of minimal quantity cocrystals due to its time consuming process and depend up on the temperature-dependent change in solubility to achieve cocrystal formation. An amount of the drug and co-former was dissolved in a particular solvent volume at 40.0 ± 0.5^{o}C. The solution was cooled in a water bath to 10.0 ± 0.5^{o}C with continuous stirring, at the cooling rate of about 0.25^{o}C/min. then the prepared crystals were recovered by vacuum filtration, then washed with distilled water several times, kept at 25-30^{o}C to remove the solvent present in them and then kept in a desiccator.66.67 [25,26]

Sono-crystallization:

Sono-crystallization is crystallization induced by Ultrasound (US). In 1927 Richards and Loomis were first persons to report the effects of US on crystallization. Ultrasound (US) to produce smaller particle size and particle size distribution (PSD) and to generate of the desired morphology and is an oscillating sound pressure wave over a frequency range of 15 kHz to 10 MHz. The cocrystal size depends on the frequency of the irradiated ultrasound, and is approximately 170 µm for a 20 kHz ultrasound.[27]

API + Co-former

(Dissolved in a suitable solvent at particular temperature)

↓

Resultant solution is placed in sonicator and exposed to ultrasound pulses

↓

after few minutes later precipitation is formed then removed from sonication

↓

Precipitated solution is left overnight for drying residual solvent[28]

Characterization of Co-Crystals: [29, 30]

The characterization of co-crystals includes the study of its structural and physical properties. Different methods used for the characterization of co-crystals are

Melting point:

The Melting point was taken by a simple capillary method using melting point apparatus. The melting point of API and CCF's were noted. Each observation was made in triplicate.

FT-IR Spectroscopy:

FT-IR of all samples was performed on the FTIR instrument (SHIMADZU 2450S). FT-IR of co-crystals was taken by preparing the KBr pellet. The spectra were collected over the range of 4000-500cm^{-1}

Differential scanning Calorimetry (DSC):

Thermal analysis by DSC of Co-crystals was performed using Differential Scanning Calorimetry DSC- Mettler 1 star calorimeter. Sample powders were placed in aluminum pans, sealed and were heated from 50℃ to 250℃ under constant purging dry nitrogen flow. An empty aluminum pan was used as a reference.

Scanning Electron Microscope (SEM):

SEM is a kind of electron microscope that scans the beam of electrons across the sample. The electrons interact with the atoms that structure the sample producing signals which give information about the sample's surface topography. Specimens were mounted on the metal sample holder with a diameter of 12 mm employing a double-sided tape and coated with gold-palladium under vacuum. It is used to determine the co-crystal micrograph and particle size.

X-Ray Diffraction (XRD studies):

Powder XRD and Single crystal XRD This analytical tool is used for phase identification of unit cells related to the co-crystal. PXRD is a frequently used technique for screening the characterization of co-crystals. The PXRD patterns obtained from the diffractometer were compared to one another for analysing the structure of co-crystals. Formation of co-crystal is indicated by the various PXRD patterns of co-crystals from their components. Therefore, PXRD is employed more to confirm the development of cocrystals.

Thermal Gravimetry method:

This method is useful for determining the sample weight under the influence of temperature for a specific period of time. It gives exact drying temperature along the various reaction steps involved in the component. It is used for the prediction of stability, purity, compatibility, and solvates/hydrates forms of cocrystals.

Table No 01 Illustration of purpose of Co-crystallization along with drugs and Co-formers

Sl. No	Name of Drug	Co-formers used	Purpose of Cocrystallization	References
01	Adefovir dipivoxil	Saccharin	Enhancement of dissolution rate	**31**
02	Atorvastatin calcium	Isonicotinamide	Enhancement of solubility and dissolution rate	**32**
03	Artesunate	Nicotinamide	Enhancement of solubility and dissolution rate	**33**
04	Baicalein	Nicotinamide	Enhancement of solubility, dissolution rate and bioavailability	**34**
05	Canagliflozin hemihydrate	Thiourea	Enhancement of solubility and dissolution rate	**35**
06	Ciprofloxacin	Nicotinic acid Isonicotinic acid	Enhancement of solubility	**36**
07	Ebastine	Asparginin, L-prolin, L-Histadin	Enhancement of solubility	**37**
08	Efavirenz	Adipic acid, Tartaric acid	Enhancement of solubility and dissolution rate	**38**
09	Ezetimibe	Benzoic acid, salicylic acid	Enhancement of solubility and dissolute rate	**39**
10	Glimepiride	Oxalic acid	Enhancement of solubility and dissolution rate	**40**
11	Itraconazole	Succinic acid	Enhancement of solubility and dissolution rate	**41**
12	Nevirapine	Salicylamine, 3-Hydroxy benzoic acid	Enhancement of dissolution rate	**42**
13	Nebivolol hydrochloride	Benzoic acid, Nicotinamide	Enhancement of solubility and dissolution rate	**43**
14	Posaconazole	Adipic acid	Enhancement of dissolution rate	**44**
15	valsartan	Succinic acid, fumaric acid, oxalic acid	Enhancement of solubility and dissolution rate	**45**

Marketed formulation of cocrystals: [46]

- Co-crystals of theophylline
- Co-crystals of aceclofenac
- Co-crystal of 5-nitrouracil
- Co-crystals of indomethacin
- Pharmaceutical co-crystals of carbamazepine and saccharin(Tegretol®)
- Pharmaceutical co-crystals of fluoxetine hydrochloride (Prozac®)
- Pharmaceutical co-crystals of itraconazole(Sporanox®)
- Pharmaceutical co-crystals of sildenafil (Viagra®)
- Co-crystal of melamine and cyanuric acid
- Co-crystals of Sacubritil and Valsartan (Entresto®)

Table No.2 List of recent Marketed/Patents products on cocrystal: [47]

Marketed/Patented Cocrystals	Combination	Purpose
Suglat® (2014)	Ipragliflozin+l-proline	Improvement of stability
Entresto (2015)	Valsartan+sacubitril	Improvement of bioavailability
EP3240575 A1 (November 08, 2017)	carfilzomib+maleic acid	To improve solubility
WO2017144598 A1 (August 31, 2017)	Lorcaserin hydrochloride+organic diacid	Improvement of stability
SEGLENTIS® (2021)	Celecoxib+racemic tramadol hydrochloride	To improve physicochemical properties, bioavailability and stability

Application:

- Co-crystallization technique could be a promising strategy for improving the dissolution rate using sugar-based coformers.
- When compared to other solid-state manipulation methods of a drug like complexation, solid dispersion, micelle solubilization, cosolvency, etc Co-crystals gained enormous benefits in the pharmaceutical industry due to their simple way of preparation.
- The produced co-crystal got the benefits of enhanced dissolution rate and taste masking, simultaneously. Nutraceutical, which has health benefits, also can be used as coformers for better combined health benefits along with the API.
- Recently Multi-Drug Co-crystal (MDC) is additionally gaining attraction among pharmaceutical scientists.
- When compared with pure drug components, MDC could offer potential advantages such as increased solubility, bioavailability and improved potential to stabilize unstable APIs via intermolecular Interactions.
- Co-crystals are also used for the in-process separation and purification of the API.
- Co-crystallization techniques are often used for those drugs which are weakly ionized in nature. Moreover, co-crystals can act as a crystallization inhibitor, and thereby supersaturation can be maintained for an extended time during dissolution, which successively helps to attain improved bioavailability and controlled release of the drug.[19]

Conclusion:

Cocrystal performs a major role in pharmaceuticals. By enhancing solubility, they prevent the excess use of harmful organic solvents. Also, the bio performance and bioavailability can be enhanced. Co-crystallization offers one among the foremost promising approach to enhance the physicochemical properties of APIs. Co-crystals possess much more potential use in pharmaceutical products when compared to solvates and hydrates. Pharmaceutical cocrystal is brought into consideration when a drug exhibits a complex and difficult to control polymorphism, when salts cannot be formed due to the neutrality of the compound or when the drug exhibit poor solubility. The major concern for investigators is screening of co-crystals which includes high throughput assessment of molecular structure of API and suitable co-former. There is need of development of proper screening methodology in order to ease cocrystallization and its regulatory criteria. This review offers standard description of selection of Co-formers, various methods that can be utilized in preparation of Co-crystals followed by characterization and list of marketed products.

Reference:

1. Mahapatra AP, Patil V, Patil R. Solubility enhancement of poorly soluble drugs by using novel techniques: A comprehensive review. Int J Pharm Tech Res. 2020;13(2):80-93.
2. Sharma DC, Gharge V, Tyagi P. Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs. Asian J of Pharm Res and Deve. 2021;9(4):169-71.
3. Gyawali R, Aryal S, Regmi Y, Rajarajan S. Cocrystallization: An Approach to Improve Bioavalability by Altering Physicochemical Properties of Poorly Soluble API's. 2021;20(04):381-397
4. Kumar S, Nanda A. Pharmaceutical Cocrystals: An Overview. Indian Journal of Pharmaceutical Sciences. 2017;79(6):858-871.
5. Malthankar AS, Jadhav MP, Game MD. A Brief Review On Pharmaceutical Co-crystals. Int J Crea Res Thou. 2021;9(7):370-382.
6. Raut AM , Musle DD, Chavan AA. Co-crystallization: A Technique for Solubility Enhancement. Int J Crea Res Thou. 2021;9(6):244-252.
7. Bavishi DD, Borkhataria CH. Spring and parachute: How cocrystals enhance solubility. Progress in Crystal Growth and Characterization of Materials. 2016;62(3):1-8.
8. Rodrigues M, Baptista B, Lopes JA, Sarraguça MC. Pharmaceutical cocrystallization techniques. Advances and challenges. International Journal of Pharmaceutics. 2018;547(1-2):404-20.
9. Jain S, Bansal M. An Overview of The Promising To Enhance The Physical Property of API by Pharmaceutical Co-crystallization Technique. 2020;9(4):01-07
10. Gowda BJ, Nechipadappu SK, Shankar SJ, Chavali M, Paul K, Ahmed MG, Sanjana A, Shanthala HK. Pharmaceutical cocrystals of efavirenz: Towards the improvement of solubility, dissolution rate and stability. Materials Today: Proceedings. 2022;51:394-402.
11. Adav BK, Khursheed AT, Singh RD. Cocrystals: A complete review on conventional and novel methods of its formation and its evaluation. Asian J. Pharm. Clin. Res. 2019;12(7):68-74
12. Mundhe AV. Cocrystalization: an alternative approach for solid modification. Journal of Drug Delivery and Therapeutics. 2013;3(4):166-72.
13. Vioglio PC, Chierotti MR, Gobetto R. Pharmaceutical aspects of salt and cocrystal forms of APIs and characterization challenges. Advanced drug delivery reviews. 2017;117:86-110.
14. Fukte SR, Wagh MP, Rawat S. Coformer selection: An important tool in cocrystal formation. Int. J. Pharm. Pharm. Sci. 2014;6(7):9-14.
15. Dutt B, Choudhary M, Budhwar V. Cocrystallization: An innovative route toward better medication. Journal of Reports in Pharmaceutical Sciences. 2020;9(2):256.
16. Gadade DD, Pekamwar SS. Pharmaceutical cocrystals: regulatory and strategic aspects, design and development. Advanced pharmaceutical bulletin. 2016;6(4):479-494.
17. Thayyil AR, Juturu T, Nayak S, Kamath S. Pharmaceutical co-crystallization: Regulatory aspects, design, characterization, and applications. Advanced Pharmaceutical Bulletin. 2020;10(2):203-212.
18. Mohammad MA, Alhalaweh A, Velaga SP. Hansen solubility parameter as a tool to predict cocrystal formation. International journal of pharmaceutics. 2011;407(1-2):63-71.
19. Yadav BK, Khursheed A, Singh RD. Cocrystals: A complete review on conventional and novel methods of its formation and its evaluation. Asian J. Pharm. Clin. Res. 2019;12(7):68-74.
20. Sahu S, Das R, Nahak A. An Updated Review on Pharmaceutical Co-Crystals: Characterization and Preparation. Research Journal of Pharmacy and Life Sciences: Volume. 2023;4(1):01-15.
21. Varma PN, Hemalatha M, Sai MJ, Lakshmi BD, Kavitha K, Bindu KH, Padmalatha K. Indo Amer J Pharm Sci. 2021;08(06):242-250.
22. Bhavani C, Kumar KN, Shankar KS, Srivani M, Rao TR. A Review on Cocrystallization. World J Pharm Res. 2022;12(01):1106-1122.
23. Rodrigues M, Baptista B, Lopes JA, Sarraguça MC. Pharmaceutical cocrystallization techniques. Advances and challenges. International Journal of Pharmaceutics. 2018;547(1-2):404-20.
24. Kotak U, Prajapati V, Solanki H, Jani G, Jha P. Co-crystallization technique its rationale and recent progress. World J Pharm Pharm Sci. 2015;4(4):1484-508.
25. Mr. Wagh NS , Dr. Wankhade AM , Mr. Akolkar AK, Balinge VS , Nalkande VS *et.al.*, A Review: Solubility Enhancement Techniques by Co-crystallization. Int J crea Res Thou. 2023;11(01):208-15.
26. Sahu S, Das R, Nahak A. An Updated Review on Pharmaceutical Co-Crystals: Characterization and Preparation. Res J of Pharmacy and Life Sci. 2023;4(1):01-15.
27. Radke R, Jain NK. Melt Sonocrystallization A Novel Technique of Solubility Enhancement: A Review. Int J Pharm Sci Rev Res. 2020;64(2):70-75.
28. Baby P, A.R.Shabaraya, Bhavyashree T. Pharmaceutical Cocrystals: A Novel Approach for Solubility Modification. Wold J of Pharm Res. 2021;10(04):1707-1724.

29. Ther AV, Bhogande YM, Sawkare AD. Pharmaceutical Co-Crystal of Cilnidipine-Benzoic acid (Design, Formulation and Evaluation). Int J of Pharmacy and Pharm Res. 2020; 19(01):739-754.
30. Anuja S, Viresh KC, Raheem TA, Shabaraya AR. Pharmaceutical Co-Crystals: An Overview. World J of Pharm Res. 2020; 9(11):556-569.
31. Yuan Gao, Hui Zu,Jianjun Zhang. Enhanced dissolution and stability of adefovir dipivoxil by cocrystal formation. J of Pharm and Pharmacology. 2011; 63:483-490.
32. Wicaksono Y, Wisudyaningsih B, Siswoyo TA. Enhancement of solubility and dissolution rate of atorvastatin calcium by co-crystallization. Tropical Journal of Pharmaceutical Research. 2017 ;16(7):1497-1502.
33. Setyawan D, Sari R, Yusuf H, Primaharinastiti R. Preparation and characterization of artesunate-nicotinamide cocrystal by solvent evaporation and slurry method. Asian Journal of Pharmaceutical and Clinical Research. 2013 ;7(1):62-65.
34. Huang Y, Zhang B, Gao Y, Zhang J, Shi L. Baicalein–nicotinamide cocrystal with enhanced solubility, dissolution, and oral bioavailability. Journal of pharmaceutical sciences. 2014 ;103(8):2330-2337
35. Burkhande NS, Wankhade VP, Atram SC, Bobade NN, Pande SD. Development of Co-Crystallization Technique to Improve Solubility of Anti-Diabetic Drug. Asian Journal of Pharmaceutical Research and Development. 2023;11(4):30-35.
36. De Almeida AC, Torquetti C, Ferreira PO, Fernandes RP, dos Santos EC, Kogawa AC, Caires FJ. Cocrystals of ciprofloxacin with nicotinic and isonicotinic acids: Mechanochemical synthesis, characterization, thermal and solubility study. Thermochimica Acta. 2020 ;685:178346.
37. Salih ZM, Al-Khedairy EB. Amino Acid as Co-Crystal Coformer for Ebastine Solubility Enhancement. The Egyptian Journal of Hospital Medicine. 2023 ;90(2):2900-8.
38. Gowda BJ, Nechipadappu SK, Shankar SJ, Chavali M, Paul K, Ahmed MG, Sanjana A, Shanthala HK. Pharmaceutical cocrystals of efavirenz: Towards the improvement of solubility, dissolution rate and stability. Materials Today: Proceedings. 2022;51:394-402.
39. Mulye SP, Jamadar SA, Karekar PS, Pore YV, Dhawale SC. Improvement in physicochemical properties of ezetimibe using a crystal engineering technique. Powder technology. 2012 ;222:131-8
40. Zidan MF, Afouna MI, Ismael HR, Ibrahim MF. Enhancement of Glimepiride Bioavailability by Co-Crystallization Technique. Int J of Res in Appl Sci and Eng Tech. 2023 ;11(11):561-568.
41. Shete A, Murthy S, Thorat B, Yadav A, Sajane S, Sakhare S, Doijad R. Studies on effect of hydrophilic polymers on physicochemical properties of itraconazole cocrystals. Future Journal of Pharmaceutical Sciences. 2017 ;3(2):95-102.
42. Panzade P, Shendarkar G, Kulkarni D, Shelke S. Solid state characterization and dissolution enhancement of nevirapine cocrystals. Advanced Pharmaceutical Bulletin. 2021 ;11(4):772-776.
43. Nikam VJ, Patil SB. Pharmaceutical cocrystals of nebivolol hydrochloride with enhanced solubility. Journal of Crystal Growth. 2020 ;534:125488.
44. Nijhawan M, Godugu M, Saxena T, Farheen T, Dwivedi K. Pharmaceutical co-crystals of posaconazole for improvement of physicochemical properties. Brazil J Pharm Sci. 2022 26;58.
45. Narala S, Ampati R, Nanam R. Solubility enhancement of ritonavir: Cocrystallization. J. Pharm. Res. 2019;8:630-7.
46. Nangare AA, Chopade AR, Kandle HS. A Review on Co-Crystallization: A Novel Technique for Enhancement of Solubility and Bioavailability. 2023; 8(07):1533-1537.
47. Bhattacharyya S, Manjunath A. A comprehensive review on pharmaceutical cocrystal-a subtle technique for solubility enhancement. The .Thai. J .Pharm Sci. 2023;46(6):622-30.