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IMPROVISING PULMONARY HYPERTENSION DRUG RELEASE BY CO-CRYSTALLIZATION METHOD – A REVIEW

Mahadev Prasad K.[1]*, Venkatesh[1], Salman M.[1] and Hanumanthachar Joshi[2]

[1]Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

[2]Department of Pharmacognosy, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

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Corresponding Author: Mahadev Prasad K.

Address: Department of Pharmaceutics, Sarada Vilas College of Pharmacy, Mysuru, Karnataka, India.

ABSTRACT

Cocrystals have attracted attention in early days for their ability to modify the physical properties of solid-state materials, notably pharmaceuticals. Initially, cocrystal formation was primarily pursued to enhance solubility however, recent research has expanded their applications to include flavour masking, mechanical property improvement, and intellectual property extension. In the context of pulmonary hypertension treatment, cocrystals have been explored to optimize drug performance. Increased commercialization of cocrystals has in turn necessitated additional research on methods to make cocrystals, with particular emphasis placed on emerging technologies that can offer environmentally attractive and efficient options. Methods of producing cocrystals and of harnessing the bespoke physical property adjustment provided by cocrystals are reviewed in this article, with a particular focus on emerging trends in these areas.

KEYWORDS: Pharmaceutical cocrystals (PC); Co-crystallization; Active pharmaceutical ingredient (API); Co-crystal former (CF); Novel methods.

INTRODUCTION

Arterial hypertension, commonly known as high blood pressure, is a chronic condition characterized by elevated pressure in the arteries, leading to increased risks of heart disease,

stroke, and other health complications. Effective management of arterial hypertension often involves the use of antihypertensive agents, many of which exhibit poor aqueous solubility, resulting in reduced bioavailability and therapeutic efficacy.[1] To address these challenges, various formulation strategies have been employed to enhance the solubility and dissolution rates of these agents.[2] A drug's solubility and rate of dissolution are crucial determinants of its effectiveness and activity. Traditional treatments or coincidental findings served as the foundation for early drug discovery research. However, the introduction of new ailments and the development of medications during the past 20 years have necessitated a logical approach to drug design and synthesis. Using cutting-edge methods like combinatorial chemistry and high-throughput screening, several new therapeutic targets have been found, and promising medicinal compounds have been created and their efficacy assessed. These screens are used to find lead compounds, which are getting bigger and more lipophilic. As a result, the modern world needs to employ several techniques to reduce issues with the permeability and solubility of lipophilic medications. Prodrugs, solid dispersions, size reduction, inclusion complexes with cyclodextrins, salt formation, self-emulsifying formulations, surfactants, polymorphs, nanoparticles, and multicomponent molecular crystals are some of the methods that researchers have described to improve the solubility of APIs.[3] Each of the above-mentioned methods has advantages and disadvantages of its own, but the success rate will always rely on the unique physicochemical characteristics of the polymers and APIs. Physical modification is frequently employed to increase the surface area of the particles, enhance powder solubility and/or wetting, and increase an API's stability. In the creation of novel solids, particularly in the pharmaceutical industry, multi-component crystals such solvates, hydrates, cocrystals, and salts are essential. To increase their solubility, the weakly water-soluble medications can be made into lipid formulations, crystalline solid formulations, or amorphous forms. Cocrystallization by crystal engineering is a viable method to solve drug-related issues.[4]

Role of Cocrystals

The US Food and Drug Administration (FDA) defines cocrystals as crystalline solids composed of two or more different compounds, often drug and cocrystal formers (or "coformers"), in the same crystal lattice. Pharmaceutical cocrystals have created opportunities to create solid state forms of an active pharmaceutical ingredient (API) that go beyond the usual solid-state forms, such as salts and polymorphs.[5] This means altering a drug's solubility and other physical properties without affecting its pharmacological activity. The

FDA further said that cocrystals can be designed to enhance the stability and bioavailability of therapeutic goods while also improving the processability of APIs during medicinal product manufacture. According to the literature, the first cocrystal to be synthesised was quinhydrone, a 1:1 cocrystal between benzoquinone and hydroquinone.[6]

Comparison of Co-crystal and Salt

Cocrystallization has offered the pharmaceutical business at least two benefits. The idea of cocrystallization states that any kind of molecule, including weakly ionisable and non-ionizable APIs, can form cocrystals. This is thought to be a better method for optimising the physical properties because salt formation in these APIs is either restricted or nonexistent.[7] Only basic or acid counter-ions are investigated in a typical API salt form when salt formation occurs for toxicological reasons, but a large variety of possible cocrystal coformers that are unrestricted by toxicological factors are available in the case of cocrystal screening. There are hundreds of compounds on the US Food and Drug Administration's "generally recognised as safe" (GRAS) list, which is a list of substances generally accepted as safe, that are often utilised as possible co-formers for pharmaceutical cocrystals. Cocrystals are made up of an API and a neutral molecule (coformer chemical) in the crystal lattice, as opposed to polymorphs, which only have one API.[8]

Design of Cocrystal

Because the cocrystal solid may be engineered to have better physical characteristics than either of the pure starting components, cocrystals are significant. Cocrystal formation has been shown to improve the physical properties of several agrochemicals, pigments, solid explosives, and especially medicines. Pharmaceutical companies are especially interested in improving physical properties since most medications are supplied in solid form. A pharmaceutical medication product's processing, distribution, and ultimately efficacy is all directly impacted by the physical characteristics of the solids that make up the product.[9] For instance, a solid's solubility in solution is directly impacted by its crystal structure. For drug compounds to be bioavailable in the body, they must be soluble. Eighty percent of the medications are taken orally in solid form, which is often the safest and most convenient dosing type. About 40% of them have poor solubility; in fact, between 80 and 90 percent of therapeutic candidates in the R&D pipeline suffer from this concerning characteristic, which might cause these medications to fail clinical trials in the modern day. Through altering the underlying crystal structure, cocrystal formation with an appropriate coformer provides the

possibility of increased solubility, thus making the molecule accessible. A variety of application areas for manipulating physical properties through cocrystal formation have become available as cocrystal research has grown. New uses like taste masking and intellectual property extension are being investigated, and improvements in solubility, stability, bioavailability, dissolution rate, melting point, hydroscopicity, compressibility, bulk density, friability, and mechanical properties have all been extensively documented.[10] The primary benefits of using cocrystals to change a drug's properties are as follows: the coformer is the component that modifies the drug's molecular structure, supramolecular synthons and crystal engineering principles act as a guide to control the crystal structure; and a library of synthons and coformers, along with the grammar of heterosynthon hierarchy, allows for the adjustment of the desired functional properties for a wide range of APIs[11] The process of cocrystals has been described using a variety of theoretical techniques, including the Hansen solubility parameters, pKa values, supramolecular synthon, hydrogen bonding propensity, and Cambridge Structure Database.[12] The Cambridge Structural Data (CSD) survey is typically conducted before experimental work in a crystal engineering project. Cocrystals made using the supramolecular synthesis principle offer a powerful method for finding new solid pharmaceutical phases. Cocrystals are composed of many elements in a certain ratio with a quantitative relationship, whereby entirely distinct molecular species travel via non-hydrogen bonding and chemical element bonding.[13] The style and analysis of cocrystal systems may benefit by the application of chemical element bonding rules, graph sets, and Pythons. However, it is typically impossible to forecast whether cocrystallization will occur; instead, the answer should now be found by empirical observation. Another technique to rationalise cocrystal formation would be to take into account both the bond donors and acceptors of the materials in that region to crystallise, as well as their potential motion.[14]

The ability to create cocrystals using a straightforward design based on supramolecular synthons and the design's modularity, which permits the exchange of cocrystal components with the goal of enhancing a specific solid-state property, are the two main factors contributing to the quick success of cocrystallization as a technique for creating advanced materials. Supramolecular synthons and halogen or hydrogen-bonding functional groups are constantly being added to the synthon-based design of cocrystals, increasing the variety of possible cocrystals and cocrystal components.[15]

Noncovalent interactions like hydrogen bonds, Vander Waals forces, or p-p stacking interactions are how drugs and coformers interact in cocrystals. Cocrystal formation is a result of hydrogen bonding, which is significant. Interactions between functional groups on the coformer and the API are followed by interactions between additional functional groups. The common functional groups of APIs and coformers that participate in cocrystal formation include carboxylic acids, amides, and alcohols. The most prevalent supramolecular synthons in crystal engineering are as follows: while heterosynthons are created when carboxylic acid and amide groups, carboxylic acid and cyano groups, alcohol and ether groups, carboxylic acid and hydroxyl groups, and hydroxyl and aromatic nitrogen/pyridine form hydrogen bonds, homosynthons are created when (a) carboxylic acid dimers, (b) amide dimers, and (c) hydroxyl dimers. In hydrogen bonding, all suitable proton donors and acceptors are employed.

A useful resource for figuring out the intermolecular interactions in crystals is the Cambridge Structure Database (CSD). The creation of the Cambridge Structure Database (CSD) is significant for the fields of structural chemistry, material science, and biology, particularly the development of new drugs. With over 40,000 new structures added annually from journals or supplemental papers, the CSD is a well-curated and updated program. All of the data was meticulously examined for typographical mistakes and for scientific integrity. With the goal of ensuring that the strongest hydrogen bonding motifs endure over a family of related structures, the CSD may be used to anticipate the stable motifs.[16]

Research teams can use virtual screening approaches to identify suitable cocrystal forming pairs by statistical analysis of cocrystal data on the CSD. This enables the creation of cocrystals using molecular modelling, which reduces experimental costs and research time. In order to better understand the behaviour of molecules and intermolecular interactions within a crystal, the CSD makes it possible to quickly and reliably retrieve, visualise, and analyse experimentally obtained crystallographic data. This provides details about the kinds of supramolecular synthons involved, the directional features, geometrical preferences, and the sort of intermolecular interaction. [17]

Different Strategies of Cocrystals Formation

Researchers have reported using entirely distinct methods to create cocrystals. The response was not well supported by prior methods, and grinding has been documented for cocrystal formation. Both solvent-based and solid-based techniques can be used to create cocrystals.[18]

Various approaches have been used, including suspension conversion methodology, anti-solvent addition, crystallisation technique, solvent evaporation, and reaction crystallisation methodology. Recent years have seen the emergence of several novel cocrystal production techniques, including the hot soften extrusion approach, the crucial fluid atomisation technique, and the area unit ultrasonic assisted methodology. Methods for these have been published, but there is still no uniformity in how various preparation techniques are used or even in the language used to refer to the same information. Frequently, information on the recovery method, equilibration period, target molecule/coformer concentration, and solvent selection has been omitted. It is challenging to replicate or compare cocrystal production techniques due to this lack of uniformity and knowledge, which will unavoidably cause confusion for those new to this field of study. In order to standardise the advancements made so far in this developing field, the goal of this study is to comprehensively outline all of the documented cocrystal production methods and applications in one place.

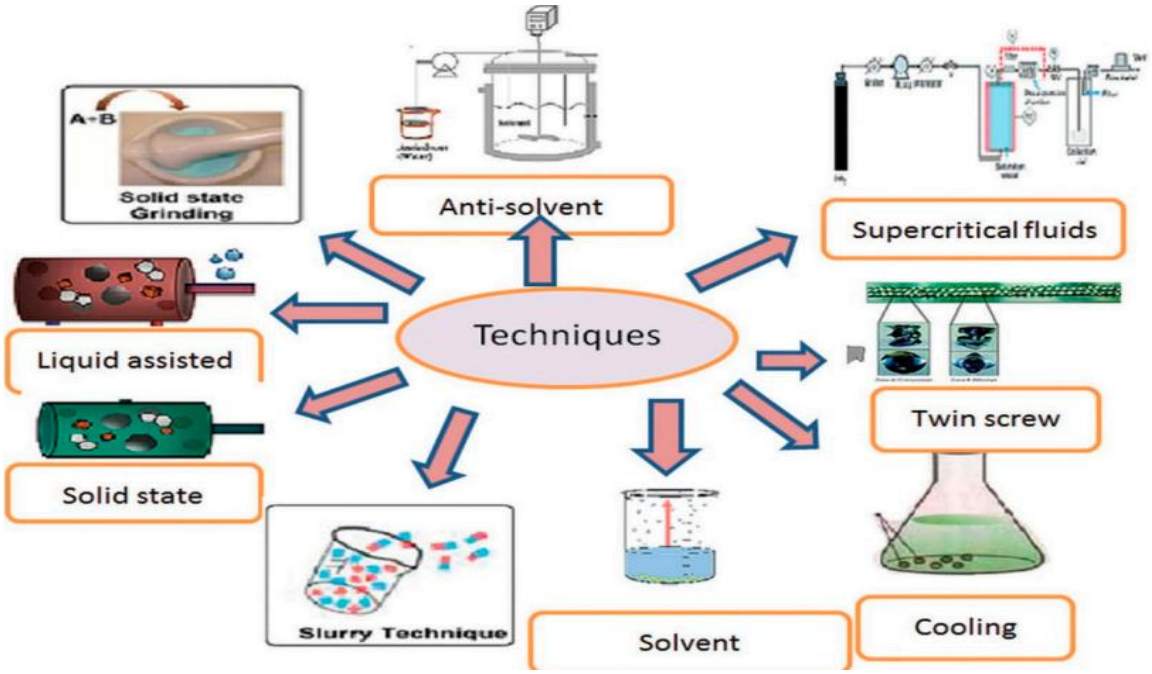

Figure 1: Techniques of Cocrystal Formation.

Solvent evaporation

This is most conventional technique of cocrystallization which includes super saturation of solution by evaporation, cooling and addition of solubility changing solvent or substance.[19] The series of events that are follows in solvent evaporation are preparation of two or more suspensions by dissolution of stoichiometric amounts of materials in a solvent, mixing of suspensions and storage under suitable temperatures for co-crystallization. In this process the

solution of multiple molecules in suitable amounts are assumed to undergo hydrogen bonding.[20] This method used for increase intrinsic solubility of Fluoxetine hydrochloride by using multiple coformers like succinic acid, fumaric acid and benzoic acid. Norfloxacin cocrystals were synthesized with Isonicotinamide, Malonic acid and maleic acid as coformers.[21]

Solid State methods

Solid-state grinding, first mentioned in the late 19th century, has gained attention for pharmaceutical cocrystal production. Adding small solvent amounts improves kinetics and facilitates cocrystal formation.[21] Techniques like solid-phase grinding, melt extrusion, and sonication operate at 80–85°C, melting and mixing coformers with APIs. Though scalable and continuous, this method is unsuitable for thermolabile compounds. Premilled reactants show higher cocrystallization rates than unmilled ones, especially at elevated temperatures and humidity. Moisture-driven cocrystallization follows three stages: moisture uptake, reactant dissolution, and cocrystal nucleation and growth. Controlled air settings also enable spontaneous cocrystal formation, enhancing pharmaceutical applications.[22]

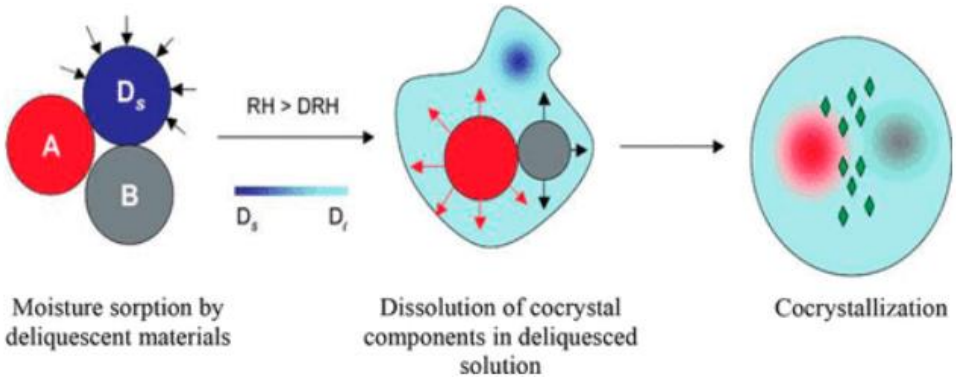

Figure 2: Schematic Representation of the Moisture Uptake.

Contact Formation

Pure API and coformers can spontaneously form cocrystals in a controlled atmosphere without mechanical force. However, premilling individual components before mixing significantly enhances the cocrystallization rate. Additionally, higher temperatures and relative humidity further accelerate the process, regardless of mechanical activation. These factors suggest that optimizing environmental conditions and reactant preparation can improve cocrystal formation efficiency, making it a valuable approach for pharmaceutical applications.[23]

Solid state grinding

Solid-state grinding is commonly used for cocrystal production, employing neat (dry) or liquid-assisted grinding. Dry grinding, a solvent-free process, involves mixing solid components in stoichiometric ratios and crushing them with a mortar, ball mill, or vibrator mill for 30–60 minutes. It enhances selectivity by increasing the surface area for intermolecular bonding. While simple and efficient, challenges include incomplete conversion, crystalline defects, and amorphous content. Partial cocrystal formation results in a mix of products, requiring extra purification. Despite these limitations, dry grinding is valuable for rapid cocrystal preparation and studying hydrogen bond preferences in pharmaceutical applications.[24]

Liquid-Assisted Grinding

Liquid-assisted grinding enhances cocrystal formation by adding a small solvent amount during grinding, significantly improving kinetics. The solvent acts catalytically, facilitating molecular diffusion or forming multi-component frameworks without integrating into the final product.[25] This method improves crystallinity, controls polymorph production, and broadens coformer compatibility. It is particularly useful for cocrystals with poor formation rates under neat grinding, ensuring high-purity products in less time. Additionally, it enables polymorphic interconversion based on solvent polarity.[26] However, its limitations include small-scale applicability, high energy consumption, and lower product purity, making it less efficient for large-scale pharmaceutical manufacturing.[27]

Slurry Crystallization

Slurry crystallization is the method during which suspension is prepared by the addition of various solvents within the mixture of API and appropriate coformers. The solvent is decanted and then the solid material is dried under a flow of nitrogen for 5 min and characterized by using PXRD. This methodology is used for the preparation of cocrystals once the drug and coformer could be stable within the solvent.[28]

Anti-Solvent Method

In this method, A solvent in which the compound is less soluble is often added to another solution, favoring the precipitation of the solids. During this process, supersaturation is generated by adding a second liquid to a solution of the drug-conformer to be crystallized, which is miscible with the solvent and in which the cocrystals are insoluble or sparingly soluble. The resulting suspension is filtered, and the collected solid can be characterized by

XRPD. Disadvantages of this method are its lower performance as compared to grinding as well as the large volume of solvent required. In these studies, the construction of phase solubility diagrams was an integral part of the methodology for identifying the optimal concentration (e.g., ratio of solvent to antisolvent) for the formation of cocrystals. Generally, However, in many cases, a coformer solution is added to the drug organic solution to facilitate cocrystallization. This phenomenon is particularly used for the precipitation or recrystallization of the former and active pharmaceutical ingredients of the cocrystal.[29]

Hot melt extrusion

Extrusion is useful method for synthesis of cocrystals, it involves highly efficient mixing and improved surface contacts, Co-crystals are prepared without use of solvent.[30] The selection of this method is primarily depending on thermodynamic stability of compound. This method was studied with the use of four models for cocrystal formation. Solvent drop extrusion technique used to optimize and make the process more flexible. Solvent drop extrusion technique gives an advantage to carry out process at lower temperature. Hot melt extrusion method was used in synthesis of Carbamazepine nicotinamide cocrystals with polymer as former. Continuous cocrystallization, API and conformer poured in the twin extruder. As a result of continuous addition of mixture, the barrel temperature also increases [31]

Freeze Drying

Freeze drying or lyophilization is an approach that has been used for the formation of pharmaceutical cocrystals. Recently, attempts have been made to adapt freeze drying for cocrystallization after it has already become an established process with several applications in biotechnology, pharmaceutical, diagnostics and food industries. Freeze drying is multistep operation by means of drying accomplished by freezing of a wet substance followed by ice sublimation directly to vapour by applying low partial pressure of water vapour. This method used as a processing technique to preserve a wide variety of products including food and pharmaceuticals. Recently, this method has also been demonstrated to be feasible for the preparation of new solid forms of cocrystal systems.[32]

Evaluation of Cocrystals

i Fourier-Transform Infrared Spectroscopy:

It is widely used process for the prediction and determination of chemical conformation, intermolecular interactions, and communion study between API and coformers. Analysis of the API, coformers, and cocrystals has been performed by FTIR in the wavelength range of

400–4000 cm−1. This method is quick, non-destructive, prone to changes in molecular structure and can also detect a functional group.

ii SEM

It is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is used to determine the cocrystal micrograph and particle size.[33]

iii Dissolution Study

It can be defined as "the quantity of drug substance that changes into a solution in a unit time in specific conditions of liquid/solid interface, solvent composition, and temperature." In-vitro dissolution study of any solid drug is carried out to evaluate the dissolution efficacy of formulated drug. This study is performed on the dissolution apparatus in the suitable dissolution medium as per official compendia. The samples are collected at specified time interval are analyzed by HPLC or UV spectrophotometer. Solubility study Higuchi and Connors method is used to determine solubility of cocrystals. Solubility of cocrystals, pure API and physical mixture of API and coformer are determined in water and different medium as mentioned in official compendium.

iv Stability Study

It is also one of the potent parameters for the evaluations of cocrystals as it gives information about different climatic storage conditions and shelf life of the drug or drug products. There are various parameters that affect the stability of drug such as humidity, light, and temperature. Stability studies are performed at particular temperature and humidity conditions for predetermined time intervals which gives an idea about cocrystal product shelf life at various storage conditions.[34]

How design of a cocrystal bring a change in formulation

- Co-crystals offer stability, broad drug compatibility, and designability via crystal engineering, making them patentable and expandable in IP portfolios. They enable green, high-yield solid-state synthesis without solvents or by-products
- Cocrystal formation offers advantages in drug discovery, delivery, and chiral resolution over other solid-state modifications. Experts suggest it enhances the pharmaceutical IP landscape through innovative co-crystallization. [35]

Conclusions and Future Outlook of Cocrystallization method in the modernization process.

Cocrystals especially Pharmaceuticals, have become an important solid form in pharmaceutical space. It is evident from the number of research papers, review articles which are published in various journals as well as organization of conferences, symposiums and workshops in last decade. From the industrial point of view the number of patents filed throughout the world by various pharmaceutical industries and research groups are also increasing at a fast rate, since there is both regulatory and intellectual property relevance. Cocrystals are an excellent alternative for drug development in order to enhance solubility, bioavailability, stability and processability. However, several challenges remain, including coformer selection, physicochemical characterization and formulation. Careful drug conformer screening and formulation design can lead to successful cocrystals development. In this review, we discuss in detail a wide range of technologies applied for the experimental screening, synthesis and manufacturing of pharmaceutical cocrystals in order to overcome poor physical properties of APIs. This review insight is provided on the proposed mechanisms of cocrystallization to be formed by different techniques. During early development, cocrystallization processes mainly focus on traditional methods, such as solvent evaporation, grinding and the slurry method. However, as time has gone by and the field has progressed, scientists in this field have developed newer methods which are increasingly simple to enable the cocrystallization processes to overcome their previous limitations. Novel methods that can be used for cocrystallization are hot melt extrusion, spray-drying, supercritical fluid technology, laser irradiation, freeze-drying, microfluidic and jet dispensing, etc. These methods successfully form various kinds of pharmaceutical cocrystals. However, every method still needs to be thoroughly investigated in order to better understand the clear cocrystallization mechanism for each method. It is quite evident from the amount of interest shown by both academia and pharmaceutical industry that in near future pharmaceutical cocrystals will be one of the viable and important solid forms of pharmaceuticals for (i) Reformulation of existing drugs for improved performance. (ii) Life cycle management with recently approved drugs. (iii) Enabling novel development compounds; performance and purification. (iv) Green chemistry and synthesis with cocrystals as intermediates.

REFERENCE

1. Duarte AR, Ferreira AS, Barreiros S, Cabrita E, Reis RL, Paiva A. A comparison between pure active pharmaceutical ingredients and therapeutic deep eutectic solvents: Solubility

and permeability studies. European Journal of Pharmaceutics and Biopharmaceutics, 2017 May 1; 114: 296-304.

2. Butler JM, Dressman JB. The developability classification system: application of biopharmaceutics concepts to formulation development. Journal of pharmaceutical sciences, 2010 Dec 1; 99(12): 4940-54.
3. Shan N, Zaworotko MJ. The role of cocrystals in pharmaceutical science. Drug discovery today, 2008 May 1; 13(9-10): 440-6.
4. Bagde SA, Upadhye KP, Dixit GR, Bakhle SS. Formulation and evaluation of co-crystals of poorly water-soluble drug. International Journal of Pharmaceutical Sciences and Research, 2016 Dec 1; 7(12): 4988.
5. Brittain HG. Cocrystal systems of pharmaceutical interest: 2010. Crystal growth & design, 2011, 12 Feb 1; 12(2): 1046-54..
6. Jones W, Motherwell WS, Trask AV. Pharmaceutical cocrystals: An emerging approach to physical property enhancement. MRS bulletin, 2006 Nov; 31(11): 875-9.
7. Aakeröy CB, Fasulo ME, Desper J. Cocrystal or salt: does it really matter?. Molecular Pharmaceutics, 2007 Jun 4; 4(3): 317-22.
8. Pindelska E, Sokal A, Kolodziejski W. Pharmaceutical cocrystals, salts and polymorphs: Advanced characterization techniques. Advanced drug delivery reviews, 2017 Aug 1; 117: 111-46.
9. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Advanced drug delivery reviews, 2007 Jul 30; 59(7): 617-30.
10. Billot P, Hosek P, Perrin MA. Efficient purification of an active pharmaceutical ingredient via cocrystallization: From thermodynamics to scale-up. Organic Process Research & Development, 2013 Mar 15; 17(3): 505-11.
11. Steed JW. The role of co-crystals in pharmaceutical design. Trends in pharmacological sciences, 2013 Mar 1; 34(3): 185-93.
12. Blagden N, Berry DJ, Parkin A, Javed H, Ibrahim A, Gavan PT, De Matos LL, Seaton CC. Current directions in co-crystal growth. New Journal of Chemistry, 2008; 32(10): 1659-72.
13. Buddhadev SS, Garala KC. Pharmaceutical cocrystals—a review. In Proceedings, 2021 Mar 8; 62(1): 14. MDPI.
14. Douroumis D, Ross SA, Nokhodchi A. Advanced methodologies for cocrystal synthesis. Advanced drug delivery reviews, 2017 Aug 1; 117: 178-95.

15. Mohana M, Muthiah PT, McMillen CD. Supramolecular hydrogen-bonding patterns in 1: 1 cocrystals of 5-fluorouracil with 4-methylbenzoic acid and 3-nitrobenzoic acid. Acta Crystallographica Section C: Structural Chemistry, 2017 Mar 1; 73(3): 259-63.
16. Oswald ID, Motherwell WS, Parsons S. Formation of quinol co-crystals with hydrogen-bond acceptors. Acta Crystallographical Section B: Structural Science, 2005 Feb 1; 61(1): 46-57.
17. Othman MF, Jamburi N, Anuar N, Rahim SA, Rohalim NH. Ibuprofen-amino acids co-crystal screening via co-grinding methods. InMATEC Web of Conferences, 2016; 69: 03002. EDP Sciences.
18. 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 Dec 20; 7(1): 62-5.
19. Basavoju S, Boström D, Velaga SP. Pharmaceutical cocrystal and salts of norfloxacin. Crystal growth & design, 2006 Dec 6; 6(12): 2699-708.
20. Chow SF, Chen M, Shi L, Chow AH, Sun CC. Simultaneously improving the mechanical properties, dissolution performance, and hygroscopicity of ibuprofen and flurbiprofen by cocrystallization with nicotinamide. Pharmaceutical research, 2012 Jul; 29: 1854-65.
21. Mundhe AV. Cocrystalization: an alternative approach for solid modification. Journal of Drug Delivery and Therapeutics, 2013 Jul 14; 3(4): 166-72.
22. Friscic T, Jones W. Recent advances in understanding the mechanism of cocrystal formation via grinding. Crystal Growth and Design, 2009 Mar 4; 9(3): 1621-37.
23. Chavan DD, Thorat VM, Shete AS, Bhosale RR, Patil SJ, Tiwari DD. Current Perspectives on Development and Applications of Cocrystals in the Pharmaceutical and Medical Domain. Cureus, 2024 Sep 27; 16(9): e70328.
24. Jayasankar A, Good DJ, Rodríguez-Hornedo N. Mechanisms by which moisture generates cocrystals. Molecular pharmaceutics, 2007 Jun 4; 4(3): 360-72.
25. Padrela L, de Azevedo EG, Velaga SP. Powder X-ray diffraction method for the quantification of cocrystals in the crystallization mixture. Drug development and industrial pharmacy, 2012 Aug 1; 38(8): 923-9.
26. Trask AV, Motherwell WS, Jones W. Pharmaceutical cocrystallization: engineering a remedy for caffeine hydration. Crystal Growth & Design, 2005 May 4; 5(3): 1013-21.
27. Kumar S, Nanda A. Approaches to design of pharmaceutical cocrystals: A review. Molecular Crystals and Liquid Crystals, 2018 May 24; 667(1): 54-77.

28. Friscic T, Jones W. Recent advances in understanding the mechanism of cocrystal formation via grinding. Crystal Growth and Design, 2009 Mar 4; 9(3): 1621-37.
29. Li S, Yu T, Tian Y, Lagan C, Jones DS, Andrews GP. Mechanochemical synthesis of pharmaceutical cocrystal suspensions via hot melt extrusion: enhancing cocrystal yield. Molecular pharmaceutics, 2017 Nov 22; 15(9): 3741-54.
30. Moradiya HG, Islam MT, Halsey S, Maniruzzaman M, Chowdhry BZ, Snowden MJ, Douroumis D. Continuous cocrystallisation of carbamazepine and trans-cinnamic acid via melt extrusion processing. CrystEngComm., 2014; 16(17): 3573-83.
31. Dhumal RS, Kelly AL, York P, Coates PD, Paradkar A. Cocrystalization and simultaneous agglomeration using hot melt extrusion. Pharmaceutical research, 2010 Dec; 27: 2725-33.
32. Ober CA, Gupta RB. Formation of itraconazole–succinic acid cocrystals by gas antisolvent cocrystallization. Aaps Pharmscitech., 2012 Dec; 13: 1396-406.
33. Qiao N, Li M, Schlindwein W, Malek N, Davies A, Trappitt G. Pharmaceutical cocrystals: An overview. International journal of pharmaceutics, 2011 Oct 31; 419(1-2): 1-1.
34. Prasad RV, Rakesh MG, Jyotsna RM, Mangesh ST, Anita PS, Mayur PK. Pharmaceutical cocrystallization: a review. Int J Pharm Chem Sci., 2012 Jul; 1(3): 725-36.
35. Yadav 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 Jun; 12(7): 68-74.