J. Pharm. Tech. Res. Management Vol. 10, No. 2 (2022), pp.141–149

CHITKARA

Journal of Pharmaceutical Technology Research and Management

Journal homepage: https://jptrm.chitkara.edu.in/

Co-Crystallization: Approaches, Characterization and Applications in Drug Delivery

Sayali T. Patil[1], Monika S. Mane[2], Kshitija S. Desai[3], Satyajeet R. Jagdale[4], Pankaj A. Jadhav[5] and Harshada A. Patil[6]

Department of Pharmaceutics, Dr. Shivajirao Kadam College of Pharmacy, Kasabe Digraj, Sangli. 416305, Maharashtra, India

pankajjadhav85@gmail.com (Corresponding Author)

ARTICLE INFORMATION

Received: July 20, 2022
Revised: August 11, 2022
Accepted: September 23, 2022
Published Online: November 10, 2022

Keywords:
Crystal engineering, Co-crystals, Co-formers, Poorly water-soluble, Dissolution enhancement, Hydrogen bonding

DOI: 10.15415/jptrm.2022.102004

ABSTRACT

Co-crystals play a significant role in the pharmaceutical sector. Medicinal co crystals are multicomponent systems with at least one active therapeutic ingredient and the rest of the constituents being pharmaceutically acceptable. Co crystallization of a medicinal material with a coformer is a potential and growing method for improving pharmaceutical performance in areas such as solubility, dissolution profile, pharmacokinetics, and stability.. A key barrier to developing novel API compounds is poor bioavailability and water solubility, which can limit the effectiveness of new drugs or prevent their approval for the market. In terms of the significant enhancement in solubility profiles compared to the single- active pharmaceutical ingredients, co-crystals provide a distinct and competitive edge over other traditional approaches.

1. Introduction

Co-crystals are crystalline substances that contain two or more distinct molecules (such as co-formers and drugs) within the same crystal lattice. Co-crystals have become highly crucial in the pharmaceutical industry due to their capacity to tailor the physicochemical features of medications. These pharmaceutical co-crystals have been defined specifically by regulatory organizations like the European Medicine Agency and the United States Food and Drug Administration. According to the United States Food and Drug Administration, co-crystals are crystalline materials composed of two or more molecules arranged in the same crystal lattice. (Guo, et al., 2021)

Co-crystals, as defined by European Medicine Agency, are homogenous (single phase) crystalline formations comprised of two or more components in a specific stoichiometrically ratio, where the organization in the crystal lattice is not reliant on ionic bonding (as with salts). The strong nano-covalent adhesive contacts of short-range order that exist between the drug and co-former molecules are primarily responsible for stabilizing co-crystals. Friedric Wohler used benzoquinone undhydroquinone in the year 1844 to create the first known co-crystal known as quinhydrone. It was the initial co-crystal structure that the Cambridge Structural Database had received reports on. A co-crystallization event's successful co-crystal formation is determined by intermolecular interactions, structural compatibility, and stoichiometry of drug and co-former molecules. (Ngilirabanga, *et al.,* 2021)

Drugs are categorized into four main groups according on their solubility and permeability behavior using the Bio Pharmaceutics Classification System (BCS). Poor aqueous solubility affects BCS Class II and Class IV medications. Hydrophobic drugs with poor water solubility may have poor absorption, limited bioavailability, and present challenges during the drug development process. The efficacy of BCS class II and BCS class IV medications must consequently be improved by increasing their bioavailability. One of the main issues the pharmaceutical industries encounter during the drug discovery and development processes is improving the aqueous solubility of poorly water-soluble medicines without sacrificing stability. Physicochemical features of Active Pharmaceutical Ingredients , such as melting point, dissolving rate, aqueous solubility, refractive index, surface activity, habit and density, electrostatic, mechanical, and optical properties, can be tailored using the instrument of crystal engineering. (Kulkarni, *et al.,* 2019)

Co-crystallization is one of the crystal engineering techniques used to create multi-component pharmaceutical crystals that can improve the dissolution rates of drugs that aren't very water-soluble without compromising their intrinsic features. As crucial as the capacity to produce the solid dosage form at scale is the solubility and dissolution

©Author(s) 2022. This article is published with open access at https://jptrm.chitkara.edu.in.
ISSN No.: 2321-2217(Print) ISSN No.: 2321-2225(Online); Registration No. : CHAENG/2013/50088

rate of the pharmaceutical solid. Companies invest a lot of time and energy searching for polymorphs, salts, and co-crystals of their active pharmaceutical ingredients in an effort to develop a solid with the appropriate characteristics and manufacturability. (Schultheiss, *et al.,* 2009)

A co-crystal is a uniformly crystalline substance kept together by non-covalent bonds between a neutral target and a neutral co-former. It is crucial that the co-formers have generally acknowledged as safe status for pharmaceutical applications. The inherent actions of these drug compounds are unaffected by changes to the physicochemical features of drugs. Pharmaceutical co-crystals are stable and high energy forms from a thermodynamic perspective. They may therefore affect the drug's solubility and rate of dissolution. The technique uses drug co-former combinations that could result in interactions that are both energetically and structurally robust.

Pharmaceutical co-crystals frequently rely on stoichiometrically precise hydrogen-bonded assemblies between a bilk molecule and a co-former. Co-formers with functional groups that can interact (i.e. form H-bonds) with the functional groups on the target API are of interest to us. Common functional groups, such amides, alcohols, and carboxylic acids, frequently interact with one another in co-crystals. The physical properties of the crystalline form may be modified by co-crystallizing an active pharmaceutical ingredient with an appropriate conformer. Although the range of solid forms and physicochemical properties available compared to those provided by the free molecule and potential salts is significantly expanded, the choice of potential co-formers for pharmaceutical applications is limited to those that are generally recognized as safe. (Buddhadev, *et al.,* 2021)

Non-covalent interactions, such as hydrogen bonds, ionic interactions, van der Waals interactions, and -interactions, are how the components communicate with one another. Physical and chemical qualities that are different from the characteristics of the individual components can be produced through the intermolecular interactions and crystal formations that result. Melting point, solubility, chemical stability, and mechanical qualities are a few examples of these characteristics. Some co-crystals have been found to exist as polymorphs, and depending on the crystal's shape, these polymorphs may exhibit various physical characteristics. Thermal microscopy's "contact method" phase diagrams are useful in the identification of co-crystals. The alteration in melting point during co-crystallization allows for the development of these phase diagrams. On opposite side of a microscope slide, two crystalline materials are placed, and then they are successively melted and resolidified. Each component is formed into thin films using this method, each with a contact zone in the centre. By slowly heating the slide under a microscope and observing the melting points of the different parts of the slide, a melting point phase diagram may be created. If only one eutectic point is seen in a simple binary phase diagram, the substances do not co-crystallize. If two eutectic points are seen, the co-composition crystal's is that which lies between the two points.

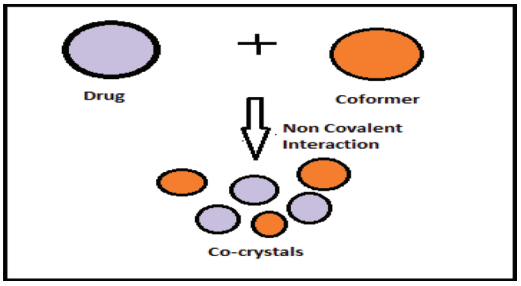

Figure 1: Co-crystals Formation.

3. Advantages

Advantages of co-crystals include their crystalline form that is stable (as compared to amorphous solids). Theoretically, all sorts of bulk molecules (weakly ionizable/non-ionizable) can form co-crystals without the need to form or break covalent bonds. Food additives, preservatives, and other drugs are numerous potential counter-molecules, and the only solid form that can be designed using crystal engineering is patentable and expands IP portfolios. Solid state synthesis is also a green manufacturing method with a high yield and no solvent or byproduct.

2.1. Melting Point

Sharp melts are a physical characteristic of solids that are used to assess the product's purity. The novel materials are thermodynamically stable as evidenced by their high melting points. That is, choosing a co-former with a high melting point can boost the thermal stability of an drug. Analysis of the melting points of about co-crystals revealed that 51% of them had melting points between API and co-former. Compared to API or co-crystals, 39% co-crystals have a melting point that is lower**.** Fenofibrate crystals were created employing a variety of coformer, such as para amino, benzoic acid and salicylic acid, and based on the findings, the melting point of Fenofibrate levels were lower than those of individual conformers and pure forms. (Diksha J. Patel, *et al.,* 2020)

2.2. Permeability

The permeability of pharmaceuticals across biological membranes is a major factor in medication absorption

and distribution. The partition of n-octanol and water is the primary factor influencing medication permeability. Coefficient based on log P and (C log P for the unmodified form of the drug. The co-crystallization of 5-fluorouracil, a BCS class-Ill pharmaceutical, with multiple conformers, including 3-hydroxybenzoic acid, 4-aminobenzoic acid, and cinnamic acid, enhanced the drug's permeability. Using Franz diffusion cells, the permeability of hydrochlorothiazide and co-crystals with various co-formers was investigated. Except for succinamide co-crystals, all co-crystals had higher drug flow levels than pure drugs. Because of the development of a hetero synthon between the drug and the co-former, co-crystals permeability was increased.

2.3. Solubility

Solubility is a crucial criterion to consider when examining medication formulations for poorly soluble substances. Co-crystallization is one method among many that have been employed by researchers to increase the solubility of pharmaceuticals, including salt creation, solid dispersion, particle size reduction, and others. By synthesizing salts and co-crystals, respectively, the solubility of the antifungal medication ketoconazole was raised 53 and 100 times in comparison to ketoconazole. As a result, Co-crystals produced a medication that was more soluble than salt formation. Co-crystals of apixaban demonstrated faster dissolution than pure drug, and their solubility was improved by nearly two times. By creating co-crystals of pterostilbene and piperazine instead of the medication being precipitated, the solubility improvement was measured to be six times greater. If inter conversion to the most stable form occurs in the GI lumen, improvements to dissolution rate, absorption, and bioavailability become meaningless. Utilizing citric acid monohydrate and oxalic acid dihydrate, co-crystals of efavirenz were created. Conformers to increase its rate of dissolution and solubility. (Patel, *et al.,* 2020)

2.4. Stability

Stability study is crucial for the creation of novel dosage formulations. Several stability tests, including relative humidity stress, chemical stability, thermal stability, solution stability, and photo stability study, should be carried out throughout the creation of pharmaceutical co-crystals. Automated water sorption/desorption tests are carried out under relative humidity stress to ascertain the impact of water on the formulation. The behavior of co-crystals under relative humidity stress conditions was investigated by a number of researchers. Co-crystals of glutaric acid and 2- [4-(4- chloro-2 fluorophenoxy) phenyl] pyrimidine-4 carboxamide demonstrated 0.08% moisture at high 95% relative humidity and were discovered to be stable under various circumstances. During relative humidity investigations, indomethacin-saccharin co-crystals displayed low water sorption and under experimental parameters, neither a separation nor a change took place. The results demonstrated an improvement in the stability and physical properties, particularly by preventing hydrate formation. Any alteration or chemical degradation during chemical stability tests should be examined in the formulation, primarily under an accelerated stability condition. Malic and tartaric acid were used as a co-former in the racemic co crystal, which was exposed to relative humidity levels of 43, 75, and 98% for up to 7 days. Theophylline co crystal's stability can be seen in the racemic co crystal's resistance to hydration compared to that of a single enantiomer.(Karimi-Jafari, *et al.,* 2018)

2.5. Bioavailability

Bioavailability is the term used to describe the rate and volume of pure medicine that is absorbed into the bloodstream. One of the biggest problems when designing a novel formulation is the low oral bioavailability of drug . The primary application of crystal engineering is the design and synthesis of co-crystals with improved water stability and oral bioavailability. According to a pharmacological study, carbamazepine: saccharine (1:1) co crystals had better oral absorption and in-vitro dissolution. The oral bioavailability of apixaban when combined with oxalic acid co-crystal is 2.7 times higher in beagle dogs, according to a pharmacokinetic research. In rats, a co-crystal of meloxicam and aspirin had greater oral bioavailability than a topically applied medication. (Ming Lu, *et al.,* 2015)

2.6. Tabletability

Crystal packing, tabletability, and compaction, which are crucial factors in Preformulation studies, might be impacted by the co-crystallization of the drug and co-former. The tabletability of co-crystal was higher than that of co-formers or pure drugs. The compaction behavior of the co-crystal of paracetamol with trimethyl glycine and oxalic acid was shown to be superior to that of the pure drug. When formed using 4 amino benzamide and isoniazide, co crystal demonstrated higher tabletability than either pure or co formers, demonstrating the increased tabletability of resveratrol. (Nitin Pawar, *et al.,* 2021)

3. Co-Crystals Preparation Methods

There are several ways to make Co-crystals. The procedures are listed below.

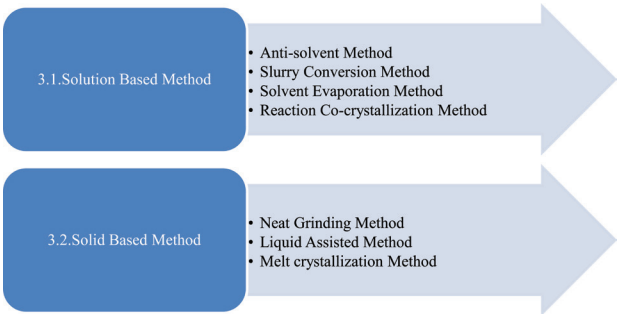

Figure 2: Co-Crystals Preparation Methods.

3.1. Solution Based Method

3.1.1. Anti-solvent Method

Water (anti-solvent) was then added to the solution vessel using a peristaltic pump at a stirring speed of 300 rpm while the mixture was being heated to 25 °C for one hour. The drug and co-former were combined with the solvent first. Better dissolving rates were attained with rod- or column-shaped co-crystals. By adding anti-solvent to obtain super-saturation during the crystallization process, the solubility of co-crystals is decreased, which causes co-crystals to precipitate. (Erriguible, *et al.,* 2015)

Advantage-

1. Well-established tools and methods.
2. Control over the morphology, size, and polymorphic form of the control is reasonable.
3. Crystals of extreme purity.

Disadvantage-

1. Crystal separation from the mother liquor.
3. Disposal or recycling of solvents.

3.1.2. Slurry Conversion Method

Use the slurry conversion method by dissolving 1 g of the medication in 20 ml of ethanol. Including 1 gram of co-former the suspension's formation was stirred. Sort the suspension mentioned above. Evaporate the ethanol following filtration. Crystals start to form and dry it out. Keep in a tamper-evident container. (Setyawan, *et al.,* 2020)

Advantage-

1. Both in batch and continuous modes, easily scalable.
2. Screening effectiveness.

Disadvantage-

1. Batch Time technique is limited.

3.1.3. Solvent evaporation Method

Using a 1:1 molar ratio of drug and co-former that had been dissolved in 60 ml of the solvent, co-crystals were created. The solution was then put into a round-bottom flask and connected to a rotator evaporator that was rotating at 90 revolutions per minute. 23°C and 55°C were used as the room temperature ranges for the solvent evaporation. The APIs were then manually combined in a 1:1 molar ratio using a mortar and pestle to create a physical combination. (Samineni, *et al.,* 2019)

Advantages-

1. Excellent control over material characteristics and chemical purity.
2. Repeatability is simple.

Disadvantages-

1. To measure the ternary phase diagram, numerous tests are required.
2. Possible considerable variation between the API and the co-solubility former's.
3. Environmental destruction.
4. Risk of solvate production during solvent removal.
5. A challenge to scale up.

3.1.4. Reaction Crystallization Method

By adding the drug and co-former to a flask containing 3 ml of ethyl acetate, the reaction crystallization method was used to create the 1:1 co-crystal at room temperature. In ethyl acetate, the solubility values of the drug and co-former are roughly 7.5 and 182 mg/ml (25°C), respectively. The suspensions were filtered using a quantitative paper filter while under vacuum after being stirred magnetically for 24 hours at ambient temperature. Using RCM, a yield of about 90% (1%) was attained. XRPD, FTIR, DSC, and HPLC were used to assess the identification and purity of co-crystals (see specific section). The powders of the medication and the co-crystal were sieved through a 60 mesh (250 m) sieve. (Samineni, *et al.,* 2019)

Advantages-

1. Ability to form co-crystals without the need for individual components to crystallize.
2. Relevance to the creation of in-situ methods for selecting high-quality co-crystals.
3. Potential large-scale production.
4. Cheaper in terms of both time and materials.

Disadvantages-

1. The solvent must be removed from the co-crystals after they have formed.

2. Additionally, unfavorable solvated or hydrated co-crystals can be produced.
3. If non-ecological solvents are utilized, waste will be produced.

3.2. Solid Based Method

3.2.1. Neat grinding Method

Dry grinding and wet grinding are two different types of grinding procedures. In dry grinding, the medication and the co-former are combined in a very precise quantitative relationship and pulverized in a ball mill or mortar and pestle. By adding a few drops of solvent to the mixture, wet grinding was carried out in an extremely similar way to neat grinding. (Samineni, *et al.,* 2019)

Advantages

1. Little to no solvent is required.
2. Creates phases that can't be created using the solvent technique.
3. Reduces the production of solvates.

Disadvantages –

1. Challenging to scale up
2. Not suitable for medications that are thermally labile.
3. Poor crystal characteristics control.

3.2.2. Liquid - assisted grinding Method

As co-formers, two organic bases and two organic acids were selected. Liquid assisted grinding was used to create co-crystals. In agate mortar and pestle, drops of ethanol were used to dissolve a 1:1 M ratio of the drug and the aforementioned conformers, which were subsequently crushed for 30 minutes. Following overnight vacuum drying, Powder x-ray diffraction and differential scanning Calorimetry were used to characterize the resultant solid phases. Before the experiment, the samples were run through an 80 mesh filter to reduce particle size. a physical mixture made by mixing the drug and the co-former in a 1:1 (mmol/mmol) ratio for one minute in a plastic bag. (Kulkarni, et al., 2019).

Advantages-

1. Fast co crystal screening is appropriate for the procedure.
2. Decreased thermal stability
3. Easy to scale
4. Fewer chances of contamination.

3.2.3. Melt Crystallization Method

The physical mixture of the drug and co-former was melted at 160°C, and the melt was subsequently cooled to the ambient temperature for crystal formation.

Advantages-

1. Drug and coformer thermal stability should be thoroughly assessed beforehand.

4. Characterization of Co-Crystals

Various methods used for characterization of co-crystals. The Characterization are given below.

4.1. Dissolution Study

In the USP (United States of Pharmacopoeia) dissolution test apparatus II, dissolving investigations were conducted for 45 minutes. The dissolving rate experiments were carried out in 900 ml of phosphate buffer 6.8 maintained at a constant 50 rpm and 37+/- 0.5 ℃ Co-crystal and drug were put to dissolution media in two distinct jars, and samples were taken at the proper intervals. Fresh 5ml of buffer solution is substituted to change the dissolving medium's volume. The samples were filtered, appropriately diluted, and subjected to first order spectroscopy at 255 nm and 291 nm for analysis. The acquired information was statistically verified.

4.2. Powder X-ray Diffraction

The key premise of X-ray diffraction is the constructive interference of monochromatic X-rays with a crystalline material. A cathode ray tube generates these X-rays, which are then filtered to create monochromatic radiation, collimated to concentrate, and directed toward the sample**.** By displaying various peak patterns, Powder X-ray Diffraction was utilized to evaluate the presence of co-crystal in the samples. The following conditions were used to operate a RIGAKU (Miniflex II) diffract meter: (Cu K radiation, 30kV voltage, 15mA current, 0.01/s step size, and a 30–400 angular range at 2 scales.

4.3. Differential Scanning Calorimetry (DSC)

A technique in which the difference in thermal energy applied to the sample and the reference material per unit of time is measured as a function of temperature in order to rebalance their temperatures, while the temperature of the sample unit, formed by the sample and the reference material, is varied in a projecting. The melting point of the co-crystal was ascertained using differential scanning Calorimetry, differential scanning Calorimetry model G1000 with series no. Q1000-0567. The samples (1-3 mg) were compressed, and then heated under nitrogen purge at a flow rate of 50 ml/min at a heating rate of 100°C/min, in aluminium pans with lids.

4.4. Fourier Transform Infrared (FT-IR)

Fourier Transform Infrared used to investigate and identify the mobility of molecules, intermolecular interactions,

and H-bond directed molecular associations, as well as to determine the solid state form of Active pharmaceutical ingredients and pharmaceutical excipients. One of the simplest techniques for distinguishing polymorphs and co-crystals is vibrational spectroscopy. They are also used to determine the hydrogen bond pattern in multicomponent molecular crystal structures. In order to identify the presence of specific functional groups in a molecule, the samples were analyzed using Fourier transform infrared .The analysis was carried out using an FT-IR model from the 50 series linked to a diamond detector, employing 32 scans per spectra with a resolution of 4000-600 cm-1 for each sample.

4.5. Thermo gravimetric analysis (TGA)

A TGA analysis is carried out by progressively raising the temperature of a sample in a furnace while its weight is monitored on an analytical balance outside of the furnace. TGA detects mass loss when a heat event results in the loss of a volatile component. Thermal analysis is used to assess the physical and chemical characteristics of solids as a function of temperature (with a constant heating rate) or of time (with a constant temperature and/or constant mass loss). Thermo gravimetric analysis may be an appropriate tool for determining the presence of volatile elements, the type of co-crystals that they form, or the temperature at which they decompose or sublimate. Thermo gravimetric analysis study predicts co-crystal purity, thermal stability, and compatibility. The heavy losses in sample mass during the Thermo gravimetric analysis are a sign of volatile component loss or co-crystal breakdown.

4.6. Solid-state NMR

Nuclear magnetic resonance (NMR) spectroscopy of solids and semi-solids is an atomic-level approach for determining the chemical composition, 3D structure, and dynamics. This Primer highlights the fundamental concepts of NMR spectroscopy as they apply to a wide variety of solid systems. Sold State NMR is used to characterize solid phases that SXRD is unable to study. Solid-state NMR was used to explore the characteristics of complexes with significant nucleon transfer. solid-state NMR is a key instrument for identifying salt or co-crystals as a result. The co-crystal structure can be evaluated using solid-state NMR by calculating chemical element bonding and native conformation changes through coupling. (Kumar, *et al.,* 2021)

5. Applications of Co-Crystals

5.1 A different method to improve the solubility and bioavailability of pharmaceuticals that are poorly water soluble is co-crystallization, particularly for substances that are neutral or weakly ionized in nature. Additionally, co-crystallization offers the chance to change and improve melting point, tablet ability, solubility, stability, bioavailability, and permeability. (Kulkarni, *et al.,* 2019).

5.2 Co-crystallization offers a flexible method for adjusting the physicochemical characteristics of pharmaceuticals, such as solubility and rate of disintegration. Depends in particular on the co-former that co-crystallizes with the drug , the pace at which the drug dissolves increases or decreases can be made in water or a buffer solution over time. (Blagden, *et al.,* 2007).

5.3 Medication dissolution rate should be prioritized over equilibrium solubility, and co-crystals may be superior to salt forms of the drug.

5.4 By modifying drug solubility, pharmacokinetics, and bioavailability, crystals have the potential to improve the delivery and clinical efficacy of pharmaceutical products. Using co-crystals in particular to enhance the oral medication absorption of BCS class II and IV Drugs. (Samineni, *et al.,* 2019).

5.5 Systems that have been used to combine numerous active pharmaceutical ingredients in a single delivery system include salts, mesoporous complexes, co-amorphous systems, and co-crystals. Compared to co amorphous, multidrug co-crystals have advantages. Technologies in terms of their improved payload stability and lower weight weighed against the mesoporous complexes.

5.6 Long-term oral treatment of high dosages of meloxicam may result in gastrointestinal problems such as stomach discomfort, diarrhoea, dyspepsia, ulceration, bleeding, and gastrointestinal perforation, despite its great efficacy.

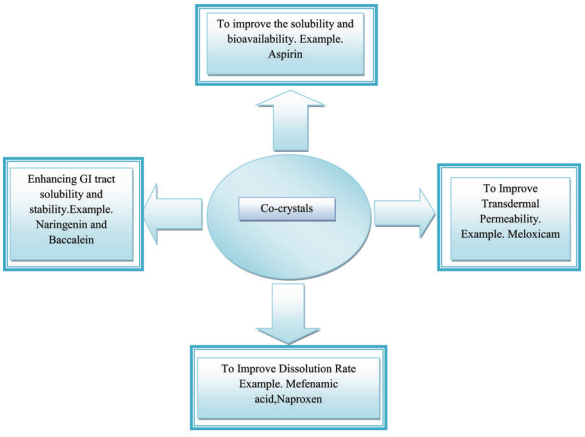

Table No 1: Examples of Marketed Co-crystals:

Drug	Brand Name	Manufacture
Carbamazepine	TEGRETOL	Novartis
Fluoxetine Hydrochloride	PROZAC	Eli lilly
Itraconazole	SPORANOX	Janssen pharma
Sildenafil	VIAGRA	Pfizer
Sacubritil + Valsartan	ENTRESTO	Novartis
Sodium valproate + Valporic acid	DEPAKOTE	Abbott
Escitalotran oxalic	LEXAPRO	Forest Lab.

Figure 3: Example of co-crystals.

5.7 Furthermore, meloxicam pH-dependent solubility complicates the creation of novel oral formulations. Transdermal distribution of this medication has been proposed as a solution to these restrictions. The co crystallization method can be utilised effectively to increase meloxicam cutaneous permeability by using salicylic acid as a coformer. (Tatiane Machado, *et al.,* 2018).

5.8 By implementing the solvent volatilization process, flavonoids (naringenin and baccalein) were used to create oxaliplatin co-crystals with the goal of enhancing GI tract solubility and stability while minimising adverse/toxic effects. (Ritu Rathi, *et al.,* 2022).

Table No 1: Examples of Marketed Co-crystals.

Drug	Brand Name	Manufacture
Carbamazepine	TEGRETOL	Novartis
Fluoxetine Hydrochloride	PROZAC	Eli lilly
Itraconazole	SPORANOX	Janssen pharma
Sildenafil	VIAGRA	Pfizer
Sacubritil + Valsartan	ENTRESTO	Novartis
Sodium valproate + Valporic acid	DEPAKOTE	Abbott
Escitalotran oxalic	LEXAPRO	Forest Lab.

Conclusion

Co-crystallization is one of the most promising methods for enhancing the physicochemical characteristics of active pharmaceutical ingredients. Co-crystals can be used in the medical and pharmaceutical fields to enhance a variety of qualities, including melting point, solubility, dissolving rate, chemical stability, and dose reduction. A crystal engineer can modify the physical characteristics of solid materials by co-crystallization. The results of co-crystallization applications in medicines are now only useful at the microscopic level.

Acknowledgements

We would like to thanks our colleagues, parents and friends who helped us a lot in finishing this work in limited time.

Authorship contribution

Sayali T. Patil
Monika S. Mane
Kshitija S. Desai
Satyajeet R. Jagdale
Dr. Pankaj A. Jadhav
Dr. Harshada A. Patil

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

References

Bijay Kumar Yadav, Atif Khursheed, & Rattan Deep Singh. (2019). Cocrystals: A Complete Review on Conventional And Novel Methods of Its Formation And Its Evaluation. *Asian Journal of Pharmaceutical And Clinical Research*, 68–74. https://doi.org/10.22159/Ajpcr.2019.V12i7.33648

Biscaia, I. F. B., Oliveira, P. R., Gomes, S. N., & Bernardi, L. S. (2021). Obtaining cocrystals by reaction crystallization method: Pharmaceutical applications. In *Pharmaceutics*, *13*(6). https://doi.org/10.3390/pharmaceutics13060898

Blagden, N., de Matas, M., Gavan, P. T., & York, P. (2007). Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. In *Advanced Drug Delivery Reviews, 59*(7), 617–630. https://doi.org/10.1016/j.addr.2007.05.011

Buddhadev, S. S., & Garala, K. C. (2021). *Pharmaceutical Cocrystals—A Review*, 14. https://doi.org/10.3390/proceedings2020062014

Erriguible, A., Neurohr, C., Revelli, A. L., Laugier, S., Fevotte, G., & Subra-Paternault, P. (2015). Cocrystallization induced by compressed CO2 as antisolvent: Simulation of a batch process for the estimation of nucleation and growth parameters. *Journal of Supercritical Fluids*, *98*, 194–203. https://doi.org/10.1016/j.supflu.2014.12.013

Fontana, F., Figueiredo, P., Zhang, P., Hirvonen, J. T., Liu, D., & Santos, H. A. (2018). Production of pure drug nanocrystals and nano co-crystals by confinement methods. In *Advanced Drug Delivery Reviews,* 131, 3–21. https://doi.org/10.1016/j.addr.2018.05.002

Guo, M., Sun, X., Chen, J., & Cai, T. (2021). Pharmaceutical cocrystals: A review of preparations, physicochemical properties and applications. In *Acta Pharmaceutica Sinica B 11*(8), 2537–2564. https://doi.org/10.1016/j.apsb.2021.03.030

Karimi-Jafari, M., Padrela, L., Walker, G. M., & Croker, D. M. (2018). Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. In *Crystal Growth and Design*, *18*(10), 6370–6387. https://doi.org/10.1021/acs.cgd.8b00933

Kulkarni, D., Pekamwar, S., Santosh, S., & Kulkarni, M. D. (2019). Crystal Engineering an Approach for Solubility Enhancement of Poorly Water Soluble Drugs Crystallographic Modification Approach For Solubility Enhancement View project Crystal Engineering an Approach for Solubility Enhancement of Poorly Water Soluble Drugs. *Journal of Medical and Pharmaceutical Innovation*, *6*. https://www.researchgate.net/publication/344801748

Kumar, A., & Nanda, A. (2021). In-silico methods of cocrystal screening: A review on tools for rational design of pharmaceutical cocrystals. In *Journal of Drug Delivery Science and Technology*, 63. https://doi.org/10.1016/j.jddst.2021.102527

Nascimento, A. L. C. S., Fernandes, R. P., Charpentier, M. D., ter Horst, J. H., Caires, F. J., & Chorilli, M. (2021). Co-crystals of non-steroidal anti-inflammatory drugs (NSAIDs): Insight toward formation, methods, and drug enhancement. *Particuology*, *58*, 227–241. https://doi.org/10.1016/j.partic.2021.03.015

Nguyen, T. A., Pham, V. N. T., Le, H. T., Chau, D. H., Mittova, V. O., Tr Nguyen, L. T., Dinh, D. A., Nhan Hao, T. v., & Mittova, I. Y. (2019). Crystal structure and magnetic properties of LaFe1-xNixO3 nanomaterials prepared via a simple co-precipitation method. *Ceramics International*, *45*(17), 21768–21772. https://doi.org/10.1016/j.ceramint.2019.07.178

Ngilirabanga, J. B., & Samsodien, H. (2021). Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy. *Nano Select*, *2*(3), 512–526. https://doi.org/10.1002/nano.202000201

Lu, M. (2015). Chapter 5. Continuous Co-crystallization of Poorly Soluble Active Pharmaceutical Ingredients to enhance dissolution Pharmaceutical Applications of Hot-melt Extrusion View project Drug Polymorphism based on Melt Crystallization. View project. https://www.researchgate.net/publication/280558640

Patel, D. J., & Puranik, P. K. (2020). Pharmaceutical Co-crystal : An Emerging Technique to enhance Physicochemical properties of drugs. *International Journal of ChemTech Research*, *13*(3), 283–290. https://doi.org/10.20902/ijctr.2019.130326

Pawar, N., Saha, A., Nandan, N., & Parambil, J. v. (2021). Solution cocrystallization: A scalable approach for cocrystal production. In *Crystals, 11*(3). https://doi.org/10.3390/cryst11030303

Rathi, R. , Kushwaha, R., Goyal, A. and Singh, I., 2022. A Review on Cocrystals of Herbal Bioactives for Solubility Enhancement: Preparation methods and Characterization Techniques. *Crystal Growth and Design, 22*(3), 2023-2042.

Rathi, R. , Kushwaha, R., Goyal, A. and Singh, I. (2022). Oxaliplatin- Flavones Pharmaceutical co-crystal-CN111205332 A: patent spotlight. *Pharmaceutical Patent Analyst, 11*(5), 147-154.

Samineni, R., Chimakurthy, J., Sumalatha, K., Dharani, G., Rachana, J., Manasa, K., & Anitha, P. (2019). Co-crystals: A review of recent trends in co crystallization of bcs class ii drugs. In *Research Journal of Pharmacy and Technology, 12*(7), 3117–3124. https://doi.org/10.5958/0974-360X.2019.00527.4

Schultheiss, N., & Newman, A. (2009). Pharmaceutical cocrystals and their physicochemical properties. In *Crystal Growth and Design, 9*(6), 2950–2967. https://doi.org/10.1021/cg900129f

Setyawan, D., Paramanandana, A., Erfadrin, V. E., Sari, R., & Paramita, D. P. (2020). Compression force effect on characteristics of loratadine-succinic acid cocrystal prepared by slurry method. *Journal of Research in Pharmacy*, *24*(3), 410–415. https://doi.org/10.35333/jrp.2020.163

Soares, F. L. F., & Carneiro, R. L. (2014). Evaluation of analytical tools and multivariate methods for quantification of co-former crystals in ibuprofen-nicotinamide co-crystals. *Journal of Pharmaceutical and Biomedical Analysis*, *89*, 166–175. https://doi.org/10.1016/j.jpba.2013.11.005

Thakuria, R., Delori, A., Jones, W., Lipert, M. P., Roy, L., & Rodríguez-Hornedo, N. (2013). Pharmaceutical cocrystals and poorly soluble drugs. In *International Journal of Pharmaceutics, 453*(1), 101–125. https://doi.org/10.1016/j.ijpharm.2012.10.043

Tatiane, C., M.,, Angélica, B., G., Juliana,R., Simone, G., C., Thiago, C.,(2018) Cocrystallization as a novel approach to enhance the transdermal administration of meloxicam. *European Journal of Pharmaceutical Sciences,* 128, 184-190. https://doi.org/10.1016/j.ejps.2018.07.038

Örn Almarsson, Shrewsbury, MA ;Magali Bourghol Hickey, Medford, MA

;Matthew L. Peterson, Framingham, MA; Michael J.Zaworotko, Tampa, FL; Brian Moulton, Providence, RI; Nair Rodriguez-Hornedo, Ann Arbor, MI 2011. PHARMACEUTICAL CO-CRYSTAL composition *US7927613 patent*.

Journal of Pharmaceutical Technology, Research and Management

Chitkara University, Saraswati Kendra, SCO 160-161, Sector 9-C, Chandigarh, 160009, India

Volume 10, Issue 2 **November 2022** **ISSN 2321-2217**

Copyright: [©2022 Pankaj A. Jadhav et al.,] This is an Open Access article published in Journal of Pharmaceutical Technology, Research and Management (J. Pharm. Tech. Res. Management) by Chitkara University Publications. It is published with a Creative Commons Attribution- CC-BY 4.0 International License. This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.