

# Pharmaceutical Co-crystals: A Systematic Review

Puneeth Jayram, Preethi Sudheer\*

Department of Pharmaceutics, Krupanidhi College of Pharmacy, Chikkabellandur, Bangalore, Karnataka, INDIA.

## ABSTRACT

Low aqueous solubility and concomitant oral bioavailability are the major glitches found in converting the active pharmaceutical ingredients to new pharmaceutical products. Many methods are in existence to improve the solubility of poorly water-soluble drugs. Co-crystallization is one of the unique technique that aggregates two or more different chemical entities in a crystalline lattice via non-covalent bonding. Co-crystals are multi-component system of an active pharmaceutical ingredient and a conformer. They offer products with superior physico-chemical properties such as melting point, solubility, stability, bioavailability, compaction and permeability. This paper focuses on the utility of co crystals in promoting the solubility of the active pharmaceutical ingredient with special emphasis

on the principle of co crystallization, methods of preparation and a survey on various cocrystal formulations and its application.

**Key words:** Solubility, Nano cocrystals, Coformers, Characterization, Crystallisation, Bioavailability.

## Correspondence

**Dr. Preethi Sudheer**

Professor, Department of Pharmaceutics, Krupanidhi College of Pharmacy, Chikkabellandur, Carmelaram (Hobli), Bangalore-560035, Karnataka, INDIA.

Phone no: +91 9449822912

Email: preetisudheer@gmail.com

DOI: 10.5530/ijpi.2020.3.45

## INTRODUCTION

Recent advent in synthetic, analytical, purification chemistry and specific techniques such as high throughput screening, combinatorial chemistry has a strong impact on discovery compounds entering into the development. Approximately 70% of new medicines discovered by the pharmaceutical industry do not have drug like properties such as good aqueous solubility and dissolution rate and so poor bioavailability. The drugs belong to class II and IV of bio pharmaceutics classification system (BCS), guarantees the requirement of newer technologies to overcome solubility problems.<sup>1</sup>

Several pharmaceutical methods as given in Figure 1 are used for improving the solubility. Among these cocrystals are considered to be one of the promising technique, which uses coformers to improve the physico-chemical properties of active pharmaceutical ingredient (API).

## CO-CRYSTALS

Pharmaceutical co-crystallization is a reliable method for changing the physical and technical properties of the drug without altering their pharmacological activities.<sup>2</sup> Cocrystal is a novel product to improve drug solubility and is also referred to as molecular complexes. It has witnessed increasing usage as an essential choice to polymorph during the selection of solid-phase APIs.<sup>3</sup> A schematic representation of various crystal lattice is given in Figure 2.

A drug cocrystal is a solid multi-component system of two crystalline neutral molecules, an API and a cocrystal former exists in solids at room temperature.<sup>4</sup> They are formed by attachment of molecular species in a stoichiometric ratio by non-covalent forces such as hydrogen-bonding in the crystal lattice, results in a new form of API.<sup>5</sup>

By incorporating pharmaceutically acceptable coformers, as in Figure 3, cocrystallization offers an effective way to change the physico-chemical and bio pharmaceutics properties of APIs including dissolution rate, solubility, melting point, hygroscopicity, compressibility, bulk density and bioavailability.<sup>6</sup>

## Nano cocrystals

A nano cocrystal is a crystalline material, with particle size of 1-1000 nm. Nanocrystallization is believed to be a generic method that can be applied to any drug with low solubility.<sup>7</sup>

The simultaneous use of nano sizing and cocrystal technology offers a synergistic effect in improving the solubility of poorly water-soluble drugs. The effect of nano cocrystals in comparison to API is been widely explored in conventional routes such as oral, intravenous, intramuscular, pulmonary and dermal due to its greater saturation solubility. For example, improved solubility and reduced tissue irritation is observed in cases of subcutaneous/intra muscular route of administration.<sup>8</sup>

## METHODS OF PREPARATION

The primary step involved in the preparation of co-crystal is the selection of cocrystal former that might be a drug or an excipient. The extent of co crystallization depends on the arrangement of the coformers. Certain safe partners mentioned are saccharin, nicotinamide, acetamide, isoniazid, ascorbic acid, etc.<sup>9</sup>

The choice of coformers compatible with particular APIs is a key challenge in pharmaceutical crystal growth. To gather the best coformers, the existing literature utilized various methods such as supramolecular synthone, Hansen solubility parameters, Database of the Cambridge Structure (CSD), pKa models, hydrogen bonding, Fabian process, etc. A large number of substances are available and are maintained by the USFDA can be used as a potential compatible agent for pharmaceutical cocrystals.<sup>10</sup> The various methods of preparation of cocrystals are mentioned below.

## Slurring technique

The technique of slurring utilises different organic solvents and water. The conformer is dissolved in organic solvent and the API is added. The suspension is stirred, filtered and dried. For instance, in the celecoxib-venlafaxine patent, the multi-drug cocrystal 'exhibited an increase in the therapeutic effect of anti-inflammatory agent celecoxib'.<sup>11</sup>

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

## Solution Methods

This method utilizes the uniform solubility of two components in a solvent system, lest the minimum soluble component precipitates out. However, the individual solubility will not ensure the success.<sup>12</sup>

## Cooling crystallization

The drug gets recrystallized by changing the solution temperature via supersaturation.

A sufficient amount of drug is dissolved at  $40.0 \pm 0.5^\circ\text{C}$  in a certain quantity of solvent. By continuous stirring, ( $0.25^\circ\text{C}/\text{min}$ ) the solution is then cooled in the water bath to  $10.0 \pm 0.5^\circ\text{C}$ . After vacuum filtration, the crystals are washed with distilled water and dehydrated for 24 hr at room temperature and then placed in desiccators.<sup>13</sup>

## Solution crystallization

Ten ml solution of coformer methyl paraben in methanol and API is combined in such a way that the mixture of API results in 1:1 combination of API and conformer. To facilitate slow evaporation, the solution is maintained at  $35^\circ\text{C}$  in a water bath. After 48 hr of evaporation and subsequent filtration and air-drying resulted in white and very small needle-shaped crystals.<sup>14</sup>

## Grinding Method

Grinding method leads to equally consistent products to solution methods. This is because the hydrogen-binding configuration is not defined under conditions that are exclusive and unmanageable. Many materials cannot be obtained from the solid-state process, could possibly be obtained by solution process. For instance, cocrystals formation of 2, 4, 6-trinitrobenzoic acid and indole-3-acetic acid by solvent method, was not observed in grinding process. There was no formation of co-crystals by grinding, since the initial solubility did not allow the co-crystal arrangements. The addition of small quantities of solvent during the grinding process demonstrated the cocrystal formation due to the increased kinetic motion.<sup>15</sup> The grinding techniques can be: neat/dry grinding and wet grinding.

## Dry grinding

Both coformer and drug are mixed in a well-defined ratio and grinded by utilizing mortar and pestle, vibratory mill, or a dry grinding process.<sup>16</sup>

## Liquid assisted grinding

This approach improves the grinding by assimilation and addition of a very small quantity of solvent during the process. The benefit of the method lies in their augmented performance and capacity to control polymorph production and improved product crystallization. If time and grinding process are not taken care of properly, this technique increases the speed of cocrystallization, which results in poor co-crystals of low quality. Same time, have the advantage of reduced time of cocrystals preparation. The ezetimibe and nicotinamide cocrystals are prepared via liquid assisted addition yielded white crystals of ezetimibe with high purity. API exhibited various solubility profiles in different organic solvents and evaporation time was found to be much longer.<sup>17</sup>

## Anti-solvent addition

Anti-solvent crystallization benefits from performing the procedure at temperatures similar to the atmospheric ones and is useful for heat-sensitive substances, which requires less heat energy than a solvent evaporation process. The difficulty in separation of solvents from the mixture limits its reuse.

Cocrystals of fenofibrate and nicotinamide was successfully prepared by solvent anti-solvent crystallization, in the presence of a coformer and API in solvents such as buffer and organic solvents like methanol, ethanol etc.<sup>18</sup>

## Solvent evaporation method

This method is widely used in the production of cocrystals. The required quantity of API and coformer is added to the suitable solvent to solubilise completely and evaporate fully. The evaporation processes establish the hydrogen bond between various functional groups and therefore, thermodynamically supported products are generated.<sup>19</sup>

## Super critical fluid technology

In the last two decades, super critical fluid engineering (SCF) has become a major tool for material processing. Supercritical fluids  $\text{CO}_2$  and  $\text{H}_2\text{O}$  are extensively being used in the preparation of a great variety of nano materials. (Figure 4.)

Supercritical liquids (SCL) have the unique characteristic of existing as fluids and gases above their critical point. This is considered as a green approach for enhancing the solubility of poorly soluble medicinal products and also in nanocrystal modification. SCL is a unique medium; where possibility new molecular interaction between two substances results in polymorphic co-crystals. As per the literature, SCF techniques for co-crystal formation utilises solvent, anti-solvent and enhancement of atomization. In these processes, the presence of a supercritical or near-critical fluid and the precipitation of cocrystals from a solution or suspension takes place especially through gas anti-solvent, (GAS), supercritical anti-solvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) process, which results in cocrystals. Indomethacin-saccharin cocrystals with different sizes and morphologies using SCF technique.<sup>20</sup>

## Spray drying

Spray drying is a quick and continuous process for solid engineering which produces a dry powder from a solution or suspension using a hot air stream as shown in Figure 5. This technique is used where coformer and drug exhibits unequal solubility, so pure crystal can't be formed by solvent evaporation method. The systems such as glutaric acid carbamazepine, theophylline-nicotinamide, urea, succinic acid or caffeine-glutaric acid, couldn't generate a pure cocrystal through solvent evaporation method, but spray drying resulted pure cocrystals as is the case for carbamazepine-nicotinamide.<sup>21</sup>

## Hot melt extrusion method

In this technique, cocrystals are produced by melting the medicine and coformer mixtures, which enhances surface contact without using any solvent. Only coformer and API that are heat stable are limited to molten form and should not be used in thermal-labile medicines

Hot-melt extrusion offers flexibility to customize the co-crystal purity in a single-step solvent-free continuous cocrystallization. Ibuprofen and nicotinamide co-crystals are prepared by HME using twin-screw resulted very good co-crystals due to the deep mixing of drug and cofomers The schematic diagram is shown in Figure 6.<sup>21</sup>

## ADVANTAGES OF PHARMACEUTICAL COCRYSTALS

The main advantage of cocrystal is that the API's physico-chemical properties will be augmented without modifying their physico-chemical properties which can result in improved absorption rate, enhanced oral bioavailability, instant results and, low cost.<sup>34</sup> In addition to this, it

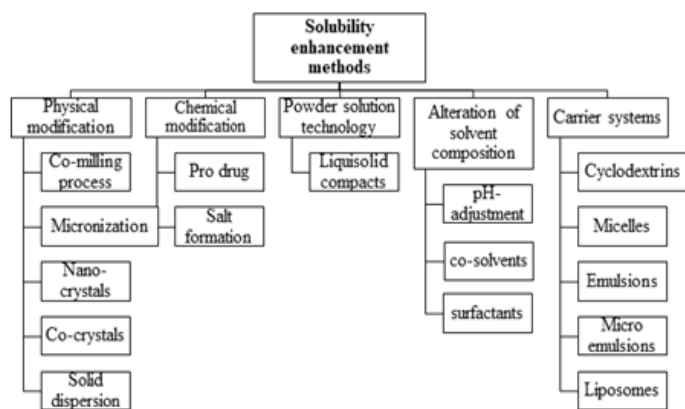


Figure 1: Solubility enhancing methods.

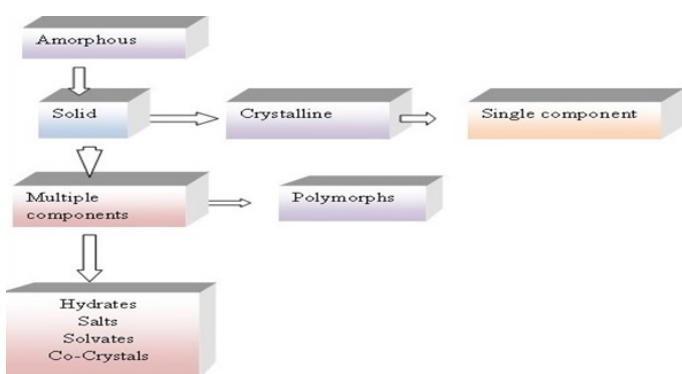


Figure 2: Types of crystal lattice.

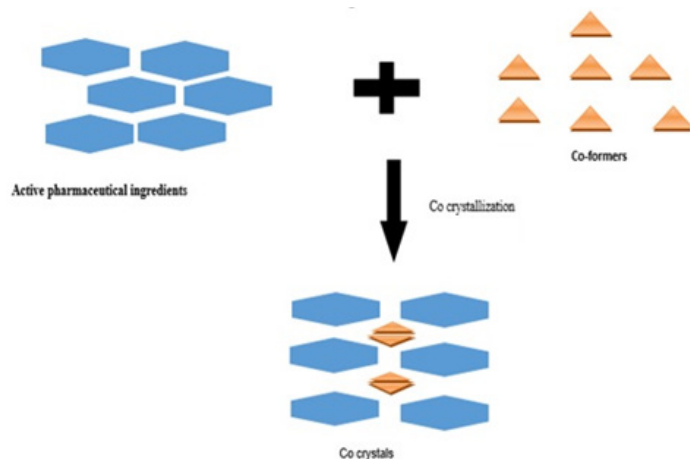


Figure 3: Schematic representation of cocrystal formation.

is suitable for all routes in any form of dosage administration. Nano-crystals can be administered through multiple routes, unlike micronized drugs. Oral administration is possible as pills, capsules, powder and, tablets. Due to very small particulate volume, nano-crystals may also be administered via the intravenous path wherein 100% bioavailability can be achieved. Moreover, the methodology is simple and scalable. However, they have the drawbacks such as sediment formation, compaction, inconsistent and inaccurate dose and proper care to be taken during the handling and shipping.<sup>22</sup>

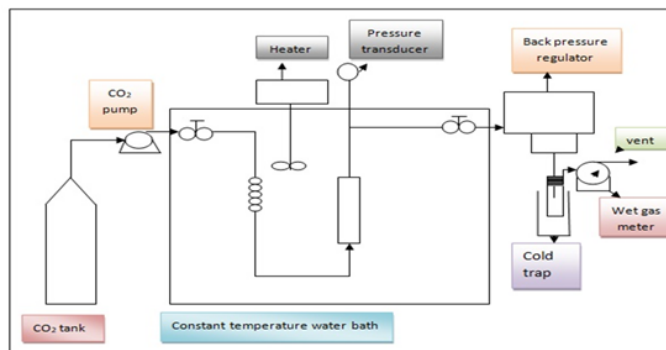


Figure 4: Super critical fluid technology.

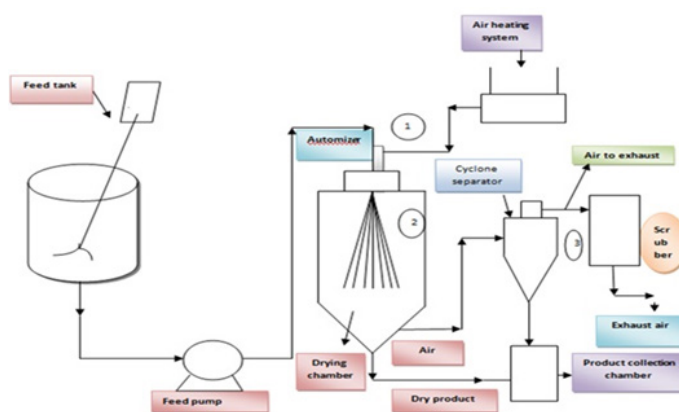


Figure 5: Spray drying.

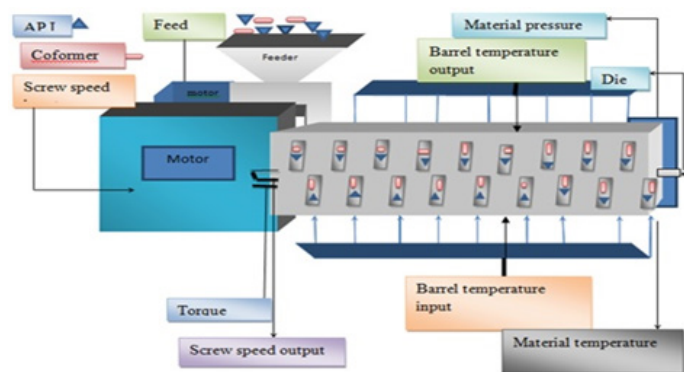


Figure 6: Hot melt extrusion.

A consolidated list of co-crystals which has been prepared for various pharmaceutical purposes is mentioned in the Table 1.<sup>23-31</sup>

## PHYSICO-CHEMICAL PROPERTIES

### Melting point

The melting point an important physical property for characterizing and identifying the purity of cocrystals and is the temperature at solid state to the liquid state transition takes place. The preferred method to obtain the melting point is differential scanning calorimetry.<sup>32</sup>

**Table 1: Cocrystal products and its applications.**

Drug	Pharmacological activity	Coformer	Authors	Year	Observation	Reference
Paracetamol	Analgesic and anti-pyretic	Caffeine	Sumera L <i>et al.</i>	2018	Improved compaction	23
Ketoconazole	Anti-fungal	Fumaric acid, Succinic acid, Adipic acid	Flavia A <i>et al.</i>	2013	Enhanced aqueous solubility	24
Itraconazole	Anti-fungal	Saccharin	Gupta RB <i>et al.</i>	2015	Improved solubility	25
Ezetimibe	Lipid-lowering	Nicotinamide	Mukherjee <i>et al.</i>	2013	Enhanced bioavailability	26
Sildenafil	Atherosclerosis	Acetyl salicylic acid	Yadav AV <i>et al.</i>	2009	Improved physico-chemical properties	27
Indomethacin	NSAIDS	Saccharin	Min-Sook J <i>et al.</i>	2010	Improved solubility, bioavailability of API	28
Meloxicam	NSAIDS	Saccharin	Cheney ML <i>et al.</i>	2011	Improved solubility and pharmacokinetics	29
Hydrochlorothiazide	Diuretic	Sucralose	Arafa MF <i>et al.</i>	2016	Enhanced aqueous solubility	30
Carbamazepine	Anti-seizure	Saccharin	Kudo S. <i>et al.</i>	2014	Improved physico-chemical properties	31

**Table 2: Marketed and Clinical Trial Cocrystals Drugs.**

SI No	Co-crystals	Uses	Status
1	Escitalopramoxalate-oxalic acid (Lexapro <sup>(R)</sup> Lundbek <sup>(R)</sup> )	Treatment of depression	Marketed
2	Sacubitril-disodium Valsartan-water ENTRESTO™	symptomatic Chronic heart failure	Marketed
3	Tremedol-celecoxib	Acute post-operative pain	Clinical trial phase 2
4	Tegreto <sup>R</sup>	Anticonvulsant	Marketed
5	(Prozac)fluoxetine hydrochloride	Treatment of depression	Marketed
6	Itraconazole (sporanox <sup>R</sup> )	Antifungal	Marketed
7	Entresto <sup>o</sup> (sacubitril-valsartan)	Heart failure	Marketed
8	Lexapro <sup>o</sup> (escitalopram oxalate)	Depression and anxiety	Marketed
9	Depakote <sup>o</sup> (valproate sodium cocrystal with valproic acid)	Seizure disorder	Marketed
10	Suglat <sup>o</sup> (ipragliflozin-L-proline) by Astellas pharma	Type 2 diabetes	Marketed
11	Entresto™	Chronic heart failure	Marketed

## Stability

The stability of a pharmaceutical co-crystal usually covers four elements: relative moisture stress, heat stress and chemical and solution stability. The presence of relative moisture assess the product's best storage state as water in the cocrystals causes the loss of its quality.<sup>32</sup>

## Photo stability

The photostability of drugs is a function of inter ring distance in the crystal lattice. Higher the ring distance more is the expected photo stability. In this manner, cocrystals of carbamazepine-saccharin and carbamazepine-nicotinamide found to overcome degradation, by repositioning the molecules in the crystal grid by the virtue of its longer ring distances.<sup>32</sup>

## Solubility

The enhanced solubility of cocrystals increases the rate of dissolution, which is the rate limiting step in gastrointestinal absorption. Co-crystals can overcome the limitation of traditional methods of solubility enhancement such as configuration of salt, solid dispersion and micronisation, etc. by thermodynamic and kinetic approaches.<sup>32</sup>

## Bioavailability

The enhanced solubility of crystals increases the bioavailable fraction of the drug that reaches systemic circulation indirectly the therapeutic efficacy of any API.<sup>32</sup>

## CHARACTERIZATION

### Fourier transform infrared spectroscopy

The co-crystalline samples are shredded dried potassium bromide using mortar and pestle and and molded into pellets in hydraulic press. After molding, pellets are scanned and registered with an infrared spectrophotometer for the range 4000-400cm<sup>-1</sup>.<sup>33</sup>

### Differential scanning calorimetry

The thermal analysis technique utilises a TA Q1000 DSC instrument contains a cooling system. DSC studies help to determine glass transition properties and the investigation of chemical reactions. Moreover, the melting and crystallization behaviour is assessed by a thermal examination of the drugs, the coformers and cocrystals. Usually, it employs 10°C / min heat flow under nitrogen flow a temperature series of 0°C-350°C.<sup>34</sup>

## Thermogravimetric analysis

Thermogravimetric analysis (TGA) is a system that calculates a substance's mass change in a regulated environment on the basis of time or temperature and is mainly used for determining the composition and thermal stability of materials. The technique classifies materials with a weight loss or gain because volatiles is sorted, /desorbed, decomposed, oxidized and reduced. These studies can provide data on the stability of materials as a function of heat, oxidative stability, the composition of multicomponent systems, estimated product life span, material decomposition kinetics, sensitive or caustic atmospheric impact on materials, the humidity and volatility of materials and physical stability. Simultaneous Shimadzu DTA/ DTG60H apparatus (Shimadzu Company, Japan) can be used in thermo gravimetric analysis.<sup>35</sup>

## Raman spectroscopy

Raman spectroscopy is an analytical method to differentiate between polymorphs, salts, cocrystals, solid solutions and hydrated salts, since the sample preparation uses only small quantity of substance. It is also a non-destructive approach for characterizing compounds, provided that the frequency of the transmitted Raman radiation is small. In particular, Raman spectra are useful for cocrystallization, because the oscillations in the cocrystals are different from the initial materials. The characteristic zones that represent the vibration of the amino and carboxyl groups in bending and stretching are moved to fewer frequencies as they form cocrystals and hydrogen bonding that results in increased belt size.<sup>36</sup>

## Powder X-ray diffraction

A Bruker D8 advance powder diffractometer with Cu K $\alpha$  radiation is used for obtaining the X ray pattern of cocrystals. The instrument is equipped with a variable settings such as a divergence slit and the anti-scattering slit for passage of light through a 20 mm sample. The tube current and voltage used are 40 mA and 40 kV respectively. The specimens are scanned from 5° to 40° at 2 $\theta$  psi. The X ray pattern explores the crystalline nature of the cocrystals.<sup>37</sup>

## Single crystal X-ray diffraction

The single crystal X-ray diffraction data were gathers the data at 170 K and 100 K, using Mo-K $\alpha$  radiation with a graphite monochromator on a Bruker Smart Apex II CCD diffractometer. For data integration and scaling, the SAINT program was used. Anisotropic displacement parameters were used to refine the non-hydrogen atoms and isotropic displacement parameters used for hydrogen atoms.<sup>37</sup>

## Scanning electron microscopic studies

Particle has to be sputtered with gold at room temperature in an argon atmosphere before morphological test. ZEISS Electron Microscope, EVO MA15 is used for studying the surface properties of the co-crystals. The specimens are scanned with an accelerating potential electric beam of 20 kV and using secondary mode, photographs are collected.<sup>38</sup>

## APPLICATIONS

Co- crystallization helps to optimize the physicochemical characteristics of a medicinal product without modifying its molecular structure. Cocrystallization also assists in improving tableability, solubility, stability and bioavailability of products.

### Solubility

Poor water solubility is an obstacle for effective drug therapy. The changes in the crystal structure of the co-crystals will possess a different solubility than any of the initial materials. The alteration of solubility

has both positive and negative effects. It is desirable to improve the solubility of the medicament as it improves the bioavailability, but excessive improvement might pose a problem because the precipitation of the starting material is undesirable because a super-saturated solution will be generated. For example, resveratrol has improved solubility 4-aminobenamide and isoniazid cocrystal forms.<sup>39</sup>

### Bioavailability

Co-crystals improve the drug product deliverance and clinical quality through modulation of pharmaceutical solubility, pharmacokinetics and bioavailability. The enhancement of oral absorption of BCS class II or IV drugs was found to increase by cocrystallization with carboxylic acids such as cinnamic and benzoic acid and amides. Stanton *et al.* observed improvements to the solubility and pharmacokinetics of AMG 517, carboxylic acid and amide form.<sup>39</sup>

### Tableability

Various prerequisites for tableting such as good mechanical strength and flowability is proposed to be increased by co-crystallization. For example, the co-crystal of carbamazepine and saccharine was found to be denser to pure carbamazepine. The compression properties of paracetamol improved in the presence of theophylline, oxalic acid, naphthalene and, phenazine.<sup>39</sup>

### Taste Masking

Oral disintegrating tablets or quick-dissolving tablets approach allows the use of tablets without chewing or water consumption and it extends to geriatric, paediatric and travelling patients. The use of sugar-based cofomer is a promising way to improve dissolution rate, for instance, when forming hydrochlorothiazide co-crystals, utilised sucralose as a cofomer. The co-crystals developed had the advantages of increased dissolution and taste masking at the same time. Theophylline is famous for its bitter flavour and it requires the usage of artificial sweetening agents such as vanilla, sodium saccharin, etc. Theophylline and saccharine 1:1 stoichiometric co-crystal prepared by liquid grinding method found to enhance the dissolution and sweetness. Co-crystals of paracetamol exhibited an improved tableability, strength, dissolution properties with a sweet taste due to the presence of trimethyl glycine (TMG).<sup>40</sup>

### Multidrug system

A popular trend in drug development has been the use of more than one APIs in a single unit dose. Besides the growing demand to help reduce costs for manufacturing drugs, there are two main reasons why multiple receptors are needed. Firstly, the effectiveness in treating complex diseases, including HIV / AIDS, cancer and diabetes. And secondly co-crystals are systems that combine multiple drugs in a single system (Multidrug Co-crystals (MDCs)) in terms of improved stability and lower payloads compared to mesoporous and cyclodextrin complexes, co-amorphous system etc. Multidrug cocrystals could provide potential benefits in relation to simple product elements such as better solutions and at least one component dissolution.<sup>41</sup>

### Controlled Release

The dissolution rate of the original API can also be reduced by cocrystal formation. For example, using cocrystallization approach the dissolution performance of ribavirin a water-soluble antiviral drug was found to be decreased (V Chen *et al.*), which reduced the fluctuations in plasma levels, from peak to trough.<sup>42</sup>

The list of marketed cocrystals pharmaceutical products are mentioned in Table 2.<sup>43-45</sup>

## CONCLUSION

Co-crystal technology is one of the latest techniques to improve the solubility of poorly soluble drugs. Cocrystals, particularly for those with neutral or weakly-ionisable product groups, is an important option to improve the bioavailability. Its promise for the future in terms of economic considerations, simple technology, use of safe agents.

## ACKNOWLEDGEMENT

Authors thank management Krupanidhi College of Pharmacy for their support.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

## ABBREVIATIONS

**API:** Active pharmaceutical ingredient; **BCS:** Biopharmaceutics classification system; **CSD:** Database of the Cambridge Structure; **USFDA:** United states food and drug administration; **PXRD:** powder X ray diffraction; **SCF:** super critical fluid engineering; **GAS:** Gas antisolvent; **SAS:** Solution enhanced dispersion by super critical fluids; **SEDS;** **HME:** Hot melt extrusion; **SXRD:** single-crystal X-ray diffraction; **FTIR:** Fourier Transform Infrared Spectroscopy; **DSC:** differential calorimetry scanning; **TGA:** Thermo gravimetric analysis; **HIV:** Human immunodeficiency virus; **AIDS:** Acquired immunodeficiency syndrome.

## REFERENCES

- Jog R, Burgess DJ. Pharmaceutical amorphous nanoparticles. *J Pharm Sci.* 2017;106(1):39-65.
- Anjana M, Joseph J, Nair SC. Solubility enhancement methods-a promising technology for poorly water-soluble drugs. *Int J Pharm Sci Rev Res.* 2013;20(2):127-34.
- Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. *Cryst Growth Des.* 2009;9(6):2950-67.
- Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. *Cryst Growth Des.* 2018;18(10):6370-87.
- Yadav AV, Shete AS, Dabke AP, Kulkarni PV, Sakhare SS. Cocrystals: A novel approach to modify physicochemical properties of active pharmaceutical ingredients. *Indian J Pharm Sci.* 2009;71(4):359-70.
- Yadav AV, Shete AS, Dabke AP, Kulkarni PV, Sakhare SS. Cocrystals: A novel approach to modify physicochemical properties of active pharmaceutical ingredients. *Indian J Pharm Sci.* 2009;71(4):359-70.
- Nagarwal RC, Kumar R, Dhanawat M, Das N, Pandit JK. Nanocrystal technology in the delivery of poorly soluble drugs: An overview. *Curr Drug Deliv.* 2011;8(4):398-6.
- Gigliobianco MR, Casadidio C, Censi R, DiMartino P. Nanocrystals of poorly soluble drugs: Drug bioavailability and physicochemical stability. *Pharmaceutics.* 2018;10(3):134. Available from: <https://doi.org/10.3390/pharmaceutics10030134>.
- Patole T, Deshpande A. Cocrystallization-a technique for solubility enhancement. *Int J Pharm Sci and Res.* 2014;5(9):3566-76.
- Steed JW. The role of cocrystals in pharmaceutical design. *Trends Pharmacol Sci.* 2013;34(3):185-93.
- Salaman CR, Ces SV, Tesson N, Castano MT. Inventors; Laboratorios del Dr Esteve SA., assignee. Cocrystals of venlafaxine and celecoxib. United States patent US 13/517 910. 2013 Aug 1.
- Good DJ, Rodriguez-HN. Solubility advantage of pharmaceutical cocrystals. *Cryst Growth Des.* 2009;9(5):2252-64.
- Sriamornsak P, Burapapadh K. Characterization of recrystallized itraconazole prepared by cooling and anti-solvent crystallization. *Asian J Pharm Sci.* 2015;10(3):230-8.
- Childs SL, Rodriguez-Hornedo N, Reddy LS, Jayasankar A, Maheshwari C, McCausland L, et al. Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. *Cryst Eng Comm.* 2008;10(7):856-64.
- Blagden N, DeMatas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. *Adv Drug Deliv Rev.* 2007;59(7):617-30.
- Kumar S. Pharmaceutical cocrystals: An overview. *Indian J Pharm Sci.* 2018;79(6):858-71.
- Sugandha K, Kaity S, Mukherjee S, Isaac J, Ghosh A. Solubility enhancement of ezetimibe by a cocrystal engineering technique. *Cryst Growth Des.* 2014;14(9):4475-86.
- Giulietti M, Bernardo A. Crystallization by antisolvent addition and cooling. *Crystallization-Science and Technology*, Marcello Rubens Barsi Andreetta, Intech Open. 2012;138. Available from: <https://www.intechopen.com/books/crystallization-science-and-technology/crystallization-by-antisolvent-addition-and-cooling>
- Weyna DR, Shattock T, Vishweshwar P, Zaworotko MJ. Synthesis and structural characterization of cocrystals and pharmaceutical cocrystals: Mechanochemistry vs slow evaporation from solution. *Cryst Growth Des.* 2009;9(2):1106-23.
- Girotra P, Singh SK, Nagpal K. Supercritical fluid technology: A promising approach in pharmaceutical research. *Pharm Dev Technol.* 2013;18(1):22-38.
- Karimi-Jafari M, Padrela L, Walker GM, Croker DM. Creating cocrystals: A review of pharmaceutical cocrystal preparation routes and applications. *Cryst Growth Des.* 2018;18(10):6370-87.
- Ross SA, Lamprou DA, Douroumis D. Engineering and manufacturing of pharmaceutical cocrystals: A review of solvent-free manufacturing technologies. *Chem Commun.* 2016;52(57):8772-86.
- Karki SFT, Fabian L, Laity PR, Day GM, Jones W. Improving mechanical properties of crystalline solids by cocrystal formation: New compressible forms of paracetamol. *Adv Mater.* 2009;21(38-39):3905-9.
- Ali S, Abolghasem J. Physicochemical characterization of new cocrystals of ketoconazole. *Powder Technol.* 2014;262:242-8.
- Ober CA, Gupta RB. Formation of itraconazole-succinic acid cocrystals by gas antisolvent cocrystallization. *AAPS Pharm Sci Tech.* 2012;13(4):1396-406.
- Wen L, Man Z, Yu-zhen Y, Yan-jie H, Xiao-hui Z, Kai S, et al. Dissolution rate enhancement of new cocrystals of ezetimibe with maleic acid and isonicotinamide. *Pak J Pharm Sci.* 2019;32(4):1501-7.
- Zegarac M, Mestrovic E, Dumbovic A, Devcic M, Tudja P. Pharmaceutically acceptable cocrystalline forms of sildenafil. London WC1X 8BT (GB); WO 2007/080362 Al. 2017.
- Basavoju S, Boström D, Velaga SP. Indomethacin-saccharin cocrystal: Design, synthesis and preliminary pharmaceutical characterization. *Pharm Res.* 2008;25(3):530-41.
- Cheney ML, Weyna DR, Shan N, Hanna M, Wojtas L, Zaworotko MJ. Supramolecular architectures of meloxicam carboxylic acid cocrystals, a crystal engineering case study. *Cryst Growth Des.* 2010;10(10):4401-13.
- Kudo S, Takiyama H. Production method of carbamazepine/saccharin cocrystal particles by using two solutions mixing based on the ternary phase diagram. *J Cryst Growth.* 2014; 392:87-91.
- Arafa MF, El-Gizawy SA, Osman MA, ElMaghraby GM. Sucralose as cocrystal coformer for hydrochlorothiazide: Development of oral disintegrating tablets. *Drug Dev Ind Pharm.* 2016;42(8):1225-33.
- Schultheiss N, Newman A. Pharmaceutical cocrystals and their physicochemical properties. *Cryst Growth Des.* 2009;9(6):2950-67.
- Pindelska E, Sokal A, Kolodziejki W. Pharmaceutical cocrystals, salts and polymorphs: Advanced characterization techniques. *Adv Drug Deliver Rev.* 2017;117:111-46.
- Araújo AA, Bezerra MD, Storpirtis S, Matos JD. Determination of the melting temperature, heat of fusion and purity analysis of different samples of zidovudine (AZT) using DSC. *Braz J Pharm Sci.* 2010;46(1):37-43.
- Trask AV, Motherwell WS, Jones W. Pharmaceutical cocrystallization: Engineering a remedy for caffeine hydration. *Cryst Growth Des.* 2005;5(3):1013-21.
- Elbagerma MA, Edwards HG, Munshi T, Hargreaves MD, Matousek P, Scowen IJ. Characterization of new cocrystals by Raman spectroscopy, powder X-ray diffraction, differential scanning calorimetry and transmission Raman spectroscopy. *Cryst Growth Des.* 2010;10(5):2360-71.
- Basavoju S, Bostrom D, Velaga SP. Indomethacin-saccharin cocrystal: Design, synthesis and preliminary pharmaceutical characterization. *Pharm Res.* 2008;125(3):530-41.
- Mureşan-Pop M, Chiriac LB, Martin F, Simon S. Novel nutraceutical myricetin composite of enhanced dissolution obtained by cocrystallization with acetamide. *Compos B Eng.* 2016;15;89:60-6.
- He H, Zhang Q, Wang JR, Mei X. Structure, physicochemical properties and pharmacokinetics of resveratrol and piperine cocrystals. *Cryst Eng Comm.* 2017;19(41):6154-63.
- Perumalla SR, Sun CC. Enabling tablet product development of 5-fluorocytosine through integrated crystal and particle engineering. *J Pharm Sci.* 2014;103(4):1126-32.
- Aitipamula S, Wong AB, Kanaujia P. Evaluating suspension formulations of theophylline cocrystals with artificial sweeteners. *J Pharm Sci.*

- 2018;107(2):604-11.
42. Chen JM, Li S, Lu TB. Pharmaceutical cocrystals of ribavirin with reduced release rates. *Cryst Growth Des.* 2014;14(12):6399-408.
  43. Malamataris M, Ross SA, Douroumis D, Velaga SP. Experimental cocrystal screening and solution-based scale-up cocrystallization methods. *Adv Drug Deliver Rev.* 2017;117:162-77.
  44. Kavanagh ON, Croker DM, Walker GM, Zaworotko MJ. Pharmaceutical cocrystals: From serendipity to design to application. *Drug Discovery Today.* 2019;24(3):796-804.
  45. Emami S, Siahi-Shadbad M, Adibkia K, Barzegar-Jalali M. Recent advances in improving oral drug bioavailability by cocrystals. *BiolImpacts: BI.* 2018;8(4):305.

**Article History:** Submission Date : 27-03-2020; Revised Date : 30-05-2020; Acceptance Date : 22-07-2020.

**Cite this article:** Puneeth J, Sudheer P. Pharmaceutical Cocrystals: A Systematic Review. *Int. J. Pharm. Investigation*, 2020;10(3):246-52.