



CODEN [USA]: IAJPBB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.5094921>Online at: <http://www.iajps.com>

Review Article

A COMPREHENSIVE REVIEW ON CO-CRYSTALS**P.M.M. Naga Lakshmi Varma^{1*}, M. Hemalatha¹, M.Jahnavi Sai¹, B.Dhana Lakshmi¹,
K.Kavitha¹, K.Hima Bindu¹, Dr.K.Padmalatha²**¹ Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Vijayawada., ² Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for Women, Vijayawada**Article Received:** May 2021**Accepted:** May 2021**Published:** June 2021**Abstract:**

Poor aqueous solubility and low oral bioavailability of an active pharmaceutical ingredient are the limitations during the growth of a new product. Co-crystal formation is a new approach to enhance the physicochemical properties of the active pharmaceutical ingredient. Co-crystallization with pharmaceutically acceptable compounds does not affect the pharmacological activity of the API but can improve the physical properties like solubility, stability and dissolution rate. Cocrystals are multi-component system of active pharmaceutical ingredient with a stoichiometric amount of a pharmaceutically acceptable coformer included within the crystal lattice. By manufacturing pharmaceutical co-crystals, the physicochemical properties of a drug can be improved thus it offers a great opportunity for the development of new drug products in the pharmaceutical industry. Most significantly, co-crystals can create new medicines with increased solubility and hence improve the efficiency and safety of the treatment. The main factor which affects co-crystal preparation is its thermodynamic stability. There are different methods used for the synthesis of co-crystal such as grinding, slurring, antisolvent, hot-melt extrusion, spray drying, etc.

KEYWORDS: Pharmaceutical co-crystals, co-crystallization, Dissolution rate, solubility, stability, solvent evaporate**Corresponding author:****P.M.M. Naga Lakshmi Varma,**
Department of Pharmaceutics,
Vijaya Institute of Pharmaceutical Sciences for Women,
Vijayawada.

QR code



Please cite this article in press P.M.M. Naga Lakshmi Varma *et al.*, **A Comprehensive Review On Co-Crystals...**, *Indo Am. J. P. Sci.*, 2021; 08(06).

1.INTRODUCTION:

In the last few years, an outsized number of medicines are discovered with low aqueous solubility. Among these, about 60-70% of the drugs belong to BCS Class II (low solubility/high permeability) and IV (low solubility/ low permeability) suffers from problems like poor aqueous solubility, poor dissolution profile and poor stability. Many Active Pharmaceutical Ingredients (API) have not been developed in formulations due to low aqueous solubility, which affects the bioavailability and therapeutic effect of drugs. Therefore, co-crystallization comes in such cases which allow using them as neutral molecules along with the cofomers without altering its biological activity.[3] Various approaches have been reported to enhance the solubility of drugs, which leads to an improvement in the bioavailability. Size reduction, solid dispersion, complexation, salt formation, cosolvency, self-emulsifying drug delivery system are some approaches used to enhance the solubility of poorly water-soluble drugs. Among all those techniques, co-crystals approach is exclusive, therein it does not affect the pharmacological properties of the drug, but it is going to modify the drugs bioavailability and also improve its physicochemical properties, like physical and chemical stability, dissolution rate and bioavailability. Hence co-crystals have developed a tremendous interest in pharmaceutical research and development because of its potential to customize physicochemical properties of the solid while maintaining the chemical integrity of the drug.

Co-crystal:

A co-crystal is a multicomponent crystal in which all components are usually solid at room temperature in a stoichiometric ratio and it involves non-covalent interactions such as hydrogen bonds, Vanderwaals bonds, ionic bonds in a crystal lattice. Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Physicochemical properties of pharmaceuticals can be improved by obtaining co-crystals using co-crystallization. Co-crystallization with pharmaceutically acceptable compounds did not affect the pharmacological activity of the API but can improve physical properties such as solubility, Hygroscopicity, compaction behaviour (Sekhon B.S *et al*; 2009).

Pharmaceutical co-crystals can be defined as crystalline materials comprised of an API and one or more unique co-crystal formers, which are solids at room temperature. The improvement of physical and

chemical property by using crystal engineering can be useful for pharmaceutical co-crystals.

1.1 ADVANTAGES OF CO-CRYSTALS

Co-crystals having advantages like stable crystalline form (as compared to amorphous solids) no need to make or break covalent bonds, theoretical capability of all types of API molecules (weakly ionized /non ionizable) to form co-crystals, the existence of numerous potential counter molecules (food additives, preservatives, pharmaceutical excipients and other APIs), the only solid form that is desirable via crystal engineering and can be produced using solid state synthesis.

There are various reasons for the improvement of solubility of poorly water-soluble drug using co-crystallization technology (Anna Karagianni *et al.*, 2018). The reasons are as follows:

Particles with reduced particle size:

Molecular dispersions as co-crystals represents the last state on particular size reduction and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium. A high surface area is formed which results an increased dissolution rate and future improved the bioavailability of the poorly water-soluble drug.

Particles with improved wettability:

The solubility enhancement of the drug is related to the drug wettability improvement verified in co-crystals.

Particles with higher porosity:

Particles in co-crystals have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. When polymers having linear structure are utilized it produces larger and more porous particle as compared with co-crystals that prepared with reticular polymers. More porous nature of the particle results higher dissolution rate.

Drugs in amorphous state:

Poorly water-soluble crystalline drugs. when in the amorphous state tend to have higher degree of solubility, Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process.

1.2 LIMITATIONS

Although preparation of co-crystals is simple but exact relationship between co-crystal structure and physical properties still unexplored. The optimum temperature range should be known for solid-state grinding method

because excessive heat may cause accidental phase transition, conglomerate crystallization or polymorphism. Solid state grinding method results in too small particle size and hence it is difficult to identify structure using X-ray crystallography. Phase separation of co-crystals into individual component upon storage at certain relative humidity condition also a concern for its applicability. Another limitation includes phase change during formulation development of API. Co-crystals may also be susceptible to counter ion displacement with excipients during manufacturing.

2. PREPARATION OF CO-CRYSTALS

The most conventional method used for crystal formation is the use of a suitable solution with a proper degree of super saturation. The solution can be supersaturated by several methods such as evaporation, cooling and incorporation of solubility lowering solvents.

Co-crystals are often prepared by solvent and solid based methods. The solid based techniques include dry grinding; solvent-assisted grinding and sonication (applied to either too wet or dry solid mixtures) 80 to 85°C. The solvent-based techniques include solvent evaporation, slurry conversion, cooling crystallization and precipitation. Solvent evaporation is the common technique used for the preparation of co-crystals.

SOLVENT SELECTION FOR CO-CRYSTALS

In order to prepare co-crystals, solvents should be selected on the basis of following criteria:

- ✦ Dissolve both drug and carrier

- ✦ Toxic solvents to be avoided due to the risk of residual levels after preparation.
E.g. chloroform and dichloromethane
- ✦ Ethanol is a less toxic alternative
- ✦ Water based systems preferable

Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass transition point.

Class I Solvents (Solvents to be avoided):

Solvents in Class I should not be employed in the manufacture of drug substances, excipients and drug products because of their deleterious environmental effect.

Class II Solvents (Solvents to be limited):

Solvents in class-II should be limited in pharmaceutical products because of their inherent toxicity.

Class III Solvents (Solvents with low toxic potential):

Solvents in class III may be regarded as less toxic and of lower risk to human health. Class III includes no solvents known as a human health hazard at level normally accepted in pharmaceuticals.

Class IV Solvents (Solvents for which no adequate toxicological data was found):

Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug products for example petroleum ether, isopropyl ether. However, no adequate toxicological data on which to base PDE was found.

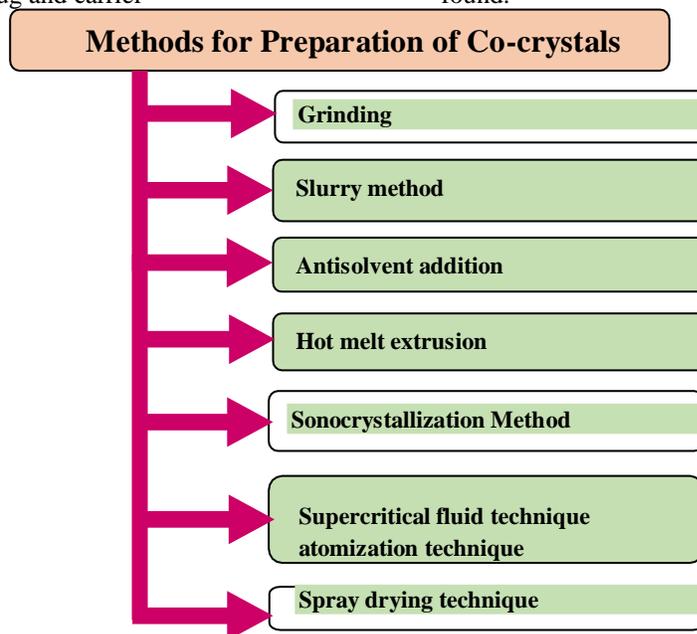


Fig No- 1: Methods of preparation of cocrystals

Grinding:

Grinding methods are widely used for the co-crystal formation in the last few years and are found to be better than the other methods (solution or melt). Grinding techniques are of two types: dry grinding and wet grinding.

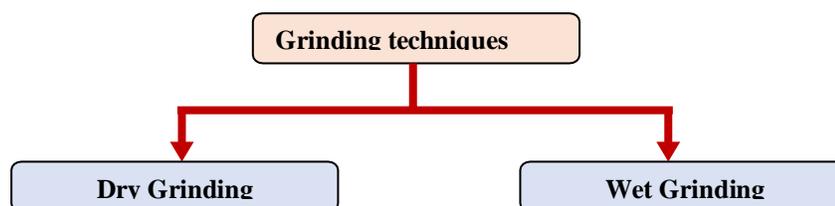


Fig No- 2: Grinding techniques for preparation of cocrystals

Dry Grinding:

Drug + Coformer
(In a stoichiometric ratio)
Grind

(Mortar and pestle or ball mill)

It is also known as solid-state grinding or mechanochemical grinding. Dry grinding can be done in different methods such as mechanical grinding using ball mill mixture, vibratory mill, or by manual grinding using mortar and Pestle.

Wet Grinding:

Drug + Coformer
(In a stoichiometric ratio)
Grind

Addition of some drops of
solvent in mixture

(Mortar and pestle or ball mill)

Liquid-assisted grinding (LAG) is an alteration of the solid-state grinding method with the incorporation of a small quantity of solvent. The solvent added acts as a catalyst for the formation of co-crystals. This method is advantageous when compared to the solvent evaporation technique due to its minimum time consumption and less requirement of the solvent. Both the drug and coformer were taken separately in a distinct molar ratio (1:1 and 1:2) in mortar and pestle for 45 min to develop co-crystals.

Slurrying:

Drug + Coformer
(In a stoichiometric ratio)

Addition of solvent to form slurry

Slurry crystallization is a simple process which includes the addition of solvent to the API along with its acceptable coformer. The choice of this method mainly depends upon the physical stability of the crystallization solvent to co-crystals and its solid former. The formation of the co-crystals is done by the addition of coformer to the solution followed by stirring. The solvent is then evaporated at room temperature to get co-crystals and may be subjected to PXRD for its characterization. Prafulla *et al.*, synthesized caffeine/maleic acid co-crystal by ultrasound-assisted slurry co-crystallization techniques. The major disadvantage of this method is that it requires a large amount of solvent.

Anti-solvent Addition:

This is one of the methods for precipitation or recrystallization of the co-crystal former and API which is an effective way for the synthesis of Micro/Nano particles.

In this co-former is dissolved in organic solvent (Anti-solvent) and API solution dispersed in co-former solution then add this solution to water so that the co-crystals are obtained.

Anti-Solvents used are buffers (pH) and organic solvents. This technique prepares co-crystals from solutions and controls the crystalline properties such as particle size and morphology.

Hot melt extrusion:

Drug + Coformer



Form co-crystal

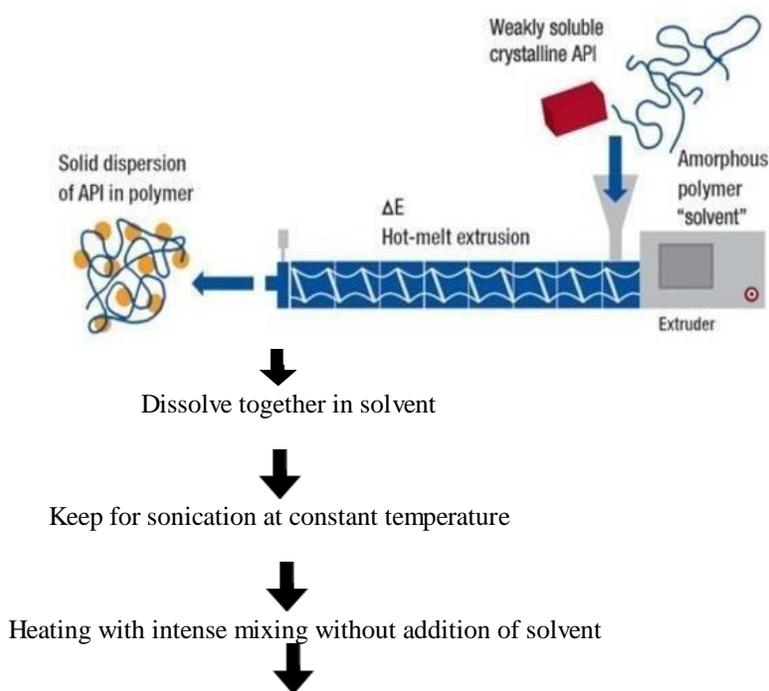
It is also known as solvent drop extrusion method. It is a process of converting the raw material into a product of uniform shape and density by forcing it through a die under controlled condition.

It involves the synthesis of co-crystals without the use of solvent which includes highly efficient mixing and improved surface contact. This method was studied with the use of four models for co-crystal formation. The selection of this method is mainly depending upon the thermostability of the compound.

Fig. No-3: Hot melt extrusion technique

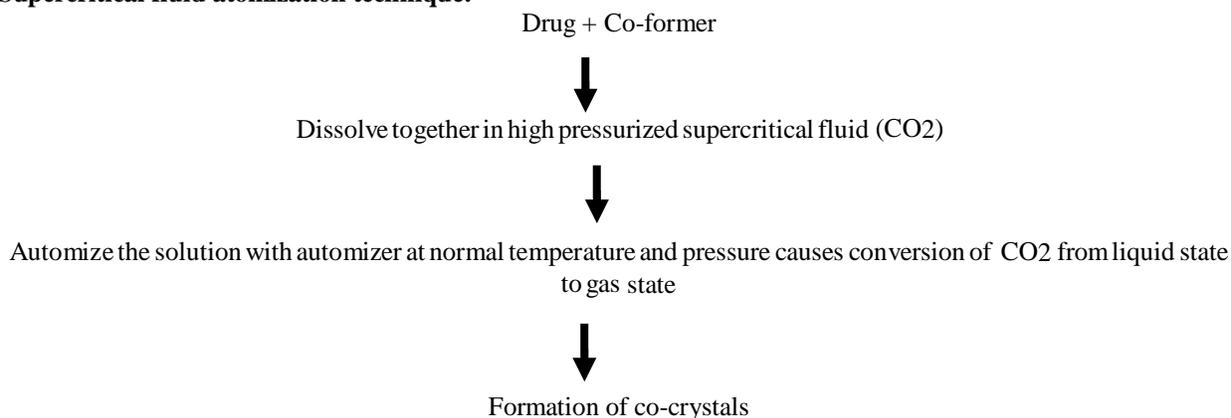
Sonocrystallization Method:

Drug + Coformer

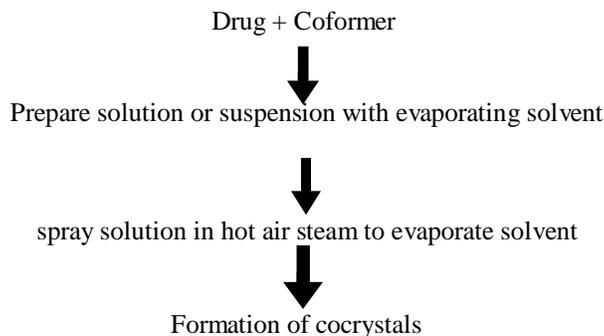


Formation of Co-Crystals

The development of sonochemical method for preparation of organic co crystals of very finite size has been done. This method was primarily developed for preparation of nanocrystals. Comparative study of method of preparation of caffeine and theophylline as API and Tartaric acid as coformer by Solvent drop grinding method and sonochemical method has been commenced. The results of methods were consistent hence sonocrystallization proves to be a significant approach (Mundhe A.V *et al.*, 2013).

Supercritical fluid atomization technique:

Supercritical fluids use offers additional advantages compared to the other co-crystal production methods. Co-crystallization by supercritical solvent (CSS) is a method where an API and a co-crystal former are mixed together by magnetic stirring after being pressurized by supercritical CO₂ in a high-pressure vessel. The Supercritical Anti-Solvent (SAS) technique explores the anti-solvent effect of supercritical CO₂ to precipitate particles (cocrystals) from solutions; the supercritical fluid enhanced atomization SEA technique explores essentially the CO₂ atomization enhancement in a spray drying process.

Spray drying technique:

Spray dryers are used for the preparation of co-crystals. It is a continuous single-step method for the transformation of liquids (solutions, suspensions, slurries) to solid powders. The cocrystals are prepared by dissolving the solution of drug and conformer in a common evaporating solvent and sprayed to a hot stream of air for evaporation of the solvent to yield good cocrystals. This is the foremost preferred technology because this is often a quick, continuous, and one-step process. Thus, the spray drying process will offer a unique environment.

3. EVALUATION OF FLOW PROPERTIES OF CO-CRYSTALS

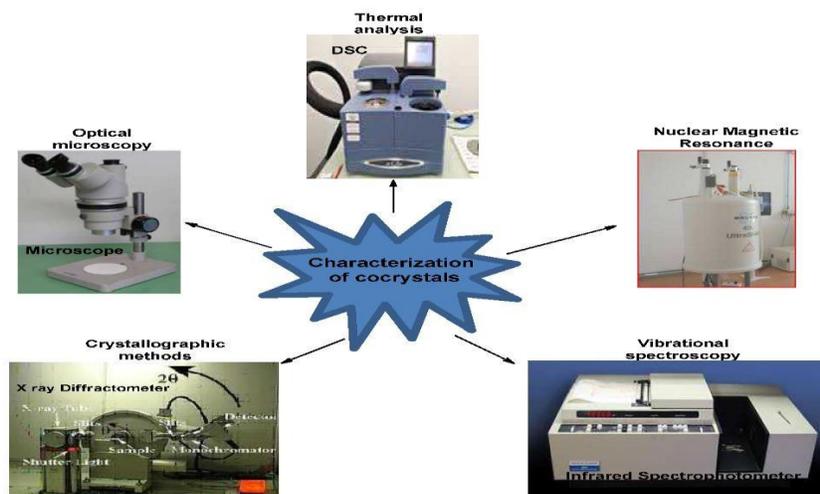


Fig.No-4: Characterization of co-crystals

Carr's Index:

$$\text{True/Tapped density } (\rho_t) = \frac{\text{Weight of microcapsules (g)} (M)}{\text{Tapped volume (ml)} (V_t)}$$

A simple test was used to evaluate the flowability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down. A useful empirical guide is given as carr's compressibility index (Leon Lachman, 1990).

$$\text{carr index} = \frac{(\text{tapped density} - \text{bulk density})}{\text{tapped density}} \times 100$$

This is a simple index that can be determined on small quantities of powders and may be interpreted as in table.

Table 1: Specifications of carr's index

CARR'S INDEX	TYPE OF FLOW
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Bulk Density:

It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume, and internal pore volume.

Tapped Density:

Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time.

Angle of Repose:

The powder flow properties were determined to know the good or bad material flow by conducting this process in which powder is taken into a funnel through which the powder to be calculated to its angle of repose is poured through funnel below this graph sheet is placed and allowed it to flow during this process material will form a heap like structure for which we can measure its radius and its height of the heap by using the formula (Leon Lachman, 1990).

$$\theta = \tan^{-1}(h/r)$$

Table 2: Specifications of Angle of repose:

Angle of repose (degrees)	Type of flow
<20	Excellent
20-30	good
30-34	Passable
>40	Very poor

Solubility:

Co-crystallization is used mainly for the enhancement of solubility of BCS class II drugs.

UV wavelength:

When the co-crystal solution is scanned in UV range, it shows the wavelength of maximum absorption similar to that of the API. If the cofomer is also an API, the scan will show two peaks or lambda max

corresponding to both API. The formation of co-crystal is concluded.

Stability:

Stability is an important parameter to be considered for any formulation. It is important to ensure the chemical stability, solution stability, thermal stability and relative humidity stability of cocrystals. The relative humidity stability of the co-crystals can be analyzed by water absorption/desorption experiments.

Melting point:

Melting point is the temperature at which solid and liquid phases of cocrystal are in equilibrium. When the co-crystal is formed, the melting point of API changes and is intermediate between the melting point of the API and the coformer.

X-Ray Diffraction (XRD studies): Powder XRD and Single crystal XRD: This analytical tool is used for phase identification of unit cells related to the co-crystal. PXRD is a frequently used technique for screening the characterization of co-crystals. The PXRD patterns obtained from the diffractometer were compared to one another for analysing the structure of co-crystals. Formation of co-crystal is indicated by the various PXRD patterns of co-crystals from their components. For powder XRD the sample is triturated to get a uniform fine powder. The selected sample must comply with Bragg's law ($n\lambda=2d \sin \theta$) for analysis. Difficulty within the procurement of one crystal is the main problem related to single crystal XRD. Therefore, PXRD is employed more to confirm the development of cocrystals.

Scanning Electron Microscope (SEM):

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

Hot stage microscopy:

A combination of both microscopy and thermal analysis is included in the hot stage microscopy study. It is used for the characterization of co-crystals as a function of temperature and time. Thermal changes like freezing point, crystalline transformations, etc are often visualized using hot stage microscopy while heating a co-crystal sample placed on a glass slide

under a microscope. When used with DSC it has expanded the optical collection capacity.

IN VITRO DISSOLUTION STUDIES:

Dissolution studies on co-crystals were performed in a calibrated 8 station dissolution test apparatus equipped with paddles (USP apparatus II method) employing 900ml of pH 6.8 buffer as a medium. The paddles were operated at 50 rpm and temperature was maintained at $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$ throughout the experiment. The samples were withdrawn up to 60 mins and replaced with equal volume of same dissolution medium to maintain the constant volume throughout the experiment. Samples with drawn at various time intervals were suitably diluted with same dissolution medium and the amount of the drug dissolved was estimated by double beam U.V spectrophotometer. The dissolution studies for all co-crystals were conducted in triplicate. From the dissolution studies, the % drug release was calculated.

4.APPLICATIONS OF CO-CRYSTALS IN PHARMACEUTICAL INDUSTRY

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

5.CONCLUSION:

Cocrystal performs a major role in pharmaceuticals. By enhancing solubility, they prevent the excess use of solvents. Also, the bioperformance and bioavailability can be enhanced. Co-crystallization offers one among the foremost promising strategy to enhance the physicochemical properties of APIs. The increased solubility, chemical and physical stability it provides are some of the most attractive properties of co-crystallized APIs. A wide range of options exists to organize co-crystals starting from routine lab-scale synthesis methods to potentially large-scale continuous production methods. This review offers a standard description of various methods that can be employed in the preparation of co-crystals followed by their characterization. Pharmaceutical co-crystals represent an advantageous class of crystal form in the pharmaceuticals. Co-crystals of drugs represent a new type of material for pharmaceutical development. Co-crystals are new aspects for pharmaceutical industries and provides new ideas to ideal with poorly soluble drugs. As compared to solvates and hydrates, co-crystals have the potential to be much more useful in pharmaceutical products.

6.REFERENCES:

- Ning Q., Mingzhong L., Walkria S., Nazneen M., Angela D., Gary T. Pharmaceutical co-crystals- An overview, *Int. J.Pharm.*, 2011, 419 (1), 1-11.
- Desale PK.: Co-crystalslization is an a novel method, *Int. J.Pharm. Invention*, 2013, 3(1), 19-26.
- Kumar S, Nanda A. Pharmaceutical cocrystals: an overview. *Indian J. Pharm. Sci.*, 2018; 79(6):858-71.
- Panzade P, Shendarkar G, Shaikh S, Rathi PB. Pharmaceutical Cocrystal of Piroxicam: Design,formulation and evaluation. *Adv. Pharm. Bull*, 2017; 7(3):399.
- Ren S, Liu M, Hong C, Li G, Sun J, Wang J, et al. The effects of pH, surfactant, ion concentration, cofomer, and molecular arrangement on the solubility behaviour of myricetin co-crystals. *Acta Pharm. Sin.* , 2019; 9(1): 59-73.
- Lahamage S, Darekar A, Saudagar R. Pharmaceutical cocrystallization. *Asian J. Res. Pharm.Sci.*, 2016; 6(1): 2231-5640.
- Aher N, Shinkar D, Saudagar R. Pharmaceutical Cocrystallization: A Review. *J Adv Pharm Edu Res*, 2014; 4(4): 388-396.
- Kotak U, Rajput V, Solanki H, Jani G, Jha P. Cocrystallization technique its rationale and recent progress, *World J Pharma Pharma Sci*, 2015; 4(4): 1484-1508.
- Fukte SR, Wagh MP, Rawat S. Cofomer selection: An important tool in co-crystal
- Formation. *Int J Pharm Sci*, 2014; 6(7): 9-14.
- Qiao N, Li M, Schlindwein W, Malek N, Davies A, Gary T. Pharmaceutical cocrystals: An overview. *Int. J Pharm*, 2011; 419(1-2): 1-11.
- Gadade DD, Pekamwar SS. Pharmaceutical cocrystals: regulatory and strategic aspects,design and development. *Adv. Pharm. Bull*, 2016; 6(4): 479.
- Panzade P, Shendarkar G. Design and Preparation of Zaltoprofen-Nicotinamide
- a. Pharmaceutical Cocrystals via Liquid Assisted Grinding Method. *Indian .Pharm. Educ. Res.*,2019; 53(4): S563-70.
- Kelly AL, Halsey SA, Bottom RA, Korde S, Gough T, Paradkar A. A novel transfectance near infrared spectroscopy technique for monitoring hot melt extrusion. *Int. J. Pharm*, 2015;496(1): 117-23.
- Sanjay A, Manohar D, Bhanudas SR. Pharmaceutical cocrystallization: A review. *J. Adv.Pharm*, 2014; 4(4).
- Aitipamula S, Vangala VR. X-ray crystallography and its role in understanding the physicochemical properties of pharmaceutical cocrystals. *J Indian Inst Sci.*, 2017; 97(2): 227-43.
- Patole T, Deshpande A. Co-crystallization-a technique for solubility enhancement. *Int. J. Pharm. Sci. Res.*, 2014; 5(9): 3566-76.
- Alatas FI, Ratih HE, Soewandhi SN. Enhancement of solubility and dissolution rate of telmisartan by telmisartan-oxalic acid cocrystal formation. *Int. J. Pharm. Res.*, 2015; 7(3): 423-6.