International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 753-761 www.ijprajournal.com ISSN: 2456-4494

Co-Crystallization: A technique to develop a better pharmaceutical formulation

Aditya Gaurav, Dr. Upendra Kumar Sharma*, Dr. Bhawna Sharma*
M.Pharm (Pharmaceutics) Department of Pharmaceutics, Institute of Pharmacy, Bundelkhand University, Jhansi, 284128, Uttar Pradesh, India.

Date of Submission: 10-05-2025 Date of Acceptance: 20-05-2025

ABSTRACT: There are many potential drug molecules which cannot be used in formulation because of poor solubility, instability, poor bioavailability etc. To resolve these problems certain techniques such as salt formation, hydrates and Co-crystallization are used. Also, this technique is used to create multidrug co-crystals and in formulation of sustained release drug. Co-crystallization is very beneficial technique in order to gain patient of co-crystal of API molecule because of the novelty of the drug. This review article is about Co-crystallization; its method of preparation like Grinding method, Solvent evaporation technique, Slurry method, Antisolvent crystallization, Supercritical fluid processing; methods of characterization of co-crystals like X-ray diffraction (XRD) studies, Differential scanning calorimetry, Spectroscopy, Field emission scanning electron microscopy (FESEM), Hot Stage Microscopy; its application in improving drug in various aspect, advantage, and limitations.

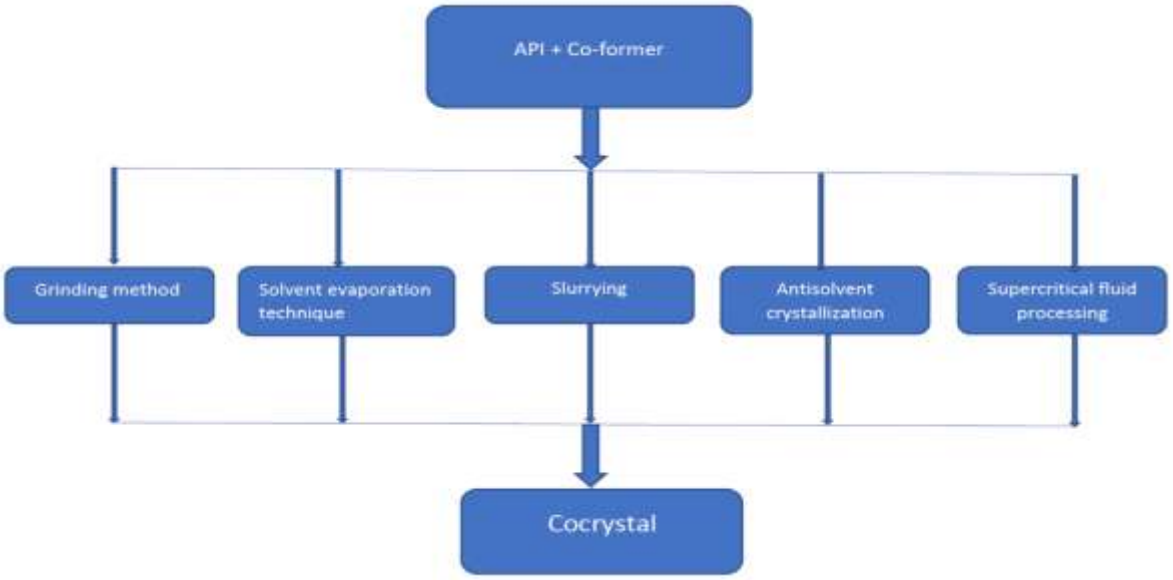
KEYWORDS: Co-crystals, Solubility, Stability, Characterization techniques, Multidrug Co-crystals

I. INTRODUCTION :

APIs (Active pharmaceutical ingredients) are the main compound responsible for the biological activity in a formulation. Few examples of APIs are Ibuprofen, Itraconazole, Atorvastatin, Naproxen Entacapone, etc. Co-formers are the compound which combines with the API to form co-crystal. Few examples of co crystals are Nicotinamide, Succinic acid, Aspartame, Theophylline, etc. There are few major forms of API available in the pharmaceutical world like salts, hydrates, and co crystals. Salts – These are chemical entity having two parts one with positive charge and another with negative charge produced by the reaction of one acid and one base. Strength or nature of a salt is dependent upon its precursor acid and base. In the case of APIs, salt formation is the most famous technique to develop most effective formulations. But this technique cannot be applied to every API molecule. Hydrates – These are a form of molecule in which water is present in the structure of the molecule. This integrated water is called as water of hydration. This gives the molecule high degree of stability. Co-crystals – US Food and Drug Administration (FDA), defines cocrystals as "solids which are crystalline materials composed of two or more molecules in the same crystal lattice" whereas EMA define it as "Homogenous (single phase) crystalline structures made up of two or more components in a definite stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonds (as with salts)". Drugs are divided into four main categories (class I, class II, class III, and class IV) according to BCS classification based on their solubility and permeability. Class II and IV medications of the Biopharmaceutics Classification System (BCS) have inadequate bioavailability due to poor water solubility. Due to their poor water solubility and hydrophobic nature, the majority of these medicines cannot be used into pharmaceutical formulations. Co-crystallization is one method for improving the aqueous solubility of medications with low water solubility, hence increasing bioavailability. Co-crystallization is an alternative to solvates, salt, and polymorphs. Synthesizing API co-crystals enables modification in physical and chemical properties without changing its biological activity. Besides APIs, co-crystallization can also be applied on food additives, preservatives, pharmaceutical excipients, vitamins, minerals, amino acids, and other biomolecules.

Methods of preparation of Co-crystals –

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 753-761 www.ijprajournal.com ISSN: 2456-4494



a) Grinding method - Mechanochemical grinding – It is otherwise called solid-state grinding or dry grinding. The API and co-former are blended and grinded by using pastel and mortar or by ball mill. Due to grinding, heat produce in this method, the produced heat cause change in properties of heat sensitive APIs which is its limitation. Accordingly high melting point drugs are mostly utilized for co-crystallization utilizing mechanochemical grinding [1]. - Liquid-assisted grinding - Liquid-assisted grinding (LAG) is a modification of solid-state grinding strategy with extra little amount of solvent during co-crystallization. Here the added solvent catalyzes cocrystals. This strategy is beneficial when thought about to the solvent evaporation technique because of its base time utilization and less necessity of the solvent [2].

b) Solvent evaporation technique - In the preparation of co-crystals, it is the most common and reliable method. In this method, the APIs and co-former are chosen in appropriate proportion and dissolved in a typical solvent. The co-crystals obtained after evaporation of solvent at room temperature. The common solvent is selected on the basis of solubility of APIs and co-former in the solvent. Co-crystals are formed by intermolecular interaction like H-bond between functional group of APIs and co-former. The limitation of this method is the requirement of more solvent in compared to LAG technique [1].

c) Slurry method – In this technique, suitable solvent is added to the APIs and its suitable conformer in specific ratio followed by stirring. Co-crystals are obtained after evaporation of solvent [3].

d) Antisolvent crystallization – In this technique, another liquid is introduced to the appropriate mixture of APIs, co-former and solvent. This another liquid helps to precipitate co-crystals by supersaturating the solution. Requirement of liquid in large quantity is limitation of this technique [4].

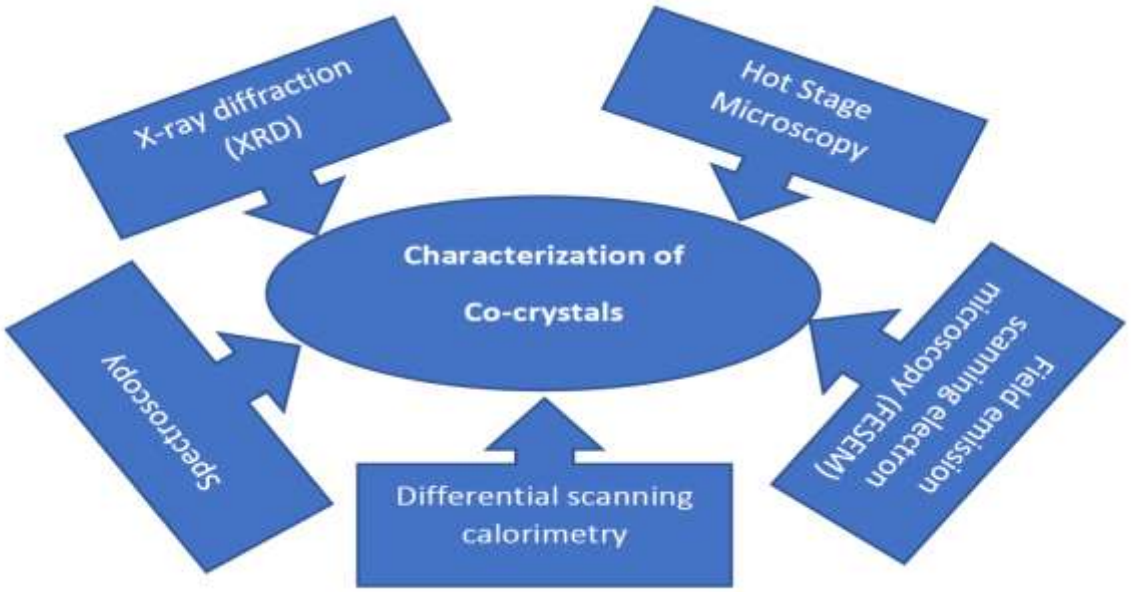
e) Supercritical fluid processing – In this technique, APIs and co-former are mixed with liquid CO2 in stainless steel container with high pressure. The co-crystals form due to rapid expansion of CO2 by reducing the pressure. Limited solubility of APIs in super critical fluids and less purity of the obtained co-crystals are the limitation of this technique [5].

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 753-761 www.ijprajournal.com ISSN: 2456-4494

API	Co-former	Method of preparation	Reference
Ibuprofen	Nicotinamide	Solvent evaporation	6
Itraconazole	Succinic acid	Solvent evaporation	7
Atorvastatin Calcium	Aspartame	Slurry method	8
Entacapone	Theophylline, Nicotinamide, Pyrazinamide, Isoniazid	Liquid assisted grinding	8
Naproxen	Tryptophan + Proline	Ball Milling	9

Table 1. Examples of methods of preparation

Characterization of co-crystals – After formation of co-crystals by different methods there is possibility of formation of different forms other than co-crystals. To identify co-crystals following methods are used –



a) XRD – The X-ray diffraction (XRD) studies - single crystalline and powder unit cell of the co-crystal is identified using this analytical tool. Powder XRD is used to identify different co-crystals while single crystalline XRD is used to recognize structure of co-crystals. Homogeneous fine powder of the sample is used in single crystalline XRD. Bragg's law ($n\lambda=2d \sin \theta$) must be obeyed by the sample [10].

b) Differential scanning calorimetry – Differential scanning calorimetry is used in determination of co-crystals. In this technique heat is applied at a controlled rate on co crystal and pure components to obtain a thermogram. Examination of thermogram confirms the possibility of presence of co-crystals [11].

c) Spectroscopy – vibrational, nuclear magnetic resonance – The energy absorbed or scattered by the co-crystals are different from the co-former and the APIs in vibrational spectroscopy which identifies the structural behavior of co-crystals. In IR spectroscopy the absorbed spectrum is different in co-crystals than in APIs and co-former due to formation of H-bonding. Solid state NMR is use in characterization of co-crystals because of the ability to provide the structural information of co-crystals [5].

d) Field emission scanning electron microscopy (FESEM) – Surface or topography of co crystals are studied by Field emission scanning electron microscopy. Micrographs of co crystals, APIs and co-formers are compared. In Field emission scanning electron microscope, electrons are emitted

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 753-761 www.ijprajournal.com ISSN: 2456-4494

by applying strong electric field, these electrons reflect from the co-crystals and get detected by an electron detector which provide topographic image of co-crystals [12].

e) Hot Stage Microscopy – In this technique, heat is given to the co-crystal and observed under the microscope. This technique helps to assess melting point, melting range and crystalline transformation. In this technique, physicochemical characteristic of a solid form is studied as a function of temperature and time [5].

Effects and applications of co-crystallization on APIs –

a) Melting point – It is a fundamental property. Melting point is the temperature at which transition between solid phase and liquid phase comes at equilibrium. Melting point is often used to identify compound and to check its purity. Melting point also influence solubility of co-crystal. It can be determined by Differential scanning calorimetry (DSC) or Kofler method.

b) Solubility – it is the amount of substance that will dissolve in given amount of solvent at fixed temperature and pressure. Co-crystallization is widely used to improve poor solubility of API. Solubility sometimes becomes bottle neck for pharmacological activities of APIs. Solubility can be increase or decrease by either adding impurities or by making co-crystal. In co-crystal, co-former acts like impurities and change its solubility in either direction. According to Hu et al., aqueous solubility of febuxostat:arginine cocrystal, increased from 7.5 mg/L to 571 mg/L.[13]

c) Controlled release – Co-crystallization technique is also used to develop controlled release formulations due to its ability to decrease solubility of APIs by choosing appropriate co-former. Chen et al. used co-crystallization technique to achieve sustain release of ribavirin (an antiviral drug). Due to this modification plasma drug concentration maintain at its therapeutic level for longer duration [14].

d) Stability – There are many factors that affects the stability of co-crystals like relative humidity, heat, light, hydrolysis. These factors can change the activities of APIs. These can be resolve using co crystallization.

i. Solution stability – It means ability of the cocrystal components to stay in the solution and not readily crystallize. When developing, it's crucial to evaluate it. This is a crucial factor to assess during the development process for solid dosage forms that will dissolve in the gastrointestinal tract as well as liquids and suspensions. Since co-crystal separation is a possibility, their development depends heavily on their stability in solution. The production of carbamazepine hydrate when the cocrystals were slurried in water for 24-48 h was assessed in a study on carbamazepine cocrystals with 18 co-formers. Seven of the investigated cocrystals still possessed their original crystalline structures, while the remaining eleven were changed into carbamazepine hydrate. The co-former's water solubility appeared to be a crucial factor in the hydrate's production. It was discovered that while cocrystals with co-formers of relatively low solubility were stable in aqueous conditions, those with relatively high solubility in water produced the hydrated form [15].

ii. Light stability – The mechanism of carbamazepine's photodegradation depends on the spacing between the rings in the crystal lattice. The photodegradation mechanism is not present in the cocrystals of carbamazepine-saccharin and carbamazepine-nicotinamide due to their greater ring lengths. Because co crystallization can alter chemical stability by rearranging molecules in the crystal lattice, the cocrystal can be shielded from undesirable processes. [16,17]

iii. Thermal stability – The physical and chemical stability of solid APIs at high temperatures are evaluated. Chen et al. looked at the cocrystal of a monophosphate salt with phosphoric acid at 60 °C, and they found no signs of degradation or form changes.[18]

iv. Relative humidity – When creating a cocrystal in solid forms, fluctuations in RH must be considered. Automated humidity sorption/desorption tests are typically carried out to identify the "problematic" circumstances and provide guidelines for more in-depth investigations, if required. By

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 753-761 www.ijprajournal.com ISSN: 2456-4494

exposing the cocrystal to a specific RH in a suitable humidity chamber and evaluating the sample once it has reached equilibrium, moisture uptake may be regulated. A thorough investigation including the co-crystallization of caffeine with different carboxylic acids, including oxalic, malonic, maleic, and glutaric acid, revealed that the cocrystals created had less hygroscopicity than the raw API. After 1, 3, and 7 weeks, the samples were taken out of each of the four RH situations and evaluated. In all RH settings, the caffeine-oxalic acid (2:1) cocrystals showed perfect stability to moisture.[19]

e) Multidrug Cocrystals – In the pharmaceutical formulation industry, combining different APIs into a single unit dose has grown in popularity. The two main factors driving this growing trend are the requirement to target many receptors for the efficient treatment of complicated illnesses including HIV/AIDS, cancer, and diabetes as well as the growing demand to facilitate the decrease of medication manufacturing costs. Multiple APIs have been combined in a single delivery method using salts, mesoporous complexes, co amorphous systems, and cocrystals.[20] Kaur et al. documented MDC of Lamotrigine and phenobarbital (both anticonvulsant). Through hydrogen binding, the two molecules combine to create heterodimers. Studies on the dissolution of cocrystals in phosphate buffer (pH 7.2) showed that they dissolved more slowly than pure phenobarbital and pure lamotrigine.

API Combination	**Therapeutic Chetegory**	**Method of preparation**	**Observations**	**Reference**
Sulfadimidine-Aspirin (1:1)	Antibacterial and NSAID	Solvent evaporation	Pharmaceutical property not evaluated	23
Tetroxoprim – Sulfametrole (1:1)	Antibacterial	Co-grinding and Solvent evaporation	Physical conditions were found that were	24, 25
Piracetam- gentisic acid (1:1)	Nootropic agent and NSAID	Co-grinding, Slurrying in water and Solvent evaporation	Determined function of the carboxylic acid primary amide dimer in the crystal designing of two polymorphic APIs	26
Lamivudine-Zidovudine (1:1)	Antiviral	Solvent evaporation	As a model for co-crystal prediction from a single molecule, established synthon theory.	27
Salfamethazine-theophylline (2:1)	Antibacterial and antiasthmatic	Solvent evaporation	In comparison to controls, the theophylline and Salfamethazine hygroscopicity of co-crystal reduced.	28
Meloxicam- aspirin (1:1)	NSAIDs	Solution crystallization, slurry and solvent drop grinding methods	Solubility increases 44 times in pH 7.4 phosphate buffer; Cmax, MRT, AUC, and MAT improved and Bioavailability improved four	29

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 753-761 www.ijprajournal.com ISSN: 2456-4494

			times	
Pyrazinamide and Diflunisal (1:1)	Antitubercular and NSAID	Ball mill grinding	Calculation based on density functional theory were performed to examine the viability of the co-crystallization of two APIs.	30

Table 2. Application of co-crystallization in preparing multi drug cocrystals

f) Bioavailability – By altering medication solubility, pharmacokinetics, and bioavailability, cocrystals have the potential to improve drug delivery and clinical performance. Utilizing cocrystals to enhance the oral medication absorption of BCS classes II and IV pharmaceuticals. Childs et al. used a suitable formulation of danazol:vanillin cocrystal that included a solubilizer (1% vitamin E-TPGS), and a precipitation inhibitor (2% Hydroxypropyl-cellulose) to increase the solubility and bioavailability of a danazol. Comparing this formulation to the poorly soluble danazol polymorph, the cocrystal's bioavailability was improved significantly by over 10 times.[21] Wang et al. improved the bioavailability of dihydromyricetin-caffeine and dihydromyricetin-urea cocrystals by inhibiting the precipitation of dihydromyricetin by using polyvinylpyrrolidone as a crystallization inhibitor. This increase bioavailability 5 times.[22]

5. API and co-former selection for co-crystallization:

To create a pharmaceutical co-crystal, two neutral substances called an API and a co-crystal former are mixed into a single crystalline solid. An excipient or another API might be the co crystal former [31]. A list of thousands of compounds that might be employed as prospective co formers for medicinal cocrystals has been kept on file by the USFDA [32]. The non-API component that is employed as a co-former must be non-toxic and free from negative effects. The cocrystal former should ideally be authorised as Generally Recognized as Safe (GRAS) or added to the US FDA's "Everything added to food in the United States" (EAFUS) list, which includes approximately 3000 substances suitable for use as food additives (GRAS). The choice of a co-former for an API is crucial for developing and screening cocrystals. The two approaches used to choose co-formers are experimental methods and knowledge-based methods. Hit and try methodology is frequently employed with all varieties of co-formers for an API, and they are distinguished by appropriate methodologies to validate the structure of cocrystals. This method is time- and money-consuming. Researchers have employed a variety of knowledge-based strategies for the selection of appropriate co-formers, including the following ones: the synthonic engineering, hydrogen-bonding propensity, Cambridge Structure Database (CSD) supramolecular compatibility, Fabian's technique, Hansen solubility parameter, conductor-like screening model for real solvents (COSMO-RS), virtual cocrystal screening, thermal analysis, saturation temperature measurement, Kofler contact method, and matching [33].

a) Hydrogen bonding propensity: In cocrystals, non-covalent interactions such as hydrogen bonds and van der Waal forces allow API and co-formers to connect with one another. For the formation of cocrystals, hydrogen bonding between API and the co-former is the most important of all of these. Etter described a graph-set notation system that has primarily been used as a theme for labelling hydrogen bonds and proposed three rules for preferable hydrogen bond formation: every acidic hydrogen molecule will be present in bond formation; all hydrogen bond acceptors will be used when hydrogen bond acceptors are available; and hydrogen bonds will be formed when there will be the best hydrogen bond donors and hydrogen bond acceptors [34].

b) Synthonic engineering: Desiraju discussed the "synthon approach" for the selection of co-formers that created a supermolecule by creating "supramolecular synthons" using particular molecular fragments within the cocrystal [35]. A co-former with the appropriate functional group will be employed for a certain API, and the functional groups present in the API and co-former will play a significant role in the creation of

International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 3 May–June 2025, pp: 753-761 www.ijprajournal.com ISSN: 2456-4494

cocrystals. Supermolecules contain synthons, which are fundamental structural constituents linked by noncovalent bonds. There are two different types of supramolecular synthon approaches: supramolecular homosynthons and supramolecular heterosynthons. In contrast to supramolecular heterosynthons, which are created by distinct functional groups like carboxylic acid-amide heterosynthons and acid-pyridine heterosynthons, supramolecular homosynthons are made up of the same functional groups that are present in API and co-former. In general, supramolecular heterosynthons are preferred over homosynthons; for instance, acid-amide and acid-pyridine heterosynthons are more frequently utilised than carboxylic acid and amide homodimers [36].

c) Cambridge Structure Database (CSD): The proven CSD tool makes it easier to statistically analyse packing patterns and reveals information about typical functional groups. Using functional groups that interact to produce supramolecular synthons, CSD is utilised to provide information about the molecular association of drugs and co-formers. CSD can create a library of appropriate co-formers for an API. This method, which is computer-based and speeds up study and experimentation, is used to identify suitable cocrystal forming pairings [35].

d) Fabian's method: The CSD was used to extract various collections of viable cocrystal-forming structures, and for each molecule, the molecular descriptors (single atom, bond, and group counts, hydrogen bond donor and acceptor counts, size and shape, surface area, and molecular electrostatic) were determined. The database listed pairs of chemicals that could form cocrystals based on computed molecular characteristics. The cocrystal formers' shape and polarity had the highest descriptive association [36].

e) Synthon matching: Synthon matching is a computational theory used for cocrystal screening that looks into the intermolecular interactions in crystal structures. This method's main drawback is that it is unable to precisely determine the in vivo properties of cocrystals. This synthon technique is used to calculate the likelihood that API and co-former will form a hydrogen bond. The conformational similarity index for proteins, graph-set analysis for hydrogen bonds, Voronoi-Dirichlet polyhedral for crystal packing, continuous symmetry measures, and the Hirshfeld surface are just a few of the methods that have emerged in recent years to determine the intermolecular interactions in crystal structures qualitatively and quantitatively. These methods use computer programs like ESCET, COMPACK, TOPOS, Xpac, Crystal Explorer, and dSNAP, respectively [37].

f) Hansen solubility parameter: Another crucial method for assessing the miscibility of drugs and co-formers used in cocrystal systems is the Hansen solubility parameter. The development of cocrystals may be predicted by the miscibility of the components in the solid state. The use of components with similar miscibility increased the success rate of the cocrystal synthesis [30].

Advantages and limitations:

Advantages – Co-crystallization enables multiple APIs to be in corporate in desired formulation for formulating multidrug dosage form. This technique overcomes the limitation of limited formulations. The APIs with disabilities like poor solubility, less bioavailability, poor stability, etc. can also be formulated with the help of co-crystallization. The product obtained by co crystallization have unique or changed characteristics from the parent molecule that maintain its novelty which can be used to extend patent of the product.

Limitations – For solid-state grinding method, optimum temperature must be known. Any excess heat may cause phase inversion or polymorphism. Also, the particle obtain from this method is too small to be identified through X-ray crystallography. Phase changes during API formulation development are still another restriction. During production, excipients may be used to counteract ion displacement in co-crystals.

II. CONCLUSION-

A class of materials known as cocrystals has the potential to solve issues with dosage form. An API cocrystal's novel crystal structures could result in improved or weakened pharmacological qualities. Co-crystallization is only beneficial when it improves the problematic feature without compromising other properties. The screening and evaluation of cocrystals must therefore take into account all important pharmacological features. Because of the benefits of both solid-state grinding and solution-mediated phase transformation, liquid-assisted grinding for co-crystallization is

successful. Cocrystal standards have altered in recent years, and regulatory organizations now offer thorough recommendations on cocrystal production and commercialization. Research into cocrystal polymorphism, higher-order cocrystals, salt cocrystals, and glassy cocrystals will all advance in the futur

REFERENCES:

[1]. Raheem Thayyil, Abdul et al. "Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications." Advanced pharmaceutical bulletin vol. 10,2 (2020): 203-212. doi:10.34172/apb.2020.024

[2]. Thenge, Raju Rameshrao, et al. "PREPARATION AND CHARACTERIZATION OF CO-CRYSTALS OF DIACEREIN." Indonesian Journal of Pharmacy/Majalah Farmasi Indonesia 28.1 (2017).

[3]. Raheem Thayyil, Abdul et al. "Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications." Advanced pharmaceutical bulletin vol. 10,2 (2020): 203-212. doi:10.34172/apb.2020.024

[4]. Raza, Syed et al. "Rapid continuous antisolvent crystallization of multi-component systems." Crystal Growth & Design 18 (2018): 210-218.

[5]. Al-Ogaili, N. A. et al "In Vitro Antibacterial Investigation and Synergistic Effect of Ficus Carica and Olea Europaea Aqueous Extracts." Research Journal of Pharmacy and Technology, vol. 13, no. 3, 2020, pp. 1198-1203.

[6]. Yuliandra, Y., Zaini, E., Syofyan, S., Pratiwi, W., Putri, L. N., Pratiwi, Y. S., and Arifin, H. "Cocrystal of Ibuprofen–Nicotinamide: Solid-State Characterization and In Vivo Analgesic Activity Evaluation." Scientia Pharmaceutica, vol. 86, no. 2, 2018, p. 23.

[7]. Alshehri, Mohammed Ahmed, et al. "Pharmacological Treatment of Metabolic Syndrome." Saudi Pharmaceutical Journal, vol. 25, no. 7, 2017, pp. 1045-1046.

[8]. Raheem Thayyil, Abdul et al. "Pharmaceutical Co-Crystallization: Regulatory Aspects, Design, Characterization, and Applications." Advanced Pharmaceutical Bulletin 10 (2020): 203 - 212.

[9]. Bi, Yanping, et al. "The Binary System of Ibuprofen-Nicotinamide Under Nanoscale Confinement: From Cocrystal to Coamorphous State." Journal of Pharmaceutical Sciences, vol. 106, no. 10, 2017, pp. 3150-3155.

[10]. Kumar, S. "Pharmaceutical Cocrystals: An Overview." Indian Journal of Pharmaceutical Sciences 79 (2017): 858-871.

[11]. Douroumis, Dennis et al. "Advanced methodologies for cocrystal synthesis." Advanced Drug Delivery Reviews 117 (2017): 178–195.

[12]. Gnanamoorthy, Palingamoorthy et al. "Field Emission Scanning Electron Microscopy (FESEM) characterisation of the porous silica nanoparticulate structure of marine diatoms." Journal of Porous Materials 21 (2014): 225-233.

[13]. Kang, Yanlei et al. "Syntheses, structure characterization and dissolution of two novel cocrystals of febuxostat." Journal of Molecular Structure 1130 (2017): 480-486.

[14]. Chen, Jia-Mei et al. "Pharmaceutical Cocrystals of Ribavirin with Reduced Release Rates." Crystal Growth & Design 14 (2014): 6399-6408.

[15]. Childs, Scott L. et al. "Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine." CrystEngComm 10 (2008): 856-864.

[16]. Spong, Barbara Rodriguez. "Enhancing the pharmaceutical behavior of poorly soluble drugs through the formation of cocrystals and mesophases." (2005).

[17]. Matsuda, Yoshihisa et al. "Pharmaceutical Evaluation of Carbamazepine Modifications: Comparative Study for Photostability of Carbamazepine Polymorphs by using Fourier- transformed Reflection- absorption Infrared Spectroscopy and Colorimetric Measurement." Journal of Pharmacy and Pharmacology 46 (1994): n. pag.

[18]. Chen, Alex M. et al. "Development of a pharmaceutical cocrystal of a

monophosphate salt with phosphoric acid." Chemical communications 4 (2007): 419-21

[19]. Trask, Andrew Vincent et al. "Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration." Crystal Growth & Design 5 (2005): 1013-1021.

[20]. Karimi-Jafari, Maryam et al. "Creating Cocrystals: A Review of Pharmaceutical Cocrystal Preparation Routes and Applications." Crystal Growth & Design (2018): n. pag.

[21]. Childs, Scott L. et al. "Formulation of a danazol cocrystal with controlled supersaturation plays an essential role in improving bioavailability." Molecular pharmaceutics 10 8 (2013): 3112-27.

[22]. Wang, Chenguang, et al. "Enhancing Bioavailability of Dihydromyricetin through Inhibiting Precipitation of Soluble Cocrystals by a Crystallization Inhibitor." Crystal Growth & Design, vol. 16, no. 9, 2016, pp. 5030-5039.

[23]. Desiraju, Gautam R "Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis." Angewandte Chemie 34 (1995): 2311-2327.

[24]. Bhatt, Prashant M. et al. "Co-Crystals of the Anti-HIV Drugs Lamivudine and Zidovudine." Crystal Growth & Design 9 (2009): 951-957.

[25]. Delori, Amit et al. "Knowledge-based hydrogen bond prediction and the synthesis of salts and cocrystals of the anti-malarial drug pyrimethamine with various drug and GRAS molecules." CrystEngComm 15 (2013): 2916-2928.

[26]. Chadha, Renu et al. "Multicomponent solids of lamotrigine with some selected coformers and their characterization by thermoanalytical, spectroscopic and X-ray diffraction methods." CrystEngComm 13 (2011): 6271-6284.

[27]. Sanphui, Palash et al. "Acemetacin cocrystals and salts: structure solution from powder X-ray data and form selection of the piperazine salt." IUCrJ 1 (2014): 136 - 150.

[28]. Lu, Jie and Sohrab Rohani. "Synthesis and preliminary characterization of sulfamethazine-theophylline co-crystal." Journal of pharmaceutical sciences 99 9 (2010): 4042-7

[29]. Cheney, Miranda L. et al. "Coformer selection in pharmaceutical cocrystal development: a case study of a meloxicam aspirin cocrystal that exhibits enhanced solubility and pharmacokinetics." Journal of pharmaceutical sciences 100 6 (2011): 2172-81

[30]. Mohammad, Mohammad Amin et al. "Hansen solubility parameter as a tool to predict cocrystal formation." International journal of pharmaceutics 407 1-2 (2011): 63-71

[31]. Sekhon, Bhupinder Singh. "Pharmaceutical co-crystals - a review." (2009).

[32]. Najar, Al and Yasser Azim. "Pharmaceutical Co-Crystals: A New Paradigm of Crystal Engineering." Journal of the Indian Institute of Science 94 (2014): 45-68.

[33]. Duggirala, Naga Kiran et al. "Pharmaceutical cocrystals: along the path to improved medicines." Chemical communications 52 4 (2016): 640-55

[34]. Desiraju, Gautam R. "Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis." Angewandte Chemie 34 (1995): 2311-2327.

[35]. Ross, Steven A. et al. "Engineering and manufacturing of pharmaceutical co-crystals: a review of solvent-free manufacturing technologies." Chemical communications 52 57 (2016): 8772-86

[36]. Fábián, László. "Cambridge Structural Database Analysis of Molecular Complementarity in Cocrystals." Crystal Growth & Design 9 (2009): 1436-1443.

[37]. Luo, Yang- Hui and Baiwang Sun. "Pharmaceutical Co-Crystals of Pyrazinecarboxamide (PZA) with Various Carboxylic Acids: Crystallography, Hirshfeld Surfaces, and Dissolution Study." Crystal Growth & Design 13 (2013): 2098-2106.