JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

CO-CRYSTALS IN PHARMACEUTICAL SCIENCE: AN UPDATED REVIEW

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Abstract : The concept of Co-crystallization discovered almost a century ago, but it has inspired a great interest of researchers in modern day due to their ability to improve physical properties of pharmaceutical active ingredients. Co-crystallization alters the molecular interactions and composition of pharmaceutical materials, and is considered better alternatives to optimize drug properties. Co-crystallization of a drug with a coformer is an emerging approach to improve the performance of active pharmaceutical ingredients (APIs), such as solubility, dissolution profile, pharmacokinetics and stability. This review article presents a comprehensive overview of pharmaceutical cocrystals, including introduction, historical background, preparation methods, applications & some discovery in Co-crystal field. Furthermore, some examples of drug cocrystals are highlighted to illustrate the effect of crystal structures on the various aspects of active pharmaceutical ingredients, such as solubility, bioavailability, meting point. In this review we have summarized recent discoveries in Co-crystal field and some examples of APIs & their coformer with therapeutic activity in tabular form.

IndexTerms- Pharmaceutical Co-crystals, Coformer, Physicochemical properties, IND-SAC Cocrystal, Crystal Engineering.

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1. INTRODUCTION

Co-crystals are the solids (crystalline in nature) which enhance the physicochemical property of drugs or the pharmaceutical products like:- solubility, stability, bioavailability, permeability, dissolution, self-emulsifying drug delivery system (SEDDS).[1] Pharmaceutical co-crystal contain the stoichiometric ratio of an active pharmaceutical ingredient (API) and co-crystal Co-former. The pharmaceutical industry and academic researcher has great interest in designing of pharmaceutical co-crystal due to excellent amplification of physicochemical properties of drug.[2] For Example:-The co-crystals of fluoxetine HCl and benzoic acid; fluoxetine HCl and succinic acid; and fluoxetine HCl and fumaric acid.[3]

The Food and Drug Administration (FDA) defined the co-crystal as "multi-component solid (Crystalline) supramolecular complexes which is made up of two or more components within the same crystal lattice where the components are in a neutral state and they interact via non-ionic interactions".[4] Co-crystals can be divided into two main groups, 1st one is molecular co-crystals and 2nd one is ionic co-crystals. Molecular co-crystals contain two or more different neutral components and are assisting by hydrogen bonds or halogen bonds. Ionic co-crystals contain minimum one ionic component and they are supported by charge-assisted hydrogen bonds or coordination bonds if metal cations are present. [5]

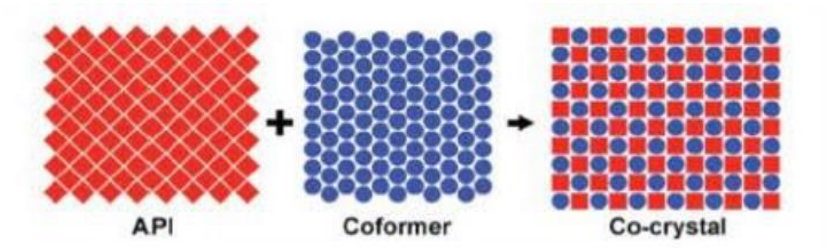

Figure 1. Schematic illustration of co-crystal formation.

2. HISTORICAL BACKGROUND

Co-crystal was first discovered in 1844; however, the structure of co-crystals was only particularized in 1958. [6] The term "cocrystal" and design rules of hydrogen bonding of an organic cocrystal was first reported by Etter. [7,8] The term "cocrystal" was not used until 1967, when it was suggested to describe a complex of hydrogen bonds that is formed between 9-methyl adenine and 1-methyl thymine. This term was spread in the 1990s by Margret Etter. [9] Desiraju was the first researcher who gave the supramolecular synthon concept of hydrogen bond formation in the crystal structures. [10] The debate on cocrystals began in 2003 with a controversial letter by Desiraju explaining his preference for it to be known as "a multi-component system held together by non-covalent interactions. [11] Reply came from Dunitz, who pointed the term included solid solutions, encapsulated compounds or amorphous solids. [12] Aakeroy proposed strict compliance with three criteria for the definition of a cocrystal :-The neutrality of the ingredients, The solid state of the components in ambient conditions and uniformity of the crystalline material and the stoichiometry of the components. [13] Disagreement comes from Andrew Bond and he suggests the term "multi-component molecular crystals" to explain a crystalline material whose component is either solid or liquid in ambient conditions. [14] In 2004 pharmaceutical cocrystal was described as a pronounced class of novel & crystalline materials which can alter the physicochemical properties of active pharmaceutical ingredients and this was the beginning of the new era of crystal engineering and cocrystal formation. [15]

3. METHODS FOR PRODUCTION OF CO-CRYSTALS: Production of cocrystal routes can classified as:-

1) Solid state method.
2) Solution based method.
3) Supercritical fluid method.

Solid-state or solution based. Solid-state methods can be differentiated as methods using very little or no solvent, with solution based methods representing production routes that involve a large excess of solvent. [16]

3.1 SOLID STATE METHOD

Solid state method is one of the type of production method of cocrystal preparation in which very little amount or no solvent is used during production.
The cocrystal forms spontaneously through direct contact or grinding with the higher energy inputs. They are reasonable alternatives to solution-based cocrystallization methods, which may generate environmental hazards due to the high solvent consumption. So many pharmaceutical cocrystals have been synthesized by solid-based methods. [17,18,19,20]
Further it is classified in to Subcategories:-

1. Contact formation.
2. Solid state grinding.
3. Extrusion.

3.1.1 CONTACT FORMATION

In contact formation it was found that the interactions between the APIs and coformer could spontaneously occur after "soft" mixing of the raw materials. [21] The spontaneous formation of cocrystals by mixing of pure active pharmaceutical ingredients and coformer under the controlled atmospheric environment. [22] It was found that there is interactions between the active pharmaceutical ingredients and coformer could spontaneously occur after soft mixing of the raw materials. [23]

Mechanism:-
The possible mechanisms explain the spontaneous crystallization by contact are vapor diffusion of the two solids moisture sorption, eutectic phase formation, amorphization and long-range anisotropic molecular migration. High humidity, high temperature and smaller particle sizes of raw materials could facilitate cocrystal formation. [24,25]
Ibrahim *et al.* studied the effect of the particle size of starting materials by spontaneous cocrystallization of urea and 2-methoxybenzamide (2-MB). It has shown that smaller particle size distributions lead to faster Cocrystal formation. A quick increase in cocrystallization rate was observed in the case of the small particle size distribution (20−45 μm) , where no buried eutectic or amorphous intermediate phase was detected. [26] Mechanism of contact formation in the presence of moisture at deliquescent conditions consists of three stages of (1) moisture uptake, (2) Dissolution of reactants, and (3) cocrystal nucleation and Growth. [27]

3.1.2 SOLID STATE GRINDING.

Solid state grinding methods have been used successfully to produce cocrystal powder samples. Two pattern are practiced 1st one is neat (dry) grinding and 2nd Liquid assisted grinding. Neat grinding involves the combination of the target molecule and coformer in their dry solid state with the application of pressure manually (mortar and pestle) or mechanical (automated ball mill) means. Dry Grinding is pronounced from melt crystallization as the solid starting materials are not expected to melt during grinding. The temperature achieved during grinding is monitored to ensure the same and will often be reported. Two Sulphathiazole:carboxylic acid cocrystals were prepared by researchers by Grinding stoichiometric equivalents of sulphathiazole with the Required carboxylic acid for 90 min in a Retch mixer mill at a 25 Hz frequency with the temperature not allowed to exceed 37 °C. [28]

It is further classified as:-

1. Neat grinding
2. Liquid assisted grinding

3.1.2.1 NEATGRINDING

Neat grinding is one of the method of Solid state grinding which include molecular diffusion and the formation of a eutectic and or a transient amorphous intermediate.[29] Molecular diffusion is a process in which a mobile solid surface is formed by grinding which causes vaporization or energy transfer. Hence high vapor pressure (range from10^{-1} to 10^{-4} mm Hg) of the solid-state components (at least one of the components) is essential in the neat grinding process.[30] Thus the cocrystals could be formed on the crystal surface due to gas phase diffusion. Furthermore, grinding can offer energy for surface diffusion and migration to remove the produced cocrystal from the reactant surface to create a fresh surface for more cocrystallization.[31] The step-by-step process of 2:1 nicotinamide–suberic acid cocrystal formation by neat grinding was observed by Karki *et al*.[32] and Halasz *et al.*[33]

3.1.2.2 LIQUID ASSISTED GRINDING

It is one of the type of solid state grinding method for the production of cocrystals. Liquid assisted grinding involves the addition of a solvent, typically in a very small amount, to the dry solids prior to the initiation of milling. The solvent has a catalytic role in assisting Cocrystal formation and should persist for the duration of the Grinding process. More efficient cocrystal formation is Suggested for liquid assisted methods than with neat methods, With a tendency for the cocrystal formation kinetics to increases as the solvent added to the grinding media is increased.[34]
For generating highly water-soluble cocrystals of a poorly soluble nutraceutical Hesperetin (HESP), the solvent Drop grinding cocrystallization method was applied. Chadha *et al*. used different coformers such as picolinic acid (PICO),Nicotinamide (NICO), and caffeine (CAFF). Their research has led to optimization of the pharmacokinetic properties by improving the bioavailability. Also, the dissolution of prepared Cocrystal in an aqueous buffer showed that the hesperetin concertation is around 4−5 times higher than that of the pure one.[35]

3.1.3 EXTRUSION

It is of two types Hot melt extrusion and twin screw extrusion.

3.2 SOLUTION BASED METHOD

This method is used to produce cocrystals which involved ternary phase (APIs, Coformer & Solvent). The perfect state of cocrystal is supersaturated while the reactants (API and coformer) are saturated or unsaturated under the experimental conditions. Hence the degree of supersaturation with respect to cocrystal in solution is the Important parameter for cocrystallization and can be adjusted by the concentrations of API and coformer.[36]
Further it is classified as:-
1.Solvent evaporation method.
2. Cooling Crystallization.
3. Reaction Crystallization.
4. Isothermal Slurry conversion.

3.2.1 SOLVENT EVAPORATION METHOD

It is the most frequent method by which we can prepare cocrystals and it is typically used to synthesis high-quality cocrystals (single-crystal) that suitable for the structural analysis by single-crystal X-ray diffraction technique.[37] The technique involves the nucleation and growth of a cocrystal form a solution of both coformers in a solvent with supersaturation provided by removal of the solvent from the solution via evaporation. Individual cocrystals or the bulk crystal sample should be harvested before the solution evaporates to dryness to ensure recovery of a clean crystal(s). A slow rate of evaporation is usually desired so as to ensure the formation of a small number of larger crystals as opposed to a high number of smaller crystals.[38]
The formation of cocrystals with the solvent evaporation method was shown by Chow *et al.* for ibuprofen–nicotinamide and flurbiprofen–nicotinamide cocrystals which exhibited higher intrinsic dissolution rates compared to the corresponding profens. Furthermore, the synthesized cocrystals shows high tabletability and less absorbed humidity as compared to the individual precursors.[39]

3.2.2. COOLING CRYSTALLIZATION

The cooling cocrystallization depend up on the temperature-dependent change in solubility to achieve cocrystal formation & the cooling crystallization is employed on an industrial level for a large number of organic molecules in the pharmaceutical and allied industries.[40]

Mechanism:-
Initially the coformers are dissolved in a solvent and then supersaturation is achieved via reducing the temperature of the solution. [41,42]The operating region for producing a specific cocrystal has to be determined based on the relative stability of all the crystal forms and their relative nucleation and growth kinetics.[43]

3.2.2 REACTION CRYSTALLIZATION

Reaction cocrystallization was used to produce cocrystals of carbamazepine:saccharin by combining individual feed solutions of either of the starting Materials.[44] The method was informed by the ternary phase diagram and illustrated a robust operating range for cocrystal formation and demonstrated the expected relationship between supersaturation and induction time. Formation of a Carbamazepine: nicotinamide cocrystal was also done by reaction cocrystallization under ambient conditions.[45]

3.2.4 ISOTHERMAL SLURRY CONVERSION

Slurry cocrystallization was first proposed as an effective cocrystal screening technique by Zhang *et al*.The process starts with a suspension of either or both of the coformer crystals in a small amount of solvent, creating a slurry. As the stable cocrystal nucleates and grows, the single component crystals dissolve in to the solution-mediated polymorphic transformation process.[46]Ahuja *et al.* reported three new cocrystals (sulfamethazine–nicotinamide, sulfamerazine–salicylamide, and sulfamerazine–anthranilic acid) using the slurry cocrystallization technique. The authors reported that the rate of cocrystal formation was higher when microwave was used as the heating. The major advantage of the method is that the cocrystals can be generated even without the knowledge of the required stoichiometric ratio of the cocrystal.[47]

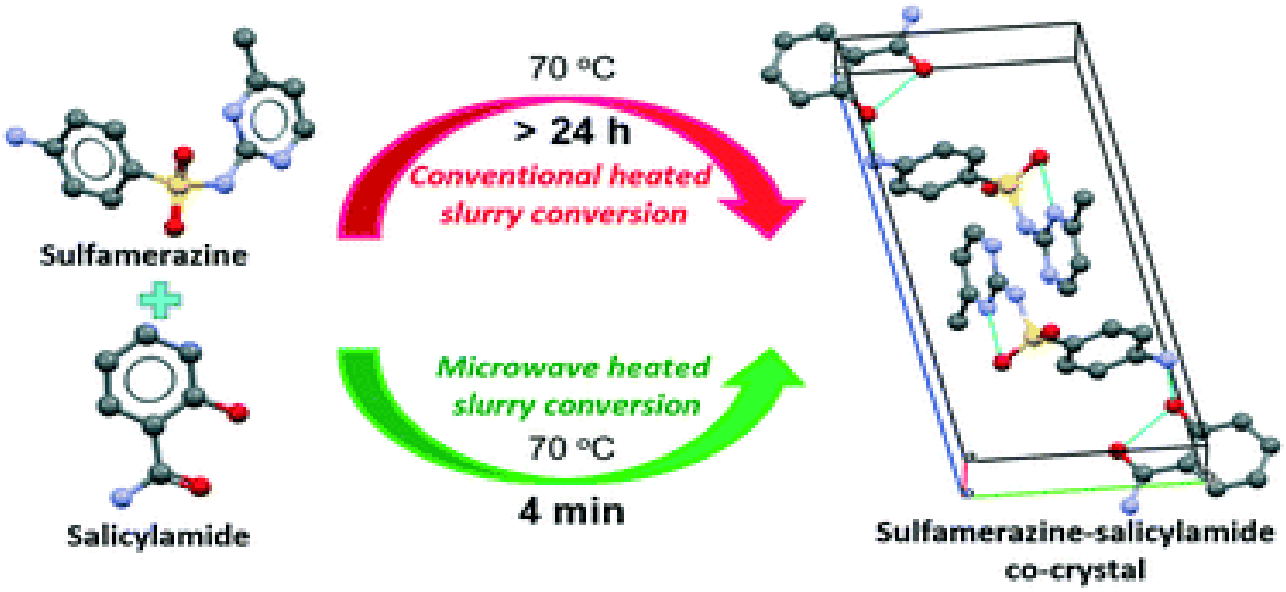

Figure 2:- Production of Cocrystal by isothermal slurry conversion.[48]

The slurry conversion method typically requires a greater amount of starting materials and will incur some material loss due to residual solubility in the solvent, it is considered one of the most promising screening techniques due to its high efficiency.[49]

3.3 SUPERCRITICAL FLUID METHOD

Supercritical fluid method is one of the way to produce Cocrystal and it is used to prepare Cocrystal with high purity. The supercritical fluid is used as solvent, anti-solvent or Cosolvent in this production method.[50]

Mechanism:-
In this method a fluid (most commonly—carbon dioxide (CO2)) is pressurized and heated above its critical point, thereby creating a supercritical phase. Beyond the critical point, fluid has the diffusivity of gas and the solvating property of liquid. The supercritical fluid is then added to the solution, containing a solvent in which the supercritical fluid is miscible. This addition causes a reduction in solubility and crystal nucleation. The low solubility of many solutes in supercritical CO2 and the low critical conditions of CO2 make it an excellent choice for the supercritical crystallization process. [51]
The supercritical fluid enhanced atomization (SEA) process was used to produce cocrystals of six different active pharmaceutical ingredients (APIs): indomethacin, theophylline, caffeine, sulfamethazine, aspirin and carbamazepine. Micrometric cocrystals using the FDA-approved sweetener saccharin (SAC) as a cocrystal former were produced from ethanol solutions using supercritical CO2 as the atomization enhancing fluid. [52]

4. SOME EXAMPLES OF OHARMACEUTICAL CO-CRYSTALS

4.1 INDOMETHACIN-SACCHARIN COCRYSTAL

IND-SAC cocrystal is obtained by solid state and liquid-assisted cogrinding methods. Various cocrystal formers, including saccharin, were used in endeavors to obtain indomethacin cocrystals by slow evaporation from a series of solvents. The melting point of crystalline phases was determined. [53]
The IND–SAC cocrystals were obtained from ethyl acetate. Physical characterization shows that the IND–SAC cocrystal is unique in thermal, spectroscopic and X-ray diffraction properties. The cocrystals were obtained in a 1:1 ratio with a carboxylic acid and

imide dimer synthons. The dissolution rate of IND–SAC cocrystal system was considerably faster than that of the stable indomethacin γ-form. The cocrystals were non-hygroscopic and it was associated with a significantly faster dissolution rate as compared to indomethacin (gamma-form). [54]

The improved aqueous solubility of the cocrystals improve the bioavailability of Indomethacin. Thus, the cocrystals are a feasible alternative solid form that can improve the dissolution rate and bioavailability of poorly soluble drugs.
1. In-vitro dissolution profiles
2. Intrinsic dissolution profiles for different formulations were analyzed.

The AUC and Cmax for IND–SAC cocrystals were consistently higher than those for PhyMix (ANOVA, $P < 0.05$) . This data confirms that the IND–SAC cocrystals offer significantly improved in-vivo exposure in dogs compared to Indomethacin. Which also confirms that improved bioavailability correlates well with the higher aqueous solubility and dissolution rate of the cocrystal.[56]

4.2 MELOXICAM-SALISYLICACID COCRYSTAL

Meloxicam is a non-steroidal anti-inflammatory drug which can selectively inhibit cyclooxygenase 2 (COX-2) due this inhibition no prostaglandin synthesized, (Due to this those substance are not synthesized which causes inflammation,) Meloxicam has high anti-inflammatory activity however, the low solubility and slow dissolution rate which slow down its role in rapid pain relief. But we can increase the pharmacological action by increasing their solubility & dissolution by Cocrystal techniques.[57]

5. APPLICATION OF CO-CRYSTAL

5.1 SOLUBILITY

The solubility of any APIs is the most important characteristics for their absorption . Solubility can also decide how much amount can be absorbed through GIT. So many APIs has low solubility due to which less absorption thorough GIT but it can be overcome by Cocrystallization method for example:- IND-SAC Cocrystal. A cocrystal will have a different solubility as compared to either of the starting materials due to the altered underlying crystal structure. [58] Zheng *et al.* reported improved solubility of resveratol by crystallization with 4-aminobenzaamide and isoniazid.[59]
Rodriguez-Hornedo has also extensively addressed cocrystal solubility and has proposed the concept of a solubility product, Ksp, which takes into account the relative concentrations of both cocrystal formers during cocrystal dissociation in a solvent.[60]

$$Ksp = [A]^a [B]^b$$

When activity coefficients are taken as unity, a & b refers as the stoichiometric number of molecules of a/b in the cocrystal. The solubility product shows the strength of cocrystal solid state interactions of the drug and ligand relative to interactions with the solvent and is also correlated to solubility, with a higher Ksp indicating higher cocrystal solubility. [61]

5.2 BIOAVAILABILITY

So many drugs has less bioavailability due many reasons in which solubility is also a reason for their fluctuation in bioavailability by Cocrystallization we can enhance their solubility & enhance the bioavailability of respective drug. Cocrystals have potential to enhance the delivery and clinical performance of drug/medicine by modulating drug solubility, pharmacokinetics, and bioavailability. [62] The approach of cocrystallization is particularly important in situations where the cocrystal transforms rapidly to a low-solubility form of the drug and is unable to maintain desired solubility levels necessary to ensure optimal absorption. Childs *et al.* improved the solubility and bioavailability of a danazol:vanillin cocrystal by using an appropriate formulation containing a combination of cocrystal, a solubilizer (1% vitamin E-TPGS (TPGS)), and a precipitation inhibitor (2% Klucel LF Pharm Hydroxypropylcellulose). [63] This formulation resulted in a high improvement in the bioavailability of the cocrystal by over 10 times compared to the poorly soluble danazol polymorph. [64]

5.3 MELTING POINT

So many APIs are in liquid form at room temperature due to their low melting point but cocrystal has ability to alter their melting point so that it can persist in solid for at room temperature. Melting point is the physical property of solids substance, which is used to determine the purity of the product with sharp melts and narrow ranges. [65]
Examples:-
Propofol is used to maintain as well as induce the general anesthesia and sedation. It is formulated as an oil-in-water (O/W) because it has low Melting point (18 °C), which results in associated problems like instability pain on injection and hyperlipidemia. McKellar et al. adopted cocrystal approach to obtain a novel solid form of Propofol using isonicotinamide as the coformer. The Propofol–isonicotinamide Cocrystal is a stable solid at room temperature due to the increased melting point (50
°C) higher melting point than that of the starting material. [66]

5.4 MULTIDRUG COCRYSTAL

Multidrug Cocrystals are systems which is used for combining multiple active pharmaceutical ingredients (APIs) in a single delivery system. The need to target multiple receptors for effective treatment of complex disorders like HIV/AIDS, cancer, and diabetes in addition to the increasing the demand for facilitating the reduction of drug manufacturing costs are the two main reasons for this growing trend. [67]

Multidrug Cocrystal offers important advantages as compared to the pure drug components, such as enhanced solubility and dissolution of at least one of the components, enhanced bioavailability. [68,69,70]

The main techniques of cocrystal synthesis is used for preparing the multidrug cocrystal (MDCs). These techniques are as follows solvent evaporation, distillation, neat and liquid-assisted grinding, slurry reaction, melting as well as cooling crystallization. Scale-up techniques such as spray-drying, [71] hot melt extrusion, [72] twin screw extrusion, [73] and high shear granulation have been used for scale-up production of cocrystals.[74]

Table No. 1: Various research in pharmaceutical co-crystals

S. No.	Researcher/year	Title of Research	Findings	Reference No.
1	Zimeng *et al. /2023*	Research Progress of Plant Active Ingredients in Pharmaceutical Cocrystal.	The effects of cocrystal in various poorly soluble herbal active ingredients of medicinal plants on their physicochemical properties and biological properties and provides references for the application of pharmaceutical cocrystal in poorly soluble active compounds of medicinal plants.	75
2	Fatima *et al.* / 2022	Glibenclamide–malonic acid cocrystal with an enhanced solubility and bioavailability.	Enhancement of Physicochemical property of Galbenclamide through Cocrystallization.	76
3	Khushbu *et al.* /2021	Improved pharmaceutical properties of ritonavir through co-crystallization approach with liquid-assisted grinding method	Improve Solubility & Bioavailability of Ritonavir by Cocrystallization (Liquid assisted grinding method).	77
4	De Almeida *et al.* /2020	Cocrystals of ciprofloxacin with nicotinic and isonicotinic acids: mechanochemical synthesis, characterization, thermal and solubility study.	Nicotinic acid (NA) and isonicotinic acid (INA) were also used as coformers with CIP.	78
5	Gajda *et al.* /2019	Continuous, One-step Synthesis of Pharmaceutical Cocrystals via Hot Melt Extrusion from Neat to Matrix-Assisted Processing.	a twin-screw extruder could be used to ensure a proper homogeneous mixture of components.	79
6	zhang *et al.* /2018	A novel cocrystal composed of CL-20 and an energetic ionic salt.	A novel nitroamine/energetic ionic salt cocrystal explosive containing CL-20 and 1-AMTN in a 1 : 1 molar ratio is presented.	80
7	Hu *et al.* /2017	Syntheses, structure characterization and dissolution of two novel cocrystals of febuxostat.	Increase in aqueous solubility from 7.5 mg/L febuxostat to 571 mg/L for a febuxostate:arginine cocrystal	81
8	Chaw *et al.* /2017	Stability of Pharmaceutical Cocrystal during Milling.	The solid-state grinding method is better than solvent-based methods for the screening of cocrystals. But sometimes solid-state grinding induces phase transformations in pharmaceutical cocrystals.	82
9	Hiendrawan *et al.* / 2016	Physicochemical and mechanical properties of paracetamol cocrystal with 5-nitroisophthalic acid.	Stability of the cocrystal was assessed by storing them at 40 °C/75% RH for one month. Compared to PCA, the cocrystal displayed superior tableting performance.	83
10	Karimi-Jafari *et al.* / 2016	Cocrystals to Facilitate Delivery of Poorly Soluble Compounds Beyond-Rule-Of-5.	Definition of Cocrystal with respect to stoichiometric ratio.	84
11	Du *et al.* / 2016	Raman and terahertz spectroscopic investigation of cocrystal formation involving antibiotic nitrofurantoin drug and coformer 4-aminobenzoic acid.	cocrystal formers bear functional groups that have the ability to form hydrogen bonds.	85
12	Shete *et al.* /2015	Cocrystals of itraconazole with amino acids: Screening, synthesis, solid state characterization, in vitro drug release and antifungal.	Synthesize Itraconazole Cocrystal with amino acid which shows Depression in melting point.	86
13	Surov *et al.* /2014	Pharmaceutical Cocrystals of Diflunisal and Diclofenac with Theophylline	Pharmaceutical cocrystals of nonsteroidal anti-inflammatory drugs diflunisal (DIF) and diclofenac (DIC) with theophylline (THP) were obtained,	87
14	Thakuria *et al.* /2013	The origin of low solubility issue of drugs is a high-throughout screening and combinatorial chemistry program	The solubility profile has to be improved without altering the chemical identity and pharmacological role of the molecule.	88

15	Feng *et al.* /2012	Structure of Entresto.	The crystal structure of Entresto® was studied	89
16	Qiao *et al.* / 2011	Pharmaceutical cocrystals: an overview.	An important parameter in the investigation of poorly soluble drugs such as BA is solubility, parameter that can be greatly improved through cocrystallization.	90
17	Kavuru *et al.*/ 2010	Cocrystal Formation of Betulinic Acid and Ascorbic Acid: Synthesis, Physico-Chemical Assessment, Antioxidant, and Antiproliferative activity.	Ascorbic acid also acted as cocrystal former for several zwitterion structures (i.e., sarcosine, nicotinic acid, betaine) leading to cocrystals that exhibit carboxylate-hydroxyl supramolecular heterosynthons	91
18	Faujan *et al.* /2009	Cocrystal Formation of Betulinic Acid and Ascorbic Acid: Synthesis, Physico-Chemical Assessment, Antioxidant, and Antiproliferative Activity	Betulinic acid is a pentacyclictriterpene of lupan skeleton with a wide range of pharmacological activities like Anti-tumor & Anti-inflammatory.	92
19	Ibrahim *et al.* /2008	The effect of particles size.	The effect of the Particle size of starting materials on spontaneous cocrystallization of urea and 2-methoxybenzamide (2-MB).	93
20	Mukharjee *et al.* /2004	Cocrystal Formation of Betulinic Acid and Ascorbic Acid: Synthesis, Physico-Chemical Assessment, Antioxidant, and Antiproliferative activity.	Betulinic acid is a pentacyclictriterpene of lupan skeleton with a wide range of pharmacological activities like anti-angiogenic.	94

Table No. 2: Examples of APIs and their coformer with therapeutic activity

S. No.	Therapeutic activity	APIs	Coformer	Reference No.
1	Arthritis	Diacerein Hesperetin	Isonicotinamide, Nicotinamide, Theophylline. Picolinic acid, Nicotinamide, Caffeine.	95 96
2	Anti-diabetic	Glibenclamide	Hippuric acid, Nicotinic acid, Theophylline, Succinic acid.	97
3	Antibacterial	Urotropine Enoxacin	Syringic acid, trans-Cinnamic acid, 4-[4-(Trifluoromethyl) phenoxy] phenol. Malonic acid, Oxalic acid, Fumaric acid.	98 99
4	Anti-cancer	5-flurouracil Tegafur	Gentisic acid, 3,4-Dihydroxybenzoic acid, 4-Aminopyridine. Syringic acid.	100 101
5	Anti-hemolytic	Chrysin	Cytosine, Thiamine hydrochloride.	102
6	Hepatoprotective	Isoniazid Pyrazinamide Riluzole	Syringic acid. Quercetin . Syringic acid .	103 104 105

6. CONCLUSION

In the past decade, cocrystal engineering has become a promising approach to improve the performance of drug substances by modifying their undesired physicochemical properties. In conclusions, this review provides detailed description and examples about preparation methods, physicochemical properties and various applications of cocrystals. More cocrystal-based drug products are believed to be commercially available for patients in the future. Two beneficial table provide us knowledge of recent discoveries in Cocrystal field & some disease, APIs & their Coformers.

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