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Pharmaceutical Cocrystals – A Review

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Abstract: Design and synthesis of pharmaceutical Cocrystals have received great interest in the recent years. Cocrystallization of drug substances offer a tremendous opportunity for the development of new drug products with superior physical and pharmacological properties such as solubility, stability, hydroscopicity, dissolution rates and bioavailability. This short review summarizes this highly topical field, covering why the topic is of interest in pharmaceutical formulation, the definitions and practical scope of cocrystals, cocrystal preparation and characterization, comparison of different (traditional and novel) methods for cocrystal formation and implications for regulatory control and intellectual property protection. Traditionally, cocrystal can be prepared by solvent evaporation method, grinding, and slurry method, but, every method has limitation for certain condition. The current trend for Cocrystal formation uses the sophisticated method such as hot-melt extrusion method, spray drying method, supercritical fluid technology and the newest, and laser irradiation method. Development of new method is not only to overcome the limitation of traditional Cocrystallization methods but also to generate a simpler step and continuous process for the production of Cocrystal product. This article gives a brief explanation of each method that can be used to generate pharmaceutical Cocrystals.

Key words: 1. Pharmaceutical Cocrystals (PC), 2.Cocrystallization, 3.Active Pharmaceutical Ingredient (API), 4. Generally recognized as safe (GRAS), 5. Cocrystal former (CF), 6. Novel methods, 7. Traditional methods

1. Introduction

Solubility and dissolution rates are key factors in determining the efficacy as well as activity of a drug. Early drug discovery studies were based on traditional remedies or serendipitous discoveries. The last two decades, however, have demanded a rational design and synthesis of drugs as a result of the emergence of new diseases and the development of drug. Many new drug targets have been identified and potential drug molecules synthesized and analyzed for efficacy employing advanced techniques such as high-throughput screening and combinatorial chemistry. The lead molecules discovered utilizing these screens is increasingly larger and more lipophilic. So, Need of today's era is to decrease problems regarding solubility and permeability of lipophilic drugs with different methods. Multi-component crystals like solvates, hydrates, Cocrystals, salts contribute key role in the design of new solids mainly in the pharmaceutical area[1-4].

Cocrystals:

According to the FDA's latest definition, "cocrystals are crystalline materials composed of two or more different molecules, typically drug and cocrystal formers ('coformers'), in the same crystal lattice. Pharmaceutical Cocrystals have opened up opportunities for engineering solid state forms beyond conventional solid-state forms of an active pharmaceutical ingredient (API), such as salts and polymorph. This includes modification of drugs to alter physical properties of a drug, especially a drug's solubility without altering its pharmacology effect. FDA also added "Cocrystals can be tailored to enhance drug product bioavailability and stability and to enhance the processability of

APIs during drug product manufacture.The first Cocrystal synthesized was quinhydrone which is a 1:1 cocrystal between benzoquinone and hydroquinone[5-6].

Comparison of Cocrystal and Salt

Cocrystallization has provided pharmaceutical industry advantages in at least two ways as compared to salt formation. (1) According to the concept of Cocrystallization, all types of molecules can form Cocrystals, including weakly ionizable and non-ionizable APIs, which is considered to be a better technique in optimization of the physical properties because salt formation is either limited or has no scope at all in such APIs (2) In case of salt formation due to toxicological reasons only or so acidic or basic counter-ions are explored in a typical API salt whereas in case of Cocrystal screening there are large number of potential Cocrystal co-formers which are free from toxicological constraints. The US Food and Drug Administration has maintained a list of substances (e.g., FDA's GRAS list–a list of substances "generally recognized as safe") which is numbering in thousands and can be used as potential co former for Pharmaceutical Cocrystals[7-8].

Importance and Design of Pharmaceutical Cocrystal

Most of the drugs are administered orally in solid form (80%), which is generally considered as convenient and usually the safest dosage form. About 40% of them have low solubility; infact and nearly 80–90% of drug candidates in the R&D pipeline have low solubility problem, which is alarming and could lead to failure of these drugs in clinical trials. The Pharmaceutical Cocrystals (PCs) have given a new paradigm in the solid-state modification, owing which the pharmaceutical industry is seriously making efforts on its utility[9-12]. As Cocrystal research has expanded so it has the range of application areas for physical property manipulation through Cocrystal formation. Improvements in solubility, stability, bioavailability, dissolution rate, melting point, hydroscopicity, compressibility, bulk density, friability and mechanical properties, have been well documented and emerging applications such as taste masking and intellectual property extension are being explored. Research in Cocrystal structure and applications has shown an exponential increase in the last decade, evident in the number of Cocrystal structures deposited in the Cambridge Structural Database and Cocrystal related patent applications [13-15]. In light of this, it is surprising that Cocrystal preparation methods have remained, until relatively recently, largely poorly defined. Limited research attention has been directed specifically at Cocrystal preparation. In this review, various techniques which are often utilized for Cocrystallization are discussed including an array of solid state, mechano-chemical and liquid assisted techniques. Additionally, a number of novel methodologies such as freeze – drying, micro fluidic and ultrasound assisted cocrystallization are evaluated for their potential in Cocrystal synthesis.

Design of Cocrystals:

The crystal engineering experiment usually involves the Cambridge Structural information (CSD) survey followed by the experimental work. Cocrystals designed on the principal of the supramolecular synthesis; it provides a strong approach for proactive discovery of novel pharmaceutical solid phases. Cocrystals incorporates multiple elements in given ratio quantitative relation, wherever completely different molecular species move by chemical element bonding and by non-hydrogen bonding. The use of chemical element bonding rules, synthons and graph sets could assist within the style and analysis of Cocrystal systems. Normally prediction of whether or not Cocrystallization can occur isn't however attainable and should, at present, be answered through empirical observation. Cocrystal formation could also be rationalized by thought of the bond donors and acceptors of the materials that area unit to be Cocrystallized and the way they may move. Etter and associates projected the rules to facilitate the deliberate style of hydrogen-bonded solids. All smart nucleon donors and acceptors area unit employed in chemical element bonding, membered ring unit chemical element bonds kind in preference to unit chemical element bonds, the most effective nucleon donor and acceptor remaining when unit chemical element-bond can form unit hydrogen bonds to 1 another (but not all acceptors can essentially move with donors). These observations facilitate to handle the difficulty of competitive bond assemblies ascertained once employing a specific Cocrystallizing agent. A detailed understanding of the supramolecular chemistry of the functional groups present in a given molecule is the prerequisite for designing the

Cocrystals because it facilitates the selection of the suitable Cocrystal former. Supramolecular synthons that can occur in common functional group in order to design new Cocrystals and certain functional groups such as carboxylic acids, amides and alcohols are particularly amenable to formation of supramolecular heterosynthon[16-18].

2. Different Strategies of Cocrystals Formation:

Till date, completely different strategies are reported for the preparation of Cocrystals by the researchers. Few ancient strategies supported the answer and grinding was reported for the synthesis of Cocrystals. Cocrystals can be prepared by solvent and solid based methods[19]. Differing kinds of strategies like solvent evaporation, crystallization technique, anti-solvent addition, suspension conversion methodology and reaction crystallization methodology are employed. Some new rising strategies used for the formation of Cocrystals area unit ultrasound aided methodology, critical fluid atomization technique spray drying technique and hot soften extrusion technique. In reported method there is little consistency in the application of different preparation methods or even in the terminology used to describe the same. Details such as solvent choice, concentration of the target molecule/co former, equilibration time, and the recovery process are often not provided. This makes it difficult to repeat or compare cocrystal preparation methods and must be confusing to a newcomer to this research area. The objective of this review is to systematically describe all reported cocrystal preparation routes and applications in a single location in an effort to standardize progress achieved to date in this evolving area.

2.1. Solid State Methods:

Solid state formation of pharmaceutical cocrystals has attracted significant interest over the last few years due to the advantages accompanied with these processes. Some of their critical features are that cocrystals are synthesised in the absence of solvents or by using negligible amounts, the excellent purity and quality, the high throughputs and the fast processing times in some occasions. Solid-based technique generally includes solid phase grinding, melt extrusion, and melts crystallization. In this method, API and coformer are melted and mixed together, resulting in the cocrystal formation in a fixed stoichiometric ratio. It is basically not suitable for thermolabile moiety, but it is easy, scalable, and continuous process. The solid based methods involve net grinding; solvent-assisted grinding and sonication (applied to either to wet or dry solid mixtures) 80 to 85° C. The spontaneous formation of cocrystals via mixing of pure API and co former under a controlled atmospheric environment has been reported. However, in some cases, brief grinding of pure components individually before mixing has been done. It was reported that the Cocrystallization rate in the case of premilled reactants was markedly faster than that of unmilled reactants Moreover, higher cocrystallization rates have been reported for the same system at higher temperatures and relative humidity, regardless of the mechanical activation. The mechanism of Cocrystallization 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 (Figure 1) [20].

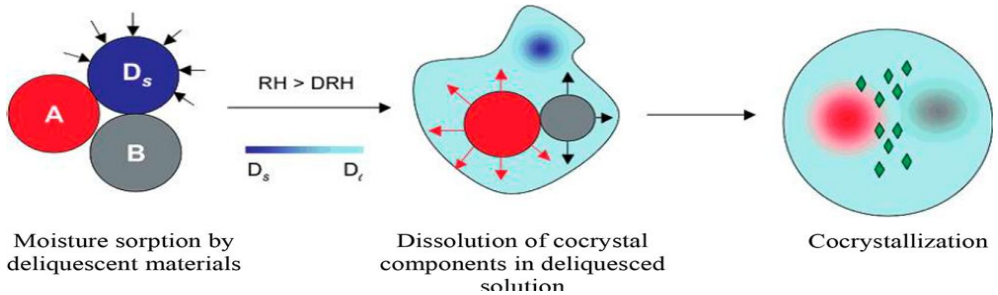

Figure 1. Illustration of the moisture uptake process leading to deliquescence, reactant dissolution, and cocrystal formation. A and B are cocrystal reactants, Ds is solid deliquescent additive, and Dl is the solution phase created by deliquescence at relative humidity greater than deliquescence relative humidity. (Reprinted with permission from ref 20. Copyright 2007 American Chemical Soceity.)

2.1.1. Contact Formation. The spontaneous formation of cocrystals via mixing of pure API and co former under a controlled atmospheric environment has been reported. In this method, no mechanical forces are applied during cocrystallization. However, in some cases, brief grinding of

pure components individually before mixing has been done. It was shown that the cocrystallization rate in the case of premilled reactants was markedly faster than that of unmilled reactants. Moreover, higher cocrystallization rates have been reported for the same system at higher temperatures and relative humidity, regardless of the mechanical activation. [20]

2.1.2. Solid State Grinding. Solid state grinding methods have been used successfully to generate cocrystal powder samples. Two formats are practiced: neat (dry) grinding and liquid assisted grinding. Neat grinding involves the combination of the target molecule and coformer in their dry solid forms with the application of pressure through manual (mortar and pestle) or mechanical (automated ball mill) means. Dry grinding is distinct from melt crystallization as the solid starting materials are not expected to melt during grinding. The temperature achieved during grinding is often monitored to ensure the same, and will often be reported. There is an efficiency associated with solid state grinding, relative to solution based methods, in that yield is not lost to the solvent due to solubility. Issues with dry grinding can include failure to form a cocrystal, incomplete conversion to the cocrystal, and crystalline defects with possible generation of some amorphous content. Incomplete conversion to the cocrystal, resulting in a mixture of cocrystals and excess starting material in the product, is not desirable as it requires the use of addition purification steps to yield a pure cocrystal product [21].

2.1.3. Liquid assisted grinding. This method 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 increase as the solvent added to the grinding media is increased, but as yet this is inconclusive. The liquid component is thought to accelerate reaction kinetics by wetting the solid surface. Liquid assisted grinding has been reported in a number of different formats.

2.1.4. Hot Melt Extrusion Technique: In hot melt extrusion technique, the Cocrystals area unit ready by heating the drug and co-formers with intense intermixture that improved the surface contacts while not use of solvent. The restrictions of this methodology embrace each coformer and API ought to be compatible in liquefied kind and not used for unstable medicine. Hot-Melt Extrusion method is a method that combined cocrystal formation and drug-formulation process, exhibit a simpler way to manufacture a drug product, involve not only drug and coformer, but also an inert matrix. The heat that used for HME method is set at a specific temperature, where only the matrix is softened/ melted. Cocrystal formation using HME method has an analogous mechanism with liquid assisting grinding method, where a catalysing agent to improve cocrystal formation played by softened/melted matrix instead of solvent. Suitable matrices for HME method must have several qualities; (1) have low glass transition (Tg) temperature, lower than melting point of cocrystal to ensure a lower processing temperature, (2) have limited non covalent interaction with drug or conformer, (3) exhibit a rapid solidification step [22].

2.2 Solution Based Methods.

A variety of methods exist to Cocrystallize from solution, and each will be discussed in the subsequent section. The driving force for crystallization is super saturation. With a cocrystal system, there are two concentrations to consider, that of the target molecule and that of the co former. The concentrations of both relative to the solubility of the cocrystal (most accurately expressed in terms of target molecule and co former) dictate the super saturation for Cocrystallization. A eutectic point will exist where at one fixed solution concentration, a mixture of Cocrystal and the target molecule is the stable solid phase for the system; a second eutectic point exists for a mixture of the Cocrystal and co former. The eutectics represent solution minima where the solvent content is at its lowest value, meaning solubility is at its highest value. The cocrystal will only be stable, less soluble than target molecule or co former, at concentrations lying between the eutectic points. Knowledge of this concentration range, termed the Cocrystal operating range, is key to designing successful solution Cocrystallization. Operation outside of this range can fail to yield a cocrystal or can yield a Cocrystal/target molecule or Cocrystal/co former mixture in the solid phase.The solubility of a cocrystal system is most accurately represented in a ternary phase diagram (TPD). This triangular diagram illustrates the solubility of the solid phases in a given solvent at a fixed temperature and

pressure and also identifies regions of stability for different solid phases in the system[23]. Figure 2 shows the typical ternary phase diagrams which describe the three-phase behavior of a multicomponent system: API, co former, cocrystal, and solvent. It is also able to predict the pathway of cocrystal formation.

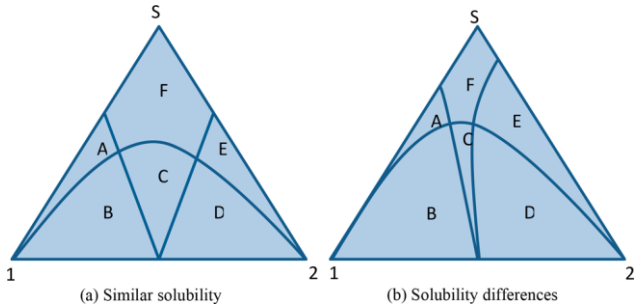

Figure 2. Schematic representation of isothermal ternary phase diagram. (a) Similar solubilities between API and coformer (1 and 2) in solvent S and (b) different solubility's of 1 and 2 in S. Region A, component 1 and solvent; B, component 1 + cocrystal; C, cocrystal; D, component 2 + cocrystal; E, component 2 and solvent; F, solution. (Modified from ref [23]. Copyright 2013 Cell Press.)

2.2.1. Slurry Crystallization: Slurry crystallization is that the method during which suspension is ready by addition of various solvents within the mixture of API and appropriate co-formers. The solvent is decanted and therefore the solid material is dried and characterized by completely different strategies for analysis. This methodology is chosen for the preparation of Cocrystals once the drug and co former ought to be stable within the solvent[15].

2.2.2. Evaporative Cocrystallization. Evaporative cocrystallization is a common method of generating Cocrystals, typically employed for generating single Cocrystals suitable for diffraction studies to elucidate cocrystal structure. The technique involves the nucleation and growth of a cocrystal from a solution of both co formers in a solvent, with super saturation 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. A slow rate of evaporation is usually desired so as to ensure formation of a small number of larger crystals as opposed to a high number of smaller crystals. This is not recommended as it tends to only yield stoichiometric Cocrystals and will not identify Cocrystals with unequal API/ co former ratios when they do exist for a cocrystal system. Ideally, evaporative cocrystallization should be performed from three solutions: 1:1 stoichiometric solution, a solution where the co former is in excess, and a solution where the target molecule is in excess[25].

2.2.3. Cooling Crystallization. A designed seeded cooling crystallization was used to prepare cocrystals of carbamazepine: nicotinamide from ethanol, in an effort to establish a scalable solution cocrystallization strategy. Solvent selection, identification of the thermodynamically stable Cocrystal operating range, and desupersaturation kinetics were considered in design of the process, which was demonstrated at 1 L scale with 90% yield and 14 L kg−1 throughout. A similar approach was taken by Holaň et al. in the preparation of agomelatine:citric acid cocrystals, and the impact of cooling rate and seed amount on the crystal size distribution in the final product was assessed[24].

2.2.4. Anti-Solvent method: Antisolvent crystallisation is another technology for the synthesis of high quality cocrystals. Generally, during the process supersaturation is generated by adding a second liquid to a solution of the drug – conformer to be crystallised, which is miscible with the solvent and in which the cocrystals is insoluble or sparingly soluble. However, in many cases, a coformer solution is added to the drug organic solution to facilitate cocrystallization.This is one in all the strategies for precipitation or recrystallization of the Cocrystal former and active pharmaceutical ingredient. The first study was reported by Chun et al. who synthesised indomethacin – saccharin cocrystals by adding water (antisolvent) in IND – SCH solvent solutions [26].

2.2.5. Crystallization by reaction: Reaction crystallization methodology is employed for speedy preparation of Cocrystals at microscopic and macroscopic scale at close temperature during which nucleation and Cocrystallization relies upon the Cocrystal elements and their solubility. The saturated of the lesser soluble part (drug) is formed in methyl alcohol and filtered, and so the

additional soluble part (coformer) is extra in a quantity just below its solubility limit. The goal isn't to own any excess drug or coformer within the beginning solutions that would be confused as a Cocrystal. What is more, by not exceptional the solubility limits of the elements, the Cocrystals that precipitate out of answer area unit pure. Answer concentrations area unit monitored by HPLC throughout the crystallization method to judge whether or not the solid ascertained gave the impression to be a fancy of the reactants (Cocrystals)[27].

2.2.6. Ultrasound Aided Cocrystallization: Sonochemical methodology has been developed for the preparation of Cocrystals of terribly little size i.e. for preparation of nanocrystals. During this methodology, API and Cocrystal former area unit dissolved along in an exceedingly solvent. Cold water is provided throughout the sonication to take care of the constant temperature of sonicator and forestall fragmentation. The energy that imparted to the sample during irradiation causing a rapid rise in temperature in short period of time, generate a melting of crystalline material, followed by material mixing, then rapid recrystallization upon cooling. A proposal condition for coformer material that can be used for this method is co former must be sublimable, to facilitate a nucleation process through vapour phase. Pure Cocrystals were obtained by this methodology[24].

2.2.7. Spray Flash Evaporation process: The technology was originally used in the file of explosives to prepare semi – crystalline nano composites and is based on the flashing behaviour of superheated liquid which is subject to a rapid pressure drop. The process favors close interactions between various drug – co former pairs and results in fast crystallization rates. The method involves dissolving the materials in a low boiling solvent (b60 °C) over-pressurized at 40–60 bars following atomization into a chamber through a heated hollow cone nozzle. Due to the sudden pressure drop, the superheated solution becomes thermodynamically unstable and the energy excess converts into latent energy inducing cocrystallization of the compounds[24]..

2.2.8. Supercritical Fluid Atomization Technique: Cocrystallization with Supercritical Solvent (CSS) technique uses the solvent power of supercritical CO2 to suspend the API and the coformer as a slurry in liquid or supercritical CO2, Rapid Expansion of Supercritical Solutions (RESS) is a process where a solution of the drug – coformer in supercritical CO2 are rapidly depressurized (10−5 s) to atmospheric conditions. Hence the solvent power of the fluid drops dramatically resulting in high super saturation of the solute in the depressurized supercritical CO2. The rapidly formed super saturation leads to nucleation and crystallisation which subsequently forces the fine particles to precipitate. The technology uses non – toxic, highly volatile solvents without leaving any solvent residues to the formed Cocrystals. Some disadvantages of RESS is the limited solubility of the drug – co former pairs in supercritical CO2 and the low product yields[28].

2.2.9. Spray drying technique: Spray – drying is a well-known process that has been used for several pharmaceutical applications such as micro and nano particles for pulmonary delivery, solid dispersions, viral vectors, and pure drug particles. In principle, spray – drying is a process of transformation of a feed from liquid stage to a dried particulate form by spraying the feed through a gaseous drying medium at elevated temperatures Although the actual mechanism of cocrystal formation was difficult to identify the authors made the following assumption: the cocrystals nucleate and grow within highly supersaturated regions of the drug substance due to rapid solvent evaporation and solidification of the generated droplets, the presence of coformer and the drug – coformer interactions in the liquid phase. For drug-conformer incongruent solubility system, where pure cocrystal can't be formed using solvent evaporation method, cocrystallization using spray drying method can be used as an alternative method. Thus, spray drying method can supply a novel atmosphere for the preparation and scale-up of Cocrystals[29].

2.3. Miscellaneous Cocrystal Preparation.

2.3.1. Laser Irradiation. This method consists of using a high-power CO2 laser to irradiate powder blends of cocrystal formers and induce their recrystallization to a cocrystal structure. Interestingly, these authors have found that the cocrystal formers need to sublime to a considerable extent for the Cocrystallization to take place, which indicated that the mechanism of the molecular rearrangement between API and coformer molecules and the nucleation of the cocrystal is likely to take place in the vapor phase. [31].

2.3.2. Resonant Acoustic Mixing: Resonant acoustic mixing has been used to mix the target molecule and coformer in the presence of a liquid to form a cocrystal in the absence of any grinding media. In this method, mechanical energy is transferred acoustically into a wetted powder mixture,

encouraging intimate mixing of the components. A range of carbamazepine cocrystals were successfully produced using a labRAM resonant acoustic mixer operating at 80−100G and 60 Hz. The cocrystal products were isolated at a range of laboratory scales, 100 mg and 1.5 and 22 g, and the technology appeared amenable to scale-up[32].

2.3.3. Freeze-Drying. Freeze-drying, technically known as lyophilization, has been mostly used as a processing technique to preserve a wide variety of products, which include food and pharmaceuticals. This process works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase. It has also has been demonstrated recently to be a feasible method for the preparation of new solid forms of cocrystal systems [32].

2.3.4. Electrospray Technology: Electrospraying is a process of simultaneous droplet generation and charging by means of an electric field. In this process, a solution containing the dissolved substances flows out from a capillary nozzle, which is maintained at high potential, through an electric field, which causes elongation of the solution droplets to form a jet. The solution jet is dried and the generated particles are collected on a charged powder collector [32].

2.3.5. Microfluidic and jet dispensing approaches: Micro fluidics is a versatile technology that allows assays to be conducted at very high throughput by running thousands of samples per second and controlling fluids in networks of micrometre – sized channels. According to this platform saturated solutions of parent compounds and coformers were dissolved in various solvents at very small quantities for a single chip through combinatorial mixing. By applying a two-phase screening process caffeine was processed with a wide range of co formers and various solvents to identify combinations with the highest propensity for Cocrystals. The parent compound (caffeine) was introduced in the chips vertically while the co formers horizontally. The results proved that Cocrystals screening using microfluidic chips is reliable and reproducible [32].

Conclusions

Cocrystals are an excellent alternative for drug development to enhance solubility, bioavailability, stability and processability. However, there are several challenges including co former selection, physicochemical characterization and formulation. Careful drug conformer screening and formulation design can lead to successful Cocrystals development. In this review,we discussed in detail a wide range of technologies applied for experimental screening, synthesis and manufacturing of pharmaceutical cocrystals in order to overcome poor physical properties of APIs. This review insight is given on the proposed mechanisms of cocrystallization in different techniques. On early development, cocrystallization processes mainly focus on traditional methods, such as solvent evaporation, grinding, and slurry method. But, as time goes by, the scientist who concern on this field then develop simpler and newer method for cocrystallization processes to overcome previous methods limitation. Novel methods that can be used for cocrystallization are hot-melt extrusion, spray drying, supercritical fluid technology, laser irradiation, freeze drying, microfluidic and jet dispensing etc. Those methods successfully form various kind of pharmaceutical cocrystal. But, every method still needs to investigate thoroughly to understand the clear cocrystallization mechanism for each method.

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Conflict Of Interest

The authors declare no conflict of interest.

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