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Review Article

A REVIEW ON ADVANCES IN PHARMACEUTICAL CO-CRYSTAL PREPARATION ROUTES, INTELLECTUAL PROPERTY PERSPECTIVE AND REGULATORY ASPECTS

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ABSTRACT

As in recent years, due to the pervasiveness of poorly soluble APIs that demonstrates poor and erratic bioavailability, pharmaceutical cocrystal's applicability to tailor the physicochemical properties has gained attention. Pharmaceutical cocrystal has been an exciting field of interest to researchers as this encouraged several regulatory bodies to create regulatory standards, which led to the approval of these crystals for marketing in various nations. With the upsurge in the growth of pharmaceutical cocrystals, the major concern is over the intellectual property perspective and regulatory status of cocrystals. With the new guidelines from the United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA), the manufacturing and characterization of cocrystal have become less complicated. In this article, various preparation routes are mentioned along with this intellectual property perspective and regulatory perspective, including regulatory guidelines, which give an idea of whether cocrystals meet the criteria for patent eligibility and how they would change the current state of the pharmaceutical industry. Here, we also reviewed some recently approved patients on pharmaceutical crystals, which provided benefits over poor physicochemical property of drug substances and also enhanced the therapeutic effectiveness of that drugs.

Keywords: Cocrystal, Crystal engineering, Regulatory guidelines, Intellectual property, Patent

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INTRODUCTION

Currently, pharmaceutical scientists use a variety of ways to change the crystal structure of APIs to get the desired properties. The ability to develop novel crystalline forms requires a thorough knowledge of the interactions in a given molecule. Crystal engineering has emerged as a significant technique in the design of novel solids in this context [1]. The majority of newly discovered chemical entities are lipophilic and face the problem of poor biopharmaceutical properties, among these properties' solubility, which remains a key issue. These entities belong to BCS class II or BCS class IV. One of the major challenges facing the pharmaceutical industry is to increase drug the water solubility of these types of drugs [2].

In such scenarios, to improve the solubility and thereby the dissolution rate, formulation scientists often turned to various basic approaches such as salt formation, changes in the solid-state structure, complexation, encapsulation, etc. Though salt formation is a widely implemented and convenient method of improving solubility, it suffers from some disadvantages, such as a lack of ionizable groups on the APIs and the availability of only a limited number of nontoxic salt formers. Further, solid-state manipulation approaches such as metastable phase formation or amorphization of APIs may increase the risk of phase conversion under normal storage conditions [3]. So the construction of pharmaceutical cocrystals to improve the solubility as well as bioavailability of these types of drugs has gained popularity in the previous decade.

Cocrystals are solids that are neutral crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. If at least one of the components is an API and the other is pharmaceutically acceptable, i.e. authorized as, Generally Recognized as Safe (GRAS) or added to the US FDA's "Everything added to food in the United States" (EAFUS) list, which contains over 3000 compounds appropriate as food additives [4], then it is recognized as a pharmaceutical cocrystal. Coformer for cocrystal development may be a polymer, amino acid, nutraceutical, another drug, etc.

Polymers as coformer

Some studies use polymeric excipients for crystalline inclusion complexes, such as cyclodextrins. However, compared to crystalline coformers, amorphous polymeric excipients have received less attention as coformers for the production of cocrystals. For the first time, Praveen *et al.* reported creating a new kind of cocrystal utilizing a few amorphous coformers. They used several grades of polyethylene glycol (PEG) to create and describe the co-crystals of the BCS Class II antibacterial medication Dapsone. The benefit of a large range of PEG molecular weights (from 600 to 35000 Dalton) allowed for the modulation of various physicochemical parameters in addition to drug solubility over a wide range. Thus, compared to small molecule coformers, this family of crystals becomes a more attractive option for better drug delivery methods. In this way, he reported that the isomorphous drug-polymer co-crystal is an emerging subset of pharmaceutical co-crystals [5].

Amino acids as conformer

The formation of cocrystal by using polymers as coformer often has problems with physical stability at relatively high humidity due to the hygroscopic nature of some of the polymers used. And the utilization of polymers leads to large bulk volume in tablets and capsule. To overcome this issue alternatively, a co-former with a low molecular weight was used to create a co-amorphous system in place of the polymer [6, 7]. Numerous studies have been done on the use of amino acids as co-formers for co-amorphous formation. It has been proven to enhance API's stability and dissolving profile when certain APIs have solubility issues [8, 9]. Along with being a co-former in co-amorphous formation, amino acids are frequently used in co-crystal structure, particularly with the "green method" co-crystallization. Because amino and carboxylic groups on amino acids can function as hydrogen bond donors and acceptors, amino acids can be used as co-formers in crystal engineering [10]. This has led many researchers to look for a co-former that is less hazardous than chemical co-formers like dicarboxylic acid and is also simple to handle [11].

Kasten *et al.* studied the capacity of the amino acids to generate potent interactions with the API by combining six APIs with 20 amino acids. This research found that non-polar amino acids are generally good co-formers [12], while acidic amino acids and polar amino acids are classified as poor co-formers [13]. Due to their capacity to offer superior dissolving rates, non-polar amino acids

with cyclic groups, such as L-phenylalanine and L-tryptophan, and non-polar amino acids with a pyrrole group, such as L-proline, should be given priority as first-choice co-formers [14].

Another drug as a conformer

Drugs can be used as coformer that lead to the formation of drug-drug co-crystal, also known as multidrug co-crystals (MDCs). Thipparaboina *et al.* defined the multidrug co-crystals as "dissociable solid crystalline supramolecular complexes comprising two or more therapeutically effective components in a stoichiometric ratio within the same crystal lattice, wherein the components may predominantly interact via non-ionic interactions and rarely through hybrid interactions (a combination of ionic and non-ionic interactions involving partial proton transfer and hydrogen bonding) with or without the presence of solvate molecules". This is one of the most recent approaches in the pharmaceutical industry [15]. Over plan drugs, MDCs have several benefits. A further benefit of MDCs over co-amorphous systems is their improved physical and chemical stability [16]. Multiple drugs are often used to target multiple sites, mainly to treat complex conditions such as HIV/AIDS, diabetes, hypertension, heart ailments, and cancers. Recently discovered drug-drug co-crystal sacubitril-valsartan is sold commercially as Entresto® tablets to treat cardiac issues [17].

Neutraceutical as conformer

The term nutraceuticals, coined by DeFelice in 1989,24 can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease" [18]. The research of nutraceuticals is a rapidly expanding field, not only because of the potential health benefits of this class of compounds but also because of their alleged therapeutic effects on several medical conditions, including pain relief, cold and flu remedies, sleep disorders, digestive problems, and the prevention of some cancers [19, 20]. However, APIs that are vulnerable to oxidation can gain stability due to the nutraceuticals' anti-oxidant properties. Additionally, the pharmaceutical industry now uses more nutraceuticals as coformers because they are patentable (meet the requirements for patents) and are easily accessible over the counter [21]. Polyphenols (such as phenolic acids, coumarins, stilbenes, flavonoids, and lignans) and vitamins are two common classes of nutraceuticals [22]. Notably, the major supramolecular motifs seen in the pure orcrystallizedd forms of nutraceuticals are exactly as predicted by known supramolecular synthons. Furthermore, ionic cocrystalsalts that have ccrystallized with either an organic molecule or an organic salt—have received much interest recently, and nutraceuticals are an obvious candidate for research in this field [23-26].

Thus by using such various types of coformers the pharmaceutical cocrystal can improve other important qualities of APIs like flowability, chemical stability, compressibility, and hygroscopicity, in addition to improving solubility, dissolving rate, bioavailability, and physical stability [2]. So the, pharmaceutical cocrystals have gained recent prominence in a flurry of research reports. Cocrystals differ from other kinds of solid forms in that they have specific scientific and regulatory advantages. These advantages are associated with intellectual property issues that present both opportunities and difficulties specific to cocrystals. Intellectual property (IP) protection is a critical element of industries where the cost of product development substantially exceeds the cost of product manufacture, including software, fashion, and medicines.

Industries in the pharmaceutical and biotechnology sectors are particularly reliant on rigorous IP protection to safeguard product revenues in a sector with numerous regulatory hurdles, high R and D costs, and inherent risks. The branch of intellectual property covering scientific and technological inventions is the patent system. Patents are a mechanism for promoting research for society's benefit: the right to exclude others from practicing a patented invention affords an economic incentive to the inventor, while the limited term of that exclusionary right ultimately delivers the invention to the public domain. Patents on novel crystal forms of an API are valuable in this regard, and the investigation of different pharmaceutical solid forms, including cocrystals, is a growing area of research in which scientific advances can afford legal advantages [27].

Regulatory bodies like the United States Food and Drug Administration (USFDA) and European Medicines Agency (EMA), have published regulatory guidelines to clarify the status of cocrystals in their respective regions. Along with the preparation routes, this article focuses on listing recent developments regarding the regulatory status of cocrystals in different regulatory regions, the effect of these regulatory guidelines, and intellectual protection in the field of crystal engineering. Another point to be probed in this article is whether cocrystals are eligible for patent protection or not as per the literature and guidelines available on pharmaceutically acceptable cocrystals [28].

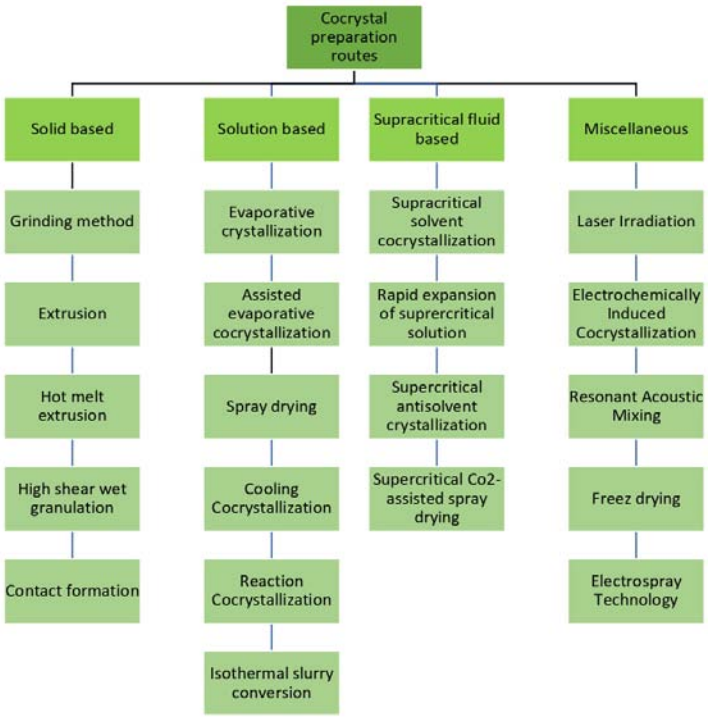

Fig. 1: Preparation routes of cocrystal

Cocrystal preparation routes

Cocrystalllization includes the methods that permit the non-covalent interaction of two or more molecules (in this case, the API and coformers) during the process. Cocrystallization methods can be classified as thermodynamic or kinetic methods depending on the driving force. Kinetic methods involve non-equilibrium conditions, depending on the system energy and reaction duration. These methods give origin principally to metastable cocrystal forms, which have higher Gibbs free energy when compared to stable ones. Grinding, slurry sonication, spray-drying, and supercritical fluid technology are some methods classified as kinetic methods. For thermodynamic methods, reactions occur in equilibrium conditions and usually take a large amount of time to be completed. Some examples are slow solvent evaporation and cocrystallization from the melt. As a result of the advancement in drug development, several techniques have been developed to prepare cocrystals, from lab-scale production to possibly large-scale manufacturing [29].

Some cocrystal preparation routes are classified here as solid-based, solution-based, supercritical fluid-based, and miscellaneous shown in fig. 1.

Solid-based methods

Critical features of this route are that cocrystals are synthesized in the absence of solvents or by using negligible amounts, excellent purity and quality, high throughputs, and the fast processing times on some occasions [30]. They are further categorized into different methods, namely neat grinding, liquid-assisted grinding (LAG), extrusion, hot-melt extrusion, and high shear wet granulation [31-35].

The neat grinding (or dry grinding) method consists of mixing the target molecule and conformer in a fixed stoichiometric ratio and grinding them for a particular period either manually or mechanically [36]. Pressure applied in this through manual (mortar and pestle) or mechanical (automated ball mill) means [37].

LAG (also known as kneading, solvent drop grinding, or wet grinding) is a modification of neat grinding by adding a small amount of solvent during the grinding process or before the initiation of milling. It has been used to enhance supramolecular selectivity, both polymorphic and stoichiometric, in crystalline systems [4].

Extrusion is the method of combining coformers in extruder equipment (may be single or twin screw) and is operated below the melting point of either starting material [38]. On the other hand, Hot-melt extrusion is a specialized technique for simultaneously melting and mixing coformers in a heated screw extruder. Cocrystalsproduced using a twin-screw extruder showed more crystallinity than crystals produced using a single screw extruder [39]. Extrusion offers highly efficient shear, close material packing, and mixing (without the use of any solvent), which increases the surface contact between cocrystal components and promotes cocrystal formation [40]. The method offers the advantages of eliminating the use of organic solvents, quick processing times, increased conversion compared to solution-based procedures, reduced waste, and technology that is ideally suited to continuous pharmaceutical processing [37].

The preparation of cocrystals recently found a use for the high shear wet granulation technique, which is typically used for drug product formulations. In this process, powder particles are aggregated with a binder (in a liquid media). In this method, high shear granulator is used, which imparts shear to the powder mixture through impellers and choppers [41, 42] A growing interest in solvent-free techniques is being seen in both academia and industry due to its beneficial connection to green chemistry principles. According to these principles, creating cocrystals efficiently and with less toxic products is advised.

Solution-based methods

A variety of solution-based routes are available for preparing cocrystals, including the evaporative method, assisted evaporative method, spray drying, isothermal slurry conversion, cooling cocrystallization, and reactive cocrystallization.

In evaporative or solution cocrystallization, the drug and coformer are dissolved in a common solvent, which is then evaporated to supersaturation. Crystal growth and nucleation are triggered by the supersaturation condition. This method is also frequently used to produce big single crystals that are suitable for use in single-crystal x-ray diffraction analysis, which is used to elucidate molecular and crystal structure. The rate of solvent evaporation affects the size of crystals. The slower the evaporation, the greater will be the size of the crystals. And faster evaporation leads to a fine powder [43].

Similar to evaporative cocrystallization, assisted evaporative cocrystallization involves evaporation but under high temperature and/or reduced pressures. The spray drying method is commercially used for obtaining amorphous solid dispersions, but recent studies show its application in drug: coformer cocrystals. It is a continuous single-step method of transforming liquids (solutions, suspensions, slurries) into solid powders by dispersing an under-saturated solution of drug and coformer through a nozzle using nitrogen where fast removal of solvent takes place [44]. The key mechanism in this method is crystallization because of supersaturation caused by fast evaporation. It is advantageous because of its continuous, highly controllable, and fast process [45].

The slurry conversion method (or isothermal slurry conversion) involves the addition of a drug to a suspension or solution of coformer for a specified period of equilibration [46]. This method doesn't need a clear starting solution, unlike evaporative cocrystallization. This method is conducted at a fixed stichometry and a constant temperature [47].

The reactive cocrystallization method involves mixing two individual solutions for drug and coformer or adding one solid coformer into a clear solution of another coformer in a solvent [48]. This induces a sudden spontaneous cocrystallization under ambient conditions.

Some compounds with temperature-sensitive solubility can be cocrystallized by cooling crystallization. The operational range for cooling crystallization must be carefully designed, which is based on the kinetics of the crystallization [49].

Supercritical fluid-based methods

The term "supercritical fluids" (SCFs) refers to highly compressed, pure substances or mixes that are above their respective critical pressure and temperature (Pc and Tc), where the liquid and gas phases are indistinguishable. Supercritical fluid-assisted crystallization is a recent exploration, which does not involve any toxic organic solvents, and hence are promising methods for synthesizing pharmaceutical cocrystals. There are three approaches; followed for crystallization by supercritical fluid methods, namely, solvent, antisolvent, and atomization enhancement [50].

Cocrystallization with supercritical solvent (CSS) involves adding an SCF (such as CO2) to a mixture of the API and coformer for a specified period. The SCF functions as a solvent and increases molecular mobility. The benefit of this method is that it is possible to fine-tune the solvent power and density of CO2 by controlling its thermodynamic conditions (like pressure and temperature), which provides control over the cocrystallization between the API and conformer [51].

In the rapid expansion of the supercritical solution (RESS) approach, supercritical CO_2($scCO_2$) is saturated with the solid drug and conformer components, then $scCO_2$ is rapidly depressurized (10^{-5}) to atmospheric conditions, resulting in high supersaturation of the solute in $scCO_2$. This supersaturation leads to nucleation and forces the fine particles to agglomerate in the form of crystals.

Two methods, namely supercritical antisolvent crystallization (SAS) and gas antisolvent crystallization (GAS), work on an exactly different approach as it employs the SCF as an antisolvent that induces precipitation of the API and coformer previously dissolved in an organic solvent by reducing solubility.

In the SAS method, the decrease in the solubility of the API and conformer upon the addition of $scCO_2$ in the precipitation chamber precipitates them into a cocrystalline structure. It is an

advantageous technique in controlling the production of polymorphs of pharmaceutical cocrystals [52].

In the GAS method, compressed CO_2 is gradually added to an API-coformer solution that is swirling in a high-pressure vessel, bringing the pressure to the desired level. The liquid solvent expands due to the $scCO_2$, which reduces the solvent's solubilizing power and speeds up the crystallization of the solutes.

Two techniques, namely atomization and antisolvent crystallization (AAS) and supercritical fluid enhanced atomization (SEA) employ the SCF as a spray enhancer that breaks up liquid jets into smaller droplets upon simultaneous depressurization with liquid solutions. Both techniques are comparable to the spray drying process discussed in the previous section, with the exception that the drying chamber is filled with supercritical CO_2 rather than nitrogen gas. However, the primary difference between these two methods is that AAS is carried out at ambient temperature while SEA is at higher. Due to the prerequisite that the starting materials (both the API and the coformer) be soluble in supercritical CO_2, these methods cannot be employed to create a variety of pharmaceutical cocrystals because, unfortunately, the majority of medication components have low solubility in CO_2 [53-55].

Some recently emerging methods, which are relatively uncommon, are also used for cocrystallization. In the laser irradiation method, the high-power CO_2 laser is used to irradiate powder mixtures of cocrystal formers (drug and conformer) and trigger cocrystal formation by inducing their recrystallization. The electrochemically induced cocrystallization method involves the principle of electrochemistry to obtain cocrystals. With the help of electrodes, the pH of the solution (containing drug and conformer) changed (temporarily) and pH change can be used as a triggering force for the cocrystal formation. In resonating acoustic mixing, the mechanical energy is transferred into wetted powder, enabling the intimate blending of drug and coformer at high frequencies, thereby it leads to cocrystals formation. Freeze-drying, technically known as lyophilization involves freezing and then reducing the surrounding pressure by applying vacuum simultaneously to enable water in the material to sublime directly from the solid phase to the gas phase, leading to the formation of lyophilized cake. It also has been demonstrated recently to be a feasible method for the preparation of cocrystals. Electrospraying is a process of simultaneous droplet generation and charging using an electric field. The solution of the drug with coformer is aspirated through a narrow capillary nozzle, which is maintained at high potential through an electric field; this kind of aspiration results in elongation of the solution droplets to form a jet. The solution jet is dried and those dried droplets are collected in the form of powder on a charged powder collector [37, 56].

Intellectual property perspective

Patentability of cocrystals

The next step after developing a pharmaceutical cocrystal with promising results is getting regulatory approval so that it can be brought to market. However, the lack of clear regulatory guidelines is a major issue to tackle [57]. A cocrystal is a distinct type of solid-state material that typically has a unique and unpredictable structure and physical property profile [58, 59].

But they should also qualify as patentable inventions. The importance of current research into this new class of pharmaceutical crystal forms is highlighted by evaluating specific characteristics that make cocrystals typically patentable. Cocrystal has undergone tremendous development over the past ten years, there are even few patents granted for cocrystals. Like the claimed subject matter of any patent application, the cocrystal must meet the three requirements of novelty, non-obviousness, and utility or usefulness to be deemed patentable [60]. Cocrystals satisfy all three requirements. Hence they are patented [56].

Novelty

Novel crystal is a new composition of matter. After USFDA guidance and the EMA reference drug designed to contain new cocrystals are accepted, screening a novelty of cocrystals, salts, and polymorphic forms offers a new opportunity to grant IP to extend patent life. This guidance raised the possibility of IP extension after the mother patent's expiration. Pharmaceutical co-crystals were described as a novel creation by Desiraju in his book "Pharmaceutical salts and co-precious stones: retrospect and potential," and as such, they should now satisfy the requirement of novelty for the grant of a patent [61]. Similar to salts, pharmaceutical co-crystals satisfy the novelty criteria, according to Andrew Trask's conclusion in his article "An Overview of Pharmaceutical Co-Crystals as Intellectual Property". According to Desiraju and Andrew co-crystals may or may not form since co-former screening is a difficult task, co-formers are chosen from a huge official list of GRAS compounds, and the outcome of co-crystallization is not always predictable. Apart from this, it is impossible to predict the properties of the synthesized co-crystals. However, the current situation is entirely different; the FDA didn't even consider co-crystals in the same class as thatsaltsor polymorphs [60].

Utility

In the case of Pharmaceutical cocrystals, the only criteria needed to be demonstrated to obtain a patent is the utility or application of the invention. Cocrystals offer opportunities similar to that of polymorphs. They are new substances, problems of inherent anticipation are not likely to arise so often and more of them can be made for any given API, expanding the pharmaceutical space around it and consequently the types of advantageous properties that may be accessed [57]. Co-crystals provide advantages over patent enhancement like thermal characterization such as melting point, solubility, mechanical property, and stability. a) Melting point: The melting point of the molecule can be correlated to the solubility of API, if API has a high melting point may have less solubility and vice versa. In case the melting point of API needs to reduce, the coformer must have a lower value which reduces the melting point and vice versa. b) Solubility: Solubility can be expressed as saturation. Intrinsic dissolution, for all the co-crystal behaviors, can be evaluated by the solid-state complex. The solubility of API can be affected by the equilibrium effect of coformers. c) Mechanical property: Mechanical property of API depends on the tensile strength, rupturing nature, elasticity, and compressibility of the molecule. Co-crystal can help improve the mechanical strength of the molecule. d) Stability: Additionally, it is reported that co-crystal helps to enhance the physical as well as chemical stability of molecules with relative humidity, thermal stress, solution stability, photostability, etc [56]. According to Trask, an API's co-crystal has the same patented therapeutic usefulness as its parent API. The extensive co-crystal research conducted over the past 10 y suggests that co-crystals offer a variety of opportunities for improving an API's properties, increasing its value and, consequently, its chances of becoming patentable [60].

Non-obviousness

Non-obviousness refers to the fact that an "innovation" would be novel but obvious to a person skilled in the relevant technology and familiar with the subject matter if they invented it relatively easily. In contrast to that formation, where acid is required to form a salt with a base, Desiraju noted that the identification of a co-former is hardly ever routine. Regardless of the existence of several co-crystal screening techniques, according to Trask, there is no reliable way to predict whether two molecules will form a hydrogen bond and a co-crystal. Several variables affect the co-crystallization process, and still, there is a need fora better understanding of this process [60, 61]. Despite many advancements in computation in the area of crystal engineering, the formation of a co-crystal remains unpredictable; hence it is not obvious.

Intellectual property opportunities and the importance of pharmaceutical cocrystal patents

Recently the cost of developing a new drug has been estimated at USD 2.8 billion [62] and the number of approved drugs per billion of spending has halved each year since the 1950s. Hence, Healthcare costs progressively increase as a result, and healthcare resources around the world are further strained. Here, crystal engineering can provide a solution as new intellectual property (IP) opportunities

exist for inventors who design cocrystals of new and old medications, especially if it results in an improvement of the API's pharmacokinetic properties. In turn, this might make it possible to manufacture the drug product, increase its purity, or use it for various indications.

In the process of claiming patients, after recognizing an API's therapeutic value, a research organization immediately submits a patent application covering its chemical structure to prevent another organization from independently filing on the same molecule. As a result, claims regarding an API's chemical structure often serve as the main basis for a patent's protection of a marketed pharmaceutical product. However, in some circumstances, further patent protection might be acquired by patenting novel solid forms of the API that were found while it was being developed. The decision of when to initiate API solid-form screening can bear on future market exclusivity. If API solid-form screening is conducted at an early stage, an application covering commercially viable solid forms can be filed together with an application covering the API chemical structure. This strategy prevents other organizations from submitting applications on the same solid forms or from attempting to create technology that gets beyond the product's intellectual property protection.

Alternatively, certain benefits and risks can accompany later-stage API solid-form screening. The effort and expense of solid-form screening may be postponed until definitive identification of the preferred final form is required for development and/or regulatory purposes. In this case, any newly discovered solid forms of the API may be covered by filings after the initial chemical-structure patent application, resulting in a solid-form patent portfolio that covers all therapeutically significant solid forms of the API, including polymorphs, hydrates, solvates, salts, and cocrystals. If the FDA-approved product involves one of the new solid forms in this portfolio, then patent protection of the solid form of the approved product may persist after the core chemical-structure patent expires, potentially leading to increased revenue and improved market position. Likewise, generic manufacturers have a chance to overcome the patent protection on existing marketed compounds by developing novel solid compounds like cocrystals [63]. Screening for solid forms is critical to ensure that the optimum form is carried forward in development and to minimize the likelihood of unexpected form conversion. This strategy adds another dimension to the importance of solid-form screening technologies. Based on the large number and variety of potential cocrystal-forming counter molecules, screens for cocrystals may demand a particularly large degree of resources and sophistication. Improvements in screening methods, including informatics-based approaches and efficient experimental techniques in consideration with proper preparation routes, should provide value to the industry from both a scientific and economic perspective.

Regulatory aspects

In 2013, USFDA was the first regulatory body to publish guidelines for pharmaceutical co-crystals; these regulations classified pharmaceutical co-crystals as drug product intermediates and treated them similarly to API-excipient molecular complexes. These guidelines are further revised in August 2016. The following information should be provided by applicants for NDAs and ANDAs that claim to contain or include a cocrystal form.

- The drug and the co-former should exist in neutral states in the co-crystal and interaction among them should be no covalent/non-ionic.

  - Δp Kavalue of drug and conformer [pKa (base)-pKa (acid)] should be less than 1 that is ΔpKa [pKa (base)-pKa (acid)]<1.

  - However, the classification of the pharmaceutical solid as salt or co-crystal is not predicated on these relative pKa values, use spectroscopic tools and other orthogonal approaches to provide evidence to the contrary

- The drug and the co-former should completely dissociate before reaching the site of pharmacological activity [64].

Many co-crystal-containing products are commercially available as a result of regulatory bodies' growing acceptance, including Beta-Chlor®, Depakote®, Cafcit®, Lexapro®, Odomzo®, Entresto®, Steglatro®, and Suglat® [65-67].

The records of regulatory consideration of cocrystal

The history of co-crystals starts with an unrecognized study discovering the first seed of co-crystals in 1844. This is mentioned in the study by Friedrich Wohler on quinhydrone during the study of quinones [68]. Furthermore, Paul Pfeiffer stated in his book "Organische Molekulverbindungen" published in 1922 that co-crystals are divided into organic and inorganic components and those composed of organic components [69]. The first co-crystal patent was filed in 1937, although the term "co-crystal" was not used until 1967 anywhere [70]. In 1958, X-ray analysis of co-crystals was reported for the first time in history to reveal the structure and intermolecular interaction of quinone and hydroquinone in a ratio of 1:1. The discussion of co-crystals was then picked up by Desiraju in2003 In his book, In"A Multi-Component System Held Together by Non-Covalent Interaction," to which Dutiz replied by stating that the term comprised solid solutions, encapsulated compounds, or amorphous solids [71]. Arakerygiven the following three criteria for making co-crystal i) the neutrality of the ingredients, ii) the solid state of the components in ambient conditions, and iii) homogeneity of the crystalline material and the stoichiometry of the components. In April 2011 the FDA first did the regulatory classification of pharmaceutical cocrystals. In this process, the FDA Center for Drug Evaluation and Research (CDER) classified cocrystals as 'drug product intermediates (DPIs)' and defined them as "solids that are crystalline materials composed of two or more molecules in the same crystal lattice" [70, 72]**.** Since cocrystals are classified as DPIs per the FDA's ruling, they can now be manufactured/engineered using a solvent-free solid-to-solid, making them suitable for production in the DPI facilities. Nonetheless, the use of solvent-free manufacturing methods in drug manufacturing facilities provides the opportunity for cocrystal manufacturing by using 'greener' manufacturing methods with better manufacturing economics and reduced development times and costs. The FDA guidance encourages the application of non-traditional synthesis techniques in the area of cocrystal production. These non-traditional manufacturing techniques can be used for commercial-scale cocrystal manufacturing, employing techniques such as hot-melt extrusion, continuous oscillatory baffled crystallization, resonant acoustic mixing techniques, and mechanochemical grinding techniques which apply both grinding stress and heat. If the guidelines issued and implemented by the FDA are fully encompassed by the pharmaceutical industry concerning cocrystal manufacturing as DPI, a significant shift in the cocrystal manufacturing process from solvent-based syntheses to solid-state manufacturing techniques will be achieved. Moreover, it is assumed that the definition of cocrystals as DPI from the FDA by itself opens the door for generic companies to develop cocrystals and follow a relatively cost-effective bioequivalence route, rather than the new chemical entity route which is often quite cost-intensive [73]. But this classification was undesirable for the industries because considering cocrystals as DPIs would require different regulatory reporting requirements, unlikesalts or polymorphs [74]. On active discussions and claims, USFDA was the first regulatory body that proposed a definition for co-crystals in 2013 and further revised it in 2016, placing co-crystals in a special solid-state similar to a different polymorphic form where data like solubility and *in vitro* dissolution prove dissociation of the drug and co-former. EMA published a paper in 2014, which classified co-crystals as the same as other salt forms [56]. A reflection paper published by EMA in May 2015 divided solid-state materials based on internal structure and addressed the application of cocrystals of APIs in medicinal products. The definition of cocrystals given by EMA is "homogeneous (single-phase) crystalline structures comprising two or more components in a specific stoichiometric ratio where the arrangement in the crystal lattice is not based on ionic bonding (as with salts)"[75]. Unlike the FDA, EMA recognizes cocrystals mainly as APIs and applies them to various formulations of the drug manufacturer can demonstrate different efficacy/or safety [76]. The USFDA published the final guidelines of 2016 on the same topic in 2018 [77].

The FDA has made numerous revisions to the definition of cocrystal. Most recently, in February 2018, the FDA defined pharmaceutical

cocrystals as "crystalline materials composed of two or more different molecules, typically an active pharmaceutical ingredient (API) and cocrystal formers ("coformers"), in the same crystal lattice."[78]. The regulations for pharmaceutical cocrystals are similar to those of polymorphs of an API because the solvates are of the initial drug substance. Specifically, it is not regarded as a new API. With this guidance, the pharmaceutical industries benefit from producing cocrystals at existing formulation facilities using APIs and coformers without any additional requirements of current good manufacturing practices (cGMPs). However, drug manufacturers should submit appropriate data for new drug applications (NDAs) and abbreviated NDAs (ANDA) containing a crystalline form supporting the structure of the cocrystals. For APIs and coformers having ionizable functional groups, data should demonstrate that no ionic interaction exists between the component API and coformers. Also, a substantial dissociation of the API from its cocrystal form should occur before reaching the site of pharmacological activity [54]. The USFDA and EMA classification of Pharmaceutical co-crystals is summarised in table 1.

Table 1: Comparison of regulatory consideration of different aspects of co-crystals between the United States Food and Drug Administration and European Medicines Agency [75, 78, 79]

Factor	US FDA	EMA
Definition	Crystalline materials are composed of two or more different molecules, one of which is the API, in a defined stoichiometric ratio within the same crystal lattice that is associated with nonionic and noncovalent bonds.	Homogenous (single-phase) crystalline structures are 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).
Regulatory status	Dug products that are designed to contain a new co-crystal are considered analogous to a new polymorph of the API. It is not regarded as a new API	Reference to the safety and efficacy documentation of an approved reference product containing the same active substance.
Regulatory regard	Similar to solvates	Similar to salts of the same API
Regulatory classification	Polymorph of Active Pharmaceutical Ingredient	Salts of Active Pharmaceutical Ingredients
Composition	Active Pharmaceutical Ingredient and a food or drug grade co-former	Active Pharmaceutical Ingredient and co-former in a fixed stoichiometric ratio
Sameness with parent API	Same	Same unless demonstrated different efficacy or safety
Conformers	A component that interacts non ironically with the API in the crystal lattice that is not a solvent (including water) and is typically non-volatile	Non-active components in a pharmaceutical Co-crystal
Co-former role	Excipient	Reagent
Co-crystal/Salt	Differences in interaction and regulatory pathways	Regulation dependent on efficacy/safety
Chemical interactions	Non-ionic/non-covalent interactions	Non-ionic/non-covalent interactions
Manufacturing sites	API manufacturing sites	API manufacturing sites
New Chemical Entity/New Active Substance Registration	No	Possible if shown difference in efficacy/safety
US-Drug master files (DMF)/EMA Active substance master file (ASMF)requirement	Not required	Possible to present a single active substance master file for a Co-crystal
Applicable Good Manufacturing Practice(GMP) regulations/guide	cGMP for drug products	Part II of EU GMP guide (active substances) and ICH Q7 and in rare cases, part I of EU GMP guide (finished drug product)

Recent patents on co-crystals (Case studies)

Pharmaceutical co-crystals have grown significantly over the past ten years, and numerous research publications and patent applications have been made worldwide. To date, several patents relating to co-crystals and multi-drug co-crystals have been approved. The case studies regarding recently approved patents on pharmaceutical co-crystals in the US are discussed here.

Cocrystals of ubiquinol and compositions comprising them

The inventors have found that ubiquinol can form a cocrystal with hydrogen bond donor conformers such as with3-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid, and 3,5-dihydroxybenzoic acid. The provision of the mentioned cocrystals of ubiquinol gives a new tool to overcome the problems associated with the stability of ubiquinol because it has been found that these cocrystals have high stability at room temperature even when exposed to air, which makes it easier to handle. This property makes the cocrystals more suitable for preparing a pharmaceutical or dietary compositions containing ubiquinol [80].

Cocrystal of telmisartan and hydrochlorothiazide

This present disclosure relates to the formation of a cocrystal of telmisartan and hydrochlorothiazide in the molar ratio of 1:1, respectively. The cocrystal of telmisartan and hydrochlorothiazide was characterized by X-ray powder diffraction (XRPD), proton nuclear magnetic resonance spectra (1H-NMR), thermal gravimetric analysis (TG), scanning differential calorimetry (DSC) and infrared (IR) spectra. The benefits of the formation of cocrystal were found that the maximum plasma concentration of the cocrystal in SD rats was higher than that of any one of hydrochlorothiazide and telmisartan itself. From this, they concluded that the formation of a cocrystal of telmisartan and hydrochlorothiazide has a simple preparation method and it gives good physical and chemical properties [81].

Memantine paroxetine cocrystal salt and its preparation method, pharmaceutical composition, and application thereof

This invention gives rise to, cocrystal salt, which is memantine paroxetine sulfate hydrate. Its mechanism of action is NMDA receptor antagonist and 5-HT inhibitor. The preliminary pharmacokinetic studies revealed that there were significant differences in the main pharmacokinetic parameters of cocrystal salt and memantine, including T1/2, Tmax, Cmax, and AUC. Additionally, the findings indicated that cocrystal salt could enhance medication bioavailability, blood drug concentration, absorption, and therapeutic impact. This gives a material basis for lowering the dosage and adverse drug effects. Furthermore, this invention's cocrystal salt can be combined with other drugs to create a compound that has remarkable therapeutic efficacy [82].

Novel crystalline varenicline oxalate hydrate, preparation method thereof, and a pharmaceutical composition comprising the same

In this invention, the cocrystal of varenicline and oxalic acid was prepared in a molar ratio of varenicline to oxalic acid of 1:1.5. It can

be in amorphous form or crystalline form, and is preferably in crystalline form, i.e., a polymorph. The invention is related to a novel crystalline varenicline oxalate hydrate, a manufacturing method thereof, and a pharmaceutical composition for assisting an antismoking agent, comprising the same as an active ingredient [83].

L-pipecolic acid cocrystal of cannabidiol

This invention relates to the preparation of a cocrystal of cannabidiol, specifically a 1:1 cannabidiol: L-pipecolic acid cocrystal. The invention also provides therapeutic uses of the 1:1 cannabidiol: L-pipecolic acid cocrystal in Dravet Syndrome, Lennox Gastaut Syndrome, myoclonic seizures, juvenile myoclonic epilepsy, refractory epilepsy, schizophrenia, juvenile spasms, West syndrome, refractory infantile spasms, infantile spasms, tuberous sclerosis complex, brain tumors, neuropathic pain, *Cannabis* use disorder, post-traumatic stress disorder, anxiety, early psychosis, Alzheimer's Disease, autism, and withdrawal from opioids, cocaine, heroin, amphetamines, and nicotine, and beneficial use in methods for its delivery, and compositions, such as pharmaceutical dosage forms, containing the cocrystal, to humans [84].

CONCLUSION

In this review, we discussed in detail a wide range of technologies applied for the manufacturing of pharmaceutical co-crystals to overcome the poor physical properties of APIs. The majority of drugs belong to BCS group II. Solubility plays a crucial role in obtaining the optimal efficacy of a drug, which leads to the cocrystal of a drug that can provide a superior solution. The intellectual property perspective includes the patentability of cocrystals, and the regulatory aspects, which the latest guidelines of the FDA (2018) and EMA (2015) mentioned, which have eased up the approval process of drug cocrystals. The pharmaceutical industries benefit from the production of cocrystals employing APIs and coformers at existing formulation facilities without any additional requirements of current good manufacturing procedures (cGMPs). But according to FDA, current good manufacturing practice (cGMP) requirements apply to co-crystals when they are categorized as a drug product intermediate. The new guidelines provide consistency among regulatory agencies and hence cocrystal characterization and/or manufacturing is less complicated and time–consuming. Pharmaceutical cocrystals generally appear patentable when evaluated against the standards of novelty, utility, and non-obviousness, as is clear from the fact that the number of patent applications filed globally by various pharmaceutical industries and research organizations is likewise increasing rapidly. From case studies of patents for cocrystals, it is concluded that cocrystals are an excellent alternative for drug development to enhance solubility, bioavailability, stability, processability, and therapeutic effectiveness.

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CONFLICT OF INTERESTS

Declared none

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