ABSTRACT

Poor aqueous solubility and low oral bioavailability of an active pharmaceutical ingredient are the major constraints during the development of new product. Various approaches have been used for enhancement of solubility of poorly aqueous soluble drugs, but the success of these approaches depends on the physical and chemical nature of molecules being developed. Cocrystallization of drug substances offers a great opportunity for the development of new drug products with superior physicochemical such as melting point, tabletability, solubility, stability, bioavailability, and permeability while preserving the pharmacological properties of the active pharmaceutical ingredient. Cocrystals are multicomponent systems in which two components, an active pharmaceutical ingredient, and a coformer were present in a stoichiometric ratio and bonded together with non-covalent interactions in the crystal lattice. This review article presents a systematic overview of pharmaceutical cocrystals. Differences between cocrystals with salts, solvates, and hydrates are summarized along with the advantages of cocrystals with examples. The theoretical parameters underlying the selection of conformers and screening of cocrystals have been summarized and different methods of cocrystal formation and evaluation have been explained.

KEYWORDS

Cocrystals, Co-crystallization, API-excipient

INTRODUCTION

Pharmaceutical cocrystals emerged in the past decade as a promising new weapon in the arsenal of drug development. The resurgence of interest in multicomponent crystal compositions has led to significant advances in the science of cocrystals design and recovery. These advances have built upon crystal engineering, which provides a deep understanding of supramolecular interactions between molecules that govern crystal packing and physicochemical properties of crystalline materials. Concomitantly, the patent landscape of pharmaceutical cocrystals developed rapidly in the last decades.

Over the course of last century of modern drug development and manufacture, drugs such as aspirin and many antibiotics have owed their purity and storage stability to their existence as crystalline solids. Crystalline solids are in which the atoms, molecules or ions pack together to form a regular repeating array that extends in three dimensions. The first reported cocrystals; Quinhydrone was studied by Friedrich in 1844. Quinhydrone, a cocrystal of quinone and hydroquinone (knows archaically as quinol). Cocrystals continued to be discovered throughout the 1900s. Some were

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discovered by chance and others by screening techniques. Knowledge of the intermolecular interactions and their effects on crystal packing allowed for the engineering of cocrystals with desired physical and chemical properties.

The inorganic: organic cocrystals include organic molecules cocry stallized with alkali and alkaline earth salts, mineral acids, and halogens as in the case of the halogenated quinones. A majority of the organic; inorganic cocrystals contained aromatic compounds, with a significant fraction containing di- or trinitro aromatic compounds. The existence of several cocrystals containing eucalyptol, a compound which has no aromatic groups, was an important finding which taught scientists that pi stacking is not necessary for the formation of cocrystals. In the last decade, there has been an enhanced interest in cocrystals that is “consist of two or more components that form a unique crystalline structure having unique properties. Due to variation in the use of the term, structures such as solvates and clathrates may or may not be considered cocrystals in a given situation.

However, the study of cocrystals has a long history spanning more than 160 years. They have found use in a number of industries, including pharmaceutical, textile, paper, chemical processing, photographic, propellant, and electronics etc. In essence, pharmaceutical cocrystals joined the arsenal of pharmaceutical R&D as a useful design tool –with patent prospects–to augment product design and elucidate new pharmaceutical product opportunities. Today, the fruits of almost 10 years of screening for pharmaceutical cocrystals is evidenced by the number of patent applications and issued patents for pharmaceutical cocrystals.

Cocrystals

Crystalline solids are formed when a solution becomes supersaturated with crystallizing solute(s) the vast majority of substances, if not all of them, will crystallize to form one or more crystalline phases under the right conditions. The cocrystals are coming under the classification of crystalline compounds. Cocrystal is a crystalline structure made up of two or more components in a definite stoichiometric ratio, where each component is defined as either an atom, ion, or molecule. Which represent the basic principles of host-guest chemistry.

Cocrystal formation from supramolecular synthons is to be considered as forming from discrete neutral molecular species that are solids at ambient temperatures, and where the cocrystal is structurally homogenous crystalline material that contains the building blocks indefinite stoichiometric amounts. Cocrystal system as a new drug substance is the promise of enhanced solubility of compounds that have inferior profiles. The dissolution of an acetaminophen/theophylline cocrystal has been compared to that of a simple physical mixture, and the faster dissolution rate of the cocrystal was confirmed.

The identification of supramolecular synthons is of great importance in crystal structure interpretation, and the transferability of multipole charge density parameters has been investigated to determine if they could be treated as modules across differing structures. When any cocrystal investigations have been concerned with the classical scope of synthon donors and acceptors, the use of halogen groups in supramolecular synthons is being investigated. Chemists and engineers in the pharmaceutical industry generally seek to deliver crystalline forms of their active compounds, mainly due to the inherent stability.
of crystalline materials and the well-established impact of crystallization processes on purification and isolation of chemical substances. Increasing attention is now being paid to the impact of material properties on drug discovery and early development as the drug substances tend to be very valuable materials. The pharmaceutical industry's mission is to rapidly advance development programs with good confidence so that formulation problems are unlikely to arise and to maximize a compound's potential as a therapeutic.

Crystal engineering is generally considered to be the design and growth of crystalline molecular solids with the aim of impacting material properties. A principal tool is the hydrogen bond, which is responsible for the majority of directed intermolecular interactions in molecular solids. Co-crystals are multi-component crystals based on hydrogen bonding interactions without the transfer of hydrogen ions to form salts; this is an important feature since Bronsted acid-base chemistry is not a requirement for the formation of a co-crystal. Co-crystallization is a manifestation of directed self-assembly of different components. Co-crystals have been described of various organic substances over the years and given various names, such as addition compounds molecular complexes and heteromolecular co-crystals.

Pharmaceutical co-crystallization, which has only recently gained widespread attention as a means of modifying the physicochemical properties of APIs, has two inherent advantages over the salt form. First, because co-crystal formation may potentially be employed with all APIs, including acidic, basic and nonionizable molecules and second is a large number of potential ‘counter molecules’ which may be considered to be nontoxic possibly increasing the scope of the pharmaceutical co-crystallization over the salt forms.

The study of model cocrystal systems is of great value in establishing an information base for the understanding of more complicated systems.

Properties

Crystal form can be crucial to the performance of a dosage form. This is especially true for compounds that have intrinsic barriers to drug delivery, such as low aqueous solubility, slow dissolution in gastrointestinal media, low permeability and first-pass metabolism. The nature of the physical form and formulation tends to exhibit the greatest effect on bioavailability parameters of water-insoluble compounds that need to be given orally in high doses. An alternative approach available for the enhancement of drug solubility, dissolution and bioavailability are through the application of crystal engineering of co-crystals. The physicochemical properties of the active pharmaceutical ingredients and the bulk material properties can be modified, whilst maintaining the intrinsic activity of the drug molecule. The intellectual property implications of creating co-crystals are also highly relevant.

Pharmaceutical active ingredients (APIs) can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drugs.

Solid form discovery and design depend on the nature of the molecule of interest and type of physical property challenges faced in its development. The preferred solid form is generally the thermodynamically most stable crystalline form of the compound. However, the stable crystal form of the parent compound may exhibit inadequate solubility or dissolution rate resulting in poor oral absorption, particularly for water-insoluble compounds. In this case, alternative solid forms may be investigated. For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. Like the parent compound, pharmaceutical salts may exist in several polymorphic, solvated and/or hydrated forms.
Phase diagrams determined from the "contact method" of thermal microscopy is valuable in the detection of cocrystals.[2] The construction of these phase diagrams is made possible due to the change in melting point upon cocrystallization. Two crystalline substances are deposited on either side of a microscope slide and are sequentially melted and resolidified. This process creates thin films of each substance with a contact zone in the middle.

A melting point phase diagram may be constructed by slow heating of the slide under a microscope and observation of the melting points of the various portions of the slide. For a simple binary phase diagram, if one eutectic point is observed then the substances do not form a cocrystal. If two eutectic points are observed, then the composition between these two points corresponds to a cocrystal.

The components interact via non-covalent interactions such as hydrogen bonding, ionic interactions, van der Waals interactions, and \( \Pi \)-interactions. The intermolecular interactions and resulting crystal structures can generate physical and chemical properties that differ from the properties of the individual components. Such properties include melting point, solubility, chemical stability, and mechanical properties. Some cocrystals have been observed to exist as polymorphs, which may display different physical properties depending on the form of the crystal.

Pharmaceutical cocrystals are of interest because they offer the advantage of generating a diverse array of solid-state forms from APIs (Active Pharmaceutical Ingredients) that lack ionizable functional groups needed for salt formation.

In cocrystals, the molecular association between an API and its excipient occurs within the same crystal lattice and is governed by nonionic interactions, unlike the ionic interaction required for salt formation required for salt formation of an API. So cocrystals are classified as dissociable “API-excipient” molecular complexes (with the neutral guest compound being the excipient). In this manner, an API that has been processed with a crystallizing excipient to generate an “API-excipient “cocrystals should be treated as a drug product intermediate.

If the API and its excipient have a \( \text{dpKa} (\text{pKa (base)} - \text{pKa (acid)}) \) greater than or “API-excipient” cocrystals that met these conditions are “pharmaceutical cocrystals”. Drug products that contain “API-excipient” cocrystals are not considered to contain new API, but rather a specifically designed component called a “cocrystals drug product intermediate.

The key benefits associated with cocrystallization approach to modify properties of pharmaceutical solids are the theoretical capability of all types of drug molecules, including weakly ionizable and non-ionizable, to form co-crystals, and the existence of numerous, potential counter-molecules, including food additives, preservatives, pharmaceutical excipient as well as other APIs, for co-crystal synthesis. The major advantage is that co-crystal synthesis may offer for the pharmaceutical industry is an opportunity to address intellectual property (IP) issues by extending the life cycles of old APIs.

**For example**

Carbamazepine can exist as four different well-characterized polymorphs and a dihydrate. Cocrystals of carbamazepine and saccharin showed one packing arrangement while the cocrystals along with N, N-bis (parabromophenyl)
melamine-diethyl barbital demonstrated how a specific heterosynthon between the two molecules is robust, but packing of the tapes into a crystalline arrangement can lead to two discrete polymorphs. Hence there may be an opportunity to reduce the practical extent of the polymorphism of drug compounds specifically by co-crystals formation although there may be some exception.

It is with the reasoning that the physical properties of pharmaceutical cocrystals could then ultimately change with varying amounts and concentrations of the individual components. One of the most important properties to change with varying the concentrations of the components is solubility. It has been shown that if the stability of the components is less than the cocrystal formed between them, then the solubility of the cocrystal will be lower than the pure combination of the individual constituents. If the solubility of the cocystal is lower, this means that there exists a driving force for the cocry stallization to occur.

Even more important for pharmaceutical applications is the ability to alter the stability to hydration and bioavailability of the API with cocystal formation, which has huge implications on drug development. The cocystal can increase or decrease such properties as melting point and stability to relative humidity compared to the pure API and therefore, must be studied on a case to case basis for their utilization in improving a pharmaceutical on the market. The extent of polymorphism of pharmaceutical is limited to the handful of the different crystal forms. The primary difference between solvates and co-crystals is the physical state of the individual components. If one component is liquid at room temperature then the crystals are designated solvates, whereas if both components are solids at room temperature then the crystals are designated as co-crystals.

Solvates are commonplace because they occur as a serendipitous result of crystallization from solution and have the potential to enhance drug dissolution rate, as shown for the solvated forms of spironolactone. Solvated crystals, however, are often unstable, leading to desolvation during storage and such solvent loss may lead to the amorphous phase crystallizing into less soluble forms. Solvent levels in solvated crystals are also often at concentrations that are not acceptable to regulatory authorities and which may also have toxicological consequences. Co-crystals, however, tend to be a product of more rational design and are more stable, particularly as the co-crystallizing agents are solids at room temperature. As with other crystalline systems, polymorphic co-crystals are not uncommon.

**Methods of Preparation of Cocrystals**

Co-crystals designed on the principal of the supramolecular synthesis; it provides a powerful approach for proactive discovery of novel pharmaceutical solid phases. The use of hydrogen bonding rules, synthon and graph sets may assist in the design and analysis of co-crystal systems. The co-crystal formation may be rationalized by consideration of the hydrogen bond donors and acceptors of the materials that are to be co-crystallized and how they might interact.

All good proton donors and acceptors are used in hydrogen bonding, six-membered ring intermolecular hydrogen bonds form in preference to intermolecular hydrogen bonds, the best proton donor and acceptor remaining after intermolecular hydrogen-bond formation will form intermolecular hydrogen bonds to one another (but not all acceptors will necessarily interact with donors). These observations help to address the issue of competing hydrogen bond assemblies observed when using a particular crystallizing agent.

Supramolecular synthon that can occur in common functional group in order to design new co-crystals and certain functional groups such as carboxylic acids, amides and alcohols are particularly amenable to formation of supramolecular heterosynthon. The strong hydrogen bond includes \((N-H\cdots O), (O-H\cdots O), (\cdot N-H\cdots N),) and \((O-H\cdots N).) The weak hydrogen bonds involve the \(-C-H\cdots O) and \(C-H\cdots O=C).
Co-crystals can be prepared by solvent and solidly based methods. The solvent-based methods involve slurry conversion solvent evaporation, cooling crystallization, and precipitation. The solid based methods involve net grinding; solvent-assisted grinding and sonication (applied to either too wet or dry solid mixtures) 80° to 85°. Cocrystals are typically generated through slow evaporation of solutions of the two components. This approach has been successful with molecules of complementary hydrogen bonding properties, in which case cocrystallization is likely to be thermodynamically favored. A multitude of other methods exists in order to produce cocrystals. Crystallizing with a molar excess of one cocrystal former may produce a cocrystal by a decrease in solubility of that one component. Another method to synthesize cocrystals is to conduct the crystallization in a slurry.

Changing the solvent will change the intermolecular interactions and possibly lead to cocrystal formation. Also, by changing the solvent, phase considerations may be utilized. A cooling molten mixture of cocrystal formers often affords cocrystals. Seeding can be useful. Another approach that exploits phase change is sublimation which often forms hydrates.

Solution co-crystallization

For solution co-crystallization, the two components must have similar solubility; otherwise, the least soluble component will precipitate out exclusively. However similar solubility alone will not guarantee success. It has been suggested that it may be useful to consider polymorphic compounds, which exist in more than one crystalline form as co-crystallizing components. If a molecular compound exists in several polymorphic forms it has demonstrated a structural flexibility and is not locked into a single type of crystalline lattice or packing mode. Thus, the chance of bringing such a molecule into a different packing arrangement in coexistence with another molecule is increased. Clearly, polymorphism alone does not guarantee the functionality of a compound to act as a co-crystallizing agent, whilst the ability of a molecule to participate in intermolecular interactions obviously plays a critical role.

Scale-up crystallization was performed in a 500 ml water-jacketed glass crystallization vessel. The temperature was maintained by a circulating water bath. A reflux column, digital thermometer, and overhead stirrer with a glass shaft and Teflon blade were attached to vessel ports. The drug and co-crystal former were added to a reaction vessel. The solids were dissolved in ethanol/methanol mixture and heated to 70° for 1 h under reflux. The temperature was decreased in 10° increments to induce precipitation in a stirred, unseeded system. Observe the appearance of the cocrystal. Literate to enhance solids recovery decrease the further temperature.

Grinding

When preparing co-crystals, the product obtained from grinding is generally consistent with that obtained from solution. This may indicate that hydrogen-bond connectivity patterns are not idiosyncratic or determined by non-specific and unmanageable solvent effects or crystallization conditions. Nevertheless, there are exceptions. Whilst many co-crystal materials can be prepared from both solution growth and solid-state grinding, some can only be obtained by solid-state grinding. An example is that in the co-crystallization of 2, 4, 6-trinitrobenzoic acid and indole-3-acetic acid, different crystal forms were obtained from solution compared with grinding. Failure to form co-crystals by grinding may be due to an inability to generate suitable co-crystal arrangements rather than due to the stability of the initial phases. When co-crystal formation has been successful from solution, but not from grinding, solvent inclusion in stabilizing the supramolecular structure may be a factor.

The recent technique of adding small amounts of solvent during the grinding process has been shown to enhance the kinetics and facilitate co-crystal formation and as lead to the increased interest of solid-state grinding as a method for co-crystal preparation. Grinding, both neat and
liquid-assisted, is employed to produce cocrystal, e.g., using a mortar and pestle, using a ball mill, or using a vibratory mill. In liquid-assisted grinding or kneading, a small or substoichiometric amount of liquid (solvent) is added to the grinding mixture. This method was developed in order to increase the rate of cocrystal formation, but has advantages over neat grinding such as increased yield, ability to control polymorph production, better product crystallinity, and applies to a significantly larger scope of cocrystal formers and nucleation through seeding.

**Slurry Conversion**

Slurry conversion experiments were conducted in different organic solvents and water. Solvent took about 100 or 200 ml. This solvent was added to the co-crystal (20 mg) and the resulting suspension was stirred at room temperature for some days. After some days, the solvent was decanted and the solid material was dried under a flow of nitrogen for 5 min. The remaining solids were then characterized using PXRD.

**Antisolvent Addition**

This is one of the methods for precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient. Solvents include buffers (pH) and organic solvents. For example preparation of co-crystals of aceclofenac using chitosan, in which chitosan solution was prepared by soaking chitosan in glacial acetic acid. A weighed amount of the drug was dispersed in chitosan solution by using high dispersion homogenizer. This dispersion was added to distilled water or sodium citrate solution to precipitate chitosan on drug.6

**Methodologies for Characterization**

Cocrystal engineering has become of such great importance in the field of pharmaceuticals that a particular subdivision of multicomponent cocrystals has been given the term pharmaceutical cocrystals to refer to a solid cocrystal former component and a molecular or ionic API. However, other classifications also exist when one or more of the components are not in solid form under ambient conditions.

For example, if one component is a liquid under ambient conditions, the cocrystal might actually be deemed a cocrystal solvate as discussed previously. The physical states of the individual components under ambient conditions is the only source of division among these classifications. The classification naming scheme of the cocrystals might seem to be of little importance to the cocrystal itself, but in the categorization lies significant information regarding the physical properties, such as solubility and melting point, and the stability of API’s.

Cocrystals may be characterized in a wide variety of ways. Powder X-Ray diffraction proves to be the most commonly used method in order to characterize cocrystals. It is easily seen that a unique compound is formed and if it could possibly be a cocrystal or not owing to each compound having its own distinct powder diffractogram. Single-crystal X-ray diffraction may prove difficult on some cocrystals, especially those formed through grinding, as this method more often than not provides powders. However, these forms may be formed often through other methodologies in order to afford single crystals.

Aside from common spectroscopic methods such as FT-IR and Raman spectroscopy, solid-state NMR spectroscopy allows differentiation of chiral and racemic cocrystals of similar structure. Other physical methods of characterization may be employed. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) are two commonly used methods in order to determine melting points, phase transitions, and enthalpic factors which can be compared to each individual cocrystal former.

A screening procedure has been developed to help determine the formation of cocrystals from two components and the ability to improve the properties of the pure API. First, the solubilities of the individual compounds are determined. Secondly, the cocrystallization of the two
components is evaluated. Finally, phase diagram screening and powder X-ray diffraction (PXRD) are further investigated to optimize conditions for cocrystallization of the components.

This procedure is still done to discover cocrystals of pharmaceutical interest including simple APIs, such as carbamazepine (CBZ), a common treatment for epilepsy, trigeminal neuralgia, and bipolar disorder. CBZ has only one primary functional group involved in hydrogen bonding, which simplifies the possibilities of cocrystal formation that can greatly improve its low dissolution bioavailability.

Theophylline crystallized rapidly from a hot ethylene glycol solution forms theophylline co-crystals. This technique was confirmed as being functional by testing for a known co-crystal of theophylline and p-nitrophenol. Salicylic acid, p-hydroxybenzoic acid, sorbic acid, 1-hydroxy-2-naphthoic acid, glycolic acid, and 2,5-dihydroxybenzoic acid were all tested as guest compounds and in each, a co-crystal formation had occurred. Raman spectra of the pure guest acid, theophylline, and the co-crystal were obtained and compared to confirm co-crystal formation. This invention provides information regarding a new method for co-crystallization i.e ethylene glycol based method.

As one aspect, novel co-crystals are provided. The novel co-crystals comprise one or more active agents, particularly of the salts of such active agents. Novel forms of salts of active pharmaceutical ingredients are provided. For example, the present invention provides novel co-crystals of fluoxetine HCl and benzoic acid; fluoxetine HCl and succinic acid; and fluoxetine HCl and fumaric acid.

Novel forms or solid state phases of active pharmaceutical ingredients may be prepared for which there are no known polymorphs, solvates or hydrates, or where such polymorphs, solvates or hydrates were disfavored. Co-crystals fulfill the criteria for patent eligibility: novelty, utility, and non-obviousness. In order to better predict the miscibility of a drug substance and a potential conformer, The use of Hansen solubility parameters has been investigated. Using Indomethacin as a model compound the parameters of over thirty conformers were calculated, and the difference in parameters between the drug and the conformers calculated using established procedures. The predicted results were found to be experimentally viable in nearly every instance, and in addition, two new cocrystals were discovered after have been predicted.

The use of non-equilibrium conditions has also been used to obtain preferential enantiomeric enrichment during the cocrystallization of racemic phenylalanine and fumaric acid. The cocrystallization of caffeine with glutaric acid from acetonitrile has been monitored using infrared absorption spectroscopy (attenuated total reflectance sampling) and particle vision measurement as a means to effect feedback control over the process. By controlling crystallization parameters, it was shown that one could eliminate nucleation of an undesirable metastable crystal form and produce large particles with a minimum content of fines.

The use of membrane-based crystallization technology has been investigated for the production of cocrystals of carbamazepine and saccharin. In this approach, as long as the initial composition of the aqueous ethanol solvent system was optimized, the membrane technology enabled one to control the degree of supersaturation during the process and thus obtain the desired product. The use of a modified planetary mill with the capacity to process 48 samples in parallel has been investigated for the carbamazepine/saccharin, caffeine/oxalic acid, caffeine/maleic acid cocrystal systems.

The use of conformer milling prior to spontaneous cocrystal formation has been investigated for a number of known systems, where the initial reactants were initially milled to particular particle size range and then allowed to form co-crystals in a solid state convection mixing apparatus. The rate of
carbamazepine and nicotinamide cocrystal formation has been found to be accelerated by the enhanced water sorption of polyvinylpyrrolidone in the reaction mixture. The mechanism for transformation of the drug/conformer/polymer ternary mixture was seen to proceed through moisture absorption by the polymer that was followed by dissolution of the components and formation of cocrystal product. The efficient formation of the cocrystal product was explained by the increased mobility of water in the ternary mixture that led to a more effective dissolution and supersaturation of the conformers.

Electrically-induced reactions have been shown to afford a possible pathway for the preparation of cocrystal products, where the principle was established using a system consisting of cinnamic acid and 3-nitrobenzamide. Cinnamate anions were neutralized by electrolytically generated hydrogen ions, whereupon the newly formed cinnamic acid was able to form a cocrystal product with the electrochemically inactive 3-nitrobenzamide. The methodology was proposed for the product removal of ionizable compounds at conditions for which conventional methods of crystallization were not practical.

**Influence of Process Variables on Cocrystal Habit**

Habit describes the external shape of a crystal, whereas polymorph state refers to the definite arrangement if molecules inside the crystal lattice. Supersaturation, nucleation and crystal growth are the basic three steps in crystallization. A thermodynamic parameter like solubility, kinetical parameter like supersaturation, nucleation rate, dissolution rate, antisolvent addition rate, and evaporation rate phenomenon governs the crystallization.\(^1\)\(^1\) Cooling a supersaturated solution of drug or pouring it into crystallizing solvent maintained at a low temperature immediately decreases the drug solubility and results in rapid deposition of drug molecules on the nuclei. Rapid cooling leads to the formation of platy or needle-shaped crystals, slow rate of cooling forms compact, symmetric or elongated prisms.

The degree of solution agitation has an influence on saturation level, high speed of agitation leads to elongated crystals with small particle size distribution having good flowability and less sedimentation in suspension. The slow speed of agitation or unstirred solution forms large platy crystals. The nature of solvent has been found to have a profound effect on the crystal habit of ibuprofen. Crystallization of ibuprofen from ethanol and acetone having high surface tension, dielectric constant and less specific gravity were thin, platy, and nearly circular in shape, while those obtained from propylene glycol and 2-propanol were rod-shaped.

When pH was decreased by the addition of hydrochloric acid to sodium hydroxide solution (pH-10) resulted in the formation of needle-shaped crystals. However, spherical agglomerates were obtained when ibuprofen was dissolved in acetonitrile because of limited miscibility with water.\(^1\)\(^2\) The low temperature of crystallizing solvent produces irregularly shaped crystals while in case of high-temperature nuclei formation is delayed and fine, symmetric crystals are produced.

Co-crystal formation during co-grinding and storage is mediated by an amorphous phase, the rate of co-crystallization is dependent on the process and storage temperature, glass transition temperatures of reactants and additives, milling time and mill type. Ions, polymeric molecules, or the other substances present in solute or solvent acts as impurities for the growing crystals and modify crystal habit. Impurity is known to modify the growing crystals into a specific morphology.

**Cocrystal System of Pharmaceutical Interest**

1:1 cocrystal of carbamazepine with indomethacin was produced by a milling process followed by exposure to 40\(^\circ\)C and 75% relative humidity for 21 days, and also by grinding in a mortar. The product was characterized by X-ray powder diffraction, and the resulting pattern indexed to a monoclinic unit cell.\(^1\)\(^3\)
The 1:1 cocrystal formed by pyrazinamide and diflunisal:

Pyrazinamide  Diflunisal

This cocrystal was able to be formed by grinding equimolar amounts of the reactants followed by thermal treatment at 80°C. The cocrystal was also obtained by means of ethanol-assisted ball mill grinding and by room temperature annealing of the mixture obtained by neat ball mill grinding. The dual-drug product was described as being of value in that side effects of pyrazinamide could be mitigated and that the aqueous solubility of diflunisal could be improved.

The structure of a 1:1 cocrystal of fluconazole with salicylic acid.

In this structure flunizole and salicylic acid molecules are each joined by hydrogen bonds into homomeric centrosymmetric dimmers, whereupon these dimmers are further linked by an additional O-H...N hydrogen bond (between one of the salicylate carboxylic acid OH groups and a nitrogen atom on a fluconazole triazole atom).

Fluconazole  Salicylic Acid

**Application of Pharmaceutical Cocrystals**

Cocrystal engineering is relevant to the production of energetic materials, pharmaceuticals, and other compounds. Of these, the most widely studied and used application is in drug development and more specifically, the formation, design, and implementation of active pharmaceutical ingredients, or API’s. Changing the structure and composition of the API can greatly influence the bioavailability of a drug. The engineering of cocrystals takes advantage of the specific properties of each component to make the most favorable conditions for solubility that could ultimately enhance the bioavailability of the drug. The principal idea is to develop superior physicochemical properties of the API while holding the properties of the drug molecule itself constant.

**Pharmaceuticals**

Cocrystal engineering has become of such great importance in the field of pharmaceuticals that a particular subdivision of multicomponent cocrystals has been given the term pharmaceutical cocrystals to refer to a solid cocrystal former component and a molecular or ionic API. However, other classifications also exist when one or more of the components are not in solid form under ambient conditions. For example, if one component is a liquid under ambient conditions, the cocrystal might actually be deemed a cocrystal solvate as discussed previously. The physical states of the individual components under ambient conditions is the only source of division among these classifications. The classification naming scheme of the cocrystals might seem to be of little importance to the cocrystal itself, but in the categorization lies significant information regarding the physical properties, such as solubility and melting point, and the stability of API’s.

The objective of pharmaceutical cocrystals is had properties that differ from that expected of the pure API’s without making and/or breaking covalent bonds. Among the earliest pharmaceutical cocrystals reported are of
sulfonamides. The area of pharmaceutical cocrystals has thus increased on the basis of interactions between API’s and cocrystal formers. Most commonly, API’s have hydrogen-bonding capability at their exterior which makes them more susceptible to polymorphism, especially in the case of cocrystal solvates which can be known to have different polymorphic forms. Such a case is in the drug sulfathiazole, a common oral and topical antimicrobial, which has over a hundred different solvates.\textsuperscript{19}

It is thus important in the field of pharmaceuticals to screen for every polymorphic form of a cocrystal before it is considered as a real improvement to the existing API. Pharmaceutical cocrystal formation can also be driven by multiple functional groups on the API, which introduces the possibility of binary, ternary, and higher ordered cocrystal forms. Nevertheless, the co-crystal former is used to optimize the properties of the API but can also be used solely in the isolation and/or purification of the API, such as separating enantiomers from each other, as well and removed preceding the production of the drug.\textsuperscript{20}

**Energetic Materials**

Two explosives HMX and CL-20 cocrystallized in a ratio 1:2 to form a hybrid explosive. This explosive had the same low sensitivity of HMX and nearly the same explosive power of CL-20. Physically mixing explosives creates a mixture that has the same sensitivity as the most sensitive component, which cocrystallization overcomes.\textsuperscript{21}

Crystal form can be crucial to the performance of a dosage form. This is especially true for compounds that have intrinsic barriers to drug delivery, such as low aqueous solubility, slow dissolution in gastrointestinal media, low permeability and first-pass metabolism. The nature of the physical form and formulation tends to exhibit the greatest effect on bioavailability parameters of water-insoluble compounds that need to be given orally in high doses.\textsuperscript{22}

An alternative approach available for the enhancement of drug solubility, dissolution and bioavailability are through the application of crystal engineering of co-crystals. The physicochemical properties of the active pharmaceutical ingredients and the bulk material properties can be modified, whilst maintaining the intrinsic activity of the drug molecule.

**Synthesis with Cocystals Green Chemistry Opportunities**

Cocrystals offer the potential to eliminate the need for use of a solvent in a chemical reaction and thereby reduce the cost of materials used in processing and all of the costs of dealing with solvent waste. Such cocrystal controlled ‘solvent-free synthesis’ approaches have already demonstrated that high yield solvent-free synthesis can be accomplished in several classes or reaction through two strategies:

- The use of conformers to serve the role of a template for aligning reactive groups, For example, photodimerization of olefins\textsuperscript{23}
- The formation of cocrystals from two reactive conformers followed by application of stress. For example, condensation.

**Future Perspective**

- Reformulation of existing drugs for improved performance
- Life cycle management with recently approved drugs
- Enabling novel development compounds; performance and purification
- Scale-up: both batch mode and continuous
- Green chemistry and synthesis with cocrystals as intermediates.

**Advantages**

- Co-crystals having advantages like stable crystalline form (as compared to amorphous solids).
- Here no need to make or break covalent bonds.
• It has theoretical capability of all types of API molecules (weakly ionizable/non-ionizable) to form co-crystals.24
• The existence of numerous potential counter-molecules (food additives, preservatives, pharmaceutical excipients, and other APIs).
• The only solid form that is designable via crystal engineering patentable expanding IP portfolios.
• Cocrystals can be produced using solid-state synthesis green technologies high yield, no solvent or by-products.

CONCLUSION

Thus cocrystal performs a major role in pharmaceuticals. By enhancing solubility they prevent the excess use of solvents. Also, the bioperformance and bioavailability can be enhanced. So that easy distribution of particular drug product may be the result. In regard to the patent landscape for pharmaceutical cocrystals, we should expect to see continued and likely accelerating activity in various regions, as it likely to continue to be the case for solid forms in general.25

Pharmaceutical co-crystals represent an advantageous class of crystal form in the context of pharmaceuticals. Co-crystals of drugs and drug candidates represent a new type of material for pharmaceutical development. Co-crystals are relatively new to the pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs. Co-crystals have the potential to be much more useful in pharmaceutical products than solvates or hydrates. The relevance of co-crystals in API formulation includes the ability to fine-tune physical properties, characterization of API, identify and develop new, proprietary forms of prescribed drugs and the opportunity to generate intellectual property.26

Further research is desirable in order to scale up co-crystal systems and implement manufacturing of final dosage forms on a commercial scale. Screening for solid forms is important to guarantee that the optimum form is carried forward in development and to minimize the likelihood of unexpected form conversion.

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