Review Article

Cocrystallization: An Innovative Route toward Better Medication

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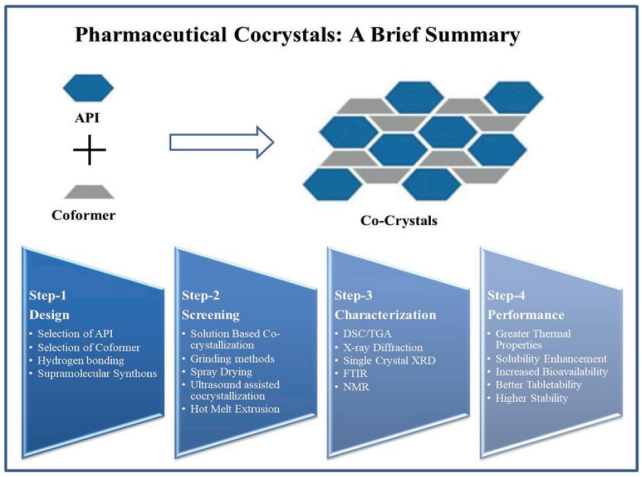
Abstract

Nowadays, poor solubility, lower bioavailability, and hindered physical, chemical, and biopharmaceutical properties of active pharmaceutical ingredients (APIs) become a very important matter of discussion for pharmaceutical scientists. It is a challenging task for pharmaceutical researchers and industry to develop a suitable formulation with improved physicochemical properties. The process of cocrystallization is long known; however, in the recent times, this approach has gained enormous importance in pharmaceuticals as a relatively new method for enhancement of solubility, bioavailability, stability, thermal properties, permeability, tablet ability, and other related physicochemical properties. Cocrystals are multicomponent systems in which two components, an API and a coformer, were present in stoichiometric ratio and bonded together with non-covalent interactions in the crystal lattice. Cocrystallization offers better optimization of not only physicochemical properties but also therapeutic response and pharmacological properties of APIs. The design of a cocrystallization experiment is based on robustness, hydrogen bonding rules, and potential intermolecular interactions. Various theoretical and experimental approaches increase the chances for selection of a suitable coformer, the most challenging step during the design of cocrystal formation. The present review covers classification of cocrystals, drug selection criteria for cocrystals, chemistry involved in cocrystal formation, methods of preparation, their characterizations, and various applications in pharmaceutical and biomedical fields.

Keywords: *Cocrystallization, cocrystals, coformer, polymorphs, salts*

Graphical abstract



Introduction

During the research and development phase, many possible promising drug candidates are eliminated from late-stage development, mainly because of poor bioavailability. To overcome these issues related to poor solubility and to tailor physical, chemical, and biopharmaceutical properties of active therapeutic ingredients, different solid-state formulation approaches of a given active pharmaceutical ingredient (API) may be explored. In this regard, crystal engineering is being commonly employed to design and synthesize the cocrystal-based pharmaceuticals.[1] Among the biopharmaceutical properties, solubility still remains a critical challenge among all the issues faced by the pharmaceutical industry

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during drug development process.[2] Approximately more than 40% of drugs in the market today have poor solubility and about 90% of APIs are not able to cross the barriers of drug development and hence fail to enter the market because of solubility-related issues. Therefore, common techniques like salts formation, solid dispersions, amorphous and polymorphic forms, and inclusion complexes are used by formulation scientists to improve solubility and dissolution rate.[3,4] Apart from these conventional methods, cocrystallization offers a diverse mechanism to tackle these issues. Cocrystallization can be employed on any API either it is acidic, basic, or ionizable one. Desiraju[5] defined "crystal engineering as the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties."

Cocrystallization

In the late 1980s, several factors contributed to the evolution of crystal engineering. Determination of crystal structure of small organic molecules is easy due to the advances in both analytical and computational methods. The most notable among them was the emergence of Cambridge Structural Database (CSD), which can be utilized for collection of data related to crystal structure information, and also used to analyze and therefore identify recurrent patterns of molecules in crystal structure.[6,7] In 1989, a book authored by G. R. Desiraju[5] entitled *Crystal Engineering: The Design of Organic Solids* showed that the designing of organic solids was considered as pioneer in providing motivation in the field of Crystal Engineering.

Cocrystallization in pharmaceuticals

Cocrystallization process design involves the following essential steps:

- Developing a rationale for selection of solvent.
- The phase diagram enables the identification of information related to the thermodynamic stability in a system containing more than one compound.
- Identification of mechanism for induction of nucleation and control of saturation kinetics for the process.

The selection of solvent is based on selecting a coformer with higher solubility than the API and cocrystal. The difference between critical concentration and solubility of the coformer, this selection of solvent being based on the equilibrium diagram of multicomponent's solid–liquid phase. Both of these steps have their own merits; the former offers higher productivity rate of cocrystals whereas the latter offers the widest window for phase-pure crystallization, both of these provide sufficient driving force for cocrystallization.

Nucleation and crystal growth kinetics are studied as a function of super-saturation as well as coformer concentration. Hence the overall cocrystallization experiment design can be summarized as follows: the preparation of a saturated solution of coformer at optimum temperature in the particular solvent, selecting a particular temperature at which to dissolve the API with heat so as to ensure that a point is reached where the concentration of the coformer is just above the critical coformer concentration in order to maximize the throughput which induces nucleation in a controlled manner so as to achieve control over particle size and purity during the growth of the crystal. Solvents in which coformers and cocrystals have low solubility are used to prepare a solution of coformer to free up the cocrystals from residual solution and to minimize the risk of conversion into pure components.[8]

Salts, solvates (hydrates), solid dispersions, polymorphs, and cocrystals

The cocrystallization process in pharmaceuticals has gained widespread attention as a new method for altering physical, chemical, and pharmacological characteristics of drugs. Cocrystallization provides a couple of benefits over other forms. First of all, cocrystallization can be used for a large number of APIs, and secondly the availability of a large number of potential coformers increases the possibility of the cocrystals that can be synthesized for an API.[9] Pharmaceutical salts and cocrystals share a common analogy, for salts, there should be at least 2-unit difference between pK_a of an acid and base while in contrast for cocrystals, the difference should be between 0 and 1 unit. This method is not applicable in case of binary acid and base combination as multiple combinations are possible for cocrystals.[10,11] An additional advantage that cocrystallization possesses is that even the properties of a non-ionizable API could be tailored.[12]

Physical state of the individual components is the primary difference between cocrystals and solvates.[13] When one component in the crystallization is liquid at 25°C, it is known as solvate, whereas if both components are solid at room temperature, cocrystals are formed. The occurrence of solvates is serendipitous during cocrystallization process[14] and can solve the solubility issue of drugs, one such example is the solvated form of spironolactone.[15] However, solvated crystals during storage may undergo desolvation making them unstable, this process of desolvation may render them into amorphous or other crystalline forms that may have less solubility and hence dissolution. From a regulatory perspective, solvent levels in solvated crystals may possess toxicological properties and hence making them unfit for regulatory approval.

Cocrystals, owing to the rationale design strategies, are comparatively more stable, also as crystalline substances; polymorphic cocrystal forms are very rare. Only 20 polymorphic cocrystals including caffeine and glutaric acid have been reported till date[16] while "co-crystals are defined by a single phase (miscible) multi-component system in the crystalline state, in the amorphous state they have been referred to as molecular dispersions" [Figure 1].[17,18] Solid dispersions and cocrystals are different substances; in case of solid dispersions, APIs are dispersed in the inert vehicle in solid form, while cocrystals involve non-covalent bonding between two or more substances, one of them being a biologically active

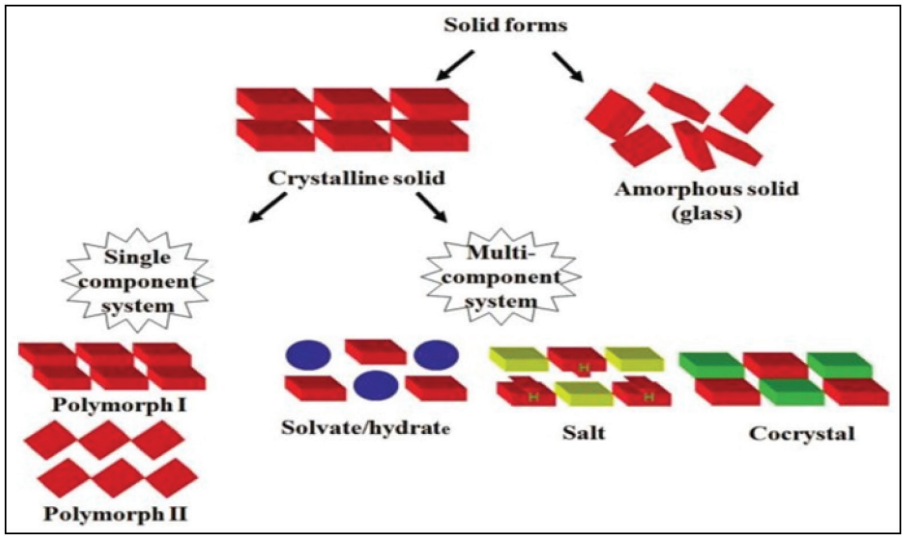

Figure 1: Various multicomponent crystalline solids

substance.[19,20] Currently, numerous methods of preparations are employed such as freeze-drying technique,[21] spray drying,[22] and by using supercritical fluids.[23,24] The key advantages related to crystallization approach to change the property of APIs are the hypothetical ability of every kind of API molecules, as well as feeble ionizable and nonionizable, to make cocrystals and the existence of diverse, important compounds, preservatives as well as food additives, and pharmaceutical recipients as APIs for cocrystal production. A major advantage is that cocrystallization process may provide a better opportunity to the pharmaceutical industry to obtain patents by improving the physicochemical properties of existing APIs.[25]

Pharmaceutical Cocrystals

Definition

Cocrystals belong to a class of long known but understudied compounds; one of the earliest known cocrystal, quinhydrone, was synthesized in 1844.[26,27] However, even after so many years, the definition of cocrystals still remains a debatable matter, but mainly the cocrystals are defined as "a mixed crystal or crystal that contains two different molecules."[28] Another definition that uses the concept of supramolecular chemistry is that "a co-crystal is the consequence of a molecular recognition event between different molecular species."[29] Furthermore, Aakeroy[30] suggested that cocrystals are "made from reactants that are solids at ambient temperature."[31] Aakeroy's definition excluded all hydrates and other solvates, which eliminated molecules that are typically classified as inclusion compounds or clathrates. The confusion regarding the definition of cocrystals remained 160 years until the scientists realized to clearly differentiate multicomponent crystal structures made up of more than two solids from those components that are mainly made up of more than two solids and including one liquid system. Although pharmaceutical cocrystals are defined as "co-crystals that are formed between a molecular or ionic API and a co-crystal former that is a solid under ambient conditions,"[32] FDA in its draft guidance proposed the following definition: "Solids that are crystalline materials composed of two or more molecules in the same crystal lattice." All these definitions lower the level of uncertainty, but an overlap between these classes still remains like considering ambient conditions. When a crystal substance contains one solid and other component is liquid, it is known as solvate crystal or hydrate. However, a multicomponent system made of molecular coformer and an ionic API would simply be classified as a pharmaceutical cocrystal.[33] Particularly, the concepts of supramolecular synthesis and crystal engineering to the development of pharmaceutical cocrystals largely remain unexploited.[34]

Drug and coformer selection criteria

In the crystal engineering technique, the pharmaceutical properties of drugs are changed without disturbing their inherent structures. The presence of various chemical groups such as carboxylic acids,[35] carbohydrates, amides,[36] amino acids, and alcohols in the coformers leads to the formation of cocrystals with different drugs.[37] The most frequently used functional group is carboxylic acid in cocrystal formation,[38,39] and in the USA, out of 100 most selling APIs, around 30 APIs contain this functional group.[40] So, in cocrystallization studies, the presence of carboxylic acid group plays an admirable role. Synthons are responsible for holding the molecules, when the formation of a compound occurred through non-covalent interactions. Due to strength, directionality, and higher rate of recurrence, hydrogen bonds are often used for designing of cocrystals. In 1991, Etter gives three rules for hydrogen bonding pattern[39]: (1) every available hydrogen molecule could be used in the formation of bonding, (2) every acceptor of hydrogen bond could participate if H-bond acceptors are present in the molecule, and (3) H bonding is possible when good acceptor and donor of H-bond is present in the molecule. The formations of synthons are governed by strength of hydrogen bonding between cocrystal formers, not by the total number of groups

available [Figure 2]. Based on the above-discussed rules, we can predict the formation of synthons within different functional groups. Basically, synthons are essential structural entities between supermolecules formed via non-covalent bonding and made up of molecular fragments and supramolecular links among them.[13] Supramolecular synthons could be classified into two categories: supramolecular homosynthons and supramolecular heterosynthons. The first one is composed of self-complementary functional groups whereas the second one is composed of dissimilar but complementary functional groups. Supramolecular heterosynthons formation takes place by non-covalent interaction between various drugs that leads to cocrystal formation. The concept of supramolecular approach is utilized for cocrystals screening but nowadays CSD is used for the selection of suitable coformers for various drugs.[41]

The selection of coformers [Figure 3] remains a key challenge because the physicochemical properties of coformers affect the properties of cocrystals formed. In the past, a trial-and-error

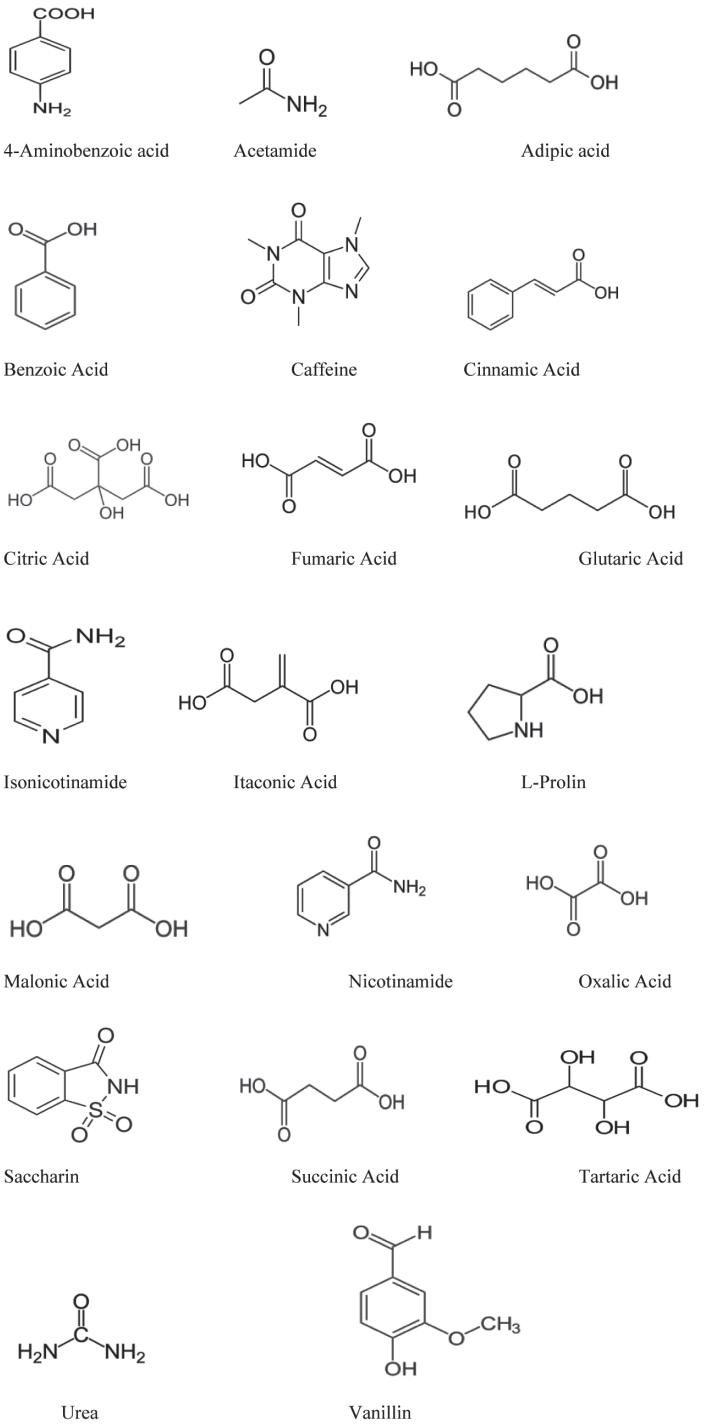

Figure 2: Various coformers used in pharmaceutical cocrystallization process

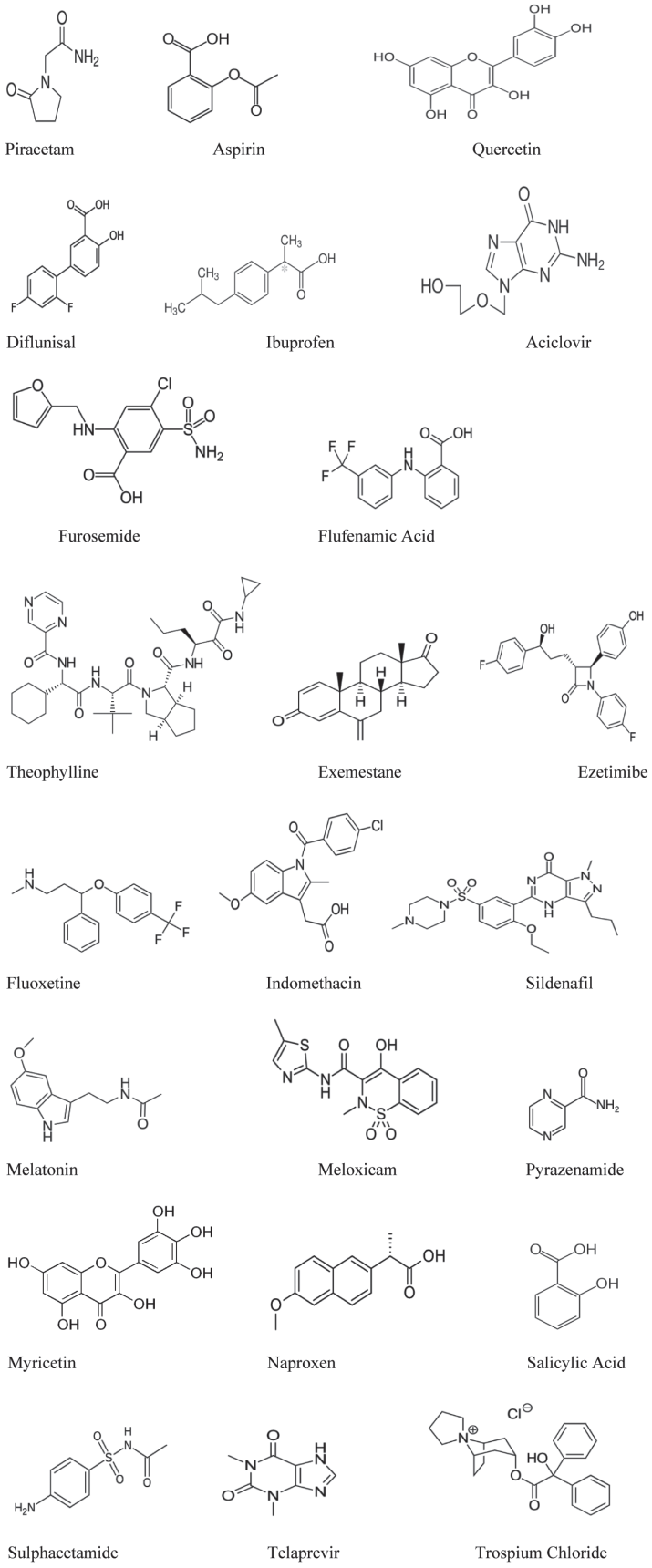

Figure 3: Examples of some drugs having poor solubility issues

technique was used for API [Figure 3] and coformer selection, but that was an expensive technique.[13] The use of statistical analysis of cocrystal details on CSD helps the researchers to find the best suited cocrystal forming pairs via molecular modeling, leading to a reduction in time and experimental costs. When molecules interact through various competing synthons, in that case a hierarchy must be established based on whatever cocrystal is being designed to do. There are lots of weak interactions between APIs and coformers which directly or indirectly effects the synthon formation process. These interactions leads to the failure of CSD analysis of cocrystals formation.[41] With the use of CSD, we can analyze the bonds, atoms, functional groups, hydrogen bond acceptors and donors, size, shape and surface area descriptors, molecular electrostatics, and polarity descriptors of compounds capable of cocrystal formation more accurately.[13,41] When there are several functional groups involved in a given molecule (drug or coformer), CSD seldom provides necessary information to tackle the hierarchy of supramolecular synthons. Meanwhile, in nucleation process of cocrystals and crystals, the role of solvents is not clearly understood, but solvents can play critical role in the preparation of cocrystals from solution.

The physicochemical properties of easily ionizable functional groups lacking drugs could be manipulated through cocrystallization process.[41]

Chemistry involved in cocrystallization

In the cocrystallization process, supramolecular chemistry is involved as a central key point, as in this process the actual idea involved is manipulation of self-assembly of crystalline solids.[31,42] The intermolecular interactions like π–π stacking interactions, van der Waals force and hydrogen bonding involved in formation of cocrystals. The changes in crystal packing of solid compounds via intermolecular interactions, *viz*., π–π stacking, van der Waals forces, halogen bonding, and hydrogen bonding lead to the formation of cocrystals.[43] In research area of cocrystallization, the term "supramolecular synthon" is frequently used and it means the construction of structural units via known conceivable synthetic operations involving intermolecular interactions.[44]

Involvement of H-bonding in process of cocrystallization

This was acknowledged in various systemic studies that almost all hydrogen bond acceptors and donors lead to the formation of hydrogen bonds. So, hydrogen donor–acceptor rule can be greatly utilized to design a particular hydrogen bond interaction.[45] Based on possible cocrystal formation, a sensible and efficient cocrystal designing approach could be utilized for increasing the experimental efficiency. This cocrystal-designing approach involved the potential robustness of intermolecular interactions, namely possibilities of formation of hydrogen bonding motifs and consideration of general hydrogen bonding rules. To analyze the robustness of intermolecular interaction CSD software could be used.[45,46] In a study, caffeine:oxalic acid (2:1) cocrystals, the anticipated OH· · ·N bond is observed in each structure, with the equivalent nitrogen on each drug molecule hydrogen bonding to the carboxylic acid. This seems to be the outcome of NH proton donor presence over theophylline. In spite of forming a weaker CH· · ·O bond, the carbonyl group of oxalic acid is focused on the second molecule of theophylline to make what seems to be a longer NH · · · O interaction. Due to the absence of a stronger donor on caffeine, this interaction could not take place.[45]

Screening Methods

ΔpK_a rule

The value of ΔpK_a is widely being used for cocrystal screening using the following equation:

$$\Delta pK_a = [pK_a\ (\text{base}) - pK_a\ (\text{acid})]$$

When the difference in pK_a values is greater than 2–3, transfer of proton will take place between acids and bases. The value of pK_a lesser than 1 exhibits the formation of cocrystals whereas the values greater than 2–3 revealed the formation of salts [Table 1].[47,48] In CSD, 6,465 possible cocrystals were studied to validate and quantify this rule.

Fabian's method

The method uses molecular descriptors (such as atoms, functional groups, bonds, hydrogen bond donors and acceptors, size, shape, and surface area descriptors) for calculation and screening of cocrystals. In this method, polarity and shape descriptors are used to predict the possible formers of cocrystals. Other molecular descriptors are also important for the prediction of cocrystal formers.[50]

Conductor-like screening model for real solvents

The method was used for checking the miscibility of coformers with super cooled liquid (melt) phase. The excess enthalpy between the pure compounds and mixture of drug and coformer reveals the capability of cocrystallization between a drug and conformer.[51]

Calculated gas phase microextraction by packed sorbent

The gas-phase microextraction by packed sorbent technique was used to calculate the difference in energy ΔE between cocrystals and pure solids in various stoichiometries to

Table 1: Relation of pK_a values with possibility of formation of complexes[49]

Possibility of formation of complexes	pK_a values
Nonionized complexes	$\Delta pK_a < -1$
Ionized complexes	$\Delta pK_a < 4$ (the possibility of formation of ionizable complex increases by 17% by increasing ΔpK_a by 1 unit from 10% at $\Delta pK_a = -1$ to 95% at $\Delta pK_a = 4$)

determine the possible formation of cocrystals between the two solids. The outcome of the study revealed that, when ΔE is more than 11 kJ/mol, the prediction of cocrystals formation increased. More than 1000 compounds were screened to validate this method (including caffeine and carbamazepine) and results were satisfactory enough.[52]

Cocrystal cocktail method

The cocrystal cocktail method is a very useful and lesser time-consuming. In this method, more than three coformers are simultaneously grounded with drug leading to the formation of homo- or heterosynthons between drug and coformers which could be analyzed using thermal analysis methods by checking their endothermic peaks.[53]

Differential scanning calorimetry

Differential scanning calorimetry (DSC) is a rapid thermal method for cocrystal screening.[54] In this method, we check the endothermic peaks for the formation of cocrystals by heating the mixture of drug and coformers in DSC pans. The hypothesis about cocrystal formation is exhibition of three endothermic and a couple of exothermic peaks in thermogram represents the formation of cocrystals with stoichiometric variety [Table 2].[55]

Hot-stage microscopy or Kofler contact method

Hot-stage microscopy or Kofler contact method offers visualization of total phase number that is exhibited by the system when two compounds are heated. When the high melting point compound starts melting and recrystallization occurs before other melted compounds come in contact with it, leading to the formation of zone of mixing.[56,57]

Saturation solubility technique

The saturation solubility technique involved the measurement of saturation solubility of APIs and conformer separately at a reference temperature. Saturation temperature of solvent system is measured by heating with the rate of 0.3°C/min. If the increase in saturation temperature is more than 10°C in comparison to reference temperature, chances for cocrystal formation increase.[58]

Methods of Preparations

There are numerous methods for formulation of cocrystals but traditionally crystallization was carried via solution with a suitable degree of supersaturation *viz*. cooling and evaporation and includes substances having properties of the solubility lowering. Cocrystallization with solvent evaporation technique did not provide favorable results.[59] Generally, two methods are used for cocrystallization: solution-based method and grinding-based method. Solution-based methods are generally preferred because of the formation of cocrystals, which can qualify the testing with single X-ray diffraction. The grinding-based methods include Neat grinding and solvent drop grinding. Currently, newer techniques are available, namely hot-stage microscopy, ultrasound assisted and cocrystallization via supercritical fluid.[60]

Table 2: Relation of cocrystal formation with DSC screening[55]

Endothermic peak	Cocrystal formation
Three endothermic and a couple of exothermic peaks	Cocrystals with stoichiometric variety
Two endothermic and one exothermic peaks	One cocrystal formation with certain molar ratio
One endothermic peak	No cocrystal formation

Grinding method

Cocrystallization product usually prepared with grinding method is consistent as compared to that prepared from solution. The main drawback of this method is its inability to prepare significant arrangements of cocrystals before due to the stability of the initial phases. Solvent method is better than the grinding method because the grinding method leads to solvent inclusion in supramolecular structure stabilization. Solvent drop grinding might enhance the kinetics and assist in the formation of cocrystals leading to increased interest as a cocrystallization technique.[61]

The neat grinding technique can be performed by using vibratory mills, mechanical grinding, or manual grinding,[59] while solvent drop grinding can be done by the addition of suitable solvent at regular intervals with grinding but make sure that the solvent should be capable of dissolving the solid material. Caffeine–glutaric acid cocrystal polymorph when compared with solvent evaporation technique is cost-effective, eco-friendly, and effective for the formation of cocrystals.[60]

Solid-state grinding

In solid-state grinding, the particulate size reduced with increased covalent reactivity within the mixture. This technique offers improvement in simplicity and selectivity over the solution-based cocrystallization technique.[59] Six cocrystals of sulfadimidine with salicylic acid and anthranilic acids were prepared using solid-state grinding technique and grinding technique, respectively. Anthranilic acid replaced salicylic acid due to general arrangement of hydrogen bonds of both cocrystals. In this technique, the major shortcoming is polymorphic transition that leads to serious side effects, causing product withdrawal from the market.[59]

Solvent drop grinding

It is almost same as the solid-state grinding method with the addition of solvent in smaller quantities. Here solvent acts as a catalytic agent.[62] Primarily, cocrystal formation occurred via solution crystal growth method. Most of the crystals grow faster with solid grinding technique whereas others proceed further slowly. For those crystals, solvent drop method is found to be effective.[59] For the preparation of cocrystals of caffeine and glutaric acid, solvent drop grinding technique is found to be suitable over solid-state grinding. Preparation of succinic

acid:anthranilic acid and indomethacin:saccharine was done using the solvent drop grinding method and optimum outcomes of the studies revealed an increase in physical stability and dissolution rates.[61]

Cocrystallization from solution

Here the key requirement is same solubility profile for both compounds undergoing cocrystallization, otherwise the least soluble compound will get precipitated out completely from the solution. However, similar solubility profile of both components could not promise a positive result. It is probably beneficial to trust polymorphic complexes that occur additionally in comparison to solitary crystalline arrangement as cocrystallizing compounds. When a molecular component occurred in various polymorphic states, it revealed a structure-based tractability and cannot be locked into a packing model.[61] For a large-scale production, a water-jacketed vessel with circulating water bath facility for temperature control was used. Teflon blades were used for continuous stirring. Drug and coformers were dissolved in alcoholic solvent at 70°C under reflux for 1 hour. Reduction in temperature with 10°C rate was done to precipitate out the cocrystals. To increase the total yield of solid product, heating rate was reduced.[61]

Solvent evaporation

This is the most traditional method used for cocrystallization, including supersaturation of solution by cooling, evaporating, and use of solvent in which the solubility of drug and coformer is higher. It is assumed that molecules undergo hydrogen bonding when mixed in appropriate quantities. Cocrystals of fluoxetine hydrochloride with different coformers, namely fumaric acid, succinic acid, and benzoic acid, were prepared by using this method for enhancing their intrinsic solubility.[59] In another study, cocrystals of norfloxacin with malonic acid, maleic acid, and isonicotinamide were also prepared with improved physicochemical properties.[61]

Slurry crystallization

The process of addition of a suitable crystallization solvent to the API and its coformer is known as slurry crystallization, the use of this process is governed by the physical stability of the crystallization solvent compared to that of the API and coformer. The synthesis of cocrystals through slurry crystallization was done with 16 coformers.[59] Different solvents could be used for slurry crystallization. Around 100 mL of liquid solvent was added and the suspension was stirred at room temperature for few days. The suspension was then allowed to decant and the cocrystals were dried under nitrogen.[61] Examples of slurry crystallization include the preparation of cocrystals for trimethoprim and sulfamethoxazole using distilled water. The major disadvantage of this method is that it requires a large amount of solvent.[59]

Hot melt extrusion

Hot melt extrusion is an efficient cocrystal synthesis method that does not require any solvents; however, the selection of this process depends on the thermodynamic stability of the API and the coformer. Holt melt extrusion can be optimized using solvent drop extrusion technique, which is an advantage to carry out hot melt at a lowest temperature. Examples include carbamazepine nicotinamide cocrystals.[59]

Sonocrystallization method

The use of sonocrystallization method to synthesize cocrystals is very rarely explored, and this method is suitable for the preparation of nanocrystals. Ultrasound method was used for the preparation of caffeine–maleic acid cocrystals, theophylline, and l-tartaric acid as a coformer.[59]

Characterization of Cocrystals

There are multiple elements that are required to be studied for the formulation of cocrystals such as incompatibility between different components, contaminations, dose, and solubility. Especially in case of polymorphs and salts, properties like solubility and stability play an important role, so these should be considered seriously, because of their effect on API's quality, effectiveness, and stability. There are numerous analytical techniques, namely thermal, spectroscopic, and biological, for characterization of cocrystals. Some of these techniques are discussed below.

Crystallographic studies

Single-crystal X-ray diffraction

Single-crystal X-ray diffraction was generally considered for studying particularly smaller crystal samples. Currently, the traditional anode has been substituted with liquid metal jet containing LaB6 cathode, thus reducing the cooling requirement of anode before operation. Commonly lower temperature studies are performed to decrease the diffuse scattering and thermal motion and also to improve the quality and quantity of data. A liquid or dry nitrogenous gas stream is maintained to set the temperature as well as for cooling the crystals. Helium gas could be used in place of nitrogen, but the temperature ranges remain lower than nitrogen (15–300 K).[63-68]

Powder X-ray diffraction

In case of crystalline substances, a graph is plotted on the intensity of the diffraction due to 2θ value or *d* spacing in cocrystals.[69-72] Subsequently, distinctive powder X-ray diffraction (PXRD) outlines relates to different crystalline arrangements, those may be deliberated as "fingerprints" of particular crystal segments. These segments may denote various drugs or different polymorphs,[63] salts, solvates,[73] and cocrystals of a given drug. So, PXRD could analyze the various phase transitions within polymorphs of same drug, by utilizing variable temperature approach, and capable of differentiating between salt and cocrystals, which basically differ because of the transfer of proton in hydrogen bonding.

Hirshfeld surfaces analysis

Hirshfeld surfaces (HS) are fashioned by segregating space in crystal into sections in which the electronic scattering of an

addition of circular atoms for molecule governs the analogous totaling over the crystal. With the help of HS analysis, we can derive the type of interactions and relative areas of surface matching to such interactions.[74]

Spectroscopic characterization

Fourier-transform infrared (FTIR) spectroscopy can predict the compatibility and possible interactions between APIs and coformers and also chemical conformation of compounds.[51] Aakeroy *et al.*[75] differentiated salts and cocrystals by using FTIR spectroscopy by studying the formation of hydrogen bonding through involvement of carboxylic functional group. Pure APIs, possible coformers, their physical mixtures, and their formulated cocrystals are analyzed and characterized using FTIR spectroscopy.[51]

Terahertz spectroscopy

The range of Terahertz spectroscopy belongs to 0.1–10 THz bands of solid molecules which are obtained from intermolecular vibrations, mainly van der Waals forces, hydrogen bonding, and intramolecular vibrations from larger fragments of macromolecules including combined phonon modes in crystalline lattices and segmental motion of polymeric chains. Temperature plays a crucial role in this technique as likely of fundamental vibrations (kT at 6.2 THz corresponds to 298 K). In this technique, very sharp bands are obtained for crystals although amorphous gives no band or very broader bands.[76-79]

Raman spectroscopy

The conventional Raman spectrum spans from many tens of centimeters to 4000/cm, therefore covers additionally the low-frequency below 400/cm, which is out-of-the-way for regular IR spectrometers.[80,81] Hence, transmission Raman chemical analysis (TRS) was utilized to faithfully determine crystalline component in samples.[82,83]

Solid-state nuclear magnetic resonance and nuclear magnetic resonance crystallography

To evaluate the compounds like polymorphs, pharmaceutical cocrystals, and salts, this methodology is habitually utilized in its high-resolution edition to interpret carbon-13 and nitrogen-15 spectra.[84-86] The quantity of signal- and position-associated intensities give data on the chemical composition of the analyzed compounds.[87-91] Interpretation of ^{13}C and ^{15}N CP/MAS NMR peak is typically complete by evaluation of the equivalent solution spectrum, through spectral editing technique by testing of reliance of the CP strength and via *ab initio* calculation of the chemical shift.[92-95]

Thermal analysis

Differential scanning calorimetry

In DSC, temperature distinction (dT/dt) among a reference and sample substances is considered and so a forethought against the time.[96] The distinction within the heat provided to the sample and the reference is recorded as a performance of temperature. The major utilization of DSC embodies the action definition, as well as temperature, glass transition, Curie temperature, determination of crystallinity, drug alteration, material procedure, and purity management. DSC is the most frequently used thermal analysis technique, mainly attributable to its speediness, ease, and handiness.[97]

Thermogravimetric analysis

It is a thermal-based method, where the mass modification and the weight change of a material are considered as performance of heat or period. Thermogravimetric analysis measurements are mainly used to see the chemical compositions of compounds and envisage their thermal steadiness. This method will describe compounds that display loss or gain of weight because of the sorption/desorption of volatiles, decomposition, oxidization, and reduction.[96,98,99]

Hot-stage microscopy

It is also referred to as thermal research or thermo-microscopy, combine research and thermal analysis. This procedure needs remarks to be created throughout the thermal process of a small amount of a compound on stage, in addition as annotations concerning the crystalline samples. HSM may be a particularly important device for the description of pharmaceutical salts, solvates, and polymorphs.[96]

Utility of Cocrystallization in Pharmaceuticals

The interest of pharmaceutical industry and researchers has been shifted toward cocrystallization and many drugs including newer and older APIs have been included in the preparation of cocrystals and eutectics as these formulations improvise the pharmaceutical issues related to these drugs without altering or modifying their therapeutic activities [Table 3].[119] The enhancements in solubility,[120] stability,[121] and aqueous solubility have been reported after cocrystallization of various APIs. With the drastically improved pharmaceutical characteristics of APIs, cocrystallization process has been considered as the most effective technique to improvise the bioavailability[122] of drugs. It is evident from the literature that by formulating cocrystals of fluoxetine hydrochloride with different coformers, the solubility of each formulation was found to be increased. The solubility of fluoxetine hydrochloride was found to be 11.6 mg/mL, whereas its cocrystals with fumaric acid and succinic acid were found to be 14.8 and 20.2 mg/ mL, respectively.[123] In another study, the solubility profile of cocrystals of Tegafure was found to be much higher in comparison to its pure amorphous state.[124] In this case, the important point is the increment in its solubility without affecting the stability of pure amorphous form of the drug. A vast literature is available containing such examples where solubility and dissolution behavior of various drugs have been modified without changing their original therapeutic properties.[125,126] If we talk about eutectics, the drug:drugs eutectics have been reported in literature. For example, 1:1 eutectic mixture of pyrazinamide and isoniazid exhibits enhanced solubility profile while of PEG and different

Table 3: Various drugs and coformers used for cocrystals formation

Drug(s)	Coformer	Method of preparation	Important points
Ezetimibe[100]	l-Proline and imidazole	Wet grinding and solution crystallization	Proline exists as zwitter ion in the crystal lattice of EZT-PRO. Carbonyl group of EZT formed CH--O bonding Imidazole. Coformer was selected on the basis of pK_a and complimentary structure. Improved solubility and solid-state stability.
Paracetamol[101]	Citric acid	Slow evaporation	Two paracetamol molecules and citric acid form hydrogen bonds
Sildenafil[102]	Acetyl salicylic acid	Solution crystallization	Sil:ASA are held together by C-H—O and C-H-- forces. 75% improved intrinsic dissolution rate.
6-Mercaptopurine[1]	Isonicotinamide	Reaction crystallization method	Cocrystals produced were less hygroscopic. Cocrystals attained maximum solubility in 5–10 min.
Theophylline[45]	Oxalic, malonic, maleic, and glutaric acids	Solid-state grinding and solution precipitation	Theophylline also possesses a good N-H hydrogen bond donor. N H· · ·O hydrogen bond is formed between NH donor of a theophylline by linking with carbonyl oxygen from an adjacent theophylline. This interaction between NH and O leads to formation of H-bond. Improvement of physical properties and avoidance of hydration.
Caffeine[103]	Maleic acid	Ultrasonic assisted solution cocrystallization	Cocrystallization with maleic acid increases solubility of caffeine, which decreases supersaturation.
Myricetin[104]	Acetamide	Solvent drop grinding	4 times increased dissolution rate.
Trospium chloride[105]	Urea	Solvent evaporation	Electronegative chloride anion accepts an H-bond from the best H-bond donor, a hydroxyl group in trospium molecule. Urea molecules form an infinite chain on which chloride anions hang over trospium. Increased intrinsic dissolution rate.
Theophylline[106]	Urea, saccharin, gentisic acid, salicylic acid, glutaric acid, sorbic acid, oxalic acid, maleic acid, and nicotinamide	Supercritical fluid enhanced atomization	Low-soluble coformers produce theophylline crystals with a low dissolving rate while use of high-soluble coformers produce faster dissolving cocrystals.
Diflunisal[107]	Nicotinamide	Supercritical fluid antisolvent precipitation	Acetone was chosen as a solvent for Diflunisal and Nicotinamide pH 7.4 phosphate buffer was used to carry out dissolution studies
Indomethacin[108]	Saccharin	Anti-solvent crystallization, solvent evaporation	N-H…O bonding was formed between the carboxylic acid dimer of Indomethacin and Saccharin imide dimer
Itraconazole[109]	l-malic acid	Gas antisolvent crystallization	The cocrystals obtained by this method were suspected to contain unquantified amount of amorphous material. Gas cocrystallization may have improved itraconazole bioavailability.
Sulfamethazine[110]	Theophylline	Neat cogrinding, solvent-drop cogrinding, and slow evaporation	The sulfamethazine form a dimer via the intermolecular O...H--N and two O...H--N and N...H—N.
Carbemazapine[111]	Saccharin	Cogrinding	Grinding-induced amorphous phases are followed by cocrystal formation. High relative humidity exposure increases rate of cocrystallization.
2-[4-(4-chloro-2-fluoropheoxy) phenyl]pyrimidine-4-carboxamide[112]	Glutaric acid	Solvent crystallization	*In vivo* bioavailability was increased. Cocrystal was found to be physically and chemically stable. Increased dissolution rate.
Ethenzamide[113]	Gentisic acid	Slow evaporation	The primary amide anti-N–H of the Ethenzamide and the 2-hydroxy group of Gentisic acid form two intramolecular N–H..O and O-H..O hydrogen bonds. Dissolution rate of Ethenzamide was improved by a factor of 2.
Artemisinin[114]	Orcinol and Resorcinol	Liquid-assisted grinding	The interaction of trimeric units is through a vast network of C–H...O bonds. Every synthon comprises of O–H...O between the OH group of Resorcinol and carbonyl moiety of Artemisinin.

Table 3: Continued

Drug(s)	Coformer	Method of preparation	Important points
Gabapentin[115]	C-propan-3-ol pyrogallol[4] arene and C-butyl pyrogallol[4] arene	Slow evaporation aided with sonication	Reported cocrystals exhibit bilayer structures comprising of networks of extensive hydrogen bonding networks between the pyrogallol[4]arene, gabapentin molecules.
S-Naproxen and RS-Naproxen[116]	d-proline	Liquid-assisted grinding	Synthon part is mainly composed of zwitterionic entity. The crystalline network in the four cocrystals formed is guided by the amino acid prolinium.
Pyrazine[117]	Dicarboxylic acid, terephthalic, phthalic, fumaric, and succinic acids.	Pyrazine cocrystals were synthesized by neat grinding	Pyridine–carboxylic acid synthon-based H-bonded chains are the backbone of the structure.
Theophylline[118]	Benzoic acid	Liquid-assisted grinding and neat grinding	Carbonyl functional group of Theophylline and COOH of Benzoic acid form an O–H…O hydrogen bond.

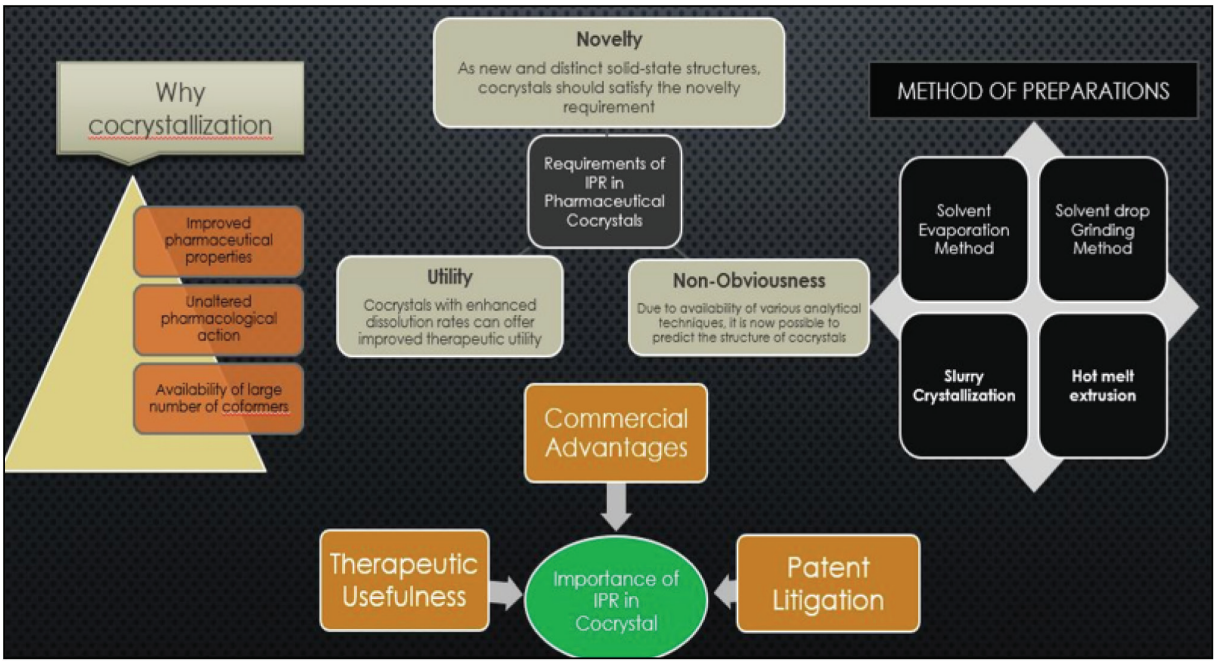

Figure 4: Application of Intellectual Property Rights in pharmaceutical cocrystals

APIs revealed enhanced pharmaceutical characteristics.[127-129] Eutectics mixture of Ibuprofen–menthol showed an improved dissolution behavior.[45] The similar improved dissolution behavior was recognized in case of 2-[4-(4-chloro-2-fluorophenoxy)phenyl] pyrimidine-4-carboxamide:glutaric acid cocrystals.[130] These examples reveal the effects of cocrystallization in improving the solubility and bioavailability of the drugs [Figure 4].[131]

The 1:1 mixture of danazol:vanillin cocrystals showed an increased solubility as compared to poorly soluble pure danazol. The stability of the drugs is also improved by cocrystallization like carbamazepine cocrystals revealed an enhanced hydrostability in comparison to the hydrate formation susceptibility of carbamazepine.[132] An improved humidity stability of theophylline and oxalic acid cocrystals has been reported as compared to their pure state.[133]

Conclusion

Cocrystals were first noticed in 1844, since then their applications to enhance the pharmaceutical properties of drugs (stability, aqueous solubility, etc.) were recognized by the pharmaceutical scientists. Pharmaceutical cocrystals are becoming increasingly important as an alternative way to improve the bioavailability of poorly water-soluble drugs, especially for these neutral compounds or those having weakly ionizable groups. There are many different ways in which

crystallization can be attempted for a single component system including cooling, solvent evaporation, dry grinding, liquid-assisted grinding, sublimation, crystallization from the melt, crystallization from gels, use of supercritical fluids, and pressurization. The additional component (or coformer) within a cocrystal adds an entirely new dimension—the number of experiments available could therefore be multiplied by the number of coformers considered. Cocrystals exhibit complex structures that can conspicuously affect the physical and chemical properties of original substance, with good clinical performance and outstanding stability during processing and storage. As a flourishing research field, cocrystals and cocrystallization technology have been applied in the field of APIs to improve the physiochemical, mechanical, and pharmacokinetic properties of the products, such as higher solubility, faster dissolution, longer shelf life, more efficient bioavailability, and more stable mechanical properties. Researchers have been putting much of their attention into exploring new cocrystals of an API. It is expected that many other pharmaceutical cocrystal systems will be explored in the near future. Meanwhile, there is an increasing need for a better understanding of the mechanism of the cocrystallization process and the theory for how pharmaceutical cocrystal improve the bioavailability of APIs. Succinctly, after achieving all these goals, cocrystals could possibly promise to be a better drug delivery system than existing ones.

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Conflict of interest

There are no conflicts of interest.

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