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A BRIEF OVERVIEW ON COCRYSTALS AND THEIR PHARMACEUTICAL APPLICATIONS

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Abstract

Cocrystals are the three dimensional arrangement of molecular complexes containing therapeutic moieties. They represent a special class of pharmaceuticals with challenging physicochemical properties. This article presents the significance and challenges which are deeply related with the synthesis and design of pharmaceutical cocrystals. The process of cocrystallization is basically dealing with a challenge for modification of physical properties like solubility, physicochemical stability etc. of active pharmaceutical ingredients in comparison to polymorphs, and pseudo polymorphs. Several synthetic methods for development of cocrystals like solid-state grinding and solvent-drop grinding, evaporation, cooling and reaction crystallization methods are discussed. The study also includes several case studies associated with the marketed samples and the future prospect of the technique.

Rezumat

Cocristalele farmaceutice sunt aranjamente tridimensionale de complexe moleculare care conțin fragmente terapeutice. Ele reprezintă o clasă specială de produse farmaceutice cu proprietăți fizico-chimice provocatoare. Acest articol prezintă semnificația și provocările care sunt profund legate de sinteza și designul de cocristale farmaceutice. Procesul de cocristalizare este de fapt o provocare de modificare a proprietăților fizice cum ar fi solubilitatea, stabilitatea fizico-chimică, etc a substanțelor farmaceutice active în comparație cu polimorfele, și pseudo polimorfele. Sunt discutate mai multe metode sintetice de dezvoltare a cocristalelor, cum sunt cele de șlefuire a stării solide, cu picătura de șlefuire, și metodele de evaporare, răcire și cristalizare. Studiul include, de asemenea, mai multe studii de caz asociate cu probele comercializate și perspectiva viitoarelor tehnici.

Keywords: cocrystals, solubility, physical stability, polymorphs, solid state grinding, solvent drop grinding.

Introduction

The therapeutic efficacies of many pharmaceuticals are declined due to their poor aqueous solubility, reduced dissolution rate, chemical stability and moisture uptake tendency. Hence the market value of such crystalline components gets reduced day by day which demands new discoveries in designing the existence of such active pharmaceutical ingredients (APIs).

Rationale behind development of crystals

The active pharmaceutical ingredients (APIs) in crystalline forms are more promising towards the stability, reproducibility and purification of the same in comparison to other types of solid forms, hence having the most priority in comparison to other forms. The properties like dissolution rate and intrinsic solubility of several crystalline forms are different and thus are playing an important role in enhancing the bioavailability. The stability with respect to temperature and humidity are more significantly depending on packaging of crystals. The conditions in which there will be legal issues and challenges towards the protection of patents of APIs in relation to unpredictable crystalline structures and physicochemical properties, [1, 2] that can be resolved by the development of pharmaceutical cocrystals (an emerging field in development of pharmaceutical APIs).

Significance of cocrystals

The development of cocrystals helps in modifying the physicochemical properties of an API without any alteration of bonds. This can be observed with the help of following applications:

1. the terminology “non covalent derivatization” is associated with stability enhancement of Polaroid film [2, 3].
2. it is also very much useful in green chemistry in the context of solid state synthesis.

There is a bunch of research which shows how non covalent interaction or coordination bonds [3] are useful in controlling the alignments of reactants. Photodimerization may be a tool in this study but the literature available does not offer much information on chemical reactions between two or more substrates. However the studies of pharmaceutical cocrystals rely on the following factors. Design: cocrystals are such a class of compounds which are well known with respect to their theoretical approach rather than practical approach. However the non covalent forces useful in three dimensional designing of crystals, justify the pattern of crystal engineering [4, 5]. The hydrogen bonding associated with the ions, salts and the APIs results in development of pharmaceutically promising cocrystals [6-8]. The Cambridge structural database is also useful in justifying the concepts of crystal engineering [9]. The APIs, associated with functional groups externally through hydrogen bonding helps in development of promising cocrystals which can be more useful in the field of pharmacy [10]. Discovery: though it had been known from the very first discovery of cocrystals by dry grinding method, but being realized and accepted recently

that the solvent drop and liquid assisted grinding are the most preferable techniques [11-13]. Diversity: it has been observed that the pharmaceutical cocrystals show several physicochemical properties in comparison to the pure form. However an API can produce thousands of cocrystals by combining with several cocrystal formers. Amongst the developed cocrystals, some of them might be useful in enhancing the solubility as well as bioavailability [14-20] or stability against hygroscopicity [21]. Development: although the development of cocrystals suggests several increment in the physicochemical as well as pharmaceutical properties of the API, not all of them can be considered for the actual purpose. The cocrystals developed from the existing APIs can be considered and permitted for patentization as a new crystalline moiety [22]. After approval of the clinical significance the moiety can be used for formulation and development or can be considered for therapeutic purpose.

Cocrystals

The APIs can be incorporated into crystalline lattice with the help of cocrystal formers for the development of new solid moiety known as cocrystals. As an alternative to the solid dosage forms, cocrystals are emphasized prominently for the development of dosage forms. With the help of such kind of modifications to the APIs, the physicochemical properties of the drug molecules can be improved significantly [23]. However the modification of drug molecules in cocrystal form does not affect their pharmacological response, rather there will be an increment in physical properties of drug molecules such as compaction behaviour, hygroscopicity and aqueous solubility [24].

In the process of cocrystallization it has been observed that there is a competition for aggregation of nuclei to develop a three dimensional lattice design either between homomers (same components) or heteromers (different components) [26]. The molecules are associated with each other with the help of hydrogen bonding. The designing of cocrystals involve a fixed stoichiometric ratio of components in association with van der Waals force of attraction, π - π bonding, ionic bonding and hydrogen bonding [25]. Normally cocrystals are found in solid form at room temperature. Cocrystals differ from conventional crystalline forms of APIs in regards of their polymorphic forms; physical properties and designs of inter molecular packing. However salts can differ from cocrystals with respect to their properties and the key point associated with such difference is the absence of ionized sites on the APIs [26]. The cocrystals of same APIs possess different solubility, dissolution rate, chemical stability and melting point in

comparison to the host crystalline moiety [12]. The study of cocrystals includes:

- selection and identification of suitable cocrystal formers for a particular API,
- screening of optimized cocrystals based on their physicochemical properties and stability,
- confirmation of procedure for the development of pharmaceutical cocrystals on the basis of reproducibility of result,
- scale up and characterization of pharmaceutical cocrystals.

Pharmaceutical cocrystals

The development of pharmaceutical cocrystals is considered to be an important approach for optimization of physical properties of the drug molecules. Two or more neutral components are held together in a crystalline geometry by the help of hydrogen bonding, resulting in the development of cocrystals [23]. The development of pharmaceutical cocrystals possesses several benefits in comparison to the conventional salt forms of the drug moiety which includes:

- both the components i.e. weakly non ionizable as well as weakly ionizable drug components are preferable for development of cocrystals, where as such kind of flexibility is not applicable for development of salts of the same;
- only 10-12 acidic or basic counter ions are there which are normally useful in the development of salts of API, but the development of cocrystals includes a huge number of potential counter molecule [27].

As per the guidelines of FDA (Food and Drug Administration), the components that are only categorized under GRAS (generally regarded as safe) category can only be used for the development of dosage forms. A huge number of components are coming under this category. Hence, a huge choice of components along with different properties can be obtained, thus the optimization of physical properties of API through development of cocrystals can be achieved. However the screening of optimized cocrystals is playing an important role.

Mechanisms involved in cocrystal synthesis

Cocrystals are very commonly developed during the process of cogrinding and storage of amorphous pharmaceuticals. The cocrystals of carbamazepine-saccharin [37], carbamazepine-nicotinamide [45], caffeine-dicarboxylic acids (maleic acid, oxalic acid etc) [41] are generated during

their solid mixing phase of components in exposed moisture uptake conditions, which results in hygroscopicity of components, solubility of cocrystals in aqueous media, dissolution and phase transmission of cocrystals [28]. During synthesis of carbamazepine-nicotinamide cocrystals, the solubility of components for crystal growth is to be reduced for better nucleation and agglomeration. It has also been observed that the development of cocrystals can be obtained by halogen bondings, which were confirmed by analysing their structural engineering. The mechanisms associated with the cocrystal development involve the affinity between the components towards bonding. eg. The bonding between N-I and S-I components. The affinity between N-I lead to development of strong molecular assemblies followed by the development of cross linking of S-I on the former molecular complex [29]. The mechanism behind enhanced dissolution rate associated with different cocrystals is different. In certain cases it may be with respect to:

- reduced particle size, eg. exemestane-maleic acid cocrystals and
- polymorphic forms of cocrystals eg. megestrol acetate-saccharin cocrystals.

However the cocrystals are considered to be more stable in the form in which the cocrystal formers are associated in huge concentration and *vice versa*. The development of cocrystals is also observed in solid mixing of reactants. The examples of cocrystals developed by such technique include carbamazepine-saccharin, carbamazepine-nicotinamide [30].

Techniques for cocrystals development

Solid-state grinding technique

Solid state grinding is basically associated with pressing, crushing and mixing of materials either manually through using the mortar and pestle or mechanically with the help of a mill. As per the development of cocrystals are concerned, solid state grinding is considered as an innovative approach, a suitable alternative of the synthetic technique like solution based cocrystallization. However in some cases the solid state grinding has proved its effectiveness more intensely in comparison to the synthetic methods. The simplicity in developing cocrystals with solid state grinding makes it the most important as well as convenient technique for screening of the same. The development of six different cocrystals of the drug "Sulfadimidine" with different cocrystal formers like anthranilic acid, salicylic acid, with the help of solid state grinding is a great example developed by Caira and coworkers [31]. The development of cocrystals

from caffeine was studied with respect to their altered physical properties and it was reported that the cocrystals can be developed by using solid state grinding technique. Etter and coworkers investigated cocrystals and found that the lattice design is a beauty of hydrogen bonding between the molecules thus agreed with the concept that the cocrystals can be generated by suitable modifications in the lattice arrangement of the parent crystalline moiety through solid state grinding. However the pharmaceutical cocrystals developed through solid state grinding technique transformed their pharmaceutical properties and this fact plays a significant role in their therapeutic efficacy and in some cases such alteration in the lattice design also effects reversely to the pharmaceuticals and leads to their withdrawal from the market [32] (e.g. cocrystals of caffeine with trifluoro acetic acid [33]).

Solvent-drop grinding technique

This technique is considered to be a very good alternative to solid state grinding in the development of pharmaceutical cocrystals. The technique involves the grinding of two different materials as that of solid state grinding along with a little quantity of solvent which is acting as a catalyst for the development of cocrystals. The technique was first demonstrated through cocrystallization of nitrogenous bases with cyclohexane tricarboxylic acid derivatives. In this cocrystal development process it was first time noticed that, the development of such cocrystals which failed in solid state grinding technique are more prominently developed in this technique with maximum purity [34]. The example under this category is the cocrystal development of caffeine: glutaric acid in a ratio of (1:1) in both form I and II. However during the course of cocrystal synthesis it has been observed that form I is more prominently developed by solid state grinding, whereas form II is more predominantly obtained through solvent drop grinding technique [38]. However there are several other examples of solvent drop grinding mediated cocrystal development which are mainly based on stoichiometric selectivity. The development of interconversions in crystalline forms are also notified in several polymorphs of succinic acid and anthranilic acid. Solvent drop grinding is not only associated with cocrystals synthesis but also in the synthesis of crystalline salts [33]. The high throughput robotics technique is extremely associated with the screening of salts optimized with their altered physical properties [35].

Evaporation cocrystallisation

Cocrystallisation by evaporation of stoichiometric solutions is based on the first strategy and it is the most important tool for cocrystal screening.

In order to design successful cocrystal screening experiments, it is very important to consider reactant solubilities, many successful cocrystal examples being obtained by this method [36].

Reaction crystallisation

If cocrystal components A and B have nonequivalent solubilities in solution, cocrystallisation through evaporation of an equimolar solution may result in the formation of single component crystals because supersaturation is generated with respect to less soluble reactants or both less soluble reactants and co-crystals. There is a risk of crystallising a single reactant or a mixture of individual reactant and cocrystal. The reaction cocrystallisation (RC) approach has been adopted for this situation. RC experiments are performed by adding reactant B to a saturated or close to saturated solution of reactant A, and then the solution becomes supersaturated with respect to cocrystal AB. This method is more effective with non-equivalent solution concentrations and when solutions are saturated with respect to reactants. In one study [23, 37] RC experiments were performed by adding carbamazepine to saturated or nearly saturated solutions of 18 coformers separately and several pure carbamazepine cocrystals were obtained.

Cooling crystallisation

Another method called cooling crystallisation involves varying the temperature of the crystallisation system, which has recently attracted much more attention for its potential of large scale cocrystal production. First, large amounts of reactants and solvent are mixed in a reactor, a typically jacketed vessel, and then the system is heated to a higher temperature to make sure all solutes are totally dissolved in the solvent and is followed by a cooling down step. Cocrystals will precipitate when solution becomes supersaturated with respect to cocrystal as the temperature drops down [38]. Cocrystals of caffeine and p-hydroxybenzoic acid were obtained through cooling crystallisation experiments. The intermolecular interactions of caffeine and p-hydroxybenzoic acid at different concentration ratios in a methanol solvent have been investigated by cooling crystallisation, showing that by understanding the details of the intermolecular interactions it not only enhances the effectiveness on cocrystal screening but also serves as a qualitative and predictive indicator for the final crystalline products. The cooling crystallisation approach can be also used in conjunction with the TPDs in depicting the regions of thermodynamic stability in a multicomponent crystal system and in predicting for the potential formation of cocrystals. Cocrystallisation of carbamazepine and nicotinamide

(CBZ/NCT) as carried out, in which the evolution of the solid phases during the cooling cocrystallisation process were monitored by an *in situ* video probe. For kinetic reasons of nucleation and growth, both metastable and stable solid phases were temporarily observed, even though only the stable phase remained at the end of the process. These results demonstrate the importance of the initial conditions on the pathway of crystallisation. In another research, [39] cooling crystallisation of concentrated CBZ/NCT slurry was monitored by using an *in situ* ATR-FTIR spectroscopy probe, in which the evolution of the CBZ and NCT concentration showed the kinetic pathways of the cocrystallisation process providing useful information on the development of the cocrystals (through nucleation and growth) on the ratio of each solid phase present in suspension. Through analysing the kinetic pathways and supersaturation levels of the components, it is possible to determine the optimal operating conditions for a cooling cocrystallisation process.

Other formation methods

Recently, several novel methods have appeared in the area of pharmaceutical cocrystallisation. The application of a supercritical fluid (SCF) technology into cocrystal formation was also carried out. The feasibility of SCF technologies in the screening and design of cocrystals was studied. The utilization of SCF is based on its three fundamental properties: solvent power, miscibility with organic liquids (anti-solvent), atomization enhancement. In this regard, indomethacin–saccharin cocrystals with different morphologies and sizes (nano-to-micron) were produced using supercritical fluid techniques, demonstrating the potential of SCF technologies as screening method for cocrystals [36]. Ultrasound has been used to prepare cocrystals from solution or suspension/slurry [40]. Ultrasound assisted solution cocrystallisation (USSC) has been studied using a noncongruently soluble pair of caffeine and maleic acid in methanol, in which pure caffeine/maleic acid 2:1 cocrystals were obtained. It is suggested that ultrasound applications in USSC must have altered supersaturation conditions of caffeine and maleic acid in solution, favoring generation of caffeine/maleic acid 2:1 cocrystal nuclei. Further investigations need to be carried out for understanding the nucleation mechanisms during USSC.

Biopharmaceutical performances solubility

Solubility is playing an important role in the development of a dosage form. The issue of solubility is a major problem which is commonly associated with biopharmaceutics classification system (BCS) class II drugs.

Both ionisable and nonionisable APIs are suitable candidates for the development of pharmaceutical cocrystals. The development of cocrystals of ionisable drugs in combination of a number of cocrystal formers suggested that, the newly developed solid moiety can overcome the problems of bioavailability [41]. However the solubility of cocrystals is mainly depending on the percentage of cocrystal formers used for the same.

Thermal analysis and prediction of solubility of cocrystals

For the prediction of ideal solubility, it has been observed that both the melting temperatures as well as enthalpies of pharmaceutical cocrystals are playing a significant role for overcoming the issue of dissolution. The drug moieties having higher melting points possess lower solubility. In an ideal solution of a solute, heat of fusion, melting point and solution temperature are playing the key role. While discussing the solubility data of a component, several considerations are to be noticed such as equilibrium solubility *vs* apparent (kinetic) solubility measurements. Kinetic solubility is one time measurement of the same whereas equilibrium solubility leads to measurement of solubility for several time periods till the achievement of equilibrium condition. Equilibrium solubility of the drug moiety is also considered as a factor for prediction of gastric as well as intestinal residence time. Thus from the above discussion it has been concluded that both factors, equilibrium solubility as well as dissolution rate, are playing significant role towards the efficacy of BCS class II drugs. Thus the development of cocrystals on the context of solubility enhancement is considered to be a novel approach.

Dissolution

The particle sizes of cocrystals are playing an important role towards the development of dissolution rate. Lesser the particle size of the cocrystals, greater will be the rate of dissolution. The dissolution mechanisms of cocrystals can be analysed by the help of powder X-ray diffraction and polarization microscopy. In general the intrinsic dissolution study is conducted for comparing the dissolution efficiency of pharmaceutical cocrystals with the host API. The paddle apparatus is normally used for studying the same. However the sink condition is maintained to predict the dissolution rate of both cocrystals and their host moiety [42]. The dissolution rate of cocrystals varies drastically in comparison to the dissolution rate of the host API. Again there is a huge variation of dissolution rate in between the cocrystals which is found to be

an effect of particle size variation/difference. However lesser the particle size of the cocrystals, greater will be its rate of dissolution as well as rate of absorption. The lesser the particle size, the greater will be its specific surface area which leads to better transformation of solid into solution. The bioavailability is the rate and extent of drug that reaches into the systemic circulation. The cocrystals in this context have a direct effect in comparison to the host API. However a very small number of *in vivo* experiments have been conducted on cocrystals, so far. The cocrystals of phosphoric acid (a monophosphate salt) have been studied *in vivo* and were found to be showing excellent results [43]. Stability is an essential tool in the field of new drug discovery. However depending upon the nature or property of drug moiety, approaches like physicochemical stability of drug molecules can be conducted either in a conventional way or in accelerated conditions to estimate their shelf life. Thermal stress studies might be conducted for hydrates and other thermolabile substances. Water uptake (hygroscopicity) study can also be conducted to confirm the packing status of the finished product. The solution stability can also be considered especially for pharmaceutical cocrystals in order to overcome the dissolution and bioavailability related difficulties. However the pH sensitivity of the drug moiety can be considered while studying several stability conditions [42].

Relative humidity stress condition

A detailed study of moisture sorption/desorption is mandatory to consider the problematic areas. The relative uptake of moisture by the dried molecules (cocrystals) during the course of experiment can be determined by exposing the same into a specific relative humidity (RH) chamber till it attains the level of equilibrium moisture content (EMC) at a fixed or variable temperature and pressure condition. The examples under study include:

- 1:1 indomethacin/saccharin cocrystals shown <0.05% water uptake in a 95% RH [36],
- 1:1 AMG 517/sorbic acid cocrystals shown a minimum of 0.7% water uptake at 90% RH,
- caffeine is found to be one of the best hygroscopic material which possesses six different cocrystals such as caffeine/oxalic acid cocrystals (2:1), caffeine/malonic acid cocrystals (2:1), caffeine/ maleic acid, caffeine/ maleic acid (1:1) and two forms of caffeine/glutaric acid (1:1) [38, 44].

By introducing such cocrystals into several RH conditions for a time period of 1, 3 and 7 weeks respectively, it has been analysed that,

caffeine/oxalic acid (2:1) is the only cocrystal amongst all six which was stable in all RH conditions. The rest of cocrystals show similar stability as that of the host caffeine. From the above discussion it has been concluded that, the cocrystals developed from strong acids like oxalic acid are more stable whereas the cocrystals developed from weak acids like glutaric acid are least stable [41].

Thermal stress condition

In accelerated stability studies the cocrystalline moieties are to be exposed at higher temperature conditions in order to observe their physicochemical stability. A very small number of studies have been carried out on such context in relation to cocrystals. The cocrystal developed from a monophosphate salt with phosphoric acid was studied with their thermal stability condition by exposing at 600°C for 8 weeks. The results obtained show no changes considering the crystallinity of the crystal moiety [43]. Four different paracetamol cocrystals have been studied for their thermal stability conditions such as 4, 4' – bipyridine, 1, 4- dioxane, N- methyl morphine, N, N- dimethyl piperazine with the help of differential scanning calorimetry (DSC). However paracetamol/4, 4'- bipyridine is the only cocrystal which is found to be stable.

Chemical stability

Chemical stability is a basic need in development of drug discovery as well as in pharmaceutical dosage form development. A very small number of cases have been reported /studied by taking cocrystals into consideration. An example under this category includes a cocrystal of phosphoric acid with a monophosphate salt, which was analysed for its chemical stability and was found that the moiety got degraded while exposed at 400°C/75% RH and at 600°C for 8 weeks [43]. The cocrystals of glutaric acid were also studied in the same conditions for 2 months and there were not registered any kind of changes with their properties [44].

Physical stability in solution

The solution stability is the stability condition in which the solute must be in solution state and should not be precipitated into crystalline form in any kind of circumstances. The solvent commonly used for studying solution stability includes water, simulated gastric fluid (SGF), simulated intestinal fluids (SIF), buffers etc. Such kind of solvents can also be used for studying solubility and dissolution of several dosage forms to note down the

behavioural changes. However the cocrystals of caffeine/oxalic acid (2:1) were found to be stable in all humidity conditions up to 98% RH while studied for 7 weeks [41]. The cocrystals of indomethacin/saccharin are used for studying the solubility property at pH 7.4 and compared with the solubility of the gamma form of indomethacin. An increased rate of solubility for the same has been observed [36].

Case studies of pharmaceutical cocrystals

Hereby the significance of pharmaceutical cocrystals can be more precisely explained with the help of following case studies.

Pharmaceutical cocrystals of carbamazepine

Carbamazepine (CBZ) is a prominent anti-epileptic drug which has been in use for the last three decades. CBZ faces several challenges like poor aqueous solubility which is associated with high dose requirement i.e. >100 mg/day for inducing therapeutic response, reduced bioavailability with limited dissolution rate and auto induced metabolism [27]. Though CBZ has a very simple molecular structure, it has a high grade of complexity with respect to its crystalline form [37, 45]. Four different polymorphs like a dihydrate, an acetone solvate and two ammonium salts of CBZ in anhydrous form have been identified. From this discovery it can be concluded that, CBZ can be considered as an ideal candidate (API) to develop pharmaceutical cocrystals and to obtain the optimum response with respect to the physicochemical properties in comparison to the existing API. Two different strategies have been adopted to develop the cocrystals of CBZ. The first one is the implementation of hydrogen bonding for building the crystalline lattice of CBZ which is absent in the existing form. The second strategy is the development of supramolecular hetero synthon amongst the cocrystal formers and CBZ by breaking the amide linkage in CBZ. Both the strategies have shown a great success in development of several cocrystals. Some of them show very good physical stability eg. CBZ: Saccharin cocrystals, [45] enhanced dissolution rate along with improved pharmacokinetics. Saccharin is showing better response with their improved physicochemical properties in comparison to the existing CBZ [45].

Pharmaceutical cocrystals of fluoxetine hydrochloride

So many APIs are currently available in their chloride salt form. Cocrystals of fluoxetine hydrochloride (fluoxetine HCl) are established by using the chloride mediated carboxylic acid supramolecular synthon [46]. Fluoxetine HCl is an antidepressant drug which is normally available in

crystalline form. The cocrystallization of the API leads to a change in physicochemical properties which is only associated with fluoxetine part and not with the hydrochloride part [46]. The cocrystals of fluoxetine HCl were developed with benzoic acid in a molar ratio of (1:1) and with fumaric acid in a molar ratio of (2:1) by using solvent evaporation condition. In all three cases it has been observed that the chloride ions are bound to the carboxylic acid through hydrogen bonding with an interaction of protonated amine [46]. The dissolution profiles of the generated cocrystals have been studied. It has been observed that the aqueous solubility of cocrystals of fluoxetine HCl: succinic acid > fluoxetine HCl: fumaric acid > fluoxetine HCl: benzoic acid. However the fluoxetine HCl: succinic acid cocrystals show twofold increase in its aqueous solubility in comparison to the existing API [46].

Pharmaceutical cocrystals of itraconazole

Itraconazole, a well-known antifungal agent is extremely water insoluble in nature and normally administered in both oral as well as parenteral route of administration [47]. However for increasing the bioavailability of the API, the drug molecule is coated on sucrose beads and dispensed in capsule forms. The co-administration of hydroxy propyl- β -cyclodextrin with the capsules enhances the absorption rate of the API. The cocrystals of itraconazole are synthesized by using 1, 4-dicarboxylic acids as cocrystal formers [47]. Each cocrystal moiety of itraconazole is comprised of two molecules of API and one molecule of the acid. However the report obtained from the dissolution study suggested that there was no such increment in the rate of dissolution of the prepared cocrystals in comparison to the pure drug. Further itraconazole: L-malic acid cocrystals were synthesized, which show similar dissolution rates as that of the pure API [41, 48].

Pharmaceutical cocrystals of sildenafil

Sildenafil is a very popular drug which is normally used in treating pulmonary arterial hypertension, atherosclerosis, peripheral vascular diseases and male erectile dysfunctioning [49]. The mechanism of action is basically associated with inhibiting cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5. The API has moderate water solubility [49]. A cocrystal form of sildenafil citrate has been developed with acetyl salicylic acid (1:1) ratio and shows an improvement in aqueous solubility. The crystallography has been studied by X-ray diffraction technique. The melting point of the cocrystal was found to be 143.8°C. The

intrinsic dissolution study report suggested that the cocrystals have improved the dissolution rate in comparison to the pure drug ($75\text{mg}/\text{min}/\text{cm}^2$ vs $6.64\text{mg}/\text{min}/\text{cm}^2$) [49].

Cocrystals of melamine and cyanuric acid

Till now whatever the discussion made on cocrystals, it was clearly understood that the development of cocrystals is a fruitful gift to the field of pharmaceutical medicinal system. But there are some cocrystals which show a reverse effect and sometimes become the key factor for undesirable side effects. The best example under such category is the development of cocrystals of melamine: cyanuric acid. Though both of them are nontoxic and safe while administered independently, but according to the report/complain made by FDA on killing of pets due to malnutritional supply in 2007 these two are the suspected elements which are commonly found in almost all animal food. The cocrystals of melamine: cyanuric acid show less aqueous solubility and might be responsible for developing kidney failure [50].

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