INTRODUCTION

Since the last decade, the interest of pharmaceutical scientists shifted toward co-crystallization (CC) process, because of their interest in improvising the physicochemical characteristics of an active pharmaceutical ingredients (API) without any alteration in its pharmaceutical activity, which led them to be a better option for patents and for development of these drugs into a newer marketable formulation. But a proper definition of co-crystals (CS) is still a matter of debate because there are only a few studies available, which significantly made differences between CS, eutectic or salts as a products of CCs. In most of the studies, it has been assumed that when heteromolecular interaction between two molecules compensate or balance the homo-molecular interactions, the resultant product will be a CS, on the other hand, when homo-molecular interaction comes into action, then chances of eutectic formation increased. Some studies also concluded that eutectic were similar to solid solutions and they called it as “conglomerates of solid solutions” formed due to interactions between couples of molecules lacking geometrical fit and on the other point CS were found to be more stable compared to eutectic as these geometrical fir components and various studies related to the CCs process have settled various parameters, which govern the formation process of CS, while in case of eutectic, solid solutions or salts, much literature is not available.

On the basis of literature, most of the studies conclude that CS are component solids carrying a crystalline structure. The latest guidelines of United States Food and Drug Administration (FDA) related to CS, these are “Crystalline materials composed of two or more molecules within the same crystal lattice”. There are numerous publications, which have provided a more constricted definition as these are crystalline substances, whose components remain solids in their pure states under ambient circumstances and all the components should be

ABSTRACT

Co-crystallization (CCs) is a less studied phenomenon related to its applicability and reliability as it is directly related to the generation of newer multicomponent solids like co-crystals (CS), eutectic, salts or solid solutions etc. Having improved physicochemical properties compared to their pure components. Further, the design and structural aspects of these multicomponent systems remain hindered compared to other techniques such as nanotechnology or solid dispersion. CC is a newer technique to modify the physicochemical as well as pharmaceutical characteristics of various drugs having issues like solubility, stability, etc. without altering or hindering their pharmaceutical activities. For drug delivery purpose, CC process has numerous advantages over nanotechnology and solid dispersion drug delivery techniques. CCs can modify the physicochemical properties of active pharmaceutical ingredients (API) have issues like sensitivity toward environmental hazards like temperature, moisture, or photostability issues. The availability of large numbers of conformers makes this technique favorable for the researchers in designing CS of newer and older. Although, solid dispersion and nanotechnology techniques are being utilized to a larger extent still there are some drawbacks of these techniques like stability, toxicological factors and protection from environmental factors need to be considered, while the CCs process drastically modifies the various pharmaceutical parameters without altering the pharmacological properties of API’s. Salts, design of CS, their methods of preparation, and their application in various fields with special emphasis on their applicability in the pharmaceutical industry.

Key words: Co-crystals, eutectic, salts, cocrystallization, chromophores, cosmetic
present in a fixed stoichiometric ratio of drug and coformers (CFs). A recent perspective, authored by 46 scientists, provided a different explanation about CS as “CS are solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio, which are neither solvates nor simple salts”. In this context, the definition of pharmaceutical CS is different compared to the definition of CS, as in the case of pharmaceutical CS, one component is drug and the other is CFs. In the crystal engineering technique, the pharmaceutical properties of drugs are changed without disturbing their inherent structures. Presence of various chemical groups’ viz. carboxylic acids, carbohydrates, amides, amino acids and alcohols in the co-crystal formers lead to the formation of CS with different drugs.

Synthons are responsible for holding the molecules, when the formation of a compound occurs through non-covalent interactions. Due to their strength, directionality and higher rate of recurrence, hydrogen bonds are often used for designing co-crystals. In 1991, Etter gave three rules for hydrogen bonding pattern every available hydrogen molecule could be used in the formation of bonding, every acceptor of hydrogen bond could participate, if an H bond acceptor is present there as well as the H bonding is possible when a good acceptor and donor H bond are present in the molecule. The formation of synthons is governed by the strength of hydrogen bonding between co-crystal formers, not by the total number of groups available. With the use of the above discussed rules, we can predict the formation of synthons within different functional groups. Synthons are essential structural entities between supramolecules that formed via non-covalent bonding and are made up of molecular fragments and supramolecular links among them. Supramolecular synthons could be classified into two categories: Supramolecular homosynthons and heterosynthons. The first one is composed of self-complementary functional groups, while the second one is composed of dissimilar but complementary functional groups. Supramolecular heterosynthons formation occur by non-covalent interactions between various drugs that leads to a co-crystal formation. The concept of the supramolecular approach is used for CS screening but now-a-days Cambridge Structural Database (CSD) is used for the selection of suitable CFs for various drugs.

So, in broad terms, CCs is the process of generation of newer crystalline substances by manipulating the intermolecular interactions of two components, which remain solids in their pure states at ambient conditions and interact with each other in a fixed stoichiometric ratio. But CS are not the only target during CCs, there are different multicomponent solids are also present viz. eutectics, salts, polymorphs, hydrates, solvates etc., which are the side products of the CC process. In the case of CS, the interaction between drug and CFs occurred through non-covalent interactions like hydrogen bonding or ionic interaction. While in case of eutectic, mostly weak van der waals interactions occurred in anunfit geometric pattern, and that’s why eutectic became less stable compared to CS. So, here in this review, we have briefly discussed various significant factors and chemistry involved during the CCs process along with the differences between CS, salts and eutectic. Screening methods for CS, their methods of preparation, and their applications CS in pharmaceutical and allied industries are been discussed in later sections. 

Co-cocrystals vs. eutectic

The literature is full of studies related to the development of newer drug delivery techniques to improvise the pharmaceutical properties of API’s including dissolution profile, ss thermostability, material compressibility during tablet production process. When we discuss crystal engineering, the most useful point is understanding of supramolecular synthon formation. These are the fundamental building blocks of the products obtained during the CCs process. When there is an interaction between two similar functional groups like the -COOH functional group of the drug and API interact, formation of homosynthons occurred, while interactions between two different functional groups lead to the generation of heterosynthons. As we discussed above in the introduction section, the chances of CS or eutectic formation depends upon these two synthons. Generally, it has been hypothesized that, heterosynthon formation leads to the generation of CS, while homosynthon formation goes to generate eutetic, but recent studies proved this wrong as numerous CS has been reported via homosynthon formation.

Eutectics are basically multi-component crystalline solids closely related to solid solutions. Both are well-documented in inorganic systems as alloys. There are numerous studies in the literature, which have defined eutectic on the basis of their lower melting point patterns and on the basis their compositions. The term eutectic was derived from the Greek term “eutectos”, which means fused. Yet the formation of eutectic has not much studied compared to solid solutions, as these are defined on the basis of their composition or arrangements of solutes and solvents in the crystalline lattice. The detaileding of internal structural composition via X-ray diffraction (XRD) studies of eutectic are rarely available compared to solid solutions. A deep analysis of structural detailing is required for eutectic in pharmaceutical scenarios the famous tin-lead eutectic was studied by inorganic chemists. In the past eutectic have been considered solid solutions and recently it has been considered CS for pharmaceuticals and organic systems. However, CS has been reported to form eutectic and solid solutions and some studies considered eutectic as an intermediate step between CS and solid solutions, which is crucial for the formation of CS, but the exact mechanism for eutectic formation still remains a matter of discussion. Thus, CS, eutectic and solid solutions are correlated with each other but most of the studies that differentiate them focused on the phase diagram studies and binary composition properties of multicomponent crystalline studies. We discussed the inter-relationships of these multicomponent solids on the basis of their intermolecular interactions and structural inter-relationships and proposed
that detailed structural data are required to differentiate between eutectic, solid solutions and CS.20

Cocrystals vs. salts
The development of a multicomponent system into CS or salts depends upon the degree of proton transfer within a hydrogen bonded synthon. To form a multicomponent crystalline system, interactions between different components at the molecular or ionic level are necessary and for multicomponent systems like CS, salts or any other type, such interactions should be non-covalent and supramolecular.21,22 The level of interactions and the geometrical arrangements between two isolated molecules (gaseous phases) comparably remain open, which makes them easy to understand, while in the case of a closed and 3D packing system, it becomes a challenging task to understand it.23 Finally, the methods like computational crystal structure prediction (CSP) methods retain the key to resolving the problems by understanding the full and clear spectrum of interactions at the intermolecular level within a crystalline system. Undeniably, it becomes the only reliable source for understanding the influence of every short- or long-range interaction made by the molecules in a crystal and this leads to predicting the most stable crystal compound.24 Even after this, the various stages in crystal developments like nucleation and growth considerations play their important roles, which cannot be explained by the experimental level studies; hence, it must understand intermolecular interactions at all points of crystal development stages. For understanding such developments, CSP method25 is not a sufficient tool, but recently, Cambridge blind tests provided some significant approaches for this.26 In case of the CSP method, the presence of additional degrees of freedom leads to the generation of a possible structure enabled by the occurrence of the second component and this made the CSP method a more discouraging technique27 while to understand the development of multicomponent systems, we required gathering of more empirical and rationalized data. However, the more precise calculation, understanding of various associated modes and inclusion of empirical data during the study, could help in the prediction of CS or salt formation.28,29 Recently, engineering of ternary CS been designed on the understanding of pKa values, supramolecular synthon history and hydrogen bond basicity. Ternary CS system like acridine-3-hydroxybenzoic acid-2-amino-4,6-dimethylpyrimidine, due to its smaller size of proton, its causes transfer of protons with small steric significance and leads to the protonation of the base by an acid. This phenomenon was a great example of understanding the electronic factors along with the solvation characteristics of acid, base and their salt.30 The pKa value represents the pH value at which all the solubilised-ionisable components are fifty percent charged and fifty percent remained protonated and it depends upon the acidic or basic strength of the molecule. The concept of prediction of salt and CS formation mainly depends upon the difference in pKa values of acid and base, which has been explained in detail in screening methods. By using the pKa value, the equilibrium concentration of ions can be calculated, and if the difference in pKa values of acidic and basic components is found to be more than 2 or 3 units, in that case proton transfer takes place31 and the chances of salt formation increase, but currently, newer theoretical and high pressure techniques based studies exhibited that proton transfer in pyridine-formic acid system depends upon the concentration of formic acid present in the solution.32 The charged ions and the polar molecules of the aqueous medium interact with each other, which makes salts more hygroscopic, especially in case of anions, they are found to be conjugated bases of strong acids like chloride and sulfates. In terms of interactions at the intermolecular level, the rationalization becomes easier in at least in broad terms (Figure 1).4

Methods of cocrystal preparation
Numerous methods for the formulation of CS, but traditional crystallization was carried via solution with suitable degrees of super saturation viz. cooling, evaporation and includes substances having properties of the solubility lowering. CCs with the solvent evaporation technique did not provide favorable results.30 Generally, two methods are used for CCs: solution-based and grinding-based techniques. Solution-based methods are generally preferred because of the formation of CS, which can qualify the testing with a single XRD (SXRD). The grinding-based techniques include neat-grinding and solvent drop-grinding techniques. Currently, newer techniques are available, viz. hot-stage microscopy, ultrasound assisted and CCs via supercritical fluid.31

Grinding method
CC products usually prepared with grinding method are consistent compared to those prepared from a solution. The main drawback of this method is its inability to prepare significant arrangements of CS before due to the stability of early phases. The solvent method is better than the grinding method in another way also as grinding method leads to solvent inclusion in supramolecular structure stabilization. Solvent drop grinding might enhance the kinetics and assist the formation of CS leading to increased interest as a CC technique.31 Neat-grinding technique can be performed by vibratory mills, mechanical-grinding or manual-grinding, while the solvent drop-

![Figure 1. An overview of pharmaceutical cocrystals](image-url)
grinding can be performed by the addition of suitable solvent at regular intervals with grinding ensure that the solvent should be capable of dissolving the solid material. Caffeine-glutaric acid CS polymorph compared with the solvent evaporation technique is cost effective, eco-friendly, and effective for CS formation.31

**Solid state-grinding**

In solid state grinding, the particulate size reduced with increased covalent reactivity within the mixture. This technique helps in improving in simplicity and selectivity over solution-based CCs technique.30 Six CS formulations of sulfadimidine with salicylic acid using solid state grinding technique while with grinding anthranilic acids were prepared and studied. Anthranilic acid replaced salicylic acid due to the general arrangement of hydrogen bonds of both CS. In this technique, the major shortcoming is that the polymorphic transition leads to serious side effects, causing product withdrawal by the market.32

**Solvent drop-grinding**

It is almost same as solid state grinding method with the introduction of the solvent in a smaller quantity. Here solvent act as catalytic agent.33 Primarily, CS formation occurred via a solution crystal growth manner. Most of the crystals grow faster with the solid grinding technique while others proceed further slowly. For those crystals, solvent drop method was found to be effective.31 For the preparation of CS of caffeine and glutaric acid solvent drop grinding technique was found to be suitable compared to solid state grinding. Preparation of succinic acid (SA):anthranilic acid and indomethacin:saccharine was done with solvent drop-grinding method and optimum outcomes of studies revealed an increment in physical stability and dissolution rates.32

**Co-crystallization from the solution**

Here the key requirement is the same solubility profile for both compounds undergoing CCs, otherwise the least soluble compound will get precipitated out completely from the solution. While similar solubility profile of both components could not promise a positive result. It is probably beneficial to trust polymorphic complexes that occur in additionally compared to solitary crystalline arrangement as CC compounds. When a molecular component occurs in various polymorphic states, it reveals a structure-based tractability and cannot be locked into a packing model.33 For large-scale production, water-jacketed vessel with a circulating water bath facility for temperature control was being used. Teflon blades were used for continues to stir. The drug and CFs were dissolved in alcoholic solvent at 70°C under reflux for 1 h. The reduction in temperature with further slowly. For those crystals, solvent drop method was found to be effective.31 For the preparation of CS of caffeine and glutaric acid solvent drop grinding technique was found to be suitable compared to solid state grinding. Preparation of succinic acid (SA):anthranilic acid and indomethacin:saccharine was done with solvent drop-grinding method and optimum outcomes of studies revealed an increment in physical stability and dissolution rates.32

**Screening of co-crystals**

Various methods for screening of CS are discussed below:

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

When the difference in pKa values is 2-3, transfer of proton will occur between acids and bases. pKa values less than 0 exhibit the formation of CS, while more than 2-3 value revealed the formation of salts.34,35 In CSD 6465 possible CS were studied to validate and quantify this rule. The increment in the pKa value of free base to one digit directly increased one unit of pH_{max}. To attain this condition practically, we need to modify the drug molecule. In the same way one-digit increment in the intrinsic solubility profile of a free base affects directly one-unit increment in pH_{max} again. This also required modification in drug molecule.36 While one decrement in salt solubility leads to an increment of one unit in pH_{max}. This characteristic can be modified using a counter ion with different properties and if salt
DUTT et al. A Talk on Multi-Component Organic Solids

formation occurred, it would be stable over a greater pH range but having a lower solubility profile (Table 1).

**Fabian’s method** used molecular descriptors, viz. (atom, functional groups, bond, hydrogen donor-acceptors, size, shape, molecular and surface area descriptors etc.) for calculation and screening of CS. In this method, mostly polarity and shape descriptors are used to predict the possible formers of CS. Other molecular descriptors are also important as well for prediction of CS formers.36

Conductor-like screening model for real solvents was used for checking the miscibility of CFs with super cooled liquid (melt) phase. The excess enthalpy, between the pure compounds and the mixture of drug and CFs reveals the capability of CCs between the drug and CFs.37

Calculated gas phase MEPS technique used the difference in energy ΔE difference between CS and pure solids in various stoichiometries, to determine the possible formation of CS between the two solids. The outcome of the study revealed that, when ΔE is more than 11 kJ/mol, chances of CS formation are enhanced by 50% more. Over 1000 compounds were screened to validate this method including (caffeine and carbamazepine) and the results were satisfactory enough.21

Co-crystal cocktail method is a very useful and smaller time-consuming method. In this method, more than three CFs were simultaneously grounded with the drug leading to the formation of homo or heterosynthons between the drug and CFs, which could be analyzed with thermal analysis methods by checking their endothermic peaks.24

Differential scanning calorimetry (DSC) is a rapid thermal method for screening of CCs.24 In this method, we check the endothermic peaks for the formation of CS by heating the mixture of drug and CFs in DSC pans. We hypothesized that CS formation is an exhibition of three endothermic and a couple of exothermic peaks in thermogram represent the formation of CS with stoichiometric variety.29 In the case of thermal techniques, it is a general hypothesis that during CCs, the melting point of CS remains between the melting points of the drug and CFs while in case of a eutectic mixture, generally the melting point of product comes before the melting point of both the drug and CFs. But there are numerous studies present in literature, where the melting point of CS comes before and after the melting points of parent components. In a study related to the behavior of melting point in CCs, Schultheiss and Newman27 in 2009 determined that around 51% of CS possess a melting points between drugs and CFs, while 6% possess greater melting points and around 39% possess lower melting points compared to drug and CF respectively. The melting point of CS is generally altered by the melting point of CFs. If we choose a CF with a higher melting point, the resultant product should possess a higher melting point and vice versa. This technique can be applied to those drugs, which have thermostability problems (Table 2).4

Hot stage microscopy or the Kofler contact method offers a visualization of the total phase number that is exhibited by the system when two compounds are heated. When the high melting point compounds start melting and recrystallization occurs before other melted compounds comes in contact with it leading to the formation of zone of mixing.39,40

Saturation solubility technique involved the measurement of the saturation solubility of API’s and conformer separately at the reference temperature. The saturation temperature of the solvent system is measured by heating with a rate of 0.3°/min. If the increase in saturation temperature is more than 10° compared to reference temperature, chances for co-crystal formation increases.41,42 The study of carbamazepine and nicotinamide-based CS revealed that the solubility profile of drug directly depends upon the concentration of CS in the drug and CF solution. This study concluded that the solubility of a drug could be increased only when it gets complexed with CFs during the CC process, otherwise the free drug had no impact on the increment of solubility profile of the parent components.4

**Applications of co-crystallization**

**Pharmaceuticals**

The interest of pharmaceutical industry and researchers have shifted toward CCs and many drugs, including newer and older APIs have been included in the preparation of CS and eutectic

---

**Table 1. Relation of pKa values with possibility of formation of complexes**

| Possibility of formation of complexes | pKa values |
|--------------------------------------|------------|
| Non-ionized complexes                | ΔpKa < -1  |
| Ionized complexes                    | ΔpKa < 4   |
|                                      |            |
| (Ionizable complex formation possibility increases by 17% by increasing ΔpKa by 1 unit from 10% at ΔpKa= -1 to 95% at ΔpKa= 4) |

**Table 2. Relation of co-crystal formation with DSC screening**

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

DSC: Differential scanning calorimetry, CS: Cocrystals
as these formulations improve the pharmaceutical issues related to these drugs without altering or modifying their therapeutic activities.\textsuperscript{43,44} The enhancements in solubility,\textsuperscript{45} stability\textsuperscript{46} and aqueous solubility have been reported after CCs of various. With the drastically improved pharmaceutical characteristics of API’s, CC process has been considered the most effective technique to improve the bioavailability of drugs.\textsuperscript{47} It is evident from literature that by developing a CS of fluoxetine hydrochloride with different CFs, the solubility of each formulation was increased. The solubility of fluoxetine hydrochloride was found to be 11.6 mg/mL while its CS with fumaric acid and SA were found to be 14.8 mg/mL and 20.2 mg/mL respectively.\textsuperscript{48} In another study, the solubility profile of CS of tegafure was found to be much higher compared to the its pure amorphous state.\textsuperscript{49} Here, the important point is the increment in its solubility without affecting the stability of the pure amorphous form of the drug. A vast literature is available containing such examples where the solubility and dissolution behavior of various drugs have been modified without changing their original therapeutic properties.\textsuperscript{50,51} If we talk about eutectic, the drug: drugs eutectic have been reported in literature like 1:1 eutectic mixture of pyrazinamide and isoniazid exhibiting enhanced solubility profiles, while in some examples, polyethylene glycol and different APIs are revealing enhanced pharmaceutical characteristics.\textsuperscript{46,52,53} Eutectic mixture of ibuprofen-menthol showed an improved dissolution behaviour.\textsuperscript{46} The similar improved dissolution behavior was recognized in the case of 2-(4-(4-chloro-2-fluorophenoxy) phenyl) pyrimidine-4-carboxamide: glutaric acid CS.\textsuperscript{3} These examples revealed the effects of CCs in improvement of solubility behavior along with bioavailability improvement of drugs.\textsuperscript{54} The 1:1 danazol: vanillin CS showed increased solubility compared to poorly soluble pure danazol. The stability of drugs is also improved by CCs like carbamazepine CS revealed enhanced hydrosolubility in caparison susceptibility hydrate formation property of carbamazepine.\textsuperscript{55} An improved humidity stability of theophylline and oxalic acid CS have been reported compared to their pure state (Figure 2).

**Mechanical properties**

In the CCs process, the API’s and CFs create new crystalline structures through non-covalently bonding resulting to a higher mechanical property. This is evident from previous studies like caffeine: Methyl gallate CS exhibited improved tabletting characteristics compared to pure caffeine, while an enhanced compressibility and mechanical strength during tabletting were observed in acetaminophen CS compared to pure acetaminophen. The plasticity and compressibility of theophylline: methyl gallate CS was found to be much higher than the theophylline alone. All these properties were improved due to the layered structures of their CS.\textsuperscript{56}

**Compression behaviors**

The poor compression and compaction of powdered API’s and ingredients is a bigger problem faced by drug formulation scientists because the compression is required at the roller stage to prepare granules, while compaction is the major requirement for making tablets by reducing the volume of powders under pressure. The compactness is the ability to compress the free flow powder in the form of a solid unit dosage form having the desired tensile strength. Therefore, the understanding of material’s characteristics becomes an important key to developing and designing newer formulations with desired physical and chemical properties. Where, a higher dose or higher amount of drug is required, than compressibility and compaction become critical parameters to study.\textsuperscript{57} To date, the focus of CS researchers mainly focused on improvement of solubility issue and tabletting property area did not get much attention. Some handful examples in the literature where this area of research touched like CS of carbamazepine with nicotinamide, and saccharin were found to have increased tensile strength of 2.00 and 2.19 times, respectively, at 1500 lb/cm\textsuperscript{2}. But the dissolution rate of these CS was found to be lesser compared to pure drugs. This signifies the relationship of higher tensile strength is directly proportional to a lower dissolution profile.\textsuperscript{58}

**Formulation and dissolution**

CS tend to have higher dissolution rates than the corresponding drugs, due to their higher solubility. However, most studies have focused on the powder dissolution profile as an indicator of CS performance. These studies did not comment on the CS solubility behavior or explain the reasons for improved dissolution rates in some. Further, suggested approaches or a mechanistic understanding of overcoming transformation challenges during dissolution were not discussed. One of the early examples is CS of itraconazole with a carboxylic acid, i.e., fumaric acid, SA, malic acid, and tartaric acid,\textsuperscript{59} all of which had higher dissolution rates than that of the crystalline drug and similar rates to that of the amorphous form of the drug.

The dissolution of fluoxetine hydrochloride was compared with that of CS made with benzoic acid, fumaric acid, or SA. The dissolution rate of the alt was about twice as high as that of the benzoic acid CS, similar to that of the fumaric acid CS and at least 3 times lower than that of the SA CS.\textsuperscript{54} Celecoxib-NIC CS had a higher dissolution rate than the drug alone. The dissolution rate of CS developed with 2% sodium dodecylsulfate and polyvinylpyrrolidone was better than that of the drug alone.
| Drug(s)          | Coformer(s)                        | Method of Preparation                        | Method of Analysis                          | Important Points                                                                                                                                                                                                 |
|-----------------|------------------------------------|----------------------------------------------|--------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ezetimibe⁵⁷     | L-proline and imidazole            | Wet-grinding and solution crystallization     | Raman spectroscopy, Infrared spectroscopy, DSC, TGA, PXRD, SCXRD | Proline exists as zwitter ion in the crystal lattice of EZT-PRO. Carbonyl group of EZT formed C-H-O hydrogen bond with imidazole. Co-former was selected on the basis of pKa and complimentary structure. Improved solubility and solid-state stability |
| Paracetamol⁵⁸   | Citric acid                        | Slow evaporation                             | Raman spectroscopy, DSC, TGA, PXRD, SCXRD  | Two paracetamol molecules forms hydrogen bonds with citric acid molecule, one of these phenolic-OH acts as hydrogen bond donor while other as acceptor                                                                 |
| Sildenafil⁵⁹    | Acetyl salicylic acid              | Solution crystallization                     | PXRD, HPLC, DSC, ATR-IR, NMR               | Sil: asa are held together by C-H-O and C-H-- forces. 75% improved Intrinsic dissolution rate                                                                                                                                 |
| 6-mercaptopurine⁶⁰ | Isonicotinamide                   | Reaction crystallization method              | DSC, TGA, DVS, FT-IR, PXRD, SCXRD         | CS produced were less hygroscopic. CS attained maximum solubility in 5-10 minutes                                                                                                                                 |
| Theophylline⁶¹  | Oxalic, malonic, maleic and glutaric acid | Solid state-grinding and solution precipitation | SCXRD                                      | Theophylline also possesses a good N-H hydrogen bond donor. N-H⁻· · ·O hydrogen bond is formed between N-H donor of a theophylline by linking with carbonyl oxygen from an adjacent theophylline. This interaction between N-H and O forms hydrogen-bonded dimers in a cyclic motif. Improvement of physical properties and avoidance of hydration |
| Caffeine⁶²      | Maleic acid                        | Ultrasonic assisted solution co-crystallization | Raman spectroscopy, PXRD                  | CCs with maleic acid increases solubility of caffeine which decreases supersaturation                                                                                                                                   |
| Myricetin⁶³     | Acetamide                          | Solvent drop grinding                        | PXRD, morphological analysis, TGA, dissolution studies, IR and NMR spectroscopy | 4 times increased dissolution rate                                                                                                                                                                                                 |
| Trospium chloride⁶⁴ | Urea                             | Solvent evaporation                          | PXRD, SCXRD, NMR, Karl Fischer coulometric titration, TGA, DSC | Electronegative chloride anion accepts an H-bond from the best H-bond donor, a hydroxyl groupin tropium molecule. Urea molecules form an infinite chain on which chloride anions hang over tropium. Increased intrinsic dissolution rate |
| Theophylline⁶⁵  | Urea, saccharin, gentisic acid, salicylic acid, glutaric acid, sorbic acid, oxalic acid, maleic acid and nicotinamide | Supercritical fluid-enhanced atomization     | PXRD, DSC, SEM, solubility and dissolution studies | Low soluble CFs produce theophylline CS with a low dissolving rate while use of high soluble CFs produce faster dissolving CS.                                                                                                                                 |
| Diflunisal⁶⁶    | Nicotinamide                       | Supercritical fluid antisolvent precipitation | XRD, DSC, FT-IR, Electron microscopy, dissolution studies | Acetone was chosen as a solvent for diflunisal and nicotinamide. pH 7.4 phosphate buffer was used to carry out dissolution studies                                                                                                                                 |
| Indomethacin⁶⁶  | Saccharin                          | Anti-solvent crystallization, solvent evaporation | XRD, DSC, DVS, Near-IR spectroscopy      | N-H⁻· · ·O bonding was formed between the caboxycylic acid dimer of IMC and SAC imide dimer                                                                                                                                 |
| Compound                          | Components | Preparation Method                                                                 | Analytical Techniques | Notes                                                                                                                                 |
|----------------------------------|------------|-------------------------------------------------------------------------------------|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Itraconazole                     | L-Malic    | Gas antisolvent crystallization                                                     | HPLC, solubility studies, XRD, DSC, SEM, powder composition study, dissolution studies | The CS obtained by this method were suspected to contain unquantified amount of amorphous material. GAS CCs may have improved itraconazole bioavailability |
| Sulfamethazine                   | Theophylline| Neat-cogrinding, solvent drop-cogrinding and slow evaporation                      | DSC, TGA, raman, PXRD, and DVS techniques                  | The sulfamethazine molecules form a dimer through the intermolecular O...H–N, and two O· · ·H–N and N· · ·H–N keeping theophylline molecule attached |
| Carbemazapine                    | Saccharin  | Cogrinding                                                                           | ATR-FTIR, PXRD, DSC  | Grinding induced amorphous phases are followed by CS formation. High relative humidity exposure increases rate of CCs                   |
| 2-[4-(4-chloro-2-fluoropheoxy)phenyl]pyrimidine-4-carboxamide | Glutaric acid | Solvent crystallization                                                              | Raman spectroscopy, SCXRD, intrinsic dissolution studies, pharmacokinetic evaluation, particle size evaluation | In vivo bioavailability was increased. CS was found to be physically and chemically stable. Increased dissolution rate |
| Ethenzamide                      | Gentisic    | Slow evaporation                                                                     | DSC, hot-stage microscopy, PXRD, SCXRD                     | The interaction of trimeric units is through a vast network of C–H: · · ·O bonds. Every synthon comprises of O–H: · · ·O hydrogen bonds formed between the OH group of resorcinol and the carbonyl moiety of artemisinin |
| Artemisinin                      | Orcinol and resorcinol | Liquid-assisted grinding                                                              | DSC, FT-IR, PXRD | The interaction of trimeric units is through a vast network of C–H: · · ·O bonds. Every synthon comprises of O–H: · · ·O hydrogen bonds formed between the OH group of resorcinol and the carbonyl moiety of artemisinin |
| Gabapentin                       | C-propan-3-ol pyrogallol[4] arene and C-butyl pyrogallol[4] arene | Slow evaporation-aided with sonication                                              | XRD                  | Reported CS exhibit bilayer structures comprising of networks of extensive hydrogen bonding networks between the pyrogallol[4]arene, gabapentin molecules |
| S-naproxen and RS-naproxen       | D-Proline   | Liquid-assisted grinding                                                              | DSC, TGA, PXRD, SCXRD | Synthon part is mainly composed of zwitterionic entity. The crystalline network in the four CS formed is guided by the amino acid prolinum |
| Pyrazine                         | Dicarboxylic acid, terephthalic, phthalic, fumaric and succinic acids. | Pyrazine CS were synthesised by neat grinding. Samples of the pyr:fum CS (50 mg), which were prepared by grinding were dissolved in a minimum amount of acetonitrile | SCXRD, PXRD, DSC and TGA measurements IR spectroscopy | Pyridine-carboxylic acid synthon-based h-bonded chains is the backbone of the structure |
| Theophylline                     | Benzoic     | Both neat-grinding and liquid-assisted grinding                                        | X-ray diffraction | Carbonyl group of theophylline and the carbonyl group of benzoic acidforms an O–H: · · ·O hydrogen bond. Another hydrogen bond is formed between acidic imidazolic nitrogen atom of theophylline and the carbonyl oxygen atom of benzoic acid |

DVS: Dynamic vapor sorption, PXRD: Powder X-ray diffraction, SCXRD: Single-crystal X-ray diffractometry, HPLC: High performance liquid chromatography, ATR-IR: Attenuated total reflectance-infrared
developed with similar excipients, and similar to that of the amorphous formulation. This was only an empirical formulation study and the mechanics of the effect of the excipient on CS behavior have not been investigated.\textsuperscript{58}

The dissolution of CS of exemestane with maleic acid and megestrol acetate with saccharinine was studied in fasted state simulated intestinal fluid. The transformation of the exemestane CS to the drug was fast and dissolution rate was similar to that of the drug when the particles were fine, whereas higher dissolution rates than those of the drug were achieved for larger particle sizes (106-150 and 150-300 \textmu m).\textsuperscript{59} The transformation of megestrol acetate CS was slow and the dissolution rate of the fine particles was much faster than for the drug, whereas that of the larger particles was similar to that of the drug.

In another study, the bioavailability of IND-saccharine CS was investigated in beagle dogs and compared with the bioavailability of both the marketed product of IND (Indomee\textsuperscript{®}) and the physical mixture of drug and CFs.\textsuperscript{45} The CS had similar pharmacokinetic data to the marketed product but significantly improved performance compared to the physical mixture. After preparing and characterizing CS of AMG517, CS of AMG517 with sorbic acid was studied \textit{in vivo} in Sprague-Dawley rats at different doses and compared with 500 mg/kg doses of the free base form of the drug. The result indicated dose-dependent pharmacokinetics (\textit{C}\textsubscript{\textit{max}} and area under the curve) for the CS.\textsuperscript{51,62}

**Cosmetics**

In the cosmetic formulation development, the focus remains on the formulation of a stable and easily applicable preparation using active ingredients. CCs and eutectic mixtures provide these basic facilities to the formulation developers. The inclusion of solid cologne in these cosmetic preparations is a challenge because a higher temperature must melt these solid components, which may directly affect the thermostability of other ingredients used. Some eutectic mixtures of standard cologne in solid form with benzophenone were developed which in result convert into liquid form and could be easily included in the formulation. The flexibility and alterability of these varieties of binary preparations were evaluated through binary formulations of solid fragrances and benzoquinone.\textsuperscript{63} The eutectic mixture based upon above idea was prepared using 12-hydroxystearic acid, as well-known benefit of 12-hydroxystearic acid on skin having a higher melting point and inadequate bioavailability. The other key benefit of CCs is availng a higher melting point crystalline substance having more stability. But higher melting point substances could be a problem for other lower melting point ingredients.\textsuperscript{44} CS-based formulation of 3-iodopropynyl butylcarbamate, an antifungal agent reported in the literature. These CS formulations exhibit higher physical and chemical stability profiles along with higher aqueous solubility and thermostability.\textsuperscript{58} These systems also provide higher flowability to powders and better compressibility during tablets or capsule formulation process. Nicotinamide: p-coumaric acid CS formulations were reported in the literature to treat acne.\textsuperscript{64} In another study, the CS of hair dye colorants exhibit better stability on hair compared to pure colorant.\textsuperscript{57} CS could be an important formulation development system in cosmetic scenario, but the higher melting point of CS plays a key role and that’s why, in the cosmetic industry, the main focus areas become eutectic systems. Butyl methoxydibenzoylmethane an ultraviolet (UV) B absorbing agent, included in the eutectic mixture with and without 12-hydroxystearic acid to overcome the challenge of the higher melting points of both components.\textsuperscript{58} An anti-sun eutectic formulation based on \textit{n}-butylphthalamide and isopropylacrylamide with 1,3,5-triazine derivatives was prepared revealing higher stability.\textsuperscript{66} The eutectic mixture preparation of monoethanolamine used in scalp itching treatment exhibits higher deposition compared to pure compound.\textsuperscript{70}

**Agricultural applications**

In the agrochemical sector, there are plentiful patents that have been completed on CS, which mainly include fertilizers, insecticides, and fungicides, etc. CS-based fungicide patent was filled containing two fungicides, namely metalaxyl and prothioconazole.\textsuperscript{57} In this preparation, the aqueous solubility of metalaxyl was drastically decreased compared with that of the pure component. The reason given behind reduced solubility was the decrement to a surplus of the fungicide in the ground water streams along with higher efficacy and less requirement of fungicides for the desired action. This CS-based formulation is a significant example of the synergistic action of two active fungicide ingredients. The CS of herbicide 3,6-dichloro-2-methoxybenzoic acid with different nitrogenous heterocycles was also reported less water solubility and higher stability.\textsuperscript{72} But there are some examples of various herbicides suffer from the Ostwald effect (large size crystals growth) with time, which has deleterious effects during the storage and processability of product in production and efficacy during use. Here CS provides significant improved stability to overcome these issues. 4-Hydroxybenzoic acid-based CS with different agrochemicals effectively overcome the above discussed problems.\textsuperscript{73} The increased melting points insecticides were reported by CCs of these insecticides with oxalic acid. The higher melting point provides shelf stability and prevents the clumping or Ostwald effect on pure insecticides with time. A recent patent on CS of 4-\textit{[(6-chloropyrid-3-yl) methyl] (2,2-difluoroethyl) amino} furan- 2(5H)-one with salicylic acid was filled higher melting point and stability.\textsuperscript{58,75}

**Chromophores**

Pigments are a principally fascinating chromophore application of CS. According to Skočepová et al.,\textsuperscript{53} it is impossible to prepare novel pigments in high amounts only through solvent methods, it can be prepared in high yield through mechanoc hemical grinding. The three-colour tuned fluorescein CS formulation supports this argument mainly. Chromophore CS of titanyl fluoroalane with titanyl fluorocytosine was developed by dry milling and heating. The novel CS has a novel spectrum along with enhanced sensitivity toward electrophotography and less dark decay. Bicomponent diazo eutectic was prepared as red textile pigments. These eutectic pigments exhibit an equal performance compared to highly toxic dyes in relation...
to thermostability, color fastness, acidic and alkali resistance, and solubility profile. In another study, proved that CS can be utilized at a much higher level than just tuning the solubility, stability, and colour of chromophores. They formulated a series of CS based upon stilbene-type molecules with different CFs. The results exhibited a significant and remarkable change in the form of UV or visible absorbance, quantum yield, and luminescence emissions.63

Food industry

CS has created a place in food additives. The yerba mate (an antioxidant) along with sucrose induce CS show a better flow property and good hygroscopicity during the production process compared to their pure state.59 It is also evident that the antioxidant properties of yerba mates remain stable in their CS form. In another example, ethyl much vanilla are required in mixture form to provide a better taste and fragrance, but during the manufacturing process, clumping occurred in a simple mixture of both these substances. But CCs of these compounds at the individual level provide their powder form carrying good flow properties and weak clump formation tendency. Menthol: xylitol-based CS is another good example of CS having optimum flow properties and weak clump formation tendency.52,53 These CS revealed a higher solubility profile compared to pure menthol and lesser hygroscopicity compared to pure xylitol.

Solubilization of cocrystals

CS has risen as a method for the modification of dissolvability, disintegration, bioavailability, and other physicochemical properties of drugs, without changing their pharmacological properties.53 CS are a class of multicomponent solids containing at least two diverse crystalline components in a solitary homogeneous system in a fixed stoichiometry ratio. They are distinguished from solvates in that the CS components are solids at room temperature. Pharmaceutical CS are generally made of a hydrophobic drug molecule and a hydrophilic CFs molecule.54 The mechanism by which CS go into solution involves three main steps: (1) Breaking intermolecular bonds in the CS, (2) breaking intermolecular bonds in the solvent, and (3) forming intermolecular bonds between the CS molecules and solvent molecules. The limiting step in dissolving the CS of hydrophobic drug molecules in aqueous media has been shown to be solvation and not breaking away from the crystal lattice. CFs appear to decrease the solvation barrier of CS of hydrophobic drugs to an extent proportional to that of the pure CFs. Consequently, CF aqueous solubility is correlated with CS solubility. However, melting points are not good indicators of CS aqueous solubility, since it is drug hydrophobicity and not CS lattice strength that limits solubility (Table 3).55

CONCLUSION

In the crystal engineering technique, the pharmaceutical properties of drugs are changed without disturbing their inherent structures. Presence of various chemical groups’ viz. carboxylic acids, carbohydrates, amides, amino acids, and alcohols in the co-crystal formers lead to the formation of CS with different drugs. So, in CC studies, the presence of a carboxylic acid functional group plays an admirable role. Synthons are responsible for holding the molecules, when the formation of a compound occurs through non-covalent interactions. Due to their strength, directionality and higher rate of recurrence, hydrogen bonds are often used for the design of CS. Generally, two methods are used for CCs: Solution-based techniques and grinding based techniques. Solution-based methods are generally preferred because of the formation of CS, which can qualify the testing with a SXRD. The grinding techniques include neat-grinding and solvent drop-grinding techniques. Currently, newer techniques are available viz. hot-stage microscopy, ultrasound-assisted, and CCs via supercritical fluid. CS offers numerous commercial applications, which are under study or less developed. In spite of their less patent activities, these are potentially critical binary systems because of their prominent effects. CCs can be used in almost all API’s including acidic, basic, or non-ionic drugs. The availability of a large number of CFs allowed this technique to be used broadly. It is evident from previous and recent studies that CC materials carry higher electrical conductivity compared to their parent components. So, this is an area of research because of its potential in the power production sector.

ACKNOWLEDGMENTS

Authors want to thank the Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak, for providing all necessary facilities to conduct this work.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.D., Design: V.B., Data Collection or Processing: B.D., Analysis or Interpretation: M.C., Literature Search: B.D., Writing: B.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Cherukuvada S, Nangia A. Eutectics as improved pharmaceutical materials: design, properties and characterization. Chem Comm (Camb). 2014;50:906-923.
2. Berry DJ, Steed JW. Pharmaceutical cocrystals, salts and multicomponent systems; intermolecular interactions and property based design. Adv Drug Deliv Rev. 2017;117:3-24.
3. Blagden N, Berry DJ, Parkin A, Javed H, Ibrahim A, Gavan PT, De Matos LL. Current directions in cocrystal growth. New J Chem. 2008;32:1659-1672.
4. Brittain HG. Cocrystal systems of pharmaceutical interest. Cryst Growth Des. 2012;12:5823-5832.
5. Cherukuvada S, Row TNG. Comprehending the formation of eutectics and cocrystals in terms of design and their structural interrelationships. Cryst Growth Des. 2014;14:4187-4198.
23. Aitipamula S, Banerjee R, Bansal AK, Biradha K, Cheney ML, Choudhury
22. Cannon AS, Warner JC. Noncovalent derivatization: green chemistry
21. Childs SL, Stahly GP, Park A. The salt-cocrystal continuum: the influence
20. Moore MD, Wildfong PLD. Aqueous solubility enhancement through
19. Huang N, Rodríguez-Hornedo N. Effect of micellar solubilization on
cocrystal solubility and stability. Cryst Growth Des. 2010;10:2050-2053.
18. Mohammad MA, Alhalawe H, Bashimam M, Al-Mardini MA, Velaga S.
Utility of hansen solubility parameters in the cocrystal screening. J Pharm
Pharmaceutical applications. J Pharm Sci. 2010;99:4453-4457.
17. Good DJ, Rodríguez-Hornedo N. Cocrystal eutectic constants and
prediction of solubility behaviour. Cryst Growth Des. 2010;10:1028-1032.
16. Stevens JS, Byard SJ, Schroeder SLM. Characterization of proton
transfer by X-Ray photoelectron spectroscopy (XPS). Cryst Growth Des.
2010;10:1435-1442.
15. Stevens JS, Byard SJ, Schroeder SLM. Salt or cocrystal? determination
of protonation state by X-ray photoelectron spectroscopy (XPS). J Pharm
14. Fábían LS. Cambridge structural database analysis of molecular
complementarity in cocrystals. Cryst Growth Des. 2009;9:1436-1443.
13. Ying Hsi KH, Chadwick A, Fried M, Kenny AS, Myerson AS. Separation
of impurities from solution by selective co-crystal formation. Cryst Eng
Comm. 2012;14:2386-2388.
12. Aakeröy CB, Rajbanshi A, Li ZJ, Desper J. Mapping out the synthetic
landscape for recrystallization, cocrystallization, and salt formation.
Cryst Growth Eng. 2010;12:4231-4239.
11. Merz K, Vasylyeva V. Development and boundaries in the field of
supramolecular synthons. Cryst Eng Comm. 2010;12:3989-4002.
10. Stevens JS, Byard SJ, Schroeder SLM. Salt or cocrystal? determination
of protonation state by X-ray photoelectron spectroscopy (XPS). J Pharm
Sci. 2010;99:4453-4457.
9. Sreekanth BR, Vishweshwar P, Vyas K. Supramolecular synthon
polymorphism in 2: 1 co-crystal of 4-hydroxybenzoic acid and
2,3,5,6-tetramethylpyrazine. Chem Commun (Camb). 2007;2375-2377.
8. Ross SA, Lamprou DA, Douroumis D. Engineering and manufacturing
of pharmaceutical co-crystals: a review of solvent-free manufacturing
technologies. Chem Commun (Camb). 2016;52:8772-8786.
7. Shayanfar A, Jouyban A. Physicochemical characterization of a new
cocrystal of ketoconazole. Powder Technol. 2014;262:242-248.
6. Cruz-Cabeza AJ. Acid-base crystalline complexes and the pKa rule.
Cryst Eng Comm. 2012;14:6362-6365.
5. Babu NJ, Reddy LS, Nangia A. Amide N-oxide heterosynthon and amide
dimer homosynthon in cocrystalsof carboxamide drugs and pyridine
N-oxides. Mol Pharm. 2007;4:417-434.
4. Trask AV, Motherwell WD, Jones W. Solvent-drop grinding: green
crystallisation. Chem Commun (Camb). 2004;7:890-891.
3. Friscic T, Jones W. Recent advances in understanding the mechanism of
cocrystal formation via grinding. Cryst Growth Des. 2009;9:1621-1637.
2. Sevukarajan M, Thamizhvanan K, Sodaapani R, SateeshBabu JB, Naveen
KB, Sreekanth Reddy B, Sethu KJ, Vivekananda U, Sarada K, Hyndavi N.
Crystal engineering technique – an emerging approach to modify physicochemical properties of active pharmaceutical ingredient.
Int J Chem Pharm Sci. 2012;3:15-29.
44. Rahman Z, Agarabi C, Zidan AS, Khan SR, Khan MA. Physico-mechanical and stability evaluation of carbamazepine cocrystal with nicotinamide. AAPS PharmSciTech. 2011;12:693-704.
45. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennerånäs H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm. 2004;1:85-96.
46. Jain S. Mechanical properties of powders for compaction and tableting: an overview. Pharm Sci Technol Today. 1999;2:20-31.
47. Hiestand EN. Dispersion forces and plastic deformation in tablet bond. J Pharm Sci. 1985;74:768-770.
48. Hiestand EN. Tablet bond. I. a theoretical model. Int J Pharm. 1991;67:217-229.
49. Hiestand EN, Smith DP. Tablet bond. II. Experimental check of model. Int J Pharm. 1991;67:231-246.
50. Blagden N, Coles SJ, Berry DJ, Pharmaceutical cocrystals- are we there yet? CrystEngComm. 2014;16:5753-5761.
51. Sun CC, Hou H. Improving mechanical properties of caffeine and methyl gallate crystals by cocrystallization. Cryst Growth Des. 2008;8:1575-1579.
52. Rahman Z, Samy R, Sayeed VA, Khan MA. Physicochemical and mechanical properties of carbamazepine cocrystals with saccharin. Pharm Dev Technol. 2012;17:457-465.
53. Desiraju GR. Crystal and cocrystal. CrystEngComm. 2003;2:466-467.
54. Dunitz JD. Crystal and cocrystal: a second opinion. CrystEngComm. 2003;4:506.
55. Bond AD. What is a cocrystal? CrystEngComm. 2003;9:833-834.
56. Shimpi MR, Childs SL, Boström D, Velaga SP. New cocrystalsof ezetimibe with L-proline and imidazole. Cryst Eng Comm. 2014;16:8964-8993.
57. Elbagerma MA. Analytical method development for structural studies of pharmaceutical and related materials in solid and solution state. An investigation of the solid forms and mechanisms of formation of cocrystal systems using vibrational spectroscopic and X-ray diffraction techniques. (Doctoral dissertation, University of Bradford). 2010.
58. Zegarac M, Lekši, E, Šket P, Plavec J, Bogdanović MD, Bučar DK, Dumić L, Meštrović E. A sildenafil cocrystal based on acetylsalicylic acid exhibits an enhanced intrinsic dissolution rate. CrystEngComm. 2014;16:32-35.
59. Wang JR, Yu X, Zhou C, Lin Y, Chen C, Pan G, Mei X. Improving the dissolution and bioavailability of 6-mercaptopturine via co-crystallization with isonicotinamide. J Med Chem Lett. 2015;25:1036-1039.
60. Trask AV, Motherwell WD, Jones W. Physical stability enhancement of theophylline via cocrystallization. Int J Pharm. 2006;320:114-123.
61. Aher S, Dhumal R, Madahik K, Paradkar A, York P. Ultrasound assisted cocrystallization from solution (USSC) containing a non-congruently soluble cocrystal component pair: caffeine/maleic acid. Eur J Pharm Sci. 2010;41:597-602.
62. Mureşan-Pop M, Chiriac LB, Martin F, Simon S. Novel nutraceutical myrcitin composite of enhanced dissolution obtained by co-crystallization with acetamide. Compos B Eng. 2016;89:60-66.
63. Skořepová E, Hušák M, Cejka J, Zámotný P, Kratochvil B. Increasing dissolution of trospium chloride by co-crystallization with urea. J Crystal Growth. 2014;399:19-26.
64. Padrelo L, Rodrigues MA, Tiago J, Velaga SP, Matos HA, de Azevedo EG. Tuning physicochemical properties of theophylline by cocrystallization using the supercritical fluid enhanced atomization technique. J Supercrit Fluids. 2014;86:129-136.
65. Cuadra IA, Cabañas A, Cheda JAR, Martínez-Casado FJ, Pando C. Pharmaceutical co-crystals of the anti-inflammatory drug diflunisal and nicotinamide obtained using supercritical CO2 as an antisolvent. J CO2 Util. 2016;13:29-37.
66. Chun NH, Wang IC, Lee MJ, Jung YT, Lee S, Kim WS, Choi GJ. Characteristics of indomethacin-saccharin (IMC-SAC) co-crystals prepared by an anti-solvent crystallization process. Eur J Pharm Biopharm. 2013;85:854-861.
67. Ober CA, Montgomery SE, Gupta RB. Formation of itraconazole/L-malic acid cocrystalsby gas antisolvent cocrystallization. Powder Technol. 2013;236:122-131.
68. Lu J, Rohani S. Synthesis and preliminary characterization of sulfamethazine-theophylline co-crystal. J Pharm Sci. 2010;99:4042-4047.
69. Jayasankar A, Somwangthanaroj A, Shao ZJ, Rodríguez-Hornedo N. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. Pharm Res. 2006;23:2381-2392.
70. McNamara DP, Childs SL, Giordano J, Iarriccio A, Cassidy J, Shet MS, Mannion R, O’Donnell E, Park A. Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. Pharm Res. 2006;23:1888-1897.
71. Atipamula S, Wong AB, Chow PS, Tan RB. Pharmaceutical cocrystalsof ethenzamide: structural, solubility and dissolution studies. CrystEngComm. 2012;14:8515-8524.
72. Karki S, Friščič T, Fábián L, Jones W. New solid forms of artemisinin obtained through cocrystallisation. CrystEngComm. 2010;12:4038-4041.
73. Fowler DA, Tian J, Barnes C, Teat SJ, Atwood JL. Cocrystallization of C-butyl pyrogallol [4] arene and C-propan-3-ol pyrogallol [4] arene with gabapentin. CrystEngComm. 2011;13:1446-1449.
74. Tilborg A, Springle G, Norberg B, Wouters J, Leyssens T. On the influence of using a zwitterionic coformer for cocrystallization: structural focus on naproxen–proline cocrystals. CrystEngComm. 2013;15:3341-3350.
75. Aranghel七月sik M, Lloyd GO, Jones W. Mechanochemical synthesis of pyrazine: dicarboxylic acid cocrystalsand a study of dissociation by quantitative phase analysis. CrystEngComm. 2012;14:5203-5208.
76. Heiden S, Tröbs L, Wenzel KJ, Emmerling F. Mechanochemical synthesis and structural characterisation of a theophylline-benzoic acid cocrystal (1:1). CrystEngComm. 2012;14:5128-5129.