ORIGINAL ARTICLE
DOI: 10.4274/tjps.galenos.2020.78700

A Brief Discussion about Multicomponent Organic Solids: Key Emphasis on Cocrystallization

Çok Bileşenli Organik Katılar Üzerine Kısa Bir Tartışma: kokristalizasyon Üzerine Temel Vurgu

Running Title:
A Talk on Multi-component Organic Solids
Koşu Başlığı:
Çok Bileşenli Organik Katılar Üzerine Bir Konuşma

Brahamdutt[1], Manjusha Choudhary[2],Vikas Budhwar[1*]
[1]Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak, Haryana, India-124001
[2]University Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India-136119
Dr. Vikas Budhwar
Assistant Professor (Pharmaceutics)
Department of Pharmaceutical sciences
Maharishi Dayanand University, Rohtak, Haryana, India-124001
Contact No: +91-9466673246
Email: vikaasbudhwar@yahoo.com
0000-0003-2461-4405
04.05.2020
03.12.2020

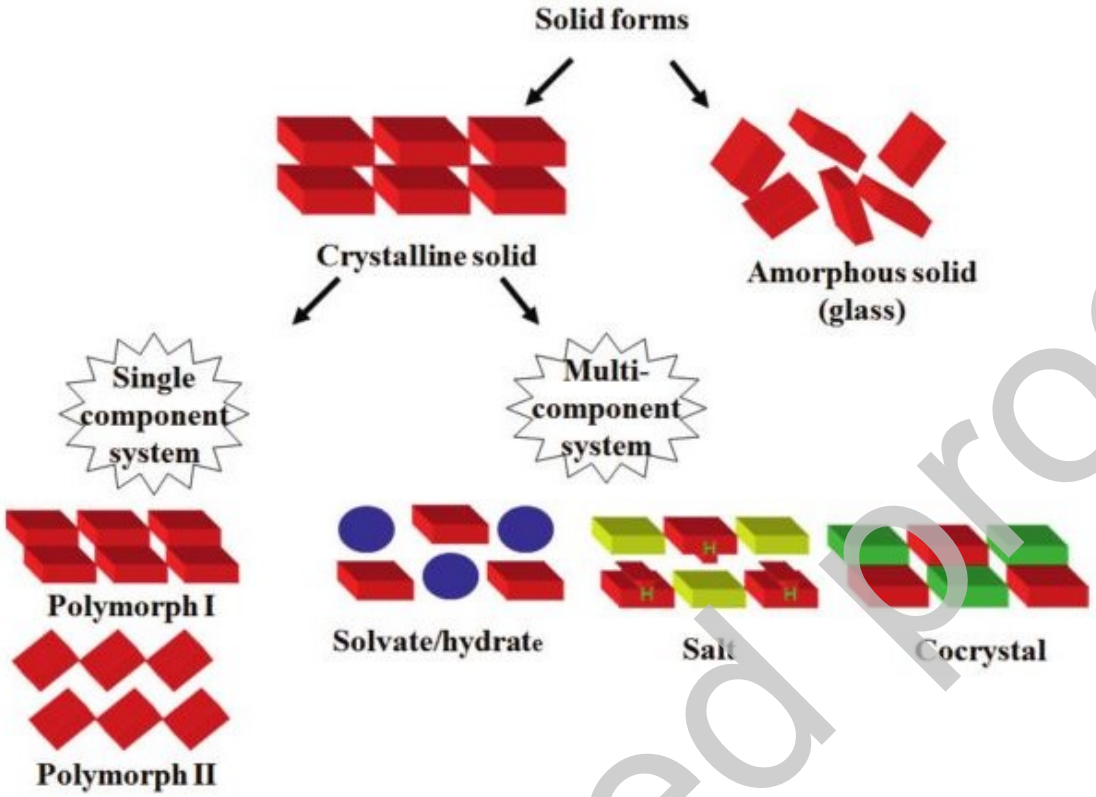
Abstract:
Cocrystallization (CCs) is the less studied phenomena related to its applicability and reliability as it directly related to the generation of newer multicomponent solids like cocrystals (CS), eutectics, salts or solid solutions etc having improved physicochemical properties compared to their pure components. Further, the designing and structural aspects of these multicomponent systems remain hindered as compared to other techniques such as nanotechnology or solid dispersions. As CCs 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 pharmacological activities. For drug delivery purpose, CCs process has numerous advantages over nanotechnology and solid dispersions drug delivery techniques. CCs can modify the physicochemical properties of active pharmaceutical ingredients (API) are having issues like sensitivity toward environmental hazards like temperature, moisture or photostability issues. The availability of large amount of coformers (CFs) makes this technique to be favourable for the researchers in designing CS of newer and older API's. Although, solid dispersions and nanotechnology techniques are being utilised to a larger extent but still there are some drawbacks of these techniques like stability, toxicological factors and protection from environmental factors

needs to be considered, while CCs process drastically modifies the various pharmaceutical parameters without altering the pharmacological properties of API's. Salts and eutectics are other multicomponent systems, which are the outcomes of CCs process. In this review, we have briefly discussed about CS, salts and eutectics, designing of CS, their methods of preparations and their application in various fields with special emphasis on their applicability in pharmaceutical industry.
Keywords: Cocrystals, Eutectics, Salts, Cocrystallization, Chromophores, Cosmetic
Abbreviations: CCs: Cocrystallization, CFs: Coformers, CS: Cocrystals

Öz:
kokristalizasyon, saf bileşenlerine kıyasla iyileştirilmiş fizikokimyasal özelliklere sahip yeni kristaller, ötektikler, tuzlar veya katı çözeltiler gibi daha yeni çok bileşenli katıların üretilmesiyle doğrudan ilgili olduğu için uygulanabilirliği ve güvenilirliği ile ilgili daha az çalışılan fenomendir. Ayrıca, bu çok bileşenli sistemlerin tasarımı ve yapısal yönleri, nanoteknoloji veya katı dispersiyonlar gibi diğer tekniklerle karşılaştırıldığında engellenmeye devam etmektedir. kokristalizasyon, farmakolojik aktivitelerini değiştirmeden veya engellemeden çözünürlük, stabilite vb. İlaç dağıtımı amacıyla, birlikte kristalleştirme işleminin nanoteknoloji ve katı dispersiyon ilaç verme tekniklerine göre çok sayıda avantajı vardır. Kokristalizasyon, aktif farmasötik bileşenlerin (API) fizikokimyasal özelliklerini değiştirebilir; sıcaklık, nem veya fotostabilite sorunları gibi çevresel tehlikelere karşı duyarlılık gibi sorunlar vardır. Büyük miktarda ortak oluşturucunun mevcudiyeti, bu tekniği araştırmacılar için daha yeni ve eski API'lerin ortak kristallerini tasarlarken avantajlı kılmaktadır. Katı dispersiyonlar ve nanoteknoloji teknikleri daha büyük ölçüde kullanılmasına rağmen, yine de bu tekniklerin stabilite, toksikolojik faktörler ve çevresel faktörlerden korunma gibi bazı dezavantajları vardır ve birlikte kristalleştirme işlemi, çeşitli farmasötik parametreleri değiştirmeden büyük ölçüde değiştirir. API'lerin farmakolojik özellikleri. Sorunları olan çeşitli ilaçların fizikokimyasal ve farmasötik özelliklerini değiştirmek için daha yeni bir tekniktir. Tuzlar ve ötektikler, birlikte kristalleştirme işleminin sonuçları olan diğer çok bileşenli sistemlerdir. Bu derlemede, kokristal, tuzlar ve ötektikler, kokristallerin tasarımı, bunların hazırlanma yöntemleri ve bunların farmasötik endüstrisindeki uygulanabilirliğine özel önem verilerek çeşitli alanlarda uygulamaları tartışılmıştır.

Anahtar Kelimeler:kokristal, Ötektikler, Tuzlar, kokristalizasyon, Kromoforlar, Kozmetik

Graphical Abstract:



1.1 Introduction:

Since last decade, the interest of pharmaceutical scientists shifted toward CCs process, because of their interest to improvise the physicochemical characteristics of an API without any alteration in its pharmacological activity, which led them to be a better option for patents and also for development of these drugs into a newer marketable formulation[1]. But a proper definition of CS is still a matter of debate because there are only few studies available, which significantly made differences between CS, eutectics or salts as a product of CCs[2]. 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 cocrystal, on the other hand, when homo-molecular interaction comes into action, then chances of eutectics formation increased. Some of the studies also conclude that eutectics are similar to solid solutions and they called it as "conglomerates of solid solutions" formed due to interactions between couple of molecules lacking geometrical fit and on the other point CS were found to be more stable compared to eutectics as these are geometrically fir components as well as various studies related to CCs process had settled various parameters which

governed the formation process of CS, while in case of eutectic, solid solutions or salts,much literature is not available[3,].

On the basis of literature, most of the studies conclude that CS are multicomponent solids carrying crystalline structure[4]. The latest guidelines of USFDA (United States Food and Drug Administration) related to CS, these are ''Crystalline materials composed of two or more molecules within the same crystal lattice''[5]. But 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 present in a fixed stoichiometric ratio of drug and CFs[6].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 definition of cocrystal, as in case of pharmaceutical CS, one component is drug and other is CFs[6].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 leads to formation of CS with different drugs.

Synthons are responsible for holding the molecules, when the formation of a compound occurred through non-covalent interactions. Due to strength, directionality and higher rate of recurrence, hydrogen bonds are often utilized for designing of co-crystals. In 1991, Etter gives 3 rules for hydrogen bonding pattern[7] every available hydrogen molecule could be used in the formation of bonding, every acceptor of hydrogen bond could participate, if H bond acceptor are present there as well as the H bonding is possible when good acceptor and donor of H bond are present in the molecule. The formations of synthons are governed by strength of hydrogen bonding between co-crystal formers, not by the total number of groups available. With the use of above discussed rules, we can predict the formation of synthons within different functional groups. Basically, synthons are essential structural entities between supermolecules, that formed via non-covalent bonding and made up of molecular fragments and supramolecular links among them. Supramolecular synthons could be classified into two categories: supramolecular homosynthons and supramolecular heterosynthons. The first one is composed by self-complementary functional groups while the second one composed of dissimilar but complementary functional groups. Supramolecular heterosynthons formation take place by non-covalent interaction between various drugs that leads to co-crystal formation. The concept of supramolecular approach is utilized for CS iscreening but now-a-days Cambridge Structural Database (CSD) is used for 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 interacted 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 product of CCs process[8]. In case of CS, the interaction between drug and CFs occurred through non-covalent interactions like hydrogen bonding or ionic interaction. While in case of eutectics, mostly weak van der waals interactions occurred in anunfit geometric pattern, and that's why eutectics became less stable compared to CS[9].So, here in this review, we have briefly discussed about various significant factors and chemistry involved during CCs process along with differences between CS, salts and eutectics. Screenings methodsfor CS, their method of preparations and applications of CS in pharmaceutical and allied industries have been discussed in later sections.

1.2 Cocrystals*vs* eutectics:

The literature is full of studies related to development of newer drug delivery techniques to improvise pharmaceutical properties of API's including dissolution profile, thermostability, material compressibility during tablet production process[8].When we discussed about crystal engineering, the most useful point is understanding of supramolecular synthons formation. As these are the fundamental building blocks of products obtained during CCs process. When there is interaction between two similar functional groups like -COOH functional group of drug and API interact, formation of homosynthons occurred, while interactions between two different functional groups leads to the generation of heterosynthons. As we discussed above in introduction section, the chances of CS or eutectics formation depends upon these two synthons. Generally, it was hypothised that, heterosynthon formation leads to generation of CS while homosynthon formation goes to generation of eutectics but recent studies proved it wrong as numerous CS have been reported via homosynthon formation[9].

Eutectics are basically multi-component crystalline solids closely related to solid solutions[1,10]. Both are well-documented in inorganic systems as alloys[11]. There are numerous studies in the literature, which defined eutectics on the basis of their lower melting point patterns and on the basis their compositions. The term eutectics was derived from the Greek term "*eutectos*", which means fused[12]. Yet the formation of eutectics is not much studied compared to solid solutions, as these are defined on the basis of their composition or arrangements of solute and solvents in the crystalline lattice[14].The detailing of internal structural composition via XRD studies of eutectics are rarely available as compared to solid solution. A deep analysis of structural detailing is required for eutectics in pharmaceutical scenario like famous tin-lead eutectic was studied by inorganic chemists[15]. In the past eutectics have been considered as solid solutions and recently it has been considered as CS for pharmaceuticals and organic systems[16].However,CS have been reported to form eutectics as well as solid solutions[17] and some studies considered eutectics as an intermediate step between CS and solid solutions which is crucial for formation of CS, but exact mechanism for eutectic formation is still remain a matter of discussion[18,19].Thus, CS, eutectics and solid solutions are found to be corelated to each other but most of the studies that differentiate them focussed on the phase diagram studies and binary compositions properties of multicomponent crystalline studies. We discussed the inter-relationships of these multicomponent solids on the basis of their intermolecular interaction as well as structural inter-relationships and proposed that detailed structural data is required to differentiate between eutectics, solid solutions and CS[20].

1.3 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 molecular or ionic level is 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) are comparably remain open, which makes them easy to understand, while in case of closed and 3D packing system, it becomes a challenging task to understand it[23]. At last, the methods like computational crystal structure prediction (CSP) methods retained the key to resolve the problems to understand the full and clear spectrum of interaction at intermolecular level within a crystalline system. Undeniably, it becomes an only reliable source for understanding the influence of every short- or long-range interactions made by the molecules in crystal and this led to predict the most stable crystal compound[24]. Even after this, the various stages in crystal developments like nucleation and growth considerations plays their important roles which cannot be explained by the experimental level studies; hence it is required to understand intermolecular

interactions at all points of crystal development stages. For understanding such developments, CSP method[25] is not a sufficient tool, but recently, Cambridge Blind Tests provided some significant approaches for this[26]. In case of CSP method, the presence of additional degrees of freedom leads to the generation of possible structure enabled by occurrence of second component and this made CSP method more discouraging technique[27] while to understand the development of multicomponent systems, we required gathering of more empirical and rationalized data. However, the more précised calculation, understanding of various associated modes and inclusion of empirical data during the study, could help in prediction of CS or salts formation[28,29]. Recently, engineering of ternary CS were designed on the understanding of pKa values, supramolecular synthons history and hydrogen bond basicity. Ternary cocrystal system like acridine·3-hydroxybenzoic acid· 2-amino-4,6-dimethylpyrimidine, due to smaller size of proton its causes transfer of proton with small steric significance and leads to the protonation of base by acid. This phenomenon was a great example of understanding the electronic factors along with solvation characteristics of acid, base and their salt[30]. The pKa value represents that the pH value at which all the solubilisedionisable components are fifty percent charged and fifty percent remained protonated and it depends upon the acidic or basic strength of the molecule[1].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 details in screening methods. By using 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 place[31] and the chances of salt formation increased but currently newer theoretical and high pressure techniques based studies exhibited proton transfer in pyridine-formic acid system depends upon concentration of formic acid present in the solution[32]. The charged ions and the polar molecules of aqueous medium interact with each other which makes salts more hygroscopic especially in case of anions are found to be conjugated base of strong acids like chloride, sulphates etc. In terms of interactions at intermolecular level, the rationalization become easier in at least broad terms[4].

Figure 1. To be inserted here.

1.4 Methods of cocrystal preparation

There are numerous methods for formulation of CSbut traditionally crystallization was carried via solution with suitable degree of super saturation viz cooling, evaporation and includes substances having properties of the solubility lowering. CCs with solvent evaporation technique did not provide favourable results[30]. Generally, two methods are used for CCs: Solution based technique and grinding based techniques. Solution based methods are generally preferred because of formation of CS which can qualify the testing with single X-ray diffraction (SXRD). The grinding techniques include Neat grinding technique and solvent drop grinding technique. Currently newer techniques are available *viz* hot-stage microscopy, ultrasound assisted and CCs via supercritical fluid[31].

1.4.1 Grinding method:

CCs product usually prepared with grinding method is consistent as compared to prepare from solution. The main drawback of this method is its inability to prepare significant arrangements of CS before due to the stability of early phases. Solvent method is better than 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 formation of CS leading to increased interest as CCs technique[31].

Neat grinding technique can be performed by vibratory mills, mechanical grinding or manual grinding, while solvent drop grinding can be done by addition of suitable solvent in regular interval with grinding but make sure that the solvent should be capable of dissolving the solid

material. Caffeine-glutaric acid cocrystal polymorph when compared with solvent evaporation technique is cost effective, eco-friendly, and effective for cocrystal formation[31].

1.4.1.1 Solid state grinding:

In solid state grinding, the particulate size reduced with increased covalent reactivity within the mixture. This technique helps in improvement in simplicity and selectivity over solution-basedCCs 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 general arrangement of hydrogen bonds of both CS. In this technique, the major shortcoming is polymorphic transition leads to serious side effects, causing product withdrawal from the market[32].

1.4.1.2 Solvent drop grinding:

It is almost same as solid state grinding method with introduction of solvent in smaller quantity. Here solvent act as catalytic agent[33]. Primarily cocrystal formation occurred via solution crystal growth manner. Most of crystals grow faster with solid grinding technique while others proceed further slowly. For those crystals, solvent drop method found to be effective[31]. For preparation of CS of caffeine and Glutaric acid solvent drop grinding technique was found to suitable in comparison to solid state grinding. Preparation of succinic acid: 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].

1.4.2 Cocrystallization from Solution:

Here the key requirement is same solubility profile for both compounds undergoing CCs, otherwise least soluble compound will get precipitate out completely from the solution. While similar solubility profile of both components couldn't promise a positive result. It is probably beneficial to trust polymorphic complexes that occur in additionally in comparison to solitary crystalline arrangement as CCs compounds. When a molecular component occurred in various polymorphic states, it revealed a structure-based tractability and cannot be locked into a packing model[33]. For large scale production, a water jacketed vessel with circulating water bath facility for temperature control was being used. Teflon blades were used for continues stirring. Drug and CFs were dissolved in alcoholic solvent at 70º C under reflux for 1 hour. Reduction in temperature with 10º C rate was done to precipitate out the co-crystals. Literary to increase solids retrieval reduced the surplus heat[31].

1.4.2.1 Solvent Evaporation:

This is the most traditional method used for CCs, including super saturation of solution by cooling, evaporating and solvent addition having solubility changing properties. It is assumed that molecules undergo hydrogen bonding when mixed in appropriate quantities. CS of Fluoxetine hydrochloride with different CFs*viz* fumaric acid, succinic acid and benzoic acid were prepared by using this method for enhancing their intrinsic solubility[31]. In another study, CS of norfloxacin with Malonic acid, maleic acid and Isonicotinamide were also prepared with improved physicochemical properties[33].

1.4.2.2 Slurry Crystallization:

The process of addition of a suitable crystallization solvent to the API and its co-former is known as Slurry crystallization, the use of this process is governed by the physical stability of the crystallization solvent compared to that of the API and CFs. The synthesis of CS through slurry crystallization was used with sixteen CS system[31]. Different solvents can be used for slurry crystallization, around 100 ml of liquid solvent is poured and for few days, stirring was done to the suspension room temperature. The Suspension is then allowed to decant and the CS was dried under nitrogen[33]. Examples of slurry crystallized includes CS of Trimethoprim and sulfamethoxazole using distilled water. Slurry Crystallization possess one major disadvantage that it requires a large amount of solvent[31].

1.4.3 Hot melt extrusion:
Hot melt extrusion an efficient cocrystal synthesis method which do not require any solvents;however, the selection of this process depends on the thermodynamic stability of the API and the CFs. Holt melt extrusion can be optimized using solvent drop extrusion technique, which an extra advantage to carry out hot melt at a lowest temperature. Examples include Carbamazepine Nicotinamide CS[31].

1.4.4 Sonocrystallization Method:
The use of sonocrystallization to synthesize CS is very rarely explored, this method is suitable for the preparation of nanocrystals. Ultrasound method was used for the preparation of Caffeine-maleic acid CS, Theophylline and L-tartaric acid as a CFs[32].

1.5Screening of Cocrystals:
Various methods for screening of CS were discussed below:

1.5.1 ΔpKa rule is widely being utilized for CS screening by using the following equation.
Δp*K*a=[p*K*a (base)–p*K*a (acid)]
When difference in p*K*a values is >2-3, transfer of proton will take place between acids and bases. p*K*a values lesser than 0 exhibits formation of CS while more than 2-3 value revealed formation of salts[34,35]. In CSD 6465 possible CS were studied to validate and quantify this rule. The increment in pKa value of free base to one digit directly increased one unit of pH_{max}. For attaining this condition practically, we required to modify the drug molecule. In the same way one-digit increment in intrinsic solubility profile of a free base effects directly one-unit increment in pH_{max} again. This also required modification in drug molecule[36].While one decrement in salt solubility leads to increment of one unit in pH_{max}. This characteristic can be modified by using a counter ion with different properties and if salt formation occurred, it would be stable over greater pH range but having lower solubility profile.

Table 1. To be inserted here

1.5.2 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 cocrystal. Other molecular descriptors are also important as well for prediction of cocrystal formers[36].

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

1.5.4 Calculated gas phase MEPS technique used the difference of energy ΔE difference between CS and pure solids in various stoichiometries, to determine the possible formation of CS between two solids. The outcome of study revealed that, when ΔE is more than 11 kJ/mol, chances of cocrystal formation enhanced 50% more. Over 1000 compounds were screened to validate this method including (caffeine and carbamazepine) and results were satisfactory enough[38].

1.5.5 Co-crystal cocktail method is very useful and lesser time-consuming method. In this method more than three CFs are simultaneously grounded with drug leading to formation of homo or heterosynthons between drug and CFs which could be analysed with thermal analysis methods by checking their endothermic peaks[39].

1.5.6 Differential scanning calorimetry is a rapid thermal method for screening of CCs[39]. In this method, we check the endothermic peaks for formation of CS by heating the mixture of drug and CFs in DSC pans. The hypothesis about CS formation is exhibition of three endothermic and a couple of exothermic peaks in thermogram represent formation of CS with

stoichiometric variety[40]. In case of thermal techniques, it is a general hypothesis that during CCs, the melting point of CS remain between melting points of drug and CFs while in case of eutectic mixture, generally the melting point of product comes before the melting point of both 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 behaviour of melting point in CCs, Schultheiss and Newman in 2009 determined that around 51% of CS possess melting point between drug and CFs while 6% possess greater melting point and around 39% possess lower melting point compared to drug and CFs melting point respectively. The melting point of CS generally get altered by the melting point of CFs. If we choose a CFs with 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[4].

Table 2. To be inserted here.

1.5.7 Hot stage microscopy or Kofler contact method offers visualization of total phase number that is exhibited by the system when two compounds are heated. When the high melting point compound start melting and recrystallization occur before other melted compound comes in contact with it leading to the formation of zone of mixing[41,42].

1.5.8 Saturation solubility technique involved measurement of saturation solubility of API's and conformer separately at reference temperature. Saturation temperature of solvent system is measured by heating with rate of 0.3°/min. If the increase in saturation temperature is more than 10° in comparison to reference temperature, chances for co-crystal formation increases[43,44]. The study of carbamazepine and nicotinamide-basedCS revealed that solubility profile of drug directly depends upon the concentration of CS in the drug and CFs solution. This study conclude that the solubility of drug could be increased only when it gets complexed with CFs during the CCs process, otherwise the free drug had no impact on increment of solubility profile of parent components[4].

1.6 Applications of cocrystallization:

1.6.1 Pharmaceuticals:

The interest of pharmaceutical industry and researchers have been shifted toward CCs and many drugs including newer and older API's have been included in preparation of CS and eutectics as these formulations improvise the pharmaceutical issues related to these drugs without altering or modifying their therapeutic activities[45,46]. The enhancements in solubility[47], stability[48] and aqueous solubility have been reported after CCs of various API's. With the drastically improved pharmaceutical characteristics of API's, CCs process have been considered as the most effective technique to improvise the bioavailability[49] of drugs. It is evident from literature that by formulating CS of fluoxetine hydrochloride with different CFs, the solubility of each formulation was found to be increased. The solubility of fluoxetine hydrochloride was found to be 11.6 mg/mL while its CS with fumaric acid and succinic acid were found to be 14.8mg/mL and 20.2 mg/ mL respectively[50]. In another study, the solubility profile of CS of Tegafure was found to be much higher in comparison to the its pure amorphous state[51]. In this case, the important point is the increment in its solubility without effecting the stability of pure amorphous form of drug. A vast literature is available containing such examples where solubility and dissolution behaviour of various drugs have been modified without changing their original therapeutic properties[50,51]. While if we talk about eutectics, the drug: drugs eutectics have been reported in literature like 1:1 eutectic mixture of pyrazinamide and isoniazid exhibiting enhanced solubility profile while in some examples PEG and different API's revealing enhanced pharmaceutical characteristics[52-54]. Eutectics mixture of Ibuprofen-menthol showed an improved dissolution behaviour[55]. The similar improved dissolution behaviour was recognized in case of 2-[4-(4-chloro-2-

fluorophenoxy) phenyl] pyrimidine-4-carboxamide: glutaric acid CS[56]. These examples revealed the effects of CCs in improvement of solubility behaviour along with bioavailability improvement of drugs[57]. The 1:1 danazol: vanillin CS showed an increased solubility as compared to poorly soluble pure danazol. The stability of drugs is also improved by CCs like carbamazepine CS revealed an enhanced hydro stability in caparison to susceptibility of hydrate formation property of carbamazepine[58]. An improved humidity stability of theophylline and oxalic acid CS have been reported as compared to their pure state.

Figure 2. To be inserted here.

1.6.1.2Mechanical properties

In 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 paracetamol CS compared to pure paracetamol. The plasticity and compressibility of theophylline: methyl gallate CS were found to be much higher than theophylline alone. All these properties improved due to layered structures of their CS[58].

1.6.1.3 Compression behaviours

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 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 solid unit dosage form having desired tensile strength. So, the understanding of material's characteristics becomes an important key to develop and design a newer formulation with desired physical and chemical properties. Where, a higher dose or higher amount of drug is required, than compressibility and compaction become very important parameters to study[59]. Till date, the main focus of CS researchers mainly focussed on improvement of solubility issue and tabletting properties area did not get much attention. There are some handful examples in the literature where this area of research touched like CS of carbamazepine with nicotinamide and saccharin were found to have an increased tensile strength of 2.00 and 2.19 times, respectively at 1500 lb/cm3. But the dissolution rate of these CS were found to be lesser compared to pure drug. This signify the relationship of higher tensile strength is directly proportional to lower dissolution profile[58].

1.6.1.4 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 profiles as an indicator of cocrystal performance. These studies did not comment on the cocrystal solubility behaviour 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, succinic acid (SA), malic acid, and tartaric acid[60], 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[55]. Celecoxib-NIC CS had a higher dissolution rate than the drug alone. The dissolution rate of CS formulated with 2% sodium dodecylsulfate and polyvinylpyrrolidone (PVP) was better than that of the drug alone formulated 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 cocrystal behaviour have not been investigated[62].

The dissolution of CS of exemestane with maleic acid and megestrol acetate with SAC was studied in Fasted State Simulated Intestinal Fluid (FaSSIF). 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 μm)[63]. 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-SAC CS was investigated in beagle dogs and compared with the bioavailability of both the marketed product of IND (Indomee®) and the physical mixture of drug and CFs[64]. The CS had similar pharmacokinetic data to the marketed product but significantly improved performance compared to the physical mixture. After preparing and characterising CS of AMG517, CS of AMG517 with sorbic acid were studied 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 (C_{max} and AUC) for the CS[65,66].

1.6.2Cosmetics

In the cosmetic formulation development, the main focus remains on the formulation of a stable and easily applicable preparation using active ingredients. CCs and eutectic mixture provide these basic facilities to the formulation developers. The inclusion of solid colognes in these cosmetic preparations is a challenge because a higher temperature is required to melt these solid components, which may directly affect the thermostability of other ingredients used. Some eutectic mixtures of standard colognes in solid form with benzophenone were formulated 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[67]. The eutectic mixture based upon above idea was prepared by using 12-hydroxystearic acid, as well-known benefits of 12-hydroxystearic acid on skin having higher melting point and inadequate bioavailability. The other key benefit of CCs is availing a higher melting point crystalline substance having more stability. But higher melting point substances could be a problem for other lower melting point ingredients[68]. Cocrystal 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[69]. These systems also provide higher flowability to powders and better compressibility during tablets or capsules formulation process. Nicotinamide: p-coumaric acid cocrystal formulations were reported in literature to treat acne[70]. In another study, the CS of hair dye colorants exhibit better stability on hair compared to pure colorant[71]. CS could be an important formulation development system in cosmetic scenario, but the higher melting point of CS plays the key role and that's why, in cosmetic industry, the main focussed area become eutectic systems. Butyl methoxy-dibenzoylmethane (BMDM) an UVB absorbing agent, included in eutectic mixture with and without 12-hydroxystearic acid to overcome the challenge of higher melting point of both components[72]. Anti-Sun Eutectic formulation based on n-butylphthalamide and isopropylphthalamide with 1,3,5-triazine derivatives was prepared revealing higher stability[73]. The eutectic mixture preparation of monoethanolamides used in scalp itching treatment exhibit higher deposition compared to pure compound[74].

1.6.3Agricultural Applications

In the agrochemical sector, there are plentiful patents have been filled on CS, which mainly include fertilizers, insecticides and fungicides etc. CS based fungicide patent was filled containing two fungicides namely metalaxyl and prothioconazole[75]. In this preparation, the aqueous solubility of metalaxyl was drastically decreased compared to the pure component. The reason given behind reduced solubility was the decrement to surplus of the fungicide in

the ground water streams along with higher efficacy and less requirement of fungicides for desired action. This cocrystal based formulation is a significant example of synergistic action of two active fungicide ingredients. CS of herbicide 3,6-dichloro-2-methoxybenzoic acid with different nitrogenous heterocycles were also reported having less water solubility and higher stability[76]. But there are some examples of various herbicide suffering from Ostwald effect (large size crystals growth) with time, which have deleterious effect during the storage and processability of product in production and efficacy during use. Here CS provide significant improved stability to overcome these issues. 4-hydroxybenzoic acid based CS with different agrochemicals effectively overcome the above discussed problems[77]. The increased melting point insecticides were reported by CCs of these insecticides with oxalic acid. The higher melting point provide shelf stability and prevent the clumping or Ostwald effect on pure insecticides with time. A recent patent on CS of 4-{[(6-chloropyrid-3-yl) methyl] (2,2-difluoroethyl) amino} furan- 2(5H)-one with salicylic acid was filled having higher melting point and stability[78,79].

1.6.4Chromophores

Pigments are a principally fascinating chromophore application of cocrystal. According to Bucar et al., it is not possible to prepare novel pigments in high amount only through solvent methods, it can be prepared in high yield through mechanochemical grinding. The three-colour tuned fluorescein CS formulation support this argument mainly. Chromophore CS of titanyl fluorothalocyanine with titanyl fluorocyanine were formulated by dry milling and heating. The novel CS have a novel spectrum along with enhanced sensitivity toward electrophotography and less dark decay. Bicomponent diazo eutectics were prepared as red textile pigments. These eutectic pigments exhibit an equal performance compared to highly toxic dyes in relation to thermostability, colour fastness, acidic and alkalis resistance and solubility profile. In another study, Yen et. al., proved that CS can be utilised at much higher level than just tuning the solubility, stability and colour of chromophores. They formulate a series of CS based upon stilbene-type molecules with different CFs. The results exhibited a significant and remarkable change in the form UV or visible absorbance, quantum yield and luminescence emissions[67].

1.6.5Food Industry

CS have also create a place in food additives. The yerba mate (an anti-oxidant) along with sucrose make CS showed a better flow property and good hygroscopicity during production process compared to their pure state[63]. It is also evident that antioxidant properties of yerba mate remain stable in there CS form. In another example, ethyl vanilla and vanilla are required in mixture form to provide a better taste and fragrance, but during manufacturing process, clumping occurred in simple mixture of both these substances. But CCs of these compounds at individual level, provide their powder form carrying good flow properties and lesser clump formation tendency. Menthol: Xylitol based CS is another good example of CS having optimum flow properties used for fragrance[54-55]. These CS revealed a higher solubility profile in comparison to pure menthol and lesser hygroscopicity compared to pure xylitol.

1.6.6 Solubilization of CS

CS have risen as a method for modification of dissolvability, disintegration, bioavailability, and other physicochemical properties of drugs, without changing their pharmacological properties[57]. CS are a class of multicomponent solids containing at least two diverse crystalline components in a solitary homogenous system in a fixed stoichiometry ratio. They are distinguished from solvates in that the cocrystal components are solids at room temperature.Pharmaceutical CS are generally made of a hydrophobic drug molecule and a hydrophilic CFs molecule[58]. The mechanism by which CS go into solution involves three main steps: (1) breaking intermolecular bonds in the cocrystal, (2) breaking intermolecular bonds in the solvent, and (3) forming intermolecular bonds between cocrystal molecules and

solvent molecules. The limiting step in dissolving 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, CFs aqueous solubility is correlated with cocrystal solubility. On the other hand, melting points are not good indicators of cocrystal aqueous solubilities, since it is drug hydrophobicity and not cocrystal lattice strength that limits solubility[59].

Table 3. To be inserted here

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 leads to formation of CS with different drugs. So, in CCs studies presence of carboxylic acid functional group plays an admirable role. Synthons are responsible for holding the molecules, when the formation of a compound occurred through non-covalent interactions. Due to strength, directionality and higher rate of recurrence, hydrogen bonds are often utilized for designing of CS. Generally, two methods are used for CCs: Solution based technique and grinding based techniques. Solution based methods are generally preferred because of formation of CS which can qualify the testing with single X-ray diffraction (SXRD). The grinding techniques include Neat grinding technique and solvent drop grinding technique. 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 less patent activities, these are potentially very important binary systems because of their prominent effects. CCs can be used in almost all API's including acidic, basic or non-ionic drugs. Availability of large number of CFs, allowed this technique to be used broadly. It is evident from previous and recent studies that CCs materials carry higher electrical conductivity compared to their parent components. So, this is an area of research because of its potential in power production sector.

Funding Source: None

Conflict of Interest: None

Acknowledgements: Authors want to thank Department of Pharmaceutical Sciences, Maharishi Dayanand University, Rohtak for providing all necessary facilities to carry out this work.

References:

1. Cherukuvada S, Nangia A. Eutectics as improved pharmaceutical materials: design, properties and characterization. Chem. Commun 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, *et al,* 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(11):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.
6. Ross SA, Lamprou DA, Douroumis D. Engineering and manufacturing of pharmaceutical co-crystals: a review of solvent-free manufacturing technologies.Chem. Commun. 2016; 52:8772-8786.
7. Shayanfar A, Jouyban A. Physicochemical characterization of a new cocrystal of ketoconazole. Powder Technol. 2014; 262:242-248.
8. Ganduri R, Cherukuvada S, Sarkar S, *et al,* Manifestation of cocrystalsand eutectics among structurally related molecules: towards understanding the factors that control their formation, Cryst Eng Comm 2017; 19: 1123.
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 2007; 2375–2377.
10. Cherukuvada S, Kaur R, Tayur NGR. Co-crystallization and small molecule crystal form diversity: from pharmaceutical to materials applications. CrystEngComm2016; 18: 8528.
11. Merz K, Vasylyeva V. Development and Boundaries in the Field of Supramolecular Synthons. Cryst Eng Comm 2010; 12: 3989−4002.
12. Aakeröy CB, Rajbanshi A, Li ZJ, Desper J. Mapping out the Synthetic Landscape for Recrystallization, Cocrystallization, and Salt Formation. Cryst Eng Comm 2010; 12: 4231−4239.
13. Hsi K, Chadwick A, Fried M, Kenny AS. Separation of impurities from solution by selective co-crystal formation. Cryst. Eng. Commun. 2012;14:2386–2388.
14. Fábián LS. Cambridge structural database analysis of molecular complementarity in cocrystals, Cryst. Growth Des. 2009;9: 1436–1443.
15. Stevens JS, Byard SJ, Schroeder SLM. Characterization of Proton Transfer by X-Ray Photoelectron Spectroscopy. Cryst. Growth Des. 2010; 10: 1435−1442.
16. Stevens JS, Byard SJ, Schroeder SLM. Salt or Cocrystal? Determination of Protonation State by X-Ray Photoelectron Spec- troscopy. 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.
18. Mohammad MA, Alhalaweh A, Bashimam M, Al-Mardini MA, VelagaS. Utility of Hansen Solubility Parameters in the Cocrystal Screening. J. Pharm. Pharmacol. 2010; 62: 1360−1362.
19. Huang N, Rodríguez-Hornedo N. Effect of Micellar Solubilization on Cocrystal Solubility and Stability. Cryst. Growth Des. 2010; 10: 2050−2053.
20. Moore MD, Wildfong PLD. Aqueous Solubility Enhancement through Engineering of Binary Solid Composites: Pharmaceutical Applications. J. Pharm. Innov. 2009; 4: 36–49.

21. Childs SL, Stahly GP, Park A. The Salt-Cocrystal Continuum: The Influence of Crystal Structure on Ionization State. Mol. Pharm. 2007; 4: 323–338.
22. Cannon AS, Warner JC. Noncovalent Derivatization: Green Chemistry Applications of Crystal Engineering. Cryst. Growth Des. 2002; 2: 255–257.
23. Aitipamula S, Banerjee R, Bansal AK, *et al.* Polymorphs, Salts, and cocrystals: What's in a Name? Cryst. Growth Des. 2012; 12: 2147–2152.
24. Cruz-Cabeza AJ. Acid–Base Crystalline Complexes and the pKa Rule. CrystEngComm 2012; 14: 6362–6365.
25. 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.
26. Etter MC, Reutzel SM. Hydrogen Bond Directed Cocrystallization and Molecular Recognition Properties of Acyclic Imides. J. Am. Chem. Soc. 1991; 113: 2586–2598.
27. Schultheiss N, Newman A. Pharmaceutical cocrystalsand Their Physiochemical Properties. Cryst. Growth Des. 2009; 9: 2950–2967.
28. Kuroda R, Imai Y, Tajima N. Generation of a Co-Crystal Phase with Novel Coloristic Properties via Solid State Grinding Procedures. Chem. Commun. 2002; 23: 2848–2849.
29. Cherukuvada S Nangia A. Fast Dissolving Eutectic Compositions of Two Anti-Tubercular Drugs. CrystEngComm 2012; 14: 2579–2588.
30. Vitthalrao MA, Kumar FN, Radheshyam BK. Reviw article cocrystalization : an alternative approach for solid modification. J drug delivther. 2013; 3(4):166–72.
31. Raghuram Reddy Kothur AS, Swetha NPB. An Outline Of Crystal Engineering Of Pharmaceutical Co- Crystals And Applications: A Review. Int J Pharm Res Dev. 2012;4(0974):84–92.
32. Sevukarajan M, Thamizhvanan K, Sodanapalli R, SateeshBabu JM, 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(1):15–29.
33. Trask AV, Motherwell WDS, Jones W. Solvent-drop grinding: green polymorph control of cocrystallisation. ChemCommun (Camb). 2004;7;(7):890–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15045115.
34. Friscic T, Jones W. Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. Cryst. Growth Des. 2009; 9: 1621–1637.
35. Aakeröy CB, Grommet AB, Desper J. Co-Crystal Screening of Diclofenac. Pharmaceutics 2011; 3: 601–614.
36. Swapna B, Maddileti D, Nangia A. Cocrystalsof the Tuberculosis Drug Isoniazid: Polymorphism, Isostructurality, and Stability. Cryst. Growth Des. 2014; 14: 5991–6005.
37. Bhogala BR, Basavoju S, Nangia A. Tape and layer structures in cocrystalsof some di- and tricarboxylic acids with 4,4-bipyridines and isonicotinamide. From binary to ternary CS. CrystEngComm. 2005;7:551-62.
38. Childs SL, Stahly GP, Park A. The salt- cocrystalscontinuum: The influence of crystal structure on ionization state. Mol Pharm. 2007; 4:323-38.
39. Cruz-Cabeza AJ. Acid-base crystalline complexes and the pKa rule. CrystEngComm. 2012; 14:6362-5.
40. Laszlo F. Cambridge structural database analysis of molecular complementarity in cocrystals. Cryst Growth Des. 2009;9(3):1436-43.
41. Kumar S and Nanda A. Pharmaceutical cocrystals: An Overview, Indian J. Pharm. Sci. 2017;79(6):858-871.
42. Musumeci D, Hunter CA, Prohens R, Scuderi S, McCabe JF. Virtual cocrystal screening. ChemSci. 2011; 2:883-90.

43. Yamamoto K, Tsutsumi S, Ikeda Y. Establishment of cocrystal cocktail grinding method for rational screening of pharmaceutical cocrystals. Int J Pharm. 2012;437:162- 71.
44. Lu E, Rodriguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. CrystEngComm. 2008;10:665-68.
45. Trask AV, Motherwell WDS, Jones W. Physical Stability Enhancement of Theophylline via Cocrystallization. Int. J. Pharm. 2006; 320: 114–123.
46. 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.
47. Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernäs H, Hussain AS, et al. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. Mol Pharm. 2003;1:85–96.
48. Jain S Mechanical properties of powders for compaction and tableting: an overview, Pharmaceutical Science & Technology Today, 1999; 2:20-31.
49. Hiestand EN. Dispersion forces and plastic deformation in tablet bond, Journal of Pharmaceutical Sciences, 1985;74:768-770.
50. Hiestand EN. Tablet bond. I. a theoretical model, International journal of pharmaceutics, 1991;67:217-229.
51. Hiestand EN, Smith DP, Tablet bond. II. Experimental check of model, International journal of pharmaceutics, 1991;67:231-246.
52. Blagden N, Coles SJ, Berry DJ, Pharmaceutical cocrystals- are we there yet?, CrystEngComm, 2014;16: 5753-5761.
53. Sun CC, Hou H, Improving Mechanical Properties of Caffeine and Methyl Gallate Crystals by Cocrystallization, Crystal Growth & Design, 2008;8: 1575-1579.
54. 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.
55. Rahman Z, Samy R, Sayeed VA, Khan MA. Physicochemical and mechanical properties of carbamazepine cocrystalswith saccharin, Pharmaceutical Development and Technology, 2012;17:457-465.
56. N. Blagden et al. Current directions in co-crystal growth, New J. Chem. 2008; 32:1659-1672.
57. Desiraju GR. Crystal and cocrystal. Cryst. Eng. Commun. 2003;2: 466–467
58. Dunitz, JD.Crystal and cocrystal: a second opinion. Cryst. Eng. Commun. 2003;4:506.
59. Bond AD. What is a cocrystal? Cryst. Eng. Commun. 2003;9: 833–834.
60. Shimpi MR, Childs SL, Boström D, Velaga S.P. New cocrystalsof ezetimibe with L-proline and imidazole. CrystEngComm 2014;16(38):8984-8993.
61. Elbagerma MA, (2010). Analytical method development for structural studies of pharmaceutical and related materials in solution and solid 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).
62. Zegarac M, Lekšić E, Šket P, Plavec J, Bogdanović MD, Bučar DK, Meštrović E. A sildenafil cocrystal based on acetylsalicylic acid exhibits an enhanced intrinsic dissolution rate. CrystEngComm 2014;16(1):32-35.
63. Wang JR, Yu X, Zhou C, Lin Y, Chen C, Pan G, Mei X. Improving the dissolution and bioavailability of 6-mercaptopurine via co-crystallization with isonicotinamide. Bio Med Chem Let 2015;25(5):1036-1039.
64. Trask AV, Motherwell WS, Jones W. Physical stability enhancement of theophylline via cocrystallization. Int J Pharm 2006 ;320(1):114-123.

65. Aher S, Dhumal R, Mahadik 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(5):597-602.
66. Mureşan-Pop M, Chiriac LB, Martin F, Simon S. Novel nutraceutical Myricetin composite of enhanced dissolution obtained by co-crystallization with acetamide. Composites Part B: Engineering 2016;89:60-66.
67. Skořepová E, Hušák M, Čejka J, Zámostný P, Kratochvíl B. Increasing dissolution of trospium chloride by co-crystallization with urea. J Crystal Growth 2014;399:19-26.
68. Padrela 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 Super Fluids 2014;86:129-136.
69. Cuadra IA, Cabañas A, Cheda JA, Martínez-Casado FJ, Pando C. Pharmaceutical cocrystalsof the anti-inflammatory drug diflunisal and nicotinamide obtained using supercritical CO 2 as an antisolvent. J CO2 Utilization 2016;13:29-37.
70. Chun NH, Wang IC, Lee MJ, Jung YT, Lee S, Kim WS, Choi GJ. Characteristics of indomethacin–saccharin (IMC–SAC) cocrystalsprepared by an anti-solvent crystallization process. Eur J Pharm Biopharm 2013;85(3):854-861.
71. Ober CA, Montgomery SE, Gupta RB. Formation of itraconazole/L-malic acid cocrystalsby gas antisolvent cocrystallization. Powder Tech 2013;236:122-131.
72. Lu J, Rohani S. Synthesis and preliminary characterization of sulfamethazine□theophylline co□crystal. J Pharm Sci 2010; 99(9):4042-4047.
73. Jayasankar A, Somwangthanaroj A, Shao ZJ, Rodríguez-Hornedo N. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. Pharm Res 2006;23(10):2381-2392.
74. McNamara DP, Childs SL, Giordano J, Iarriccio A, Cassidy J, Shet MS, Park A. Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. Pharm Res 2006;23(8):1888-1897.
75. Aitipamula S, Wong AB, Chow PS, Tan RB. Pharmaceutical cocrystalsof ethenzamide: structural, solubility and dissolution studies. CrystEngComm 2012;14(24):8515-8524.
76. Karki S, Friščić T, Fábián L, Jones W. New solid forms of artemisinin obtained through cocrystallisation. CrystEngComm 2010;12(12):4038-4041.
77. 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(5):1446-1449.
78. Tilborg A, Springuel 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(17): 3341-3350.
79. Arhangelskis M, Lloyd GO, Jones W. Mechanochemical synthesis of pyrazine: dicarboxylic acid cocrystalsand a study of dissociation by quantitative phase analysis. CrystEngComm 2012;14(16):5203-5208.
80. Heiden S, Tröbs L, Wenzel KJ, Emmerling F. Mechanochemical synthesis and structural characterisation of a theophylline-benzoic acid cocrystal (1: 1). CrystEngComm 2012;14(16):5128-5129.

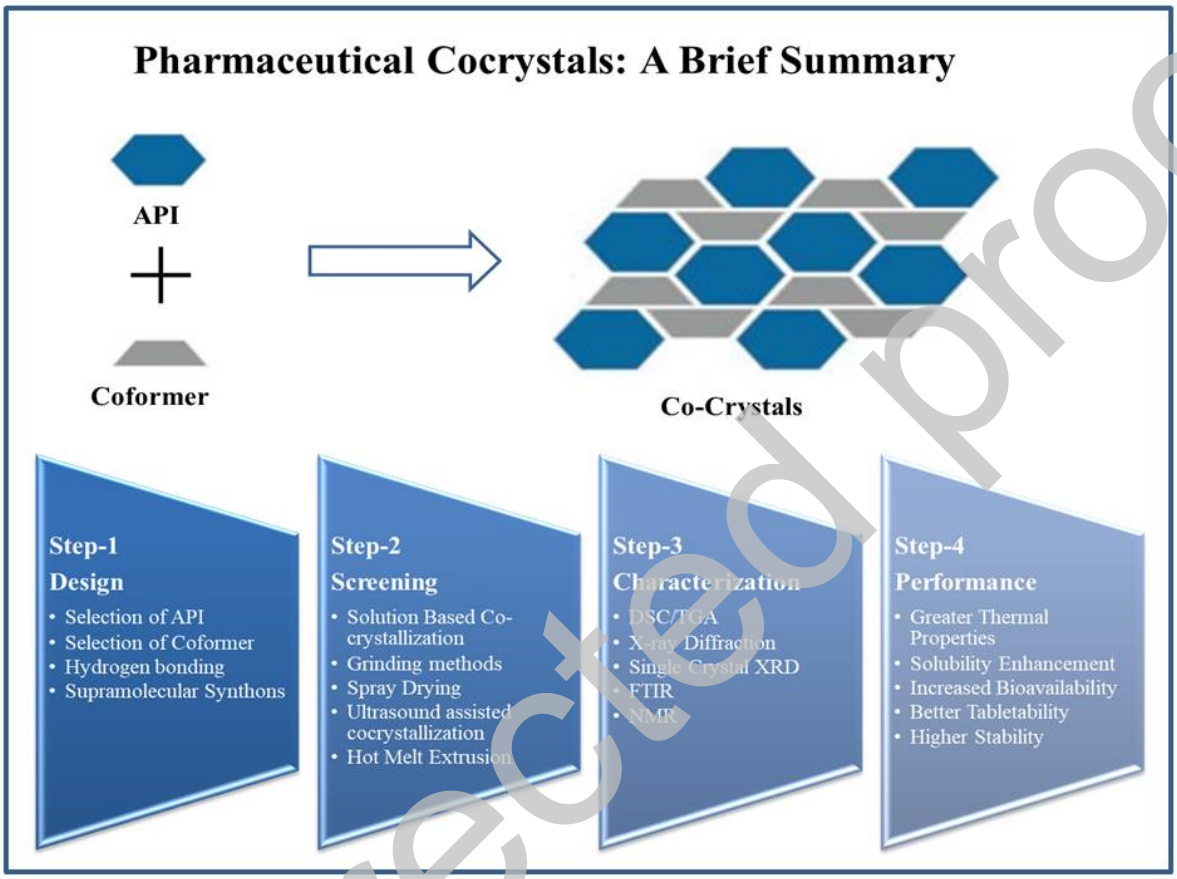


Figure 1. An overview of pharmaceutical cocrystals

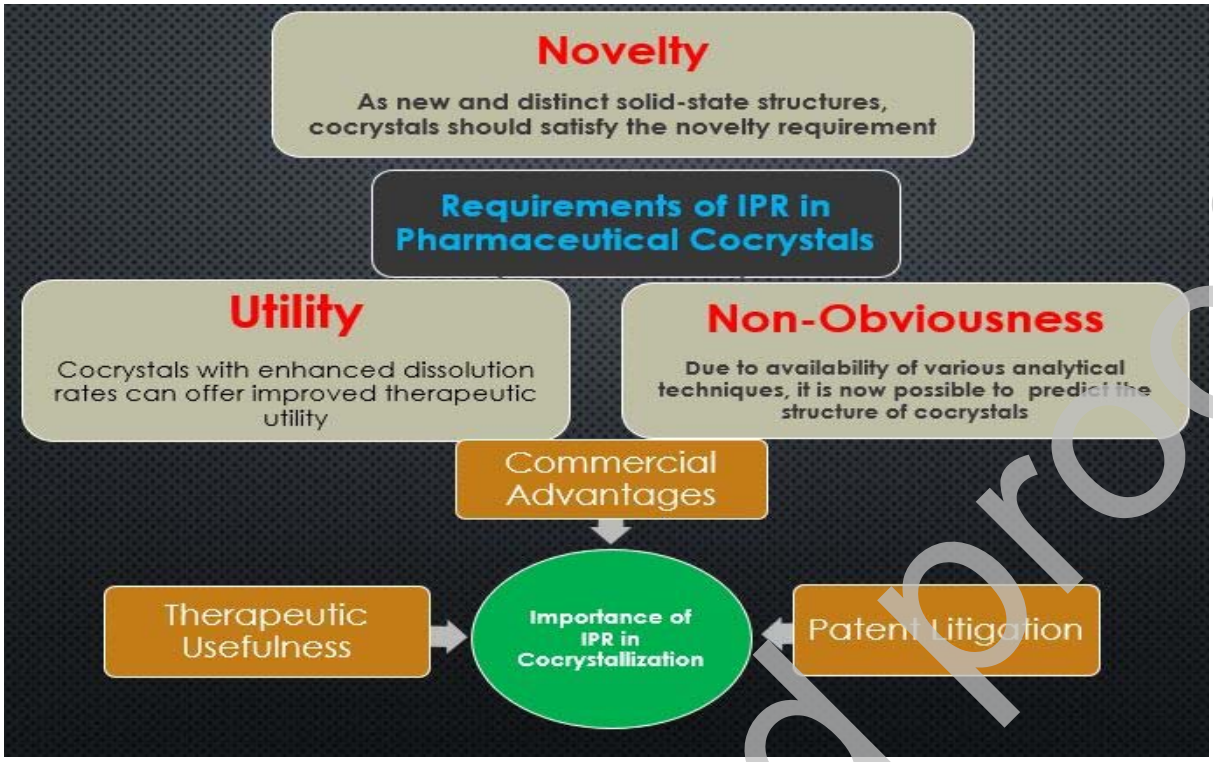


Figure 2. Application of Intellectual Property Rights in Cocrystallization

Table 1 Relation of p*K*a values with possibility of formation of complexes[32].

Possibility of formation of complexes	**p*K*a values**
Non-ionized complexes	Δp*K*a<–1
Ionized complexes	ΔpKa<4 (ionizable complex formation possibility increases by 17% by increasing Δp*K*a by 1 unit from 10% at ΔpKa=–1 to 95% at ΔpKa=4)

Table 2 Relation of Cocrystal formation with DSC screening[37].

Endothermic Peak	**Cocrystal formation**
Three endothermic and a couple of exothermic peaks	CS with stoichiometric variety
Two endothermic and one exothermic	One CSformation with certain molar ratio
One endothermic	No CS formation

Table 3. Various drugs and coformers used for cocrystals formation and chemistry involved in their formation.

Drug(s)	**Coformer (s)**	**Method of Preparation**	**Method of Analysis**	**Important Points**
Ezetimibe[60]	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.
Paracetamol[61]	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.
Sildenafil[62]	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-mercaptopurine[63]	Isonicotinamide	Reaction Crystallization method	DSC, TGA, DVS, FT-IR, PXRD, SCXRD.	CSproduced were less hygroscopic. CS attained maximum solubility in 5-10 minutes.
Theophylline[64]	Oxalic, Malonic, Maleic and Glutaric acid	Solid-state grinding andSolution precipitation	SCXRD.	Theophylline also possesses a good N-H hydrogen bond donor. N H· · ·O hydrogen bond is formed between NH donor of a theophylline by linking with carbonyl oxygen from an adjacent theophylline. This interaction between NH and O forms hydrogen-bonded dimers in a cyclic motif. Improvement of Physical properties and avoidance of hydration.
Caffeine[65]	Maleic acid	Ultrasonic assisted solution co-crystallization	Raman Spectroscopy, PXRD	CCs with maleic acid increases solubility of caffeine which decreases supersaturation
Myricetin[66]	Acetamide	Solvent drop grinding	PXRD, Morphological analysis, TGA, dissolution studies, IR and NMR spectroscopy,	4 times increased dissolution rate
Trospium	Urea	Solvent	PXRD, SCXRD,	electronegative chloride

Chloride[67]		evaporation	NMR, Karl Fischer Coulometric titration, TGA, DSC.	anion accepts an H□bond from the best H□bond donor, a hydroxyl groupin trospium molecule. Urea molecules form an infinite chain on which chloride anions hang overtrospium. Increased intrinsic dissolution rate
Theophylline[68]	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.
Diflunisal[69]	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
Indomethacin[70]	Saccharin	Anti-solvent crystallization, solvent evaporation	XRD, DSC, DVS, Near-IR spectroscopy.	N-H…O bonding was formed between the caboxcylic acid dimer of IMC and SAC imide dimer
Itraconazole[71]	L-malic acid	Gas antisolvent crystallization	HPLC, Solubility studies, XRD, DSC, SEM, Powder composition study, dissolution studies.	The CSobtained by this method were suspected to contain unquantified amount of amorphous material. GAS CCs may have improved itraconazole bioavailability.
Sulfamethazine[72]	Theophylline	Neat cogrinding, solvent-drop cogrinding and	DSC, TGA, Raman, PXRD, and dynamic vapor sorption	The sulfamethazine molecules form a dimer through the intermolecular O...H--N, and two O...H--N

		slow evaporation	(DVS) techniques	and N...H—N keeping theophylline molecule attached.
Carbemazapine[73]	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[74]	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[75]	Gentisic acid	Slow evaporation	DSC, hot-stage microscopy (HSM), PXRD, SCXRD	The primary amide anti-N–H of the ofEthenzamide and the 2-hydroxy group ofGentisic acid forms two intramolecular N–H..O and O-H..O hydrogen bonds Dissolution rate of Ethenzamide was improved by a factor of 2.
Artemisinin[76]	Orcinol and Resorcinol	Liquid-assisted grinding	DSC, FT-IR. PXRD	The interaction of trimeric units is through a vast network of C–H...Obonds. Every synthon comprises of O–H...O hydrogen bonds formed between the OH group of Resorcinol and the carbonyl moiety of Artemisinin
Gabapentin[77]	C-propan-3-ol pyrogallol[4]arene and C-butyl pyrogallol[4]arene	Slow evaporation aided with sonication	XRD	ReportedCSexhibit bilayer structures comprising of networks of extensive hydrogen bonding networks between the pyrogallol[4]arene, gabapentin molecules.
S-Naproxen and RS-Naproxen[78]	D-proline	Liquid-assisted grinding	DSC, TGA, PXRD, SCXRD	Synthon part is mainly composed of zwitterionic entity.

				The crystalline network in the four CSformed is guided by the amino acid prolinium.
Pyrazine[79]	Dicarboxylic acid, terephthalic, phthalic, fumaric and succinic acids.	PyrazineCSwere 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[80]	Benzoic acid	both neat grinding and liquid assisted grinding	X-ray diffraction (XRD)	Carbonyl group of Theophylline and the carboxyl group of Benzoic acidforms an O–H…O hydrogen bond Another hydrogen bond is formed between acidic imidazolic nitrogen atom of Theophylline and the carboxyl oxygen atom of Benzoic acid.