International Journal of
Medicinal Chemistry & Analysis
www.ijmca.com
e ISSN 2249 - 7587
Print ISSN 2249 - 7595

REVIEW ON COCRYSTAL AS AN APPROACH WITH NEWER IMPLICATIONS IN PHARMACEUTICAL FIELD

Yerram Chandramouli*, R. Gandhimathi, B. Rubia yasmeen, Amaravathi Vikram, B. Mahitha, S.M. Imroz

[1]Department of Pharmaceutics, Sree Vidyanikethan College of Pharmacy, A.Rangampet, Tirupati- 517 102, India.

ABSTRACT

Cocrystal is a crystalline structure consisting of two or more components that form a unique structure having specific properties. The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an active pharmaceutical ingredient (API) and the other a co-crystal former. This technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API. This review focuses on properties of cocrystals, their methods of synthesis and applications in the field of pharmacy.

Keywords: Cocrystal, crystal engineering, drug, solid.

INTRODUCTION

Crystal engineering is concerned with the construction of crystal structures of organic and metal organic species, using design principles that are derived from an understanding of the intermolecular interactions that prevail in molecular solids. A principal tool is the hydrogen bond, which is responsible for the majority of directed intermolecular interactions in molecular solids. The fact is that a crystal is built up from a large number of molecules and this building up need not be a smooth and continuous process in which the final structure of the crystal is established and is recognizable from the very initial stages of molecular assembly. A few molecules assemble to form a cluster; several clusters may assemble to form larger entities and these entities interact with each other through an event that we term as nucleation, which leads in turn to the first crystal. Local order and organization within the small and then the larger clusters must lead eventually to long range periodicity that one associates with the crystalline state.

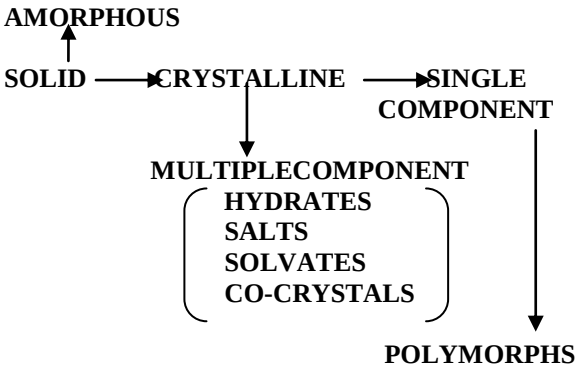
Crystal engineering is defined as 'the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design and new solids with desired physical and chemical properties.

Cocrystals

Cocrystal is a crystalline structure composed of at least two components, where the components may be atoms, ions or molecules [1]. This definition is sometimes extended to specify that the components be solid in their pure forms at ambient conditions [2]. However, it has been argued that this separation based on ambient phase is arbitrary [3]. A more inclusive definition is that cocrystals consist of two or more components that form a unique crystalline structure having unique properties [4]. Due to variation in the use of the term, structures such as solvates and clathrates may or may not be considered cocrystals in a given situation. It should be noted that the difference between a crystalline salt and a cocrystal lies merely in the transfer of a proton. The transfer of protons from one component to another in a crystal is dependent on the environment. For this reason, crystalline salts and cocrystals may be thought of as two ends of a proton transfer spectrum, where the salt has completed the proton

Corresponding Author: - **Yerram Chandramouli** Email: chandu.pharmatech@gmail.com

transfer at one end and an absence of proton transfer exists for cocrystals at the other end [5].



PHARMACEUTICAL CO-CRYSTALS

The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences [6,7]. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former [8]. Co-crystal former may be an excipient or another drug [9]. Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API. Scientists showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical co-crystal formation improved the performance of a drug known to have poor solubility [10]. Pharmaceutical co-crystallization is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability hygroscopisity, and compressibility without alternating their pharmacological behavior [11,12]. The expanding scope of crystal form selection, emergence of crystal engineering in pharmaceutical science and pharmaceutical co-crystals were reviewed [13]. Some common aspects of co-crystal formation, screening strategies and outline methodologies for co-crystal functionality were reported [14]. The use of co-crystals in drug design and delivery and as functional materials with potential applications as pharmaceuticals has recently attracted considerable interest [15]. Pharmaceutical co-crystals have been described for many drugs such as acetaminophen, aspirin, ibuprofen, flurbiprofen etc. Co-crystals of antitubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool [16]. Schematic representation of developing cocrystals into pharmaceutical products is given in figure No. 1.

CO-CRYSTALS VERSUS SOLVATES

The main difference between solvates and co-crystals is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates; if both components are solids at room temperature, the crystals are designated as co-crystals [17].

SALT VERSUS CO-CRYSTAL FORMATION

Co-crystal and salts may sometimes be confused. The understanding of the fundamental difference between a salt formation and a co-crystal is very important to both pre-formulation activities and chemical/pharmaceutical development aspects. Indeed, salts and co-crystals can be considered as opposite ends of multi-component structures [18-20]. Salts are often chosen instead of the free acid or base as these can improve crystallinity, solubility and stability of a pharmaceutical compound. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionizable sites in the API. Salt formation is an acid–base reaction between the API and an acidic or basic substance. The widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs [21,22]. Salt formation is a three component system having an acid (A), a base (B) and one or more solvents. A salt is formed by transfer of a proton (H^+) from an acid (A) to base (B).

$$A\text{-}H + B \rightarrow (A^-)(B^+ - H)$$

Proton transfer is thought to mainly depend on the pK_a values of the components. When there is no such transfer and the components are instead present in the crystal as neutral entities, the product is generally defined as a co-crystal. In other words, a co-crystal is an A-B composite in which no proton transfer occurred [23].

Salt formation is an acid–base reaction between the API and an acidic or basic substance and large numbers of crystalline salts of APIs are available in market [20,21]. The formation of a salt or co-crystal can be predicted from pKa value of acid (A) and a base (B). Salt formation generally requires a difference of about 2.7 pKa units between the conjugate base and the conjugate acid (A) i.e. [pKa (base) - pKa (acid) $\geq$ 2.7]. For example, succinic acid having pKa 4.2 form co-crystal with urea base (pKa 0.1) while succinic acid form salt with L-lysine base having pKa9.5.Generally base pKa values are not sufficiently high to allow proton transfer when co-crystal is formed [20]. Cocrystal of succinic acid-urea has two hydrogen bonds i.e. the oxygen atom in urea molecule is bonded to hydrogen atom in succinic acid molecule while oxygen atom from succinic acid molecule is bonded to hydrogen atom in urea molecule (Figure No. 3).

DESIGN OF COCRYSTAL

Cocrystals consist of a single crystalline phase of multiple components in a given stoichiometric ratio, where the different molecular species interact by hydrogen bonding or by other non-covalent bonds. Because of its strength and directionality, the hydrogen bond has been

the most important interaction in cocrystal formation [24–27]. Supramolecular arrangements in pharmaceutical crystals are often based on synthons of strong and weak hydrogen bonds as shown in Fig. 1. Strong hydrogen bonds may include N–H. . . O, O–H. . . O, N–H. . . N, and O–H. . .N while weak hydrogen bonds may include C–H . . .O–N and C–H . . .O=C.

Figure 1. Scheme of Co crystal development process

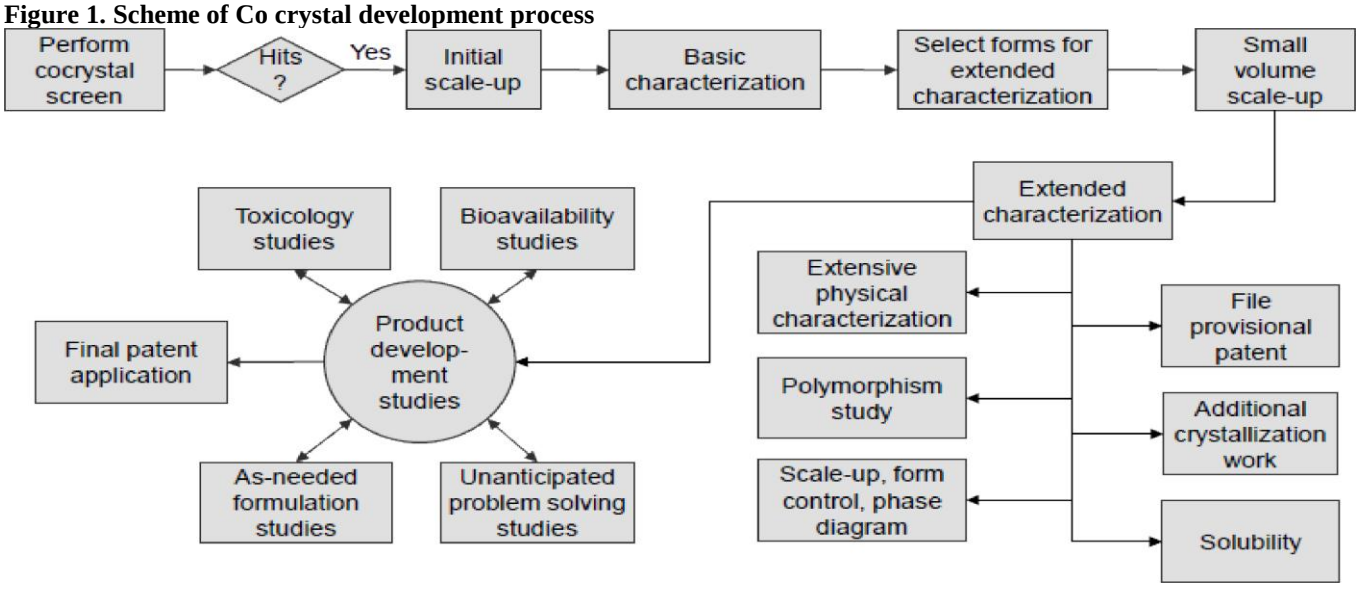


Figure 2. Example of two-component caffeine crystals, the monohydrate (A) and the co-crystal with oxalic acid (B). the unit cells of the crystals viewed along the a-axis is shown. The hydrate incorporates the solvent (water) molecule in the crystal lattice, while the co crystal consists of two solid compounds. Note that in both structures, the same hydrogen bridges (shown by dotted lines) are involved to connect the host (caffeine) with guest (water or oxalic acid) molecules.

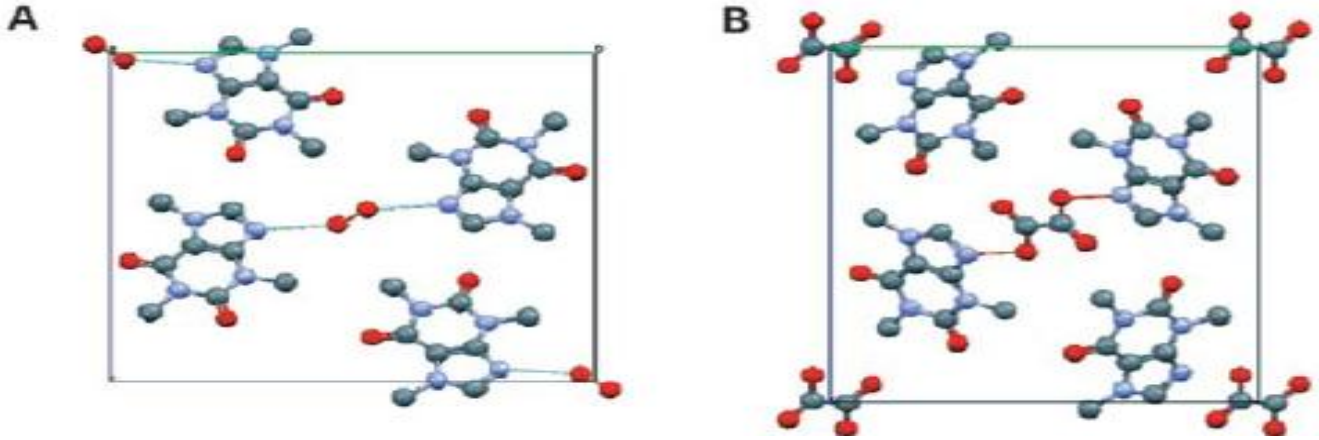


Figure 3. Structure of co-crystal of succinic acid-urea

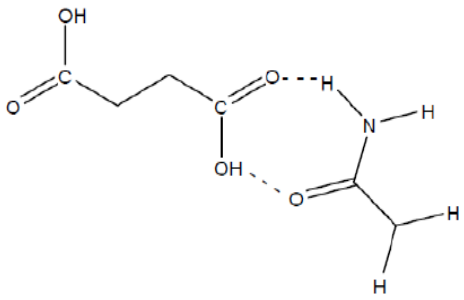


Figure 4. Common synthons found between carboxylic acid and amide functional groups

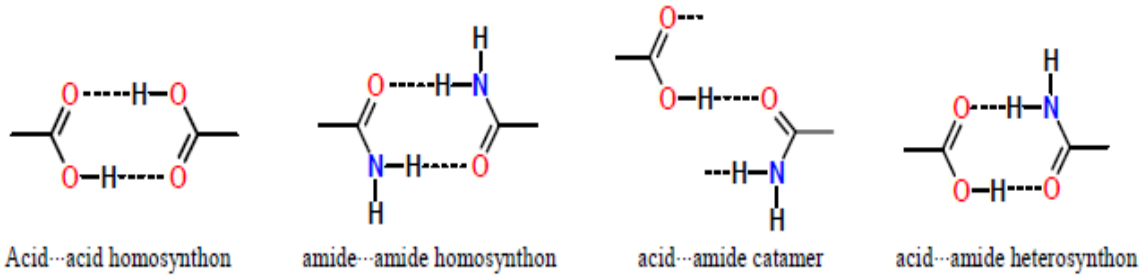


Figure 5. Molecular interactions in carbamazepine cocrystals and solvates
(a) Dihydrate, (b) Acetonesolvate, (c) Carbamazepine-saccharin, (d) Carbamazepinenicotinamide, (e) Carbamazepine-salicylic acid and (f) Carbamazepine-4-aminobenzoic acid hydrate

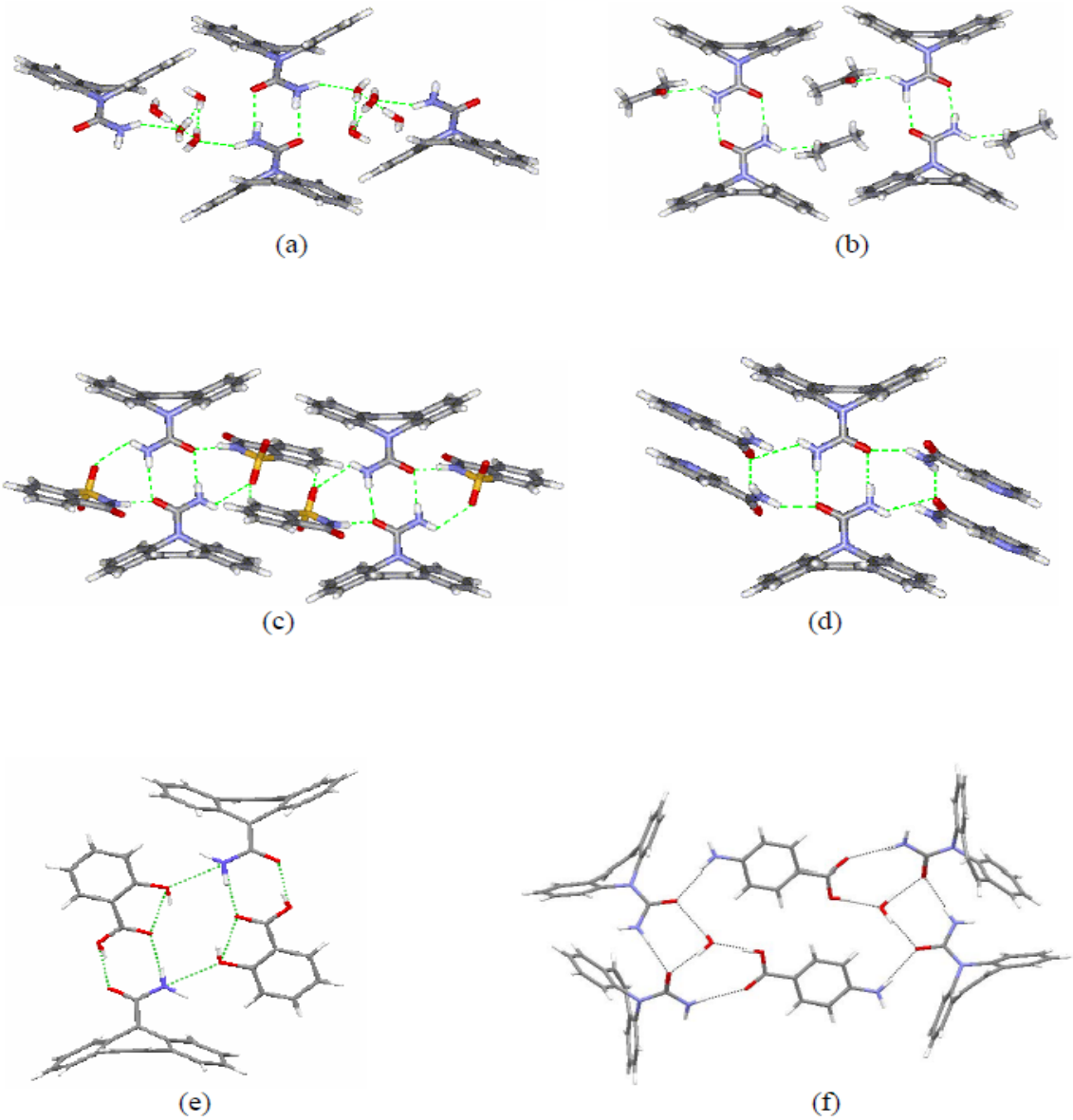


Table 1. Biopharmaceutical performance of co-crystals

Drug	Co-former	Biopharmaceutical performance			References
		Solubility	**Dissolution**	**Bioavailability**	
Fluoxetin	Benzoic acid Hydrocloride, Fumaric acid, Succinic acid	5.6 mg/ml 11.4 mg/ml 14.8 mg/ml 20.2 mg/ml	- - - -	- - - -	[15]
Itraconazole	Succinic acid, Lmalic acid, Ltartaric acid	4 - 20 fold higher than crystalline itraconazole	-	-	[11]
Piroxicam	Saccharin	No improvement	-	-	[11]
2-[4-(4-chloro-2-fluorphenoxy)phenyl] pyrimidine-4-carboxamide	Glutaric acid	-	18 times faster than parent compound	-	[20]
Exemestane	Malic acid		Same as API	-	[11]
Megestrol acetate	Saccharin	-	3-4 times higher than API	-	[11]
Celecoxib Form IV	Nicotinamide	-	Faster than Celecoxib Form III	4 times increased	[23]
Fluoxetin HCl	Succinic acid	-	3- fold increase over API	-	[11]
Fluoxetin HCl	Benzoic acid	-	Half- that of API	-	[11]
Fluoxetin HCl	Fumaric acid	-	Same as that of API	-	[11]

Cocrystals are multiple component systems where intermolecular interactions (including hydrogen bonds, van der Waals, and π-π interactions) and favorable geometries lead to a self-assembled supramolecular network. Cocrystals offer the advantage of generating solid forms of APIs even when they lack ionizable functional groups and in this way produce materials with a large range of properties that are not available in single API solid phases (polymorphs and amorphous forms), or in API solvates, or salt forms. Solvates are compounds where one of the components is liquid at room temperature, such as a hydrate. In a crystalline salt, the interactions are mostly electrostatic, and the components are ionized. A pharmaceutical co crystal contains an API and a coformer molecule(s), both of which typically exist in the neutral state and interact by hydrogen bonding or by other non-covalent bonds. A few cocrystals have been synthesized in which the API is ionized, but the coformer is still non-ionized. The term co crystal generally refers to components that in their pure states are solids at room temperature. Cocrystals may include two or more different components and in most cases to date, two and three component systems are reported with the latter being mostly cocrystalline solvates, e.g. theophylline-5-fluorouracil hydrate, carbamazepine-4-aminobenzoic acid hydrate and tetroxoprim-sulfametrole methanolate.

The field of crystal engineering has focused on understanding the intermolecular interactions and connectivities that lead to the construction of supermolecules or extended architectures. Because of its strength and directionality, the hydrogen bond has been the most important interaction in cocrystal formation. By studying the hydrogen bond patterns in crystalline solids, valuable knowledge is gained to identify hydrogen-bond preferences and reliable synthons that lead to cocrystal formation.

Guidelines for preferred hydrogen bond patterns in crystals include: [23,24]

a all acidic hydrogens available in a molecule will be used in hydrogen bonding in the crystal structure of that compound [24]

b all good acceptors will be used in hydrogen bonding when there are available hydrogen-bond donors [23]

c the best hydrogen-bond donor and the best hydrogen-bond acceptor will preferentially form hydrogen bonds to one another [23].

The presence of multiple competitive hydrogen-bond sites, conformational freedom, steric hindrances, or competing dipolar or ionic forces. These general principles nevertheless establish the basis for predicting likely and unlikely structures.

METHODS TO SYNTHESIS COCRYSTALS

Different techniques for the preparation of cocrystals are

1. Solvent evaporation technique
2. Melting technique
3. Sublimation

4. Solid state grinding or mechanical milling technique
5. Solvent reduced technique
    a. Slurrying technique
    b. Solvent drop technology
6. Super critical fluid technology
7. By using intermediate phase

1. Solvent evaporation technique

This technique is the common way to synthesize cocrystals. In this method cocrystal components or cocrystal formers are taken in stoichiometric ratio and solubilise in a common solvent. The resultant solution is allowed to evaporate slowly. This technique works on the principle that, when different molecules of complimentary functional groups afford hydrogen bonds that are more favorable than each of the individual molecular components. In this case, the cocrystal is likely to be thermodynamically favored [26].

2. Melting technique

By simply melting two cocrystal formers together and cooling, a cocrystal may be formed. If a cocrystal is not formed from a melt, a seed from a melt may be used in a crystallization solution in order to afford a cocrystal.

3. Solid state grinding technique

This technique is also called as mechanical milling or neat grinding technique. cocrystal formers are taken in stoichiometric amounts and ground together manually using a mortar and pestle, using a ball mill, or using a vibratory mill. Normal milling time is 60 minutes. It has been reported that cocrystal material at first obtained exclusively by one approach may be used as seeds to subsequently obtain that cocrystal by another method, there by potentially enabling XRD structure determination via single-crystal growth. In one alternative case, cocrystal structure determination was achieved even when material could be prepared only as crystalline powder by grinding [27].

4. Slurrying technique

Slurries-induced formation of cocrystalline phase among two or more active solid materials or between the active solid materials and the excipients. equimolar were dissolved in small amount of methanol at ambient temperature. The solution was slowly evaporated at room temperature during 48 hours to promote cocrystallization [28].

5. Solvent drop technique

This technique is also called as liquid assisted grinding or kneading. This involves the grinding of stoichiometric amounts of coformers with the aid of small amount of liquid. This method was developed in order to increase the rate of cocrystal formation, but has advantages over solid state grinding such as increased yield, ability to control polymorph production, better product crystallinity, and applies to a significantly larger scope of cocrystal formers [29]. This method also enhances the cocrystallisation selectivity.

6. Supercritical fluid technology

Pharmaceutical cocrystals can be formed also by use of supercritical fluids. Supercritical fluids act as a new media for the generation of cocrystals. Supercritical fluid technology offers a new platform that allows a single-step generation of particles that are difficult or even impossible to obtain by traditional techniques. The generation of pure and dried new cocrystals (crystalline molecular complexes comprising the API and one or more conformers in the crystal lattice) can be achieved due to unique properties of super critical fluids by using different supercritical fluid properties [30].

7. By using intermediate phase

Using intermediate phases to synthesize these solid-state compounds are also employed. Through the use of a hydrate or an amorphous phase as an intermediate during synthesis in a solid-state route has proven successful in forming a cocrystal. Also, the use of a metastable polymorphic form of one cocrystal former can be employed. In this method, the metastable form acts as an unstable intermediate on the nucleation pathway to a cocrystal. As always, a clear connection between pair wise components of the cocrystal is needed in addition to the thermodynamic requirements in order to form these compounds.

NANO CRYSTAL

A nano crystal refers to any nanomaterial with at least one dimension $\leq$ 100nm and it should be single crystalline. The production of drug nanocrystals by bottom up techniques (with main focus on particle diminution by high pressure homogenization) for many new chemical entities of very low solubility has been reported. The transfer of the liquid nanosuspensions to patient convenient oral dosage forms such as tablets and capsules have also been reported. Under microwave irradiation, nonlinear optical nanococrystals of aminonitropyridines with benzenesulfonic acids were reported. Single-component crystalline nanorods, composed of 9-methylanthracene (9-MA) and exposed to a suspension of 1,2,4,5-tetracyanobenzene (TCNB) in water formed a 1:1 charge-transfer complex within the rods, which are transformed from crystalline 9-MA into co-crystalline 9-MA/TCNB. The co-crystal nanorods were characterized by electron microscopy, X-ray diffraction, and optical spectroscopy. These studies demonstrated the importance of organic nanostructures for supporting structure-preserving chemical transformations that were not possible in larger crystals [25].

SYNTHESIS OF NANO CO CRYSTALS

1. Sonochemical synthesis

Sonochemistry became means to prepare co-crystals of nanometer scale dimensions. [25]The technique which is harsh yet transisent has afforded co-crystals with components comprised of relatively simple molecules .The method affords pharmaceutical nanococrystals with a narrow size distribution. In this process the pharmaceutically active ingredients and co-former are dissolved separately in solvents and injected in an anti solvent at 0^0C under ultrasonic radiation. After 15 s of sonication suspension is filtered [31].

2. Wet milling technique

The different wet-milling processes in miniature, middle and large preparation scales have been established in order to cover the various types of studies with wide scale. The powder of a poorly water-soluble model drug candidate, three general-purpose equipments with stirring, oscillating and turbulent motions was applied instead of the specific milling machine with high power to avoid much investment at such early development stage. The operational conditions were optimized to obtain finer particles using the middle-scaled oscillating beads-milling apparatus in particular. It was found that the nano co-crystals, which whole particle distribution was in the submicron range, was successfully produced within the running time around 10min [32].

COCRYSTALS AS AMEANS OF CONTROLLING PHYSICOCHEMICAL PROPERTIES OF DRUG:

The ability to deliver the drug to the patient in a safe, efficient and cost-effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state. This provides a significant driving force for inventing new approaches to designing pharmaceutical solid materials with specific physicochemical properties.

1. **Hydrate Formation**

API in cocrystals will not form solvates or hydrates during crystallization or upon storage. Since cocrystals are supra molecular assemblies and are designed based on functional groups and hydrogen bond complementarity, solvate formation that relies on this complementarity will be inhibited by the formation of cocrystals, given that the intermolecular interactions between the API and coformer are stronger than between the API and solvent molecule. Example: caffeine-oxalic acid cocrystal did not transform to caffeine hydrate under high relative humidity [33].

2. Chemical Stability

Cocrystal formation can also improve the chemical stability of an API when chemical reactivity requires that reactant molecules be in suitable positions in the solid state. Example: The single component carbamazepine (CBZ) polymorphs degrade by solid-state photochemical reaction, CBZ cocrystal formation with saccharin and nicotinamide inhibits photodegradation of CBZ by altering the molecular arrangements in the solid state such that the distance between the azepine rings is more than 4.1 Å, thereby preventing photodegradation [34].

3. Dissolution Rate

Cocystals show the improved dissolution rate than the pure drug depending upon the co-former used. Example: Indomethacin-saccharin cocrystal had a greater than 50 times increase in dissolution rate in a 200mM phosphate buffer (pH 7.4) compared to γ-indomethacin, the most stable polymorph [35].

4. Cocrystal Solubility

Cocrystal solubility is dependent on cocrystal component concentration, solution complexation, and ionization when one or more components are ionizable.

5. Bioavailability

If cocrystals are going to be a viable alternative for solid state forms of a drug, Bioavailability studies need to be performed. Carbamazepine-saccharin was reported to yield slightly higher plasma levels when compared to dosing carbamazepine monoclinic, form III, although the authors reported that the increase was not statistically significant.

CHARACTERIZATION OF COCRYSTALS [36- 45]

Characterization of cocrystals is of utmost importance and there are different analytical methods ranging from simple melting point determination to complete structural determination through single crystal X-ray crystallography. Other procedures like studying the morphology of crystals by microscopic methods, observing changes in crystal forms with temperature, phase transition by thermal methods, interpreting molecular motion and chemical environment by the use of vibrational spectroscopy and solid state NMR are used depending upon the information sought.

1. Crystallographic methods

Crystallographic methods include both single crystal X-ray diffraction as well as powder X-ray diffraction. A successful single crystal X-ray diffraction study can provide unambiguous atomic positions and complete structural information, but obtaining a single crystal suitable for this study becomes often the bottleneck. In such cases, powder X-ray diffraction studies using microcrystalline samples become a major tool. In fact, it has become routine to take powder diffractograms to ascertain the solid state nature and purity of every batch of synthetic drugs.

2. Optical microscopy

Another quick and efficient method is to study the crystal morphology by optical microscopy. As unit cell repetition leads to crystal formation, this feature is reflected in the outer appearance of crystals that can be observed by simple hand lens or microscope. Further, a detailed study can be performed using polarizing optical microscopy, electron microscopy and thermal microscopy.

3. Thermal analysis

The third important method, which is widely used in pharmaceutical industries for characterization of polymorphism, solvation, purity, degradation and drug compatibility, is thermal analysis, which includes Thermogravimetry, Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC).

4. Vibrational spectroscopy

The study of molecular motions by use of vibrational spectroscopy is also sometimes employed in the characterization of polymorphs. This method includes infrared absorption spectroscopy and Raman spectroscopy.

5. Nuclear magnetic resonance

Nowadays solid state NMR is also used for characterization. It studies the chemical environment of the nuclei which is different in polymorphs because of magnetic non-equivalence. Resonance peaks for the magnetically non-equivalent nuclei will differ in different polymorphs and can yield very useful information.

6. Scanning electron microscopy

Scanning electron microscopy (SEM) was conducted to characterize the surface morphology of the particles. The samples were mounted on alumina stubs using double adhesive tape, coated with gold in HUS-5GB vacuum evaporator. Then the sample was observed in Hitachi S-3000N SEM at an acceleration voltage of 10KV and a magnification of 5000X.

POLYMORPHISM OF CO-CRYSTALS

Polymorphism in multi-component crystals is gaining interest in the recent times in the context of pharmaceutical co-crystals. Polymorphs have different stabilities and may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature. In addition, they exhibit different melting points and solubilities which affect the dissolution rate of drug and thereby, its bioavailability in the body. Co-crystal polymorphs suggest additional options to modify properties, increase patent protection, and improve marketed formulations. Co-crystals of 4-hydroxybenzoic acid and 2,3,5,6-tetramethyl-pyrazine (2 : 1) exhibited the first supramolecular synthon polymorphism in a co-crystal; metastable anti-hierarchic polymorph I was converted to stable hierarchic form II [46]. Preparation of polymorphic co-crystals I and II (temozolomide: 4,4-bipyridine-*N*,*N*-dioxide (1:0.5 and 2:1) were optimized by using solution crystallization and grinding methods. The metastable nature of co-crystal II was ascribed to unused hydrogen-bond donors/acceptors in the crystal structure [47].

Two polymorphs of carbamazepine-nicotinamide co-crystals and two polymorphs of carbamazepine-saccharin co-crystals were found to be polymorphic [48]. Co-crystal polymorphs of carbamazepine and isonicotinamide having 1:1 stoichiometry were reported which were formed through a solvent-mediated transformation process upon suspending a dry mixture of the pure crystalline components in ethanol [49]. Two polymorphs of a co-crystal between 2-ethoxybenzamide and saccharin sustained by a carboxamide–imide heterosynthon involving two N–HO hydrogen bonds were prepared and structurally characterized by single crystal X-ray diffraction. The only metastable Form II was formed in the grinding experiments, whereas both polymorphs were reported by solution crystallization. It is worthy to note that the number of polymorphs of a co-crystal was more than the number of polymorphs of its parent API. The importance of this multiple screening techniques for co-crystal polymorphs sheds light on the ability of the solid-state grinding to produce the metastable polymorph of a co-crystal [50]. Co-crystals of piroxicam with carboxylic acids were prepared and various groups of co-crystals containing piroxicam and a guest carboxylic acid were differentiated by the piroxicam tautomer present in the co-crystal and the presence or absence of a strong hydrogen bond donor interacting with piroxicam's amide carbonyl group. Further, two 1:1 piroxicam/4-hydroxybenzoic acid co-crystals were found to be polymorphs [51].

PHARMACEUTICAL CO-CRYSTALS AS INTELLECTUAL PROPERTY

Compared to other classes of solid forms, co-crystals possessed particular scientific and regulatory advantages, and alongside these advantages were intellectual property issues which give co-crystals with unique opportunities and challenges. Researchers reported **t**he importance regarding patents on pharmaceutical co-crystals to the pharmaceutical industry [52]. The value of co-crystals to the pharmaceutical industry should become clearer, mainly with respect to several relevant legal and regulatory issues, as products containing co-crystal technology come out from pharmaceutical development pipelines onto the market.

APPLICATIONS OF CO-CRYSTALS

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule

synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution [53-56]. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization [52].

CONCLUSION

From physical properties outlook, a key benefit of co-crystals is the possibility of achieving the high dissolution rate comparable to that of the amorphous form, while maintaining the long-term chemical and physical stability. The major challenge with this technology lies in the selection of an appropriate cocrystal former. Cocrystal approach is also an opportunity for the research based pharmaceutical companies to expand their intellectual property portfolios.

REFERENCES

1. Stahly GP. A survey of co crystals reported prior to 2000. *Crystal Growth & Design Perspective*, 9, 2009, 4212–4229
2. Ter Horst JH, Deij MA, Cains PW. Discovering new co-crystals. *Crystal Growth & Design*, 9, 2009, 1531–1537.
3. Bond, A.D. (2007). "What is a co-crystal?". CrystEngComm 9: 833–834.
4. Stahly, G.P. (2007). "Diversity in Single- and Multiple-Component Crystals. The Search for and Prevalence of Polymorphs and Cocrystals". Crystal Growth & Design 7: 1007–1026.
5. Schultheiss N, Newman A. Pharmaceutical co-crystals and their physicochemical properties. *Cryst Growth Des*, 9, 2009, 2950–2967.
6. Tiekink ERT, Vittal JJ (Editors). Frontiers in Crystal Engineering, John Wiley & Sons, Ltd, Chapter 2: Crystal Engineering of Pharmaceutical Co-crystals, 2006, p. 25-50.
7. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. *J Pharm Sci*, 95, 2006, 499-516.
8. Rodríguez-Hornedo N, Nehm SJ, Jayasankar A. Cocrystals: design, properties and formation mechanisms, In Encyclopedia of Pharmaceutical Technology, 3rd ed, Taylor & Francis, London, 2007, 615-635.
9. Remenar JF, Morissette SL, Peterson ML, Moulton B, MacPhee JM, Guzmán H, Almarsson O, Crystal engineering of novel co-crystals of a triazole drug with 1,4-dicarboxylic acids. *J Am Chem Soc*, 125, 2003, 8456-8457.
10. Almarsson Ö, Zaworotko MJ. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem Commun*, 2004, 1889-1896.
11. Schultheiss N, Newman A. Pharmaceutical co-crystals and their physicochemical properties. *Cryst Growth Des*, 9, 2009, 2950–2967.
12. Peterson ML, Hickey MB, Zaworotko MJ, Almarsson O. Expanding the scope of crystal form evaluation in pharmaceutical science. *J Pharm Pharmaceut Sci*, 9(3), 2006, 317-326.
13. Etter MC, Reutzel SM. Hydrogen bond directed cocrystallization and molecular recognition properties of acyclic imides. *J. Am. Chem. Soc*, 113, 1991, 2586–2598.
14. Jones W, Motherwell WDS, Trask AV. Pharmaceutical co-crystals: An Emerging approach to physical property enhancement. *MRS Bull*, 31, 2006, 875-879.
15. Vishweshwar P, Nangia A, Lynch VM. Molecular complexes of homologous alkanedicarboxylic acids with isonicotinamide: X-ray crystal structures, hydrogen bond synthons, and melting point alternation. *Crystal Growth Design*, 2003.
16. Morissette SL, Almarsson O et al. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. *Advanced Drug Delivery Reviews*, 56, 2004, 275-300.
17. Aakeröy CB, Fasulo ME, Desper J. Cocrystal or salt: Does it really matter? *Mol Pharma*, 4, 2007, 317–322.
18. Stahly GP. Diversity in single-and multiple-component crystals. The search for and prevalence of polymorphs and co-crystals. *Cryst Growth Des*, 7, 2007, 1007-1026.
19. Childs SL, Stahly GP, Park A. Salts and co-crystals of theophylline. *Mol Pharma*, 4, 2007, 323-338.
20. Stahl PH, Wermuth CG, editors. Handbook of pharmaceutical salts: properties, selection, and use. New York: Wiley-VCH; 2002, p 374
21. Serajuddin ATM. Salt formation to improve drug solubility. *Advanced Drug Delivery Rev*, 59, 2007, 603-616
22. Etter MC. Encoding and decoding hydrogen bonds patterns of organic compounds. *Acc Chem Res*, 23, 1990, 120-126.
23. Donohue J. The Hydrogen Bond in Organic Crystals. *Journal of Physical Chemistry*, 56, 1952, 502-510.
24. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. *Pharmaceutical co-crystals J Pharm Sci*, 95, 2006, 499-516.
25. Caira MR, Nassimbeni LR et al. Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid State. *Journal of the Chemical Society, Perkin Transactions*, 2, 1995, 2213-2216.
26. Jayasankar A, Somwangthanaroj A et al. Cocrystal formation during cogrinding and storage is mediated by amorphous phase. *Pharmaceutical Research*, 23, 2006, 2381-2392.
27. Erizal Zaini et al. cocrystalline phase transformation of binary mixture of trimethoprim and sulfamethoxazole by slurry technique. *Asian Journal of Pharmaceutical and Clinical Research*, 3(4), 2010.

28. Tiekink ERT, Vittal JJ (Editors). Frontiers in Crystal Engineering, John Wiley & Sons, Ltd, Chapter 2: Crystal Engineering of Pharmaceutical Co-crystals, 2006, p. 25-50.
29. Jung J, Perrat M. *J. Supercritical Fluids*, 20, 2001, 179.
30. Basavoju S, Bostrom D et al. Indomethacin-saccharin cocrystal: design, Synthesis and preliminary pharmaceutical characterization. *Pharmaceutical Research*, 25, 2008, 530-541.
31. Miroshnyk et al. Nanococrystals as a formulation alternative for poorly soluble APIs, *AAPS Journal*, 2010,12(S3).
32. Trask AV, Motherwell WDS et al. Pharmaceutical Cocrystallization: Engineering a Remedy for Caffeine Hydration. *Crystal Growth & Design*, 5, 2005, 1013-1021.
33. Rodríguez-Spong B. Enhancing the Pharmaceutical Behavior of Poorly Soluble Drugs Through the Formation of Cocrystals and Mesophases, Ph.D. Thesis, University of Michigan, 2005.
34. Basavoju S, Bostrom D et al. Indomethacin-saccharin cocrystal: design, Synthesis and preliminary pharmaceutical characterization. *Pharmaceutical Research*, 25, 2008, 530-541.
35. Lowes MMJ, Caira MR et al. Physicochemical properties and X-ray structural studies of the trigonal polymorph of carbamazepine. *Journal of Pharmaceutical Sciences*, 76, 1987, 744-752.
36. Callear SK. Preparation, characterization and structural analysis of salts and co-crystals of organic compounds. University of Southampton, School of Chemistry, PhD Thesis, 2008, p.253.
37. Wenger M, Bernstein J. An alternate crystal form of gabapentin: A cocrystal with oxalic acid. *Cryst Growth Des*, 8, 2008, 1595–1598.
38. Basavoju S, Bostrom D, Velaga SP. Indomethacin-saccharin co-crystal: Design, synthesis and preliminary pharmaceutical characterization. *Pharm Res*, 25, 2008, 530-541.
39. Lu J, Rohani S. Preparation and characterization of theophylline − nicotinamide co-crystal. Org Process Res Dev, 2009.
40. Allesø M, Velaga S, Alhalaweh A, Cornett C, Rasmussen MA, Van Den Berg F, De Diego HL, Rantanen J. Near-Infrared Spectroscopy for cocrystal screening. A comparative study with Raman Spectroscopy. *Anal Chem*, 80, 2008, 7755–7764.
41. Lu E, Rodríguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. *CrystEngComm*, 10, 2008, 665- 668.
42. Variankaval N, Wenslow R, Murry J, Hartman R, Helmy R, Kwong E, Clas SD, Dalton C, Santos I. Preparation and solid-state characterization of nonstoichiometric co-crystals of a phosphodiesterase-IV inhibitor and L-tartaric acid. *Cryst Growth Des*, 6, 2006, 690-700.
43. Wang S, Chen J. Gossypol co-crystals and the use thereof. United States Patent 7432300.
44. Cooke CL, Davey RJ. On the solubility of saccharinate salts and co-crystals. *Cryst Growth Des*, 8, 2008, 3483–3485.
45. Nehm SJ, Rodríguez-Spong B, Rodríguez-Hornedo N. Phase solubility diagrams of co-crystals are explained by solubility product and solution complexation. *Cryst Growth Des*, 2008.
46. Sreekanth BR, Vishweshwar P, Vyas K. Supramolecular synthon polymorphism in 2 : co-crystal of 4-hydroxybenzoic acid and 2,3,5,6 –tetramethylpyrazine. *Chem commun*, 2007, 3375-3377.
47. Badu NJ, Reddy SL, Aitipamula S, Nangia A. Polymorphs and polymorphic cocrystals of temozolomide. *Chem Asian J*, 3, 2008, 1122–1133.
48. Porter WW, III, Elie SC, Matzger AJ. Polymorphism in carbamazepine co-crystals. *Cryst Growth Des*, 8, 2008, 14–16.
49. Ter Horst JH, Cains PW. Co-Crystal polymorphs from a solvent-mediated transformation. *Cryst Growth Des*, 8, 2008, 2537-2542.
50. Aitipamula S, Chow PS, Tan RBH. Dimorphs of a 1 : 1 co-crystal of ethenzamide and saccharin: solid-state grinding methods result in metastable polymorph. *CrystEngComm*, 11, 2009, 889-895.
51. Childs SL, Hardcastle KI. Co-crystals of piroxicam with carboxylic acids. *Cryst Growth Des*, 7, 2007, 1291–1304.
52. Trask AV. An overview of pharmaceutical co-crystals as intellectual property. *Mol Pharma*, 4, 2007, 301–309.
53. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. *Pharmaceutical co-crystals J Pharm Sci*, 95, 2006, 499-516.
54. Almarsson Ö, Zaworotko MJ. Crystal engineering of the composition of pharmaceutical phases. Do pharmaceutical co-crystals represent a new path to improved medicines? *Chem Commun*, 2004, 1889-1896.
55. Peterson ML, Hickey MB, Zaworotko MJ, Almarsson O. Expanding the scope of crystal form evaluation in pharmaceutical science. *J Pharm Pharmaceut Sci*, 9(3), 2006, 317-326.
56. Hickey MB, Peterson ML, Scoppettuolo LA., Morrisette SL, Vetter A, Guzman H, Remenar JF, Zhang Z, Tawa MD, Haley S, Zaworotko MJ, Almarsson O. Performance comparison of a co-crystal of carbamazepine with marketed product. *Eur J Pharmaceut Biopharmaceut*, 67, 2007, 112-119.