



Pharmaceutical Co-Crystals: A New Paradigm of Crystal Engineering

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Abstract | A review on pharmaceutical co-crystals, nutraceutical co-crystals and pharmaceutical co-crystal polymorphs depicting their relevance both in academia and pharmaceutical industry because of their potential as new solid forms of the active pharmaceutical ingredient. The overview of crystal engineering to design co-crystals for altered and improved physicochemical properties such as solubility, dissolution rate, bioavailability, hygroscopicity etc., with some examples present in the literature till 2013.

Keywords: *Pharmaceutical Co-crystals, Nutraceuticals, Polymorphs, Crystal Engineering, Physico-chemical Properties, Active Pharmaceutical Ingredients.*

1 Introduction

The concept of crystal engineering was introduced by Pepinsky¹ in 1955 and Schmidt implemented it further in the context of organic solid-state photochemical reactions.² Around 1980's, the development in the field of crystal engineering gained high impetus with the rise of interest from various disciplines *viz.*, crystallography, solid-state chemistry, theoretical chemistry, and inorganic chemistry etc.³⁻⁵ In 1989, Desiraju defined crystal engineering as “*the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties*”.⁶ This definition laid the foundation for the modern concept of crystal engineering and has stood fast with time. Since then *Crystal Engineering* has subsequently matured into paradigm for the preparation or supramolecular synthesis of *Organic Solids*⁷ as well as *Metal Organic Frameworks*⁸ with desired structures and properties engineered at the molecular level.⁹

Co-crystal formation by itself is not of intrinsic novelty, since molecular solids have been known for more than a century and that it contains two or more distinct chemical compounds. A very early example of a co-crystal is the 1:1 molecular complex between Benzoquinone and Hydroquinone, named Quinhydrone, reported by Wöhler in 1844.¹⁰ However, last two decades or so has seen considerable research with focus on the conditions and reasons for the formation of multicomponent crystals.¹¹

Surprisingly, this concept has been addressed very recently, in the extremely valuable, *Active Pharmaceutical Ingredients (APIs)*, via systematic approach for the formation of *Pharmaceutical co-crystal (PC)*.¹² The definition of a co-crystal is currently the focus of significant scientific debate in journal articles and presentations at conferences¹³. However, a universal and completely acceptable definition of what constitutes a co-crystal is still unavailable.¹³ Almarsson and Zaworotko proposed the least controversial definition of pharmaceutical co-crystals—*co-crystals are those that are formed between an active pharmaceutical ingredient (API) and a co-crystal former (CF), which is a solid under ambient conditions, and is not limited to two components. The components of the crystal interact by hydrogen bond or other non-covalent and non-ionic interactions.*^{12(b)} Moreover, the discussions are wide spanning from the use of hyphenation (*i.e.*, co-crystal versus cocrystal) to the nature of the interactions between components of the crystal.¹⁴ In this review, without falling in to the debate of nomenclature, co-crystal will be used rather than cocrystal for consistency.

Discovery of new chemical entity (NCE) is itself a difficult task, and if fails in clinical development phase which are usually longer, results in significant losses to the company both in terms of time and cost.^{15,16} Therefore, new methods are introduced for new solid form of APIs with significant chemical and legal advantages to extend the pharmaceutical space. These forms include polymorphs,¹⁷ pseudopolymorphs,¹⁸ solvates,¹⁹

salts¹⁹⁻²⁰ and the most recent co-crystals²¹ as shown in Figure 1.

Much importance has been gained by PCs as it offers an alternative approach to physical property (i.e., dissolution rate, solubility, hygroscopicity, physical and chemical stability, etc.) optimization during crystal form selection.²² Co-crystals provide unique opportunities and challenges when it comes to solid forms, since they possess particular scientific and regulatory advantages as well as intellectual property concerns.²³ The relevance of co-crystal in the formulation of API has led the focus to design strategies for making co-crystals to alter specific physical properties.

2 Design of Co-crystal

The foundation of crystal engineering lies in the concept of supramolecular chemistry. The basic tenet of supramolecular chemistry is the molecular

recognition between complementary molecular fragments giving rise to self-organization of molecules to give a supramolecular function.²⁴ The molecular recognition process relies on a number of factors for the assembly of a supramolecular solid-state structure, including hydrogen bonding between molecular functional groups, complementary geometry of molecules and other directing factors.²⁵ Therefore, self-organization by design of molecules in supramolecular synthesis can be considered through the selection of suitable components and interactions. This is illustrated schematically in Figure 2.

Intermolecular interactions are regarded as the communication network between molecules, and are responsible for the organization of these molecules into an anisotropic arrangement to make up the “supermolecule” or crystal. Typically, intermolecular interactions may be weak

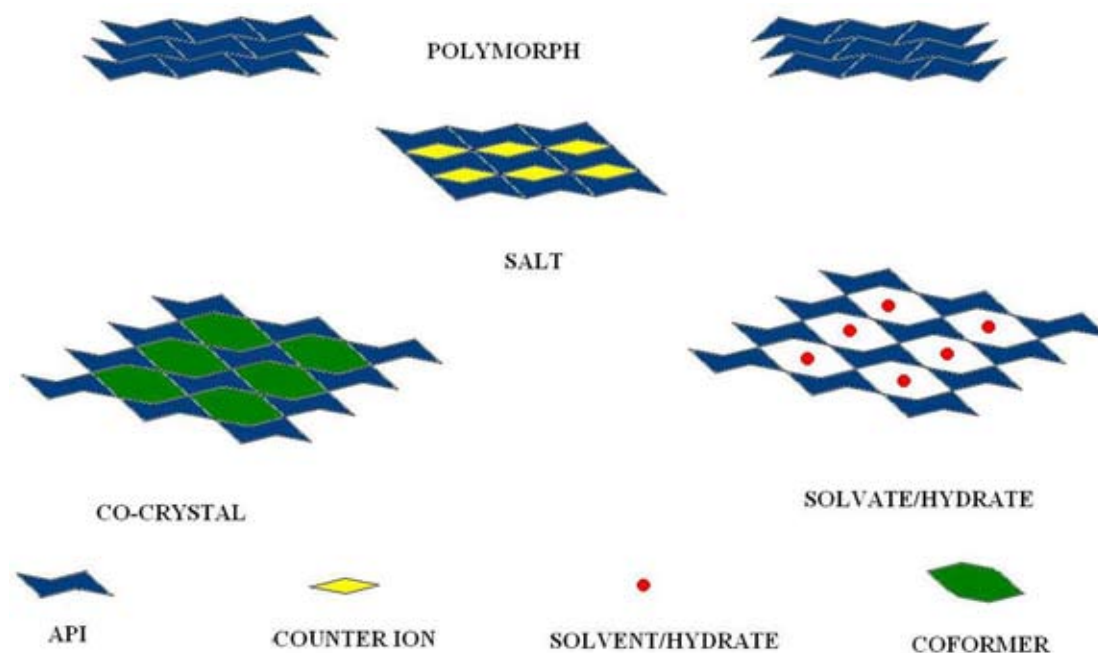


Figure 1: Possible multicomponent solid state forms: Polymorph, salt, co-crystal, solvate and pseudopolymorph.

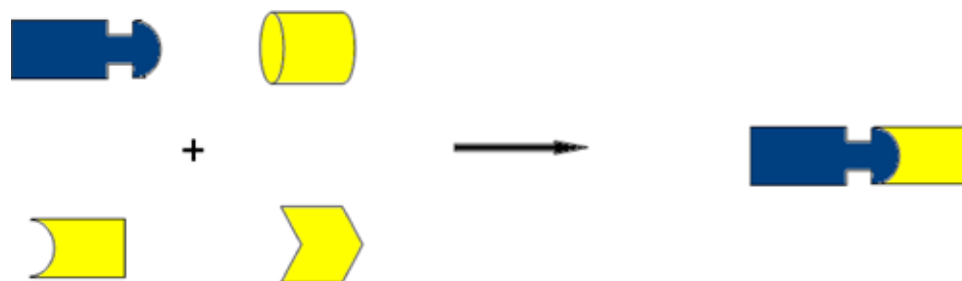


Figure 2: Schematic illustration of molecular recognition in supramolecular synthesis.

(0.5–12 Kcal mol⁻¹), medium (16–60 Kcal mol⁻¹) or strong (60–120 Kcal mol⁻¹).²⁶ Weak or medium range interactions like CH···O, π ··· π , CH··· π etc., are isotropic in nature and influence molecular

shape, size and close-packing.^{27,28} Strong interactions, on the other hand, such as NH···O, OH···O etc., taking place between heteroatoms such as N, O, S, Cl, Br, I or between these atoms and C or H,

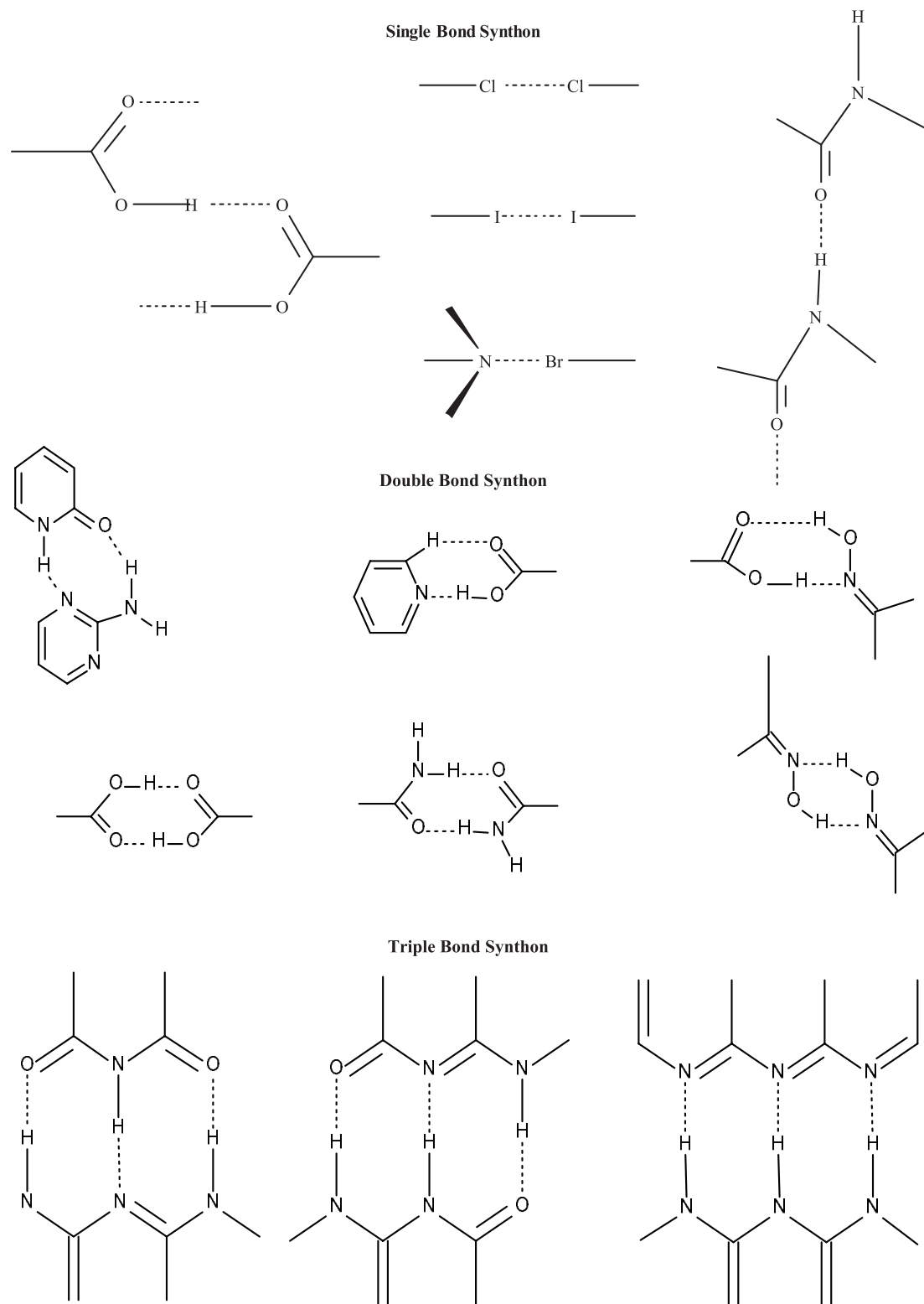


Figure 3: (Continued).

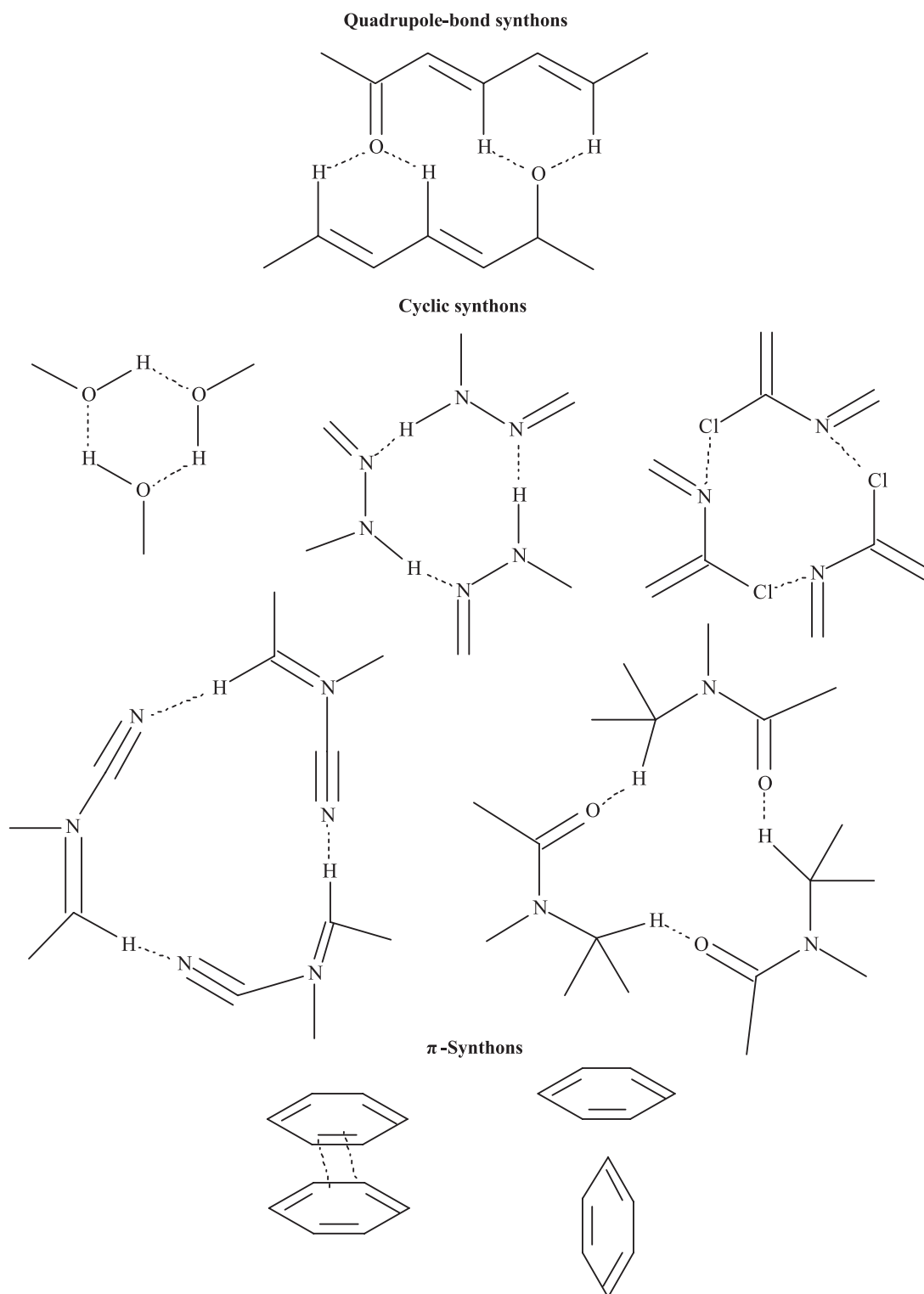


Figure 3: Some common supramolecular synthons.

are highly directional, and the energies are almost similar to that of covalent bonds leading to intermolecular orientation and function.²⁸ The directing nature of the hydrogen bond (intermolecular interactions) in the solid-state brings with it the

control over physical processes apparent in the crystalline form such as optical properties, thermal stability, solubility, color, conductivity, crystal habit and mechanical strength.²⁴ The frequent occurrence, along with the strength and directional

nature of the hydrogen bond, make it a robust and specific interaction in the supramolecular context.²⁹ These typical robust and specific interactions were termed by Desiraju, as “*Kinetically defined structural units that ideally express the core features or kernel of a crystal structure, and which encapsulate the essence of the crystal in terms of molecular recognition*”—known as supramolecular synthons.³⁰ Predictability of crystal structure is the first step towards fine-tuning of properties, and in an ideal situation, a crystal structure is held by sets of robust intermolecular interactions (supramolecular synthon) in roughly orthogonal directions, and the crystal engineer should be able to manipulate each set independently. A few examples of supramolecular synthon are shown in Figure 3.

The work carried out by Etter et al. proposed several “hydrogen-bond rules”, viz., (1) all good proton donors and acceptors are used in hydrogen bonding, (2) six membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds and, (3) the best donor typically pairs with best acceptor in a given crystal structure³¹ and the combined use of them

with geometric analysis (graph-set analysis)³² has helped implementation of rational co-crystal design in the synthesis of many new supramolecular structures. General graph set notation is written as $G^a_d(n)$, where G denotes one of four possible patterns. Intramolecular hydrogen bond is denoted by $G = S$ (self), while as intermolecular hydrogen bonds can be either C (chain), R (ring), or D (discrete). The terms **a** and **d** refer to the number of acceptors (**a**) and donors (**d**) in the repeat motif, and are omitted when $a = d = 1$. Similarly, **n** is omitted in case of D when there is only one hydrogen bond. Some examples of graph set notations are shown in Figure 4.

The analysis carried out by Allen et al.³³ within the Cambridge Structural Database (CSD), a searchable repository containing small molecule crystal structures demonstrated a quantification of the robustness of a certain class of intermolecular arrangements (supramolecular synthons) involving strong hydrogen bonded bimolecular ring motifs. The assessment of robustness of a synthon is based on the frequency of synthon formation, which is observed on its formation

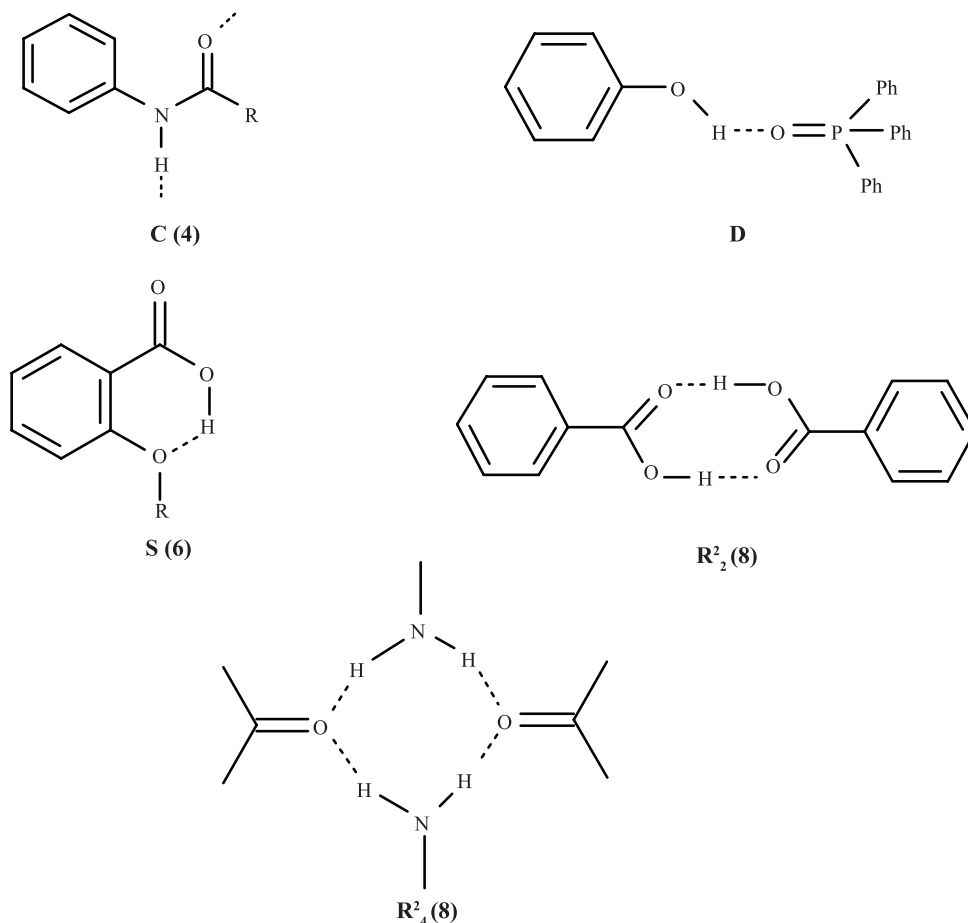


Figure 4: Graph set notation of intra- and inter-molecular hydrogen bonding.

probability among all structures containing the necessary functional group components. A higher formation probability suggested a greater utility in the design of a co-crystal.

The rise and development of supramolecular chemistry has given an opportunity to move in a completely different direction, from traditional crystallization of pure compounds to co-crystallization, which is a deliberate attempt of bringing together different molecular species as one whole entity in the crystalline lattice without making or breaking covalent bonds. Recrystallization and co-crystallization processes fundamentally differ in their outcome. The result of recrystallization is a homomeric product (self-complementary donor and acceptor groups –homo-synthon), whereas co-crystallization usually leads to a heteromeric

product (comprised of different, yet complementary donor and acceptor groups–hetero-synthon).

3 Importance and Design of Pharmaceutical Co-crystal

Solid state modifications of APIs (Figure 5) a serious concern, with respect to altering their physical properties and optimizing the APIs without changing their desirable molecular behavior. Solid forms offer a lot of advantages over other forms, but often face the problem of physical and chemical properties such as solubility, melting point, chemical interaction, stability, bioavailability etc.³⁴

Most of the drugs are administered orally in solid form (80%), which is generally considered as convenient and usually the safest dosage form. About 40% of them have low solubility; infact and

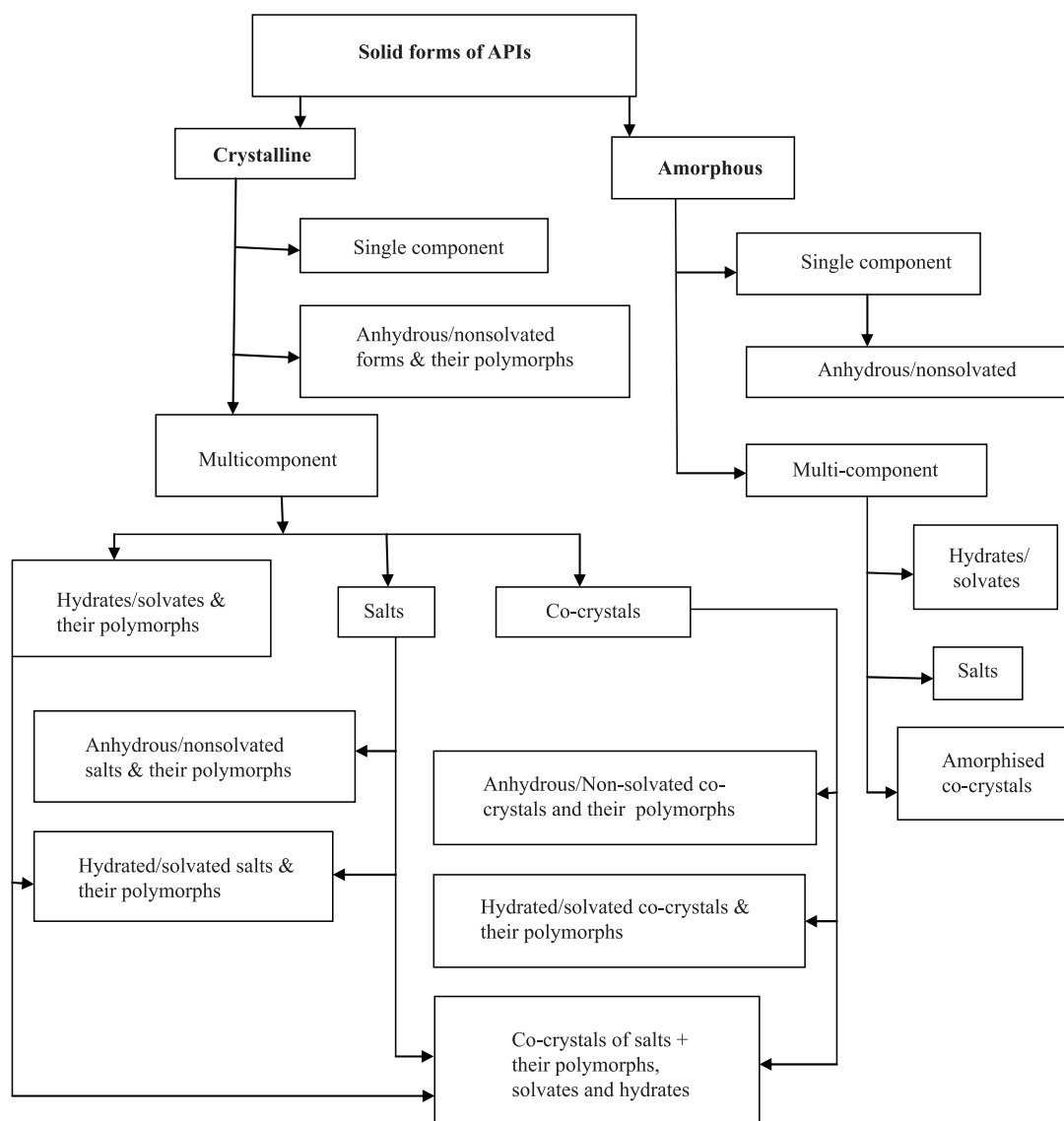


Figure 5: Different solid forms that can exist for an API.

nearly 80–90% of drug candidates in the R&D pipeline have low solubility problem, which is alarming and could lead to failure of these drugs in clinical trials.³⁵ Although remedy for the physico-chemical problems of the solid forms of the APIs are well available in the scientific literature, they are not competent enough to address them satisfactorily.³⁶

The PCs have given a new paradigm in the solid-state modification, owing which the pharmaceutical industry is seriously making efforts on its utility. The formation of API co-crystals offer a new method to modify the physical and chemical properties of drugs without changing their chemical nature, thereby maintaining its pharmaceutical importance as such.³⁷ Co-crystallization has provided pharmaceutical industry advantages in at least two ways as compared to salt formation. (1) According to the concept of co-crystallization, all types of molecules can form co-crystals, including weakly ionizable and non-ionizable APIs, which is considered to be a better technique in optimization of the physical properties because salt formation is either limited or has no scope at all in such APIs (2) In case of salt formation due to toxicological reasons only 12 or so acidic or basic counter-ions are explored in a typical API salt screen,^{38,39} whereas in case of co-crystal screening there are large number of potential co-crystal co-formers which are free from toxicological constraints. The US Food and Drug Administration has maintained a list of substances (e.g., FDA's GRAS list—a list of substances “generally recognized as safe”) which is numbering in thousands and can be used as potential CF for PCs.⁴⁰ Diversity shown by pharmaceutical co-crystals alone will afford a number of forms with a variety of CFs, which is anticipated to improve physical properties such as solubility, stability, hygroscopicity and dissolution rate etc. Isolation and purification of APIs can also be achieved through co-crystallization by discarding the co-crystal former before formulation.

The notion that co-crystals should be recognized as a distinct class of compounds has gained much support during recent past due to increased focus on PCs with a large number of special issues of journals, book chapters, review articles and research papers being published.^{13,41,42} Focus on pharmaceutical co-crystals relatively started in the year 2000 when publications demonstrated co-crystallization of the analgesic drugs—Paracetamol, Ibuprofen, and Flurbiprofen, with different co-formers having complementary hydrogen bond acceptors.^{43,44} These were some examples which gave initial breakthrough

to explore a series of co-crystals with common hydrogen bond features in APIs. From the interest of pharmaceutical industry these examples were just model systems in which most of the co-formers were not safe for human ingestion. In subsequent papers, many PCs were reported with GRAS compounds, which have been approved by FDA.⁴⁰ Recent literature shows a significant number of scientific reviews and patents of pharmaceutical co-crystals with pharmacokinetic (PK) studies supporting that pharmaceutical co-crystals are a viable option to enhance the clinical performance of poorly soluble APIs.⁴⁵ It is evident that pharmaceutical co-crystals represent an opportunity to diversify the number of crystal forms of a given API, and in turn fine tune or even customize its physicochemical and PK properties without the formation/breakage of covalent bonds.

4 Some Important Case Studies

Herein, we cite some examples of co-crystals of APIs with GRAS compounds, drug-drug co-crystals and nutraceutical co-crystals present in the literature.

On the basis of solubility and permeability drugs have been classified into four classes in BCS classification as shown in Figure 6.⁴⁶

Very recently, Nair et al.⁴⁷ examined 263 Abbreviated New drug Applications (ANDA) under development in USA, based on the WHO Model List of Essential Medicines (EML) having sufficient solubility and permeability data for BCS classification to evaluate the approvals

	High Solubility	Low Solubility
High Permeability	<p><i>Class I</i></p> <p>High Solubility</p> <p>High Permeability</p>	<p><i>Class II</i></p> <p>Low Solubility</p> <p>High Permeability</p>
Low Permeability	<p><i>Class III</i></p> <p>High Solubility</p> <p>Low Permeability</p>	<p><i>Class IV</i></p> <p>Low Solubility</p> <p>Low Permeability</p>

Figure 6: The Biopharmaceutics Classification (BCS) of drugs.

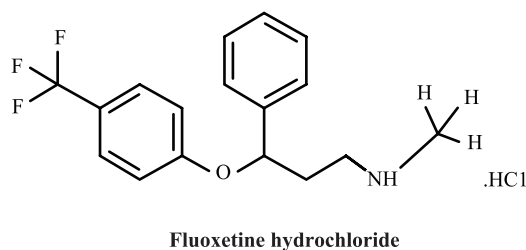
in the distribution of BCS Class 1, 2, 3, and 4 drugs.⁴⁸ During the period of 2000 to 2011, out of 263 ANDA submissions indicated 110 (41.8%) approvals for Class 1 drugs (based on both bio-waiver and in vivo bioequivalence studies),⁴⁹ 55 (20.9%) approvals for Class 2, 98 (37.3%) for Class 3, and no (0%) approvals for Class 4 drugs. From the above data it is evident that co-crystal screening could be one of the best methods available to address this issue satisfactorily.

Among many research papers published in literature for API co-crystals according to the BCS classification, a few of them have been highlighted in this review.⁵⁰

5 BCS I Class

5.1 Co-crystals of Fluoxetine Hydrochloride (Prozac)

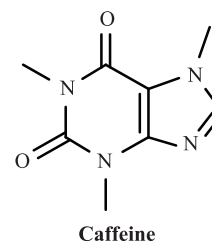
Childs et al.⁵¹ have reported three co-crystals of antidepressant drug Fluoxetine hydrochloride with coformers like Benzoic acid, Fumaric acid and Succinic acid. The co-crystal with Benzoic acid showed a decrease in solubility by about 50%, while a co-crystal with Succinic acid showed a two fold increase in solubility and co-crystal with Fumaric acid did not show any variation in aqueous solubility compared to hydrochloride salt of the API, thereby providing altered solubilities of the drug with the formation of co-crystals for variation in formulation.



5.2 Co-crystals of Caffeine

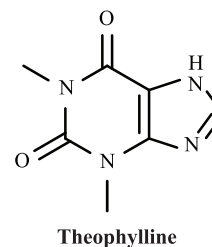
The work carried out by Trask et al.^{52(a)} resulted in the formation of co-crystals of a stimulant drug Caffeine with different dicarboxylic acid coformers *viz.*, Oxalic acid, Malonic acid, Maleic acid, and Glutaric acid, in order to look for pharmaceutically suitable and stable anhydrous forms of Caffeine. At relative humidity of 75% and below, all the co-crystals showed stability and no hydrates were formed. One of the co-crystals with Oxalic acid showed relative humidity stability up to 98% for a period of 7 weeks. Thus, co-crystals can offer resistance to hygroscopicity and result in pharmaceutically viable compounds with improved physical properties.

A recently reported 1:1 co-crystal hydrate of Caffeine with 4-hydroxybenzoic acid showed improvement in thermal stability. Thus, co-crystal promises to widen the scope in pharmaceutical development.^{52(b)}



5.3 Co-crystals of Theophylline

Another work was reported by Trask et al.^{53(a)} for the formation of co-crystals of a respiratory drug. Theophylline with some aliphatic dicarboxylic acids, showed improvement in the stability of co-crystals with respect to relative humidity as compared to the crystals of pure Theophylline. All the reported co-crystals were stable up to 75% relative humidity for a time period of 7 weeks. Among the co-crystals the 2:1 Theophylline : Oxalic acid co-crystal demonstrated stability at relative humidities up to 98% for 7 weeks time. Zhanga and Rasmuson^{53(b)} obtained 2:1 Theophylline : Oxalic acid co-crystal using slurry conversion crystallization in more benign solvents with higher yield than reported in earlier literature. Thus, attempt of getting a co-crystal with various coformers by different methodologies may lead to the variation in properties as well.

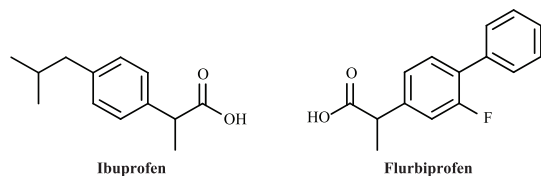


6 BCS II Class

6.1 Co-crystals of Ibuprofen and Flurbiprofen

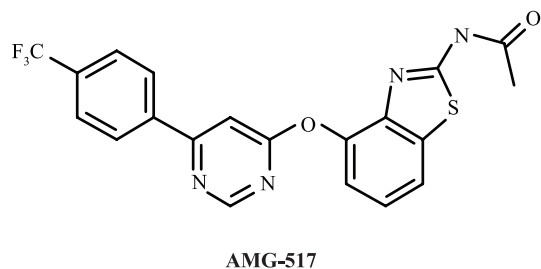
The low dissolution rates and poor aqueous solubility of the two anti-inflammatory Profens *viz.*, Ibuprofen and Flurbiprofen was improved by co-crystallizing with nicotinamide. The dissolution rate increased by 8 fold and 5 fold for Ibuprofen and Flurbiprofen co-crystals, respectively. Co-crystallization also improved other physicochemical properties like moisture sorption and

mechanical properties (tableting behavior) of the two drugs.⁵⁴



6.2 Co-crystals of AMG-517

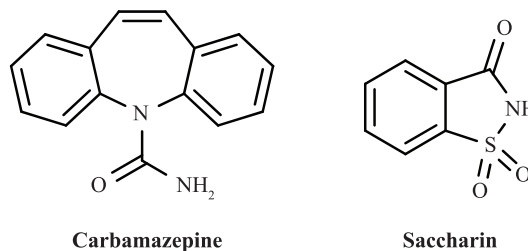
The poor aqueous solubility of AMG-517, an antagonist of transient receptor potential vanilloid 1 (TRPV1), was solved by co-crystallizing with some aliphatic and aromatic carboxylic acids. The study carried out by Stanton and Bak⁵⁵ on AMG-517 resulted in co-crystals with enhanced dissolution rates. The co-crystals with six cofomers *viz.*, Glutaric acid, Glycolic acid, Sorbic acid, *trans*-2-Hexanoic acid, Lactic acid, and Benzoic acid reach maximum solubility within 1–2 hrs. Their study also revealed that the three co-crystals with *trans*-Cinnamic acid, 2, 5-Dihydroxybenzoic acid, and 2-Hydroxycaproic acid were less soluble than the AMG-517 free base. Thus, co-crystals can decrease the required dosage by increasing the dissolution rates.



6.3 Co-crystal of Carbamazepine (Tegretol)

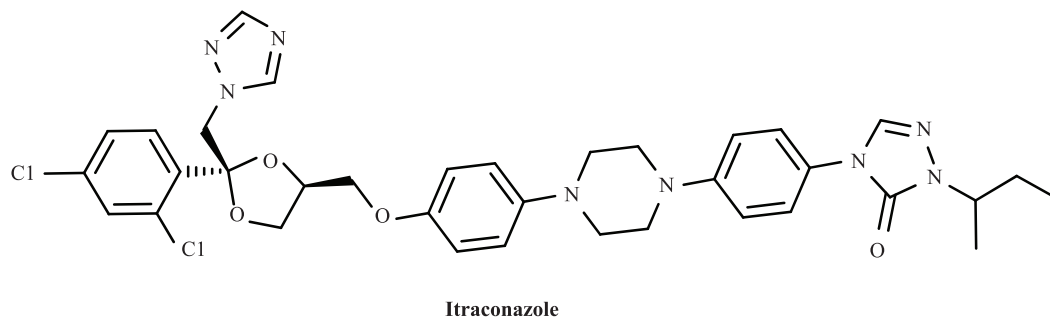
The challenges of low water solubility, dissolution limited bioavailability and requirement of high dosage in case of pure form of antiepileptic drug Carbamazepine (Tegretol) was overcome in its co-crystal with Saccharin. The

Carbamazepine : Saccharin co-crystal shows improved physicochemical properties like enhanced dissolution rate and suspension stability. As compared to the marketed form Tegretol, the co-crystal possesses higher C_{max} (maximum drug concentration) and a comparable T_{max} (time to reach peak concentration).⁵⁶



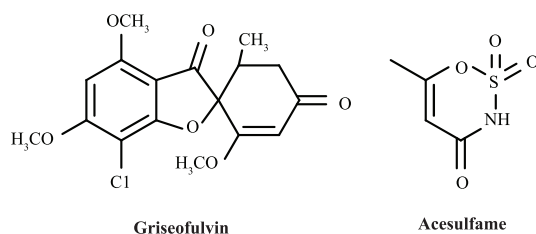
6.4 Co-crystals of Itraconazole (Sporanox)

The highly water insoluble antifungal drug Itraconazole has been co-crystallised with 1, 4-Dicarboxylic acids *viz.*, Succinic acid, L-Malic acid, and L-Tartaric acid. The Itraconazole : 1, 4-Dicarboxylic acid co-crystal forms a trimer with two API molecules and one cofomer. The dissolution of all the co-crystals was found to be comparable to that of marketed form Sporanox, while the Itraconazole : L Malic acid co-crystal was observed to have a dissolution profile almost similar to that of the marketed formulation.^{57(a)} Thus, it is evident that the co-crystal promises to be an improvement with respect to its solubility and bioavailability as compared to the pure crystalline form of the API. A recent paper by Nonappa et al.^{57(b)} reveals the new insights of the Itraconazole : Succinic acid co-crystal where they observed ambiguity in location of the elements (C, H, and N) in the 1,2,4-triazol-5-one ring as well as the uncovered the existence of C–Cl...N halogen bond. The authors believe that these new insights could be the responsible factors for the altered properties of the API.



6.5 Co-crystal of Griseofulvin

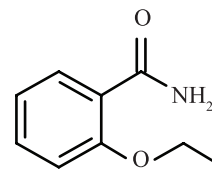
Aitipamula et al.⁵⁸ reported co-crystals of antifungal, low solubility drug Griseofulvin with coformer Acesulfame using solution crystallization technique. The co-crystal was a monohydrate with Griseofulvin and Acesulfame in 2:1 stoichiometric ratio with improved physicochemical properties. The co-crystal showed remarkable stability up to 150°C, with three fold increase in solubility and dissolution rate as low as 20 minutes as compared to the pure Griseofulvin. The co-crystal hydrate can thus find scope in getting novel formulations for the drug.



6.6 Co-crystals of Ethenzamide

Pharmaceutically important co-crystals of a poor aqueous solubility analgesic drug Ethenzamide were obtained using solid state grinding and solvent vaporization crystallization techniques with various coformers like Salicylic acid, 2-Chloro-4-

respectively in solubility and dissolution rate. API co-crystal solid forms thus offer promising improvement in physicochemical properties during drug development.⁵⁹

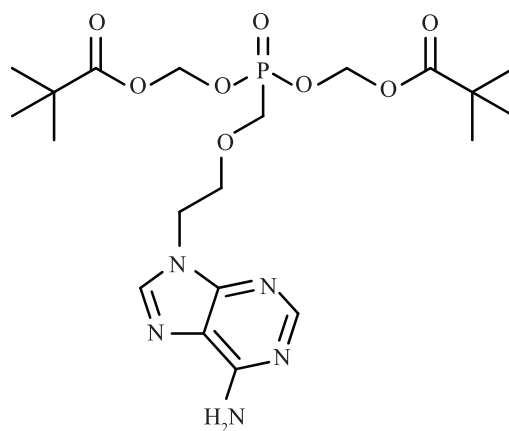


Ethenzamide

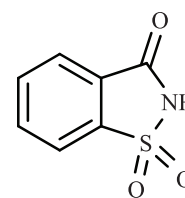
7 BCS Class III

7.1 Co-crystal of Adefovir Dipivoxil

Gao et al.⁶⁰ obtained the co-crystal of Adefovir Dipivoxil, an anti hepatitis B drug with Saccharin using solution crystallization technique. The co-crystal exhibited enhanced dissolution rate and stability as compared to the pure API. The dissolution profile of the co-crystal was found to be pH independent with a two fold increase in dissolution efficiency in water and phosphate buffer (pH 6.8) as compared to the pure compound. Their study also revealed that the co-crystal is kinetically more stable than the pure drug.



Adefovir dipivoxil



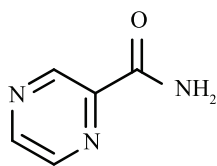
Saccharin

Nitrobenzoic acid, Vanillic acid, 4-Aminobenzoic acid, 4-Hydroxybenzoic acid, and Fumaric acid. All the co-crystals exhibited improvement in physical properties like solubility and intrinsic dissolution rate as compared to pure Ethenzamide crystals with highest increase shown by the co-crystals of Ethenzamide with 4-Hydroxybenzoic acid with almost 5-fold and 2-fold increase

7.2 Co-crystals of Pyrazinamide

Using slow evaporation technique Luo and Sun⁶¹ obtained co-crystals of anti-tuberculosis drug Pyrazinamide with co-crystal coformers like Malonic acid, Succinic acid and Glutaric acid. The co-crystals exhibited enhanced solubility as compared to the pure API. The co-crystals also showed increased dissolution rate than the pure crystals of

the Pyrazinamide. The study also revealed that the coformers with greater solubility and higher dissolution rates result in co-crystals with more solubility and higher dissolution rates than the parent compound.

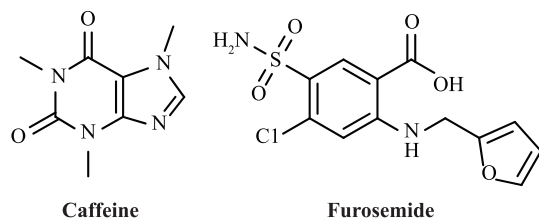


Pyrazinamide

8 BCS Class IV

8.1 Co-crystal of Furosemide

Goud et al.⁶² reported a co-crystal of Furosemide, a low soluble and low permeable antihypertensive drug with Caffeine using liquid assisted grinding. The co-crystals with improved physicochemical properties exhibited higher solubility, more stability and increased dissolution rates than the pure compound. The solubility and intrinsic dissolution rate for the co-crystal was found to be 6 and 2 times more respectively, than Furosemide.

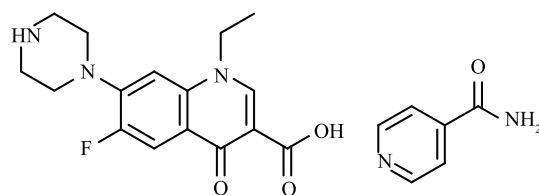


Caffeine

Furosemide

8.2 Co-crystal of Norfloxacin

Basavoju et al.⁶³ reported a co-crystal solvate of antibacterial drug Norfloxacin with coformer Isonicotinamide. Norfloxacin, a poorly soluble and low permeability drug, co-crystallizes with Isonicotinamide in trichloromethane by slow evaporation technique. The resulting co-crystal shows enhanced solubility which was reported to be 3 times more than pure crystal of Norfloxacin.



Norfloxacin

Isonicotinamide

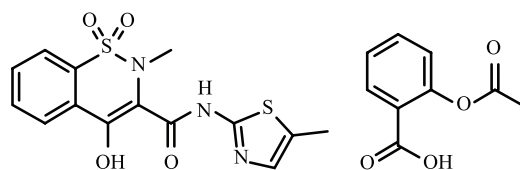
9 Drug-Drug Co-Crystals

In a drug-drug co-crystal (combination drugs) the use of a pharmaceutically acceptable GRAS (generally recognized as safe) compound as

coformer is replaced by another API. The resulting co-crystals exhibit improved physicochemical properties such as solubility, dissolution rate, hygroscopicity, compaction behavior, tableability, and stability without changing the therapeutic nature of both the APIs independently. From a drug-drug co-crystal, a patient can get one tablet containing more than one drug⁶⁴ for one or more than one ailment, thus increasing his compliance, reducing the number of prescriptions, and also lowering the administrative cost.⁶⁵

9.1 Co-crystal of Meloxicam : Aspirin

The low solubility and longer time to reach maximum solubility for Meloxicam a nonsteroidal anti-inflammatory drug was solved by co-crystallizing with Aspirin, an analgesic API which acts as a coformer. It was shown in the study carried out by Cheney et al.⁶⁶ that in acidic conditions which resemble with that of gastrointestinal tract, the solubility of the co-crystal was found to be 0.22 mg/ml as compared to 0.005 mg/ml for the pure API Meloxicam. It was also revealed that the time required to reach the maximum concentration was also decreased considerably as compared to the parent drug.

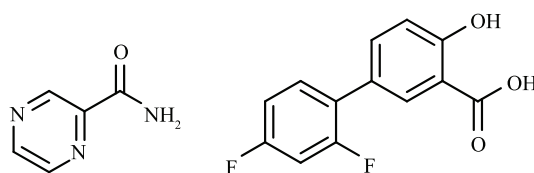


Meloxicam

Aspirin

9.2 Co-crystal of Pyrazinamide : Diflunisal

Pyrazinamide, an anti-tuberculosis drug, was co-crystallized with another API Diflunisal which is a nonsteroidal anti-inflammatory compound. The 1:1 co-crystal was reported by Evora et al.⁶⁷ using crystallization techniques like grinding, annealing and solution crystallization. In the said work the authors claim that the side effects of pyrazinamide can be decreased and also improve the aqueous solubility of Diflunisal.

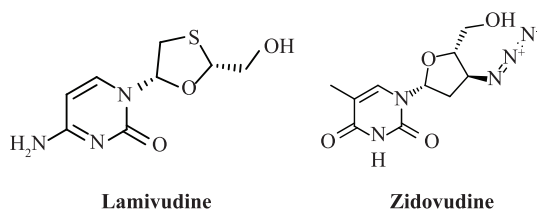


Pyrazinamide

Diflunisal

9.3 Co-crystal of Lamivudine : Zidovudine

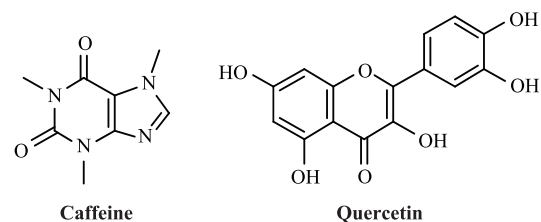
The low permeability anti-HIV drugs Lamivudine and Zidovudine are administered orally as a physical mixture of 150 mg and 300 mg respectively under the name Combivir. A successful attempt to study the co-crystal forming ability of the two drugs was carried out by Bhatt et al.⁶⁸ It was reported that using slow evaporation technique a 1:1 co-crystal hydrate was obtained.



10 Nutraceuticals

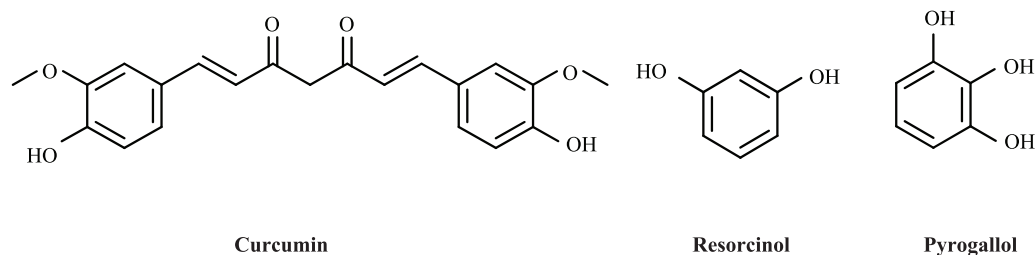
The term nutraceutical was coined by Dr. Stephen De Felice and defined as “a food, or parts of food, that provide medical or health benefits, including the prevention and treatment of disease”. So, the nutraceuticals while supplementing with nutritional values also act as drugs to prevent and cure many diseases.⁶⁹ Many nutraceuticals used as potential APIs often show poor aqueous solubility and hence less

itself. It was also revealed that T_{max} (minimum time to reach peak concentration) for Quercetin : Caffeine co-crystal and Quercetin : Caffeine methanol solvate co-crystal is 10 and 5 minutes respectively, as compared to 30 minutes for Quercetin dehydrate.⁷⁰



10.2 Co-crystals of Curcumin

The co-crystallization of anticancer nutraceutical Curcumin using liquid assisted grinding with Resorcinol and Pyrogallol resulted in co-crystals with improved aqueous solubility and intrinsic dissolution rates. The solubility for the Curcumin : Resorcinol and Curcumin : Pyrogallol co-crystals was observed to be approximately 2 times and 5 times respectively, more than Curcumin. Moreover the intrinsic dissolution rates were found to be approximately 5 and 12 times for Curcumin : Resorcinol and Curcumin : Pyrogallol co-crystals respectively than pure Curcumin.⁷¹



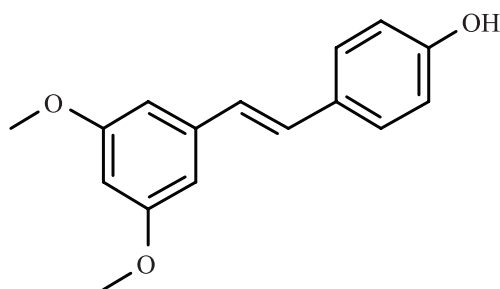
bioavailability. However, many studies carried out by scientific community resulted in co-crystals of nutraceutical with pharmaceutically accepted compounds which exhibited improved physicochemical properties. Herein are some examples that show improvement in their physicochemical properties.

10.1 Co-crystals of Quercetin

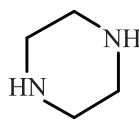
The antioxidant nutraceutical Quercetin with poor aqueous solubility and low bioavailability was co-crystallized with Caffeine, Isonicotinamide, and Theobromine. The Quercetin : Caffeine co-crystal and Quercetin : Caffeine methanol solvate co-crystal show 14 and 8 times more solubility respectively than Quercetin dihydrate

10.3 Co-crystals of Pterostilbene

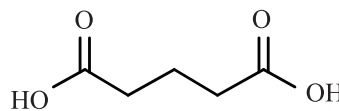
Two co-crystals of a poor aqueous solubility nutraceutical Pterostilbene (a stilbenoid found in blueberries and grapes) were reported by Bethune et al.⁷² with Piperazine and Glutaric acid. A 2:1 co-crystal of Pterostilbene : Piperazine and 1:1 co-crystal of Pterostilbene : Glutaric acid were obtained using liquid assisted grinding technique. The co-crystals exhibited physical stability at different temperatures ranging from room temperature to 65°C and relative humidities ranging from ambient to 98% for 8 weeks time. It was also found that Pterostilbene : Piperazine co-crystal enjoyed six times more solubility than pure Pterostilbene compound.



Pterostilbene



Piperazine



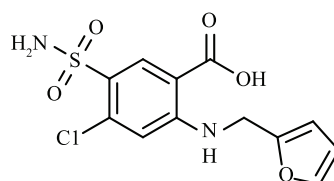
Glutaric acid

11 Polymorphism in Pharmaceutical Co-crystals

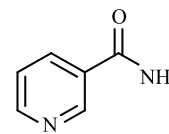
Polymorphism, which is found commonly in single component crystals than in multi-component crystals, is defined by McCrone as “A solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state” and further stated that “in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound”.⁷³ Polymorphs have different crystal structure and hence show different physical and chemical properties like solubility, stability, hygroscopicity etc.⁷⁴ It was believed that only few co-crystals exist in polymorphic forms,⁷⁵ but some recent advances in the field revealed that a good number of co-crystals can show polymorphism.⁷⁶ The increasing interest in the pharmaceutical co-crystal development has resulted in an increase in the number of co-crystal polymorphs in recent years. The number of polymorphs associated with a pharmaceutical co-crystal varies and maximum number reported till date is five for Furosemide : Nicotinamide 1:1 co-crystal⁷⁷ and three each for Barbituric acid–Urea 1:1 co-crystal,^{76(b)} Pimelic acid–4,4′-Bipyridine co-crystal,⁷⁸ and Ethenzamide–Gentisic acid 1:1 co-crystal.⁷⁹ Thus, screening of polymorphs and co-crystal characterization is finding importance due to the rise in the number of polymorphs found in the pharmaceutical co-crystals, which may lead to increase in the number of solid forms to look for better physicochemical properties and to keep a check on the undesired form.

11.1 Furosemide : Nicotinamide co-crystal

Ueto et al.⁷⁷ reported five anhydrous co-crystal polymorphs (I-V) and a hydrate in the case of a diuretic drug Furosemide with Nicotinamide using slurry method for screening.



Furosemide



Nicotinamide

Single crystal structures of four co-crystal polymorphs (I-IV) are reported leaving the fifth polymorph (V), as no single co-crystal could be obtained for this polymorph. Forms (I-III) have monoclinic crystal system with space group $P2_1/n$, while as form IV has a monoclinic crystal system but with C_2/c space group. All the polymorphs (I-IV) were having one Furosemide molecule and one Nicotinamide molecule in the asymmetric unit. The polymorph co-crystals were stabilized by different supramolecular synthons (Figure 7, A-E) resulting in to the different crystal structures *viz.*, carboxylic acid...pyridine (Synthon A), carboxylic acid...amide (Synthon B and E), sulfonamide...amide (Synthon C and D) between Furosemide and Nicotinamide molecules of the asymmetric unit (Figure B). All the synthons are not found in all of the crystal structures of the polymorphs. Robust synthon A was common in all the forms except form IV while synthons B, C, D and E were not consistent in all the crystal structures. Synthon A is the only synthon found in form I while in form II an additional synthon B is found but in form III synthon B is absent instead synthon C and D are present, whereas in case of form IV only synthon E is found. The other additional synthon F and G are consistent in all the form (I-IV) except synthon G which is absent in form IV. The crystal structural difference among the polymorphs was also attributed to the differences in conformations of Furosemide and Nicotinamide, which arises due to different torsion angles.

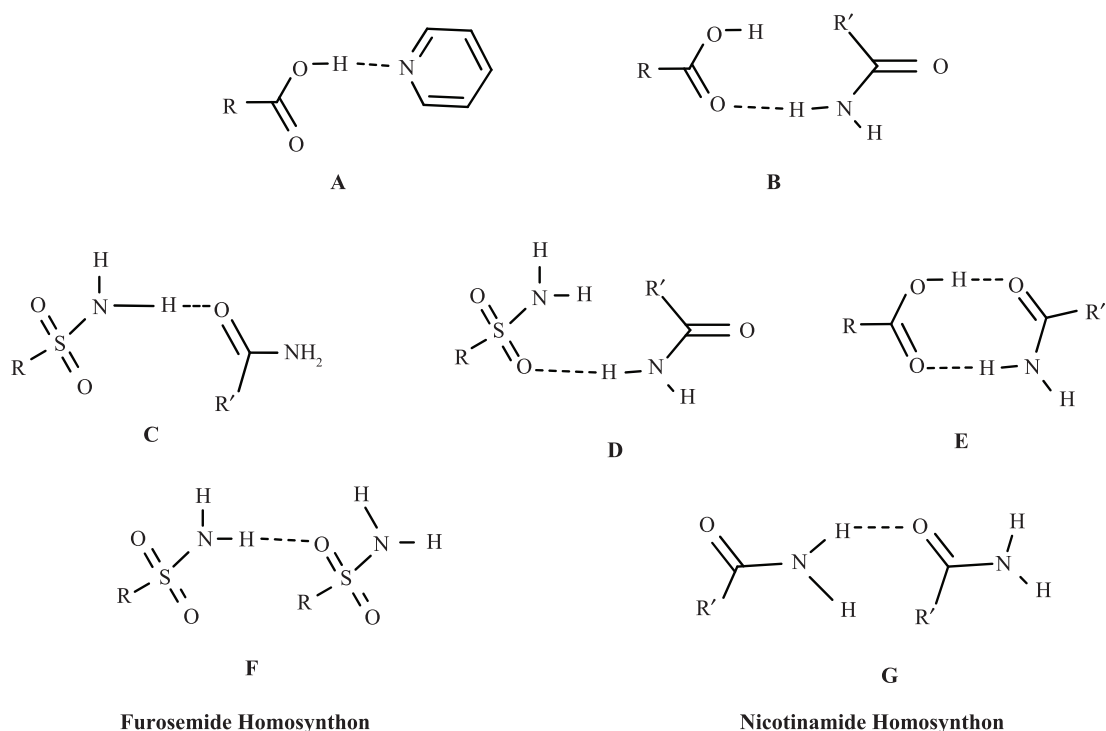
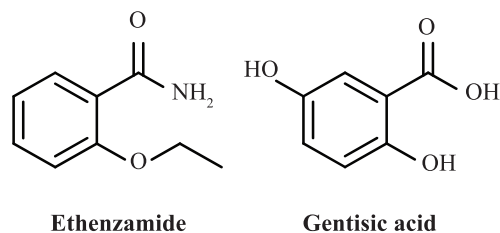


Figure 7: Synthons formed in FS–NCT 1:1 co-crystals.

11.2 Co-crystal polymorphs of Ethenzamide and Genticic acid

Aitipamula et al.⁷⁹ reported trimorphic drug-drug co-crystals of Ethenzamide (EA) and Genticic Acid (GA) both non steroidal anti-inflammatory drugs. Form I crystallizes in triclinic crystal system with P1 space group, while form II and III crystallize in monoclinic crystal system with $P2_1/c$ and $P2_1/n$ space groups respectively. The polymorphic co-crystals (I-III) were sustained by major acid-amide heterosynthon with difference in their arrangement. In form I and II the –OH groups of the GA molecule, adopts a syn-anti conformation (Fig. 8a and 9a), and form III adopts a syn-syn conformation (Fig. 9b). Form I shows a one dimensional zipper like arrangement by symmetry independent one molecule each of GA (A) and EA (C) by $\text{NH}\cdots\text{O}$ and $\text{OH}\cdots\text{O}$, and the second independent asymmetric molecule of GA (B) extends the hydrogen bonding network by $\text{OH}\cdots\text{O}$ hydrogen bond forming two inversion related tapes that are parallel to each other and $\text{OH}\cdots\text{O}$ and $\text{NH}\cdots\text{O}$ hydrogen bond further connect the zipper like network via second independent EA (D) molecule. Form II has linear tapes via $\text{OH}\cdots\text{O}$ hydrogen bonds involving –OH of GA, and in form III a tetrameric motif is formed between EA and GA by $\text{OH}\cdots\text{O}$ hydrogen bonds.



12 Conclusion and Future Outlook

Co-crystals, especially PCs per se, have become an important solid form in pharmaceutical space. It is evident from the number of research papers, review articles which are published in various journals as well as organization of conferences, symposiums and workshops in last decade or so. From the industrial point of view the number of patents filed throughout the world by various pharmaceutical industries and research groups are also increasing at a fast pace, since there is both regulatory and intellectual property relevance. Increasing number of pharmaceutically important co-crystals (including nutraceutical co-crystals) with GRAS compounds as cofomers suggest that physicochemical properties, especially solubility, have improved even for neutral APIs, as well as dissolution rate, bioavailability, hygroscopicity etc. Moreover, co-crystal screening leads to the identification of the most viable form of co-crystal, thus saving

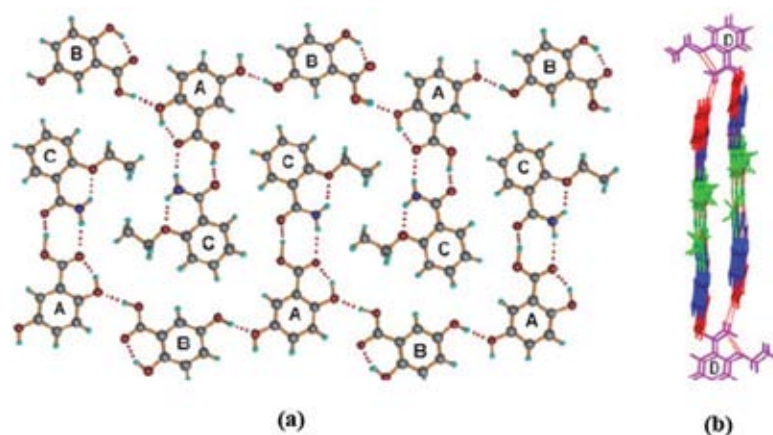


Figure 8: (a) A zipper-like structure of Form I. (b) A view of the hydrogen bonded network showing the EA molecules (C) connecting the two zipper-like networks.⁷⁹

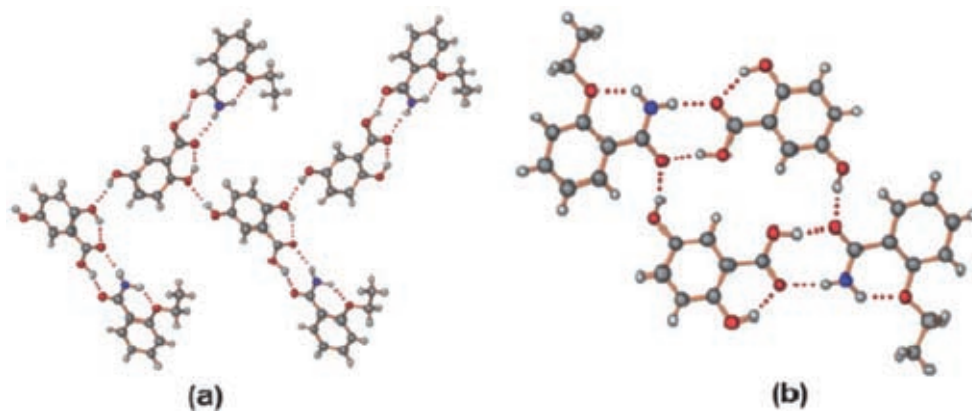


Figure 9: (a) A hydrogen bonded linear tape in the crystal structure of Form II. (b) A hydrogen bonded tetrameric motif in the crystal structure of Form III.⁷⁹

time and money. It is to be noted that, till date very few pharmaceutical co-crystals are known as compared to single component polymorphic modification of an API which does become an important issue for pharmaceutical industry.

The challenges that lie ahead include scaling up the production of the PCs, preceded by discovery of new scale up methods, and high throughput screening of the possible co-crystal with various coformers and their polymorphs. Crystal structure prediction⁸⁰ has emerged as one of the most promising methods in computational chemistry for prediction of the crystal lattice and thereby predict the likely shape of crystals, physical properties and even design the molecular arrays. But still much work has to be done in this field as the number of structures (over 600,000) present in the Cambridge Structural Database (CSD) has not proved to be enough to set rules to derive the most probable crystal structure

from these structures. The other aspect is the legal issues related to intellectual property of the existing APIs, the co-crystals, the properties, mode of action etc., as the nomenclature of the pharmaceutical co-crystal is at a debate among the Scientific Community, Pharmaceutical industry and United States Food and Drug Administration (FDA), which is not on consensus leading to a reconsideration over the nomenclature of the pharmaceutical co-crystals and existing classification of the pharmaceutical solids.

It is quite evident from the amount of interest shown by both academia and pharmaceutical industry that in near future pharmaceutical co-crystals will be one of the viable and important solid forms of pharmaceuticals sold in the market, clearing all the hurdles, be it nomenclature or classification of pharmaceutical co-crystals.

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