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Review

Drug-Drug and Drug-Nutraceutical Cocrystal/Salt as Alternative Medicine for Combination Therapy: A Crystal Engineering Approach

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Abstract: The pre-formulation of pharmaceutical cocrystals and salts is a concept of crystal engineering that has emerged as a promising technique for drug development in pharmaceutical industry. Recent introduction of pharmaceutical cocrystals in regulatory guidelines of US Food and Drug Administration (FDA) made them one of the potential alternatives when salt preparation is not feasible. Apart from generally regarded as safe (GRAS) coformers, drug-drug and drug-nutraceutical cocrystals are recent additions to pharmaceutical cocrystal family that have additional health benefits. Indeed, preparation of salt forms is a routine practice to deal with inadequacies associated with the active pharmaceutical ingredient (API) and happens to be a potentially reliable method. Amongst them, drug-drug and drug-nutraceutical cocrystals have drawn significant importance in the recent past as they reduce drug load and cost effects during multiple disease diagnosis. However, one has to be prudent in the selection of drug molecules, the presence of complementary hydrogen bond synthon, disease management during multiple disease therapy, etc. that play important roles in their preparation. That is the reason why drug–drug cocrystals are scarce in the literature compared to pharmaceutical cocrystals containing GRAS coformers and salt forms. Herein, we discuss case studies preferably the reported drug-drug, drug-nutraceutical cocrystals, and a few salts with an emphasis on their role in physicochemical property modulation.

Keywords: crystal engineering; supramolecular synthon; API; nutraceutical; pharmaceutical cocrystal; salt; solubility; dissolution; stability

1. Introduction

The breakthrough of a new drug is time consuming and staggeringly difficult task. The discovery of new drugs is gradually decreasing because of stiffened regulations and requirements imposed on drug discovery and formulation [1,2]. The subject crystal engineering has brought us an opportunity to overcome these issues by translating the idea of new pre-formulations of existing drugs based on intermolecular interactions. Novel formulation with improved pharmacological properties has a vital necessity in this context because most drug molecules have more or less inadequacies relating to their pharmacokinetic and physiological properties such as solubility, dissolution, hygroscopicity, membrane permeation, chemical stability, etc. [3–23]. They are imperative factors that essentially define the overall efficacy of the active pharmaceutical ingredient (API). One survey says that nearly 80% drugs are in solid formulations and absorbed via passive diffusion from the gastrointestinal tract [24]. Among them, over 40% of drugs that appear on the World Health Organization (WHO) Essential Drug List are known to be insoluble or poorly water-soluble, based on the Biopharmaceutics Classification System (BCS) [3,25]. Preparation of salt formulation made a drug more bio-available;

however, more than 50% of drug molecules lack an ionisable group which can make salt formation likely impossible. From these facts, it is essential to develop a new solid state formulation with trusted properties. The brilliancy of the subject of crystal engineering is that it provides a wide-range of possibilities to engineer and/or design various crystalline solid state formulations of a drug that can carry the tailored biopharmaceutical properties—for example polymorphs, pseudopolymorphs, solvates, hydrates, cocrystal, etc. They have been demonstrated as alternatives and can easily minimize major obstacles in successfully commercializing the compounds. Among them, cocrystal synthesis is relatively modern technology to modulate drug biopharmaceutical properties, in particular to treat drug resistance issues [26–29]. Fortuitously, the importance of cocrystal preparation has recently been realized in the pharmaceutical industry and many of them have started practicing in order to modify an existing API for coveted attributes. This scope continues to develop a new formulation to enhance and/or control bioavailability and essentially the efficacy of a drug. A pharmaceutical cocrystal generally incorporates API with a pharmaceutically-acceptable molecule (cocrystal former or CCF) in their crystal lattice without any structural modification of the parent drug (Figure 1) [3–23,30–35]. Preferably, the coformers are chosen from the GRAS (generally regarded as safe) list prepared by USA Food and Drug Administration (FDA) which comprises over 3000 substances [36–39]. Food additives, preservatives, excipients, vitamins, minerals, amino acids, bio-molecules, and their APIs can be selected as CCF. They are commonly prepared by a variety of techniques such as melt crystallization, grinding, and recrystallization from solvents etc. Thus, pharmaceutical cocrystal stands here as an alternate and interesting pathway to improve efficacy of a drug.

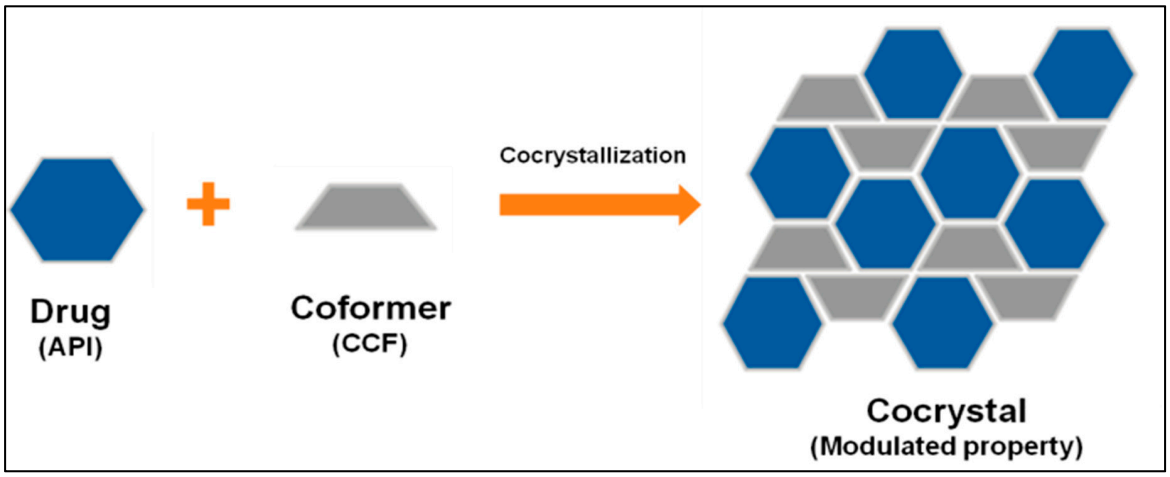


Figure 1. Typical representation of preparation of cocrystal.

Crystalline products are strongly preferred in the development of an API due to their relative ease in terms of purity, stability, and an established technology for product improvement synergistically by changing intermolecular interaction behaviors, such as drug-drug, drug-coformer and solute–solvent interactions. It is needless to mention that coformers and/or excipients play crucial roles in changing the lipophilic behaviors resulting modified physicochemical and mechanical properties. Other very important developments are to address drug resistance issues and combination therapy using cocrystals. Most bacteria, viruses, and other microbes multiply rapidly and slowly adapt resistance to the drugs designed to kill them, making the product less effective. Essentially, they develop a resistance power to that drug over time. Thus strategy to develop multicomponent drugs, especially when all components are APIs, would offer a combination drug that shows better effect than the sum of their individual effects [27–32]. A typical CCF when replaced by another drug or a nutraceutical, the resultant cocrystal is known as drug–drug and drug–nutraceutical cocrystal and they are now comprehended as alternate drugs for enhancing well-being. Down the line, we have discussed several examples from the context of pharmaceutical cocrystals that led to significant improvement in drug

properties. Entresto is one of the classic examples to receive approval as a new active substance. It is a fixed-dose combination product presented as film-coated tablets containing and valsartan as active substances as a trisodium hemipentahydrate co-crystal. Generally, three strengths are proposed containing 24.3 mg sacubitril and 25.7 mg valsartan (low dose), 48.6 mg sacubitril and 51.4 mg valsartan (medium dose), and 97.2 mg sacubitril and 102.8 mg valsartan (high dose) for the treatment of chronic heart failure [40]. In 2009, Lexapro—which is an approved cocrystal/salt of Escitalopram and oxalic acid—was mainly used for the treatment of major depressive and anxiety disorders [41]. Though most pharmaceutical cocrystals remain in 1:1 equivalency, the stoichiometric ratio in product cocrystals is an important parameter to address. Our group studied synthesis of variable stoichiometry drug cocrystals that result with different solubilities and cell membrane permeations behaviour in vitro under physiological pH conditions [7]. In a few other systems, we further examined the essence of molecular symmetry and conformational behavior of drug in presence of supramolecular entities in altering pharmacokinetic properties [5,8,42]. From the plethora of publications in the area of pharmaceutical cocrystals, it has been noticed that most pharmaceutical cocrystals were formed between organic acids or bases and the API [3–23,30–35,43–46]. So there seems to remain a scope to explore cocrystal engineering approach using inorganic acid as a cocrystal former.

From thermodynamic point of view salts, cocrystals or amorphous forms are high energy forms [12]. They are widely used to generate supersaturated aqueous solutions and improve drug bioavailability. Generation and maintenance of the metastable supersaturated state (makes the drug more bioavailable) as a strategy to improve intestinal absorption of poorly water soluble drugs, there are two essential steps need to be considered and they are termed as 'spring and parachute approach' [12]. A thermodynamically unstable, supersaturated solution of a drug can only be generated starting from a high energy form of a drug which is known as the "spring" (Figure 2). A combination of excipients like co-solvent, lipid, or polymer based formulations; coformers etc. can deliver the drug in solution as high energy solid forms that can easily provide an accelerated dissolution or a higher apparent solubility. This phenomenon is known as the 'parachute effect'. The apparent solubility is the apparent equilibrium between drug in solution and a solid whose structure is in the high energy state. A high energy form of the drug (the spring) provides the driving force to solubilize the drug at a concentration greater than its equilibrium solubility level and a similar effect resulted by the combination of excipients (the parachute) by inhibiting or retarding precipitation. Maintaining a supersaturated state for a time period sufficient for absorption may require a temporary inhibition of precipitation through the use of pharmaceutical excipients or by other components that interfere with nucleation and crystal growth. This are the 'parachutes' or precipitation inhibitors.

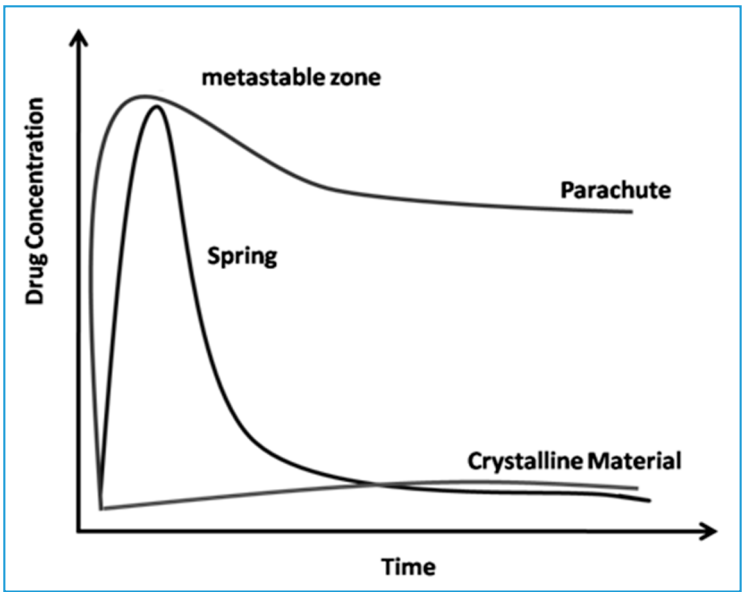


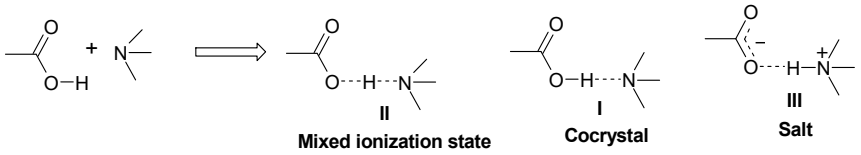
Figure 2. The 'spring and parachute' approach to promoting and maintaining supersaturation of poorly soluble drugs. Adapted with permission from *Cryst. Growth Des.*, 2011, 11 (7), 2662–2679. Copyright 2011 American Chemical Society.

The strategy involves drug-coformer combinations that have the potential of forming energetically and structurally robust interactions which are highlighted as the use of hydrogen bonding and crystal engineering strategies to improve drug profile. In the context of drug–drug and drug–nutraceutical cocrystals, literature reveals only a few cocrystal case studies with pharmacokinetic details. However, R&D departments of many pharmaceutical companies have started putting effort into cocrystal synthesis as an alternative formulation. Only a very limited number of pharmaceutical cocrystals have been approved by the FDA as drug products to date [47–54]. Of late, on 7 July 2015, Novartis gained approval for Entresto™—a cocrystal comprised of sacubitril, valsartan, and solvate water—to treat chronic heart failure [41,55]. Cafcit, which is a drug product consisting anhydrous caffeine, citric acid monohydrate, and sodium citrate dehydrate is another cocrystal formulation already available in the market [56–58]. Sodium valproate is another marketed product with a drug-drug co-crystal [59]. Dimenhydrinate is another widely used drug for the prevention of motion sickness, including nausea and vomiting which is a cocrystal of two drugs—namely, diphenhydramine and 8-chlorotheophylline. The antiemetic effect of the drug for prevention of sickness is due to the presence of diphenhydramine, but associated with the side effect of drowsiness. This cocrystal of dimenhydrinate overcomes side effects as it contains an additional stimulant, 8-chlorotheophylline [60]. The recent approval of a pharmaceutical cocrystals has attracted additional interest from the pharmaceutical industry as materials for drug formulation. Thus novelty, non-obviousness, and usefulness can make cocrystals patentable from the perspective of intellectual property as well as drug formulation. A novel cocrystal formulation can emerge as viable alternative to the traditional drugs in near future. The patent portfolios of cocrystals as drug substance not drug product infer enhancement of existing commercial value of the product. The FDA perhaps issued revised guidance to technically distinguish between salts and cocrystals based on the ionization of the components. Essentially, it abandons the position that cocrystals are drug product intermediates. Cocrystals are therefore adapted as a special case of solvates, in which the second component is nonvolatile and refers to a conformer, rather than as an excipient.

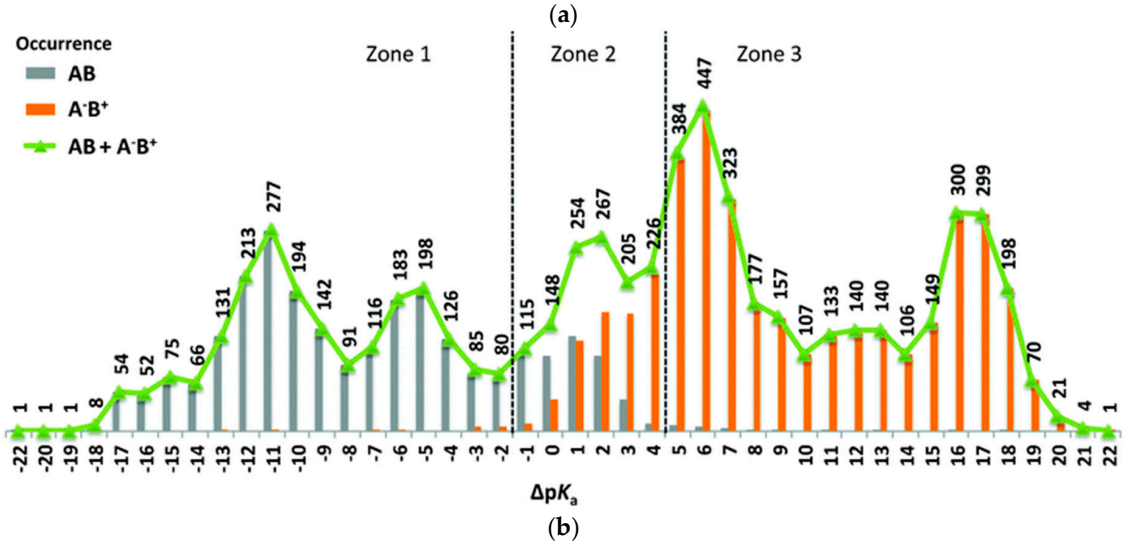
The presence of many functional groups in APIs, which may form robust supramolecular synthons defined by Desiraju [61]. Later, Zaworotko sub-classified supramolecular synthons into homosynthons and heterosynthons based on the interacting functional groups [19]. Commonly observed acid . . .

acid, acid ... pyridine, acid ... amide, amide ... amide, amide ... pyridine N-oxide, O−H···O, O−H···N, N−H···O, and N−H···N, etc. supramolecular synthons offer a great opportunity to design pharmaceutical cocrystals. Moreover, the role of molecular arrangement in the crystal lattice which is controlled by intermolecular interactions not only by hydrogen bonds—but also halogen bonds, π–π interactions [62], van der Waals interactions, metal-coordination bonding, etc.—on modifying properties of a solid crystalline substance also been studied.

As cited before salts and cocrystals can distinguish based on the ionization of the components. It is indeed essential to understand the classification of crystalline solid forms for making in order to characterize them and draw appropriate comparisons as both salts and cocrystals fall into multicomponent crystals. Cocrystals are defined as multicomponent crystal structure in which two or more compounds coexist through hydrogen bonds or non-covalent interactions and they are in neutral form. However, salt can be defined when the proton is transferred from acid to base and exists in the ionic state. Therefore, it is apparent that there exists a continuum linking cocrystals and salts based on the extent of proton transfer between acidic and basic components. When the proton resides on the base, then proton transfer has occurred and the crystalline acid–base complex is a salt and when the proton remains on the acid, then it is a cocrystal. The tendency of transferring a proton from the acidic end to the base is directly related to the p*K*a difference, which is defined as the negative logarithm of the dissociation constant [63–71]. Thus the ΔpK_a [$\Delta pK_a = pK_a(\text{base}) - pK_a(\text{acid})$] will decide the location of the transferable proton within the continuum. It has been observed that when the ΔpK_a is more than 3.75, maximum probability of the proton will reside on the base and the resultant material is a salt, which is an essential criterion while selecting the appropriate counter ions to the preparation of salts of API in order to improve its properties like solubility. Similarly, a neutral cocrystal is expected when the p*K*a difference is less than 0. The proton will have an intermediate H bond character when the transition range falls between 0 and 3.75. This intermediate situation may lead to salt as well as cocrystal. A linear relationship between ΔpK_a and the probability of proton transfer between acid-base pairs was also derived by Aurora from a CSD study of nearly 6500 crystalline complexes. The pK_a rule was validated when ΔpK_a is between −1 and +4 (Scheme 1b) [67]. The p*K*a rule of thumb to predict the proton location in a continuum is depicted in Scheme 1a. The other scale of pK_{HB} which measures the free energy of hydrogen bonded complex (1.364 $pK_{HB} = -\Delta G_{HB}$ in kcal mol^{-1}) also determines the hydrogen bond pairing that could be an appropriate scale compared to pK_a values [72]. The pK_{HB} values are sensitive to factors—like inductive effect, resonance effects, steric hindrance, lone-pair repulsion, intramolecular H-bonding, etc.—that can alter intermolecular interaction pattern.



$\Delta pK_a = pK_a$ (pyrNH$^+$) − pK_a (COOH) [$\Delta pK_a < 0$, neutral synthon; $0 < \Delta pK_a < 3.75$, mixed ionization state; $\Delta pK_a > 3.75$, ionic N$^+$–H···O$^-$]



Scheme 1. (**a**) The pKa rules of thumb to predict the H-bonding motifs in multi-component crystals. This Scheme is reproduced with a slender modification from Ph.D. thesis entitled Structural and Thermal Analysis of Organic Solids by B. Sarma, 2009, University of Hyderabad, India. (**b**) Calculated occurrence of AB (**grey**) and A$^-$B$^+$ (**orange**) as a function of the calculated ΔpK_a Inculcate from a CSD study of a set of 6465 acid-base complexes carried out by Aurora; Adapted with permission from *CrystEngComm*, 2012, 14, 6362–6365. Copyright 2012 the Royal Society of Chemistry.

2. Case Studies

2.1. Drug-Drug Cocrystal

2.1.1. Aspirin Cocrystals

Žegarac et al [73] prepared a 1:1 sildenafil–acetylsalicylic acid (more commonly known as aspirin) cocrystal and a 1:1:1 cocrystal salt involving sildenafil cation, acetylsalicylate and salicylic acid. Sildenafil is an active component of the blockbuster drug *Viagra*® used for the treatment of male erectile dysfunction. Solution crystallization resulted the 1:1 cocrystal along with accidental discovery of the 1:1:1 cocrystal salt. The 1:1 acetylsalicylic acid based cocrystal exhibits 75% improved dissolution rate compared to sildenafil citrate (the active ingredient of *Viagra*®) (Figure 3).

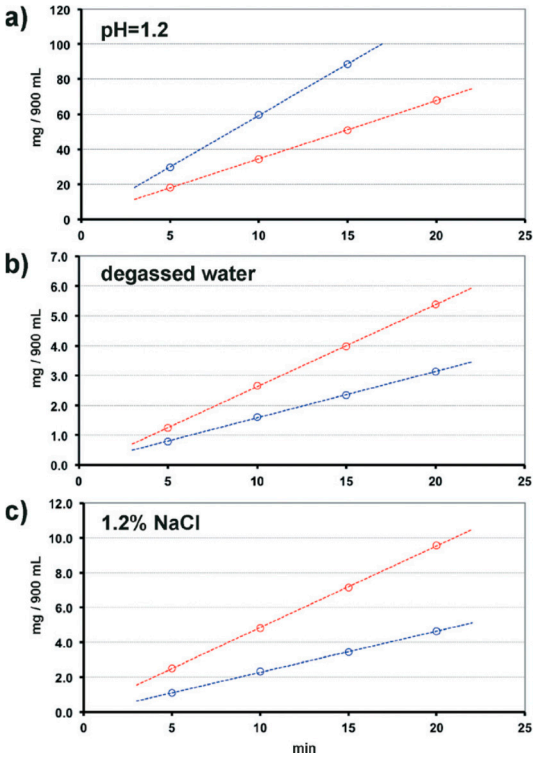


Figure 3. Dissolution rates of 1:1 sildenafil–acetylsalicylic acid cocrystal and sildenafil citrate in (**a**) an aqueous solution at a pH of 1.2, (**b**) degassed water, and (**c**) an aqueous solution containing 1.2% NaCl. Colour scheme: 1:1 cocrystal—blue, sildenafil citrate—red. Adapted with permission from *CrystEngComm*, 2014, 16, 32-35. Copyright 2014 The Royal Society of Chemistry.

Meloxicam is a non-steroidal anti-inflammatory drug with low aqueous solubility and high permeability. In order to improve its aqueous solubility, Zaworotko and coworkers prepared a 1:1 cocrystal of meloxicam and aspirin [74]. The crystal structure contains a $R_2^2(8)$ ring motif connecting aspirin and meloxicam molecule as shown in Figure 4. The resulting cocrystal exhibits superior kinetic solubility and potentiality to significantly decrease the time required to reach the human therapeutic concentration compared with the parent drug, meloxicam.

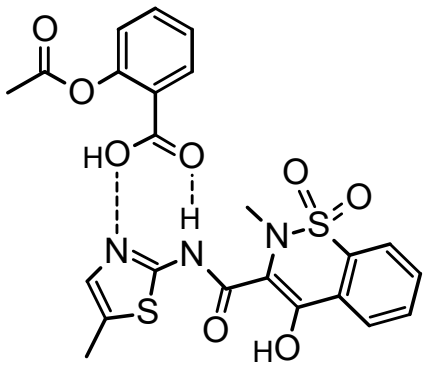


Figure 4. Supramolecular synthon present in 1:1 cocrystal of meloxicam and aspirin.

2.1.2. Anti-Tuberculosis Drug Cocrystal

Desiraju and coworker reported [75] two drug-drug cocrystals of anti-tuberculosis drugs isoniazid (INH), pyrazinamide (Pyz), and 4-aminosalicylic acid (PAS). They were successful in preparing

two drug-drug cocrystals—namely, 1:1 molecular complex of INH and PAS; and a monohydrate of 1:1 complex of Pyz and PAS—using liquid assisted grinding as well as solution crystallization. They observed that both the cocrystal system contains the most stable COOH···$N_{pyridine}$ hydrogen bond synthon. In case of INH-PAS cocrystal there are two symmetry independent COOH···$N_{pyridine}$ hydrogen bond present; one with H atom located on the carboxylic group indicative of pure cocrystal, whereas the second one shows a partial proton transfer. 3D crystal packing of INH-PAS cocrystal is shown in Figure 5. The two symmetry independent COOH···$N_{pyridine}$ hydrogen bond synthon present in INH-PAS cocrystal is shown in Figure 6. On the other hand, crystallizing Pyz with PAS in 1:1 ratio in methanol resulted a monohydrate of Pyz-PAS cocrystal. Various hydrogen bond synthon present in the cocrystal hydrate is shown in Figure 7. The water molecule actively takes part in the hydrogen bond connecting the Pyz and PAS molecules in a tetrahedral environment and acts simultaneously as two hydrogen bond donors and two hydrogen bond acceptors. Due to drug resistant TB, multidrug therapy is practiced during treatment of TB. Therefore, cocrystal of PAS with INH and Pyz may be a useful formulation for the treatment of tuberculosis.

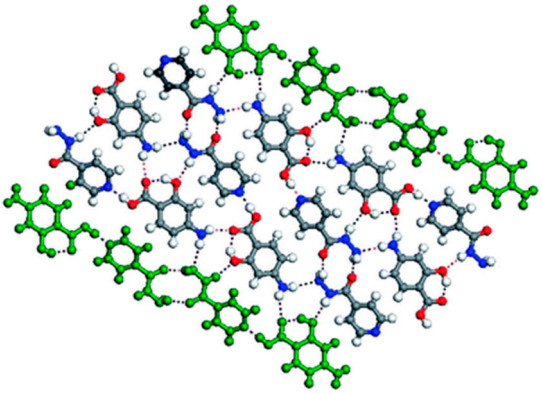


Figure 5. Hydrogen bond interaction present in INH-PAS cocrystal showing finite tetramer motif highlighted in green. Adapted with permission from *CrystEngComm*, 2011, **13**, 4358–4364. Copyright 2011, The Royal Society of Chemistry.

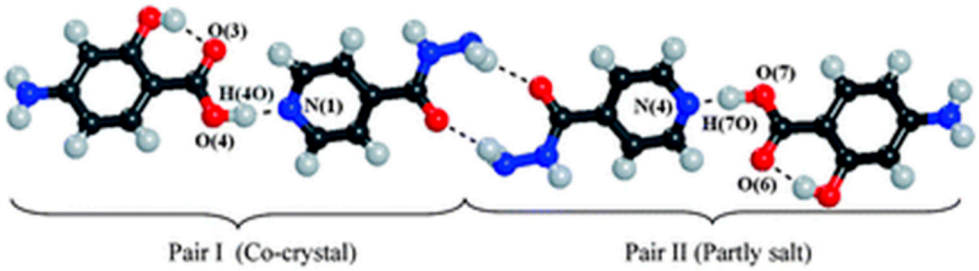


Figure 6. COOH···$N_{pyridine}$ and amide-amide dimer synthon between the symmetry independent molecules of INH-PAS cocrystal. Adapted with permission from *CrystEngComm*, 2011, **13**, 4358–4364. Copyright 2011, The Royal Society of Chemistry.

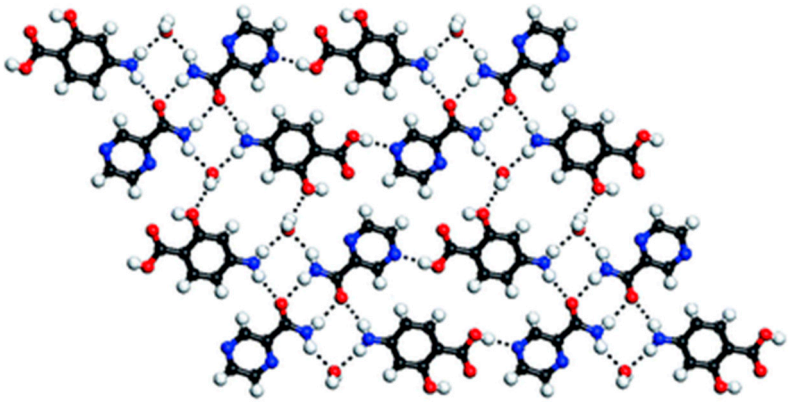


Figure 7. Hydrogen bond interaction present in Pyz-PAS-H_2O cocrystal. Adapted with permission from *CrystEngComm*, 2011, 13, 4358–4364. Copyright 2011, The Royal Society of Chemistry.

Liu et al. [76] recently designed a drug-bridged-drug ternary cocrystallization strategy to prepare a combination drug utilizing a GRAS coformer fumaric acid to connect a Pyz and INH molecule as shown in Figure 8. This is the first ternary dual-drug cocrystal reported in the literature. They highlighted that the ternary cocrystal drug exhibited optimized formulation capacity and in vitro/vivo synergistic effects.

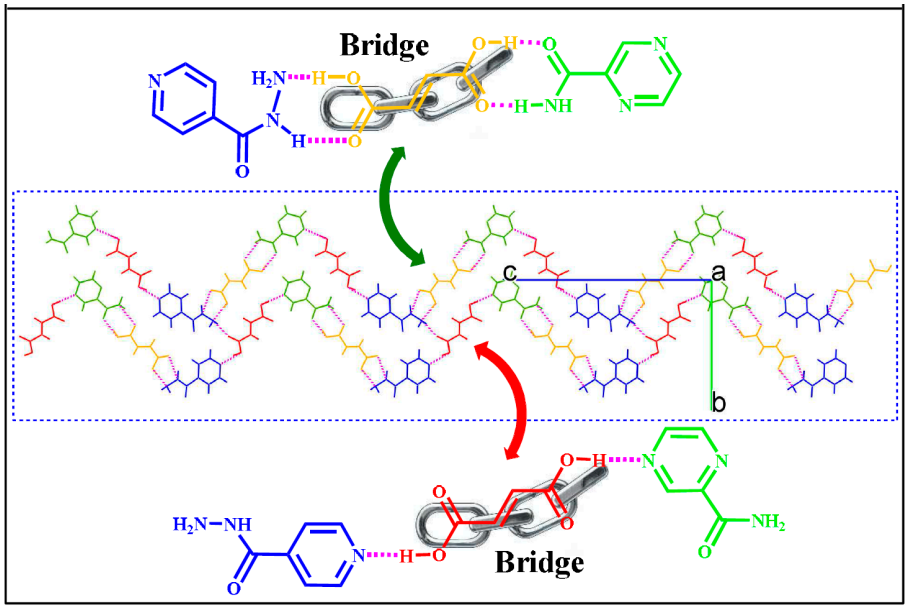


Figure 8. Molecular structures of INH, Pyz, and FA; crystal structure of INH-FA-Pyz ternary cocrystal. Adapted with permission from *Cryst. Growth Des.*, DOI: 10.1021/acs.cgd.7b01738. Copyright 2018, American Chemical Society.

2.1.3. Bicalutamide Cocrystal

Surov and coworker [77] prepared a 1:1 cocrystal of an antiandrogenic drug, bicalutamide (Bic), with salicylamide (2OHBZA) using liquid assisted grinding, slurry sonication as well as solution crystallization. Structural analysis showed that two units of each bicalutamide and salicylamide together form two ring synthon motifs with graph set notation—$R_4^4(12)$ and $R_2^2(10)$—as shown in Figure 9. From the dissolution profile (Figure 10), it was observed that cocrystal Bic with benzamide (BZA) and salicylamide have higher dissolution demonstrating a 'spring and parachute' behavior compared to the pure drug bicalutamide.

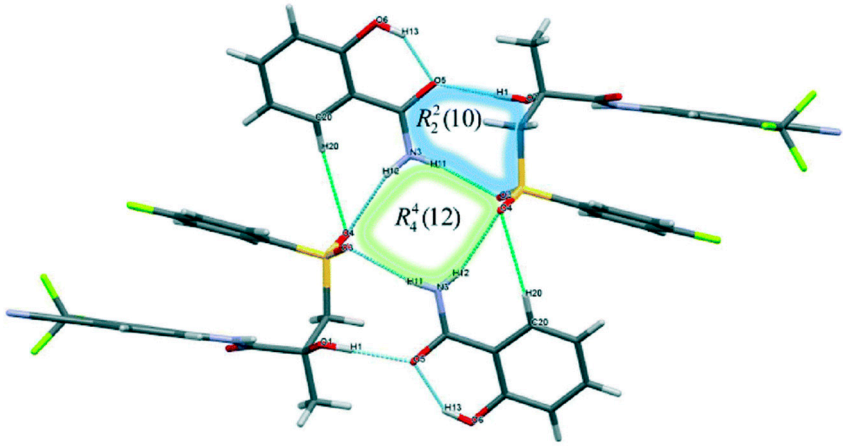


Figure 9. Two ring synthon motifs with graph set notation $R_4^4(12)$ and R_2^2 (10) between the tetrameric unit of a bicalutamide–salicylamide cocrystal. Adapted with permission from *CrystEngComm*, 2016, **18**, 4818–4829. Copyright 2016, The Royal Society of Chemistry.

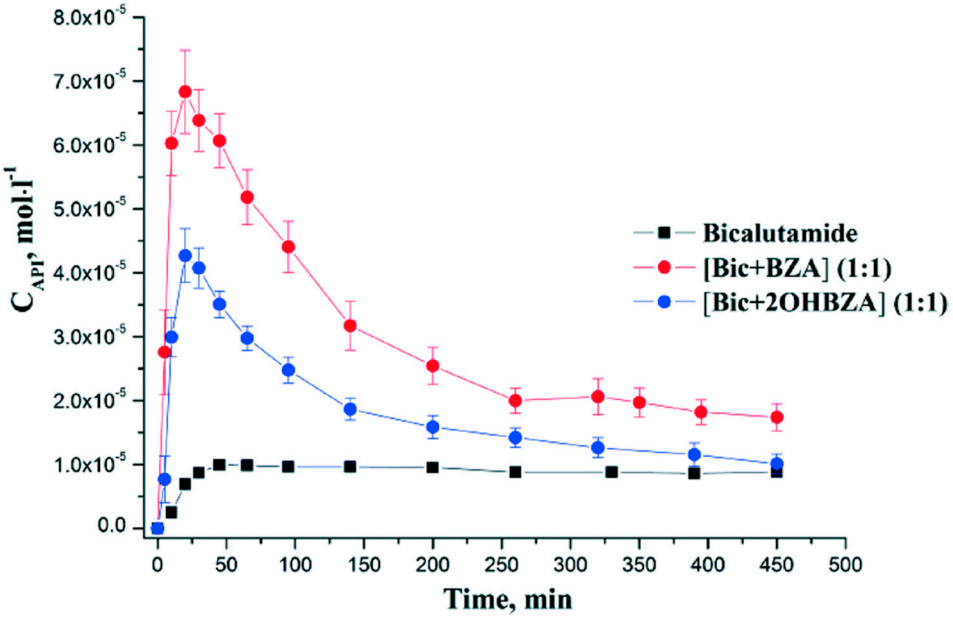


Figure 10. Dissolution profiles for the cocrystals (Bic + BZA and Bic + 2OHBZA) and pure bicalutamide in the pH 7.4 phosphate buffer at 25 °C. Adapted with permission from *CrystEngComm*, 2016, **18**, 4818–4829. Copyright 2016, The Royal Society of Chemistry.

2.1.4. Caffeine Cocrystal System

Caffeine is one of the most widely used psychoactive drug and central nervous system stimulant used as a model compound to prepare various cocrystals using GRAS coformers as well as APIs. Bucar et al. [78] prepared cocrystals of caffeine with various substituted hydroxybenzoic acid derivatives and studied their synthon preference. Among them, salicylic (2HBA) and gentisic acid (25DHBA) are two coformers of pharmaceutical importance. Cocrystals were discovered using solution mediated phase transformation and showed three different caffine-carboxylic acid heterosynthons (Figures 11 and 12).

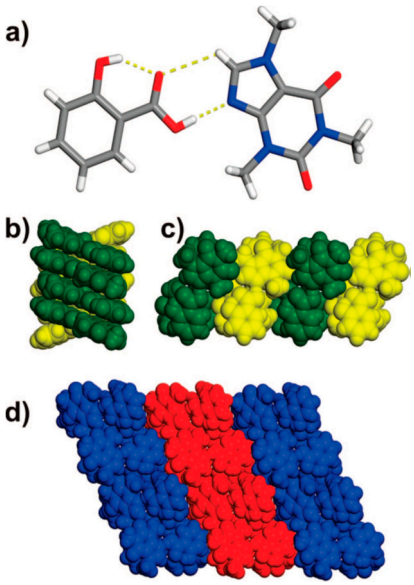


Figure 11. (**a**) Acid-imidazole synthons between 2HBA and caffeine, respectively. (**b**–**d**) Crystal packing of the resultant 1:1 cocrystal. Adapted with permission from *Cryst. Growth Des.*, 2009, 9 (4), 1932–1943. Copyright 2009, American Chemical Society.

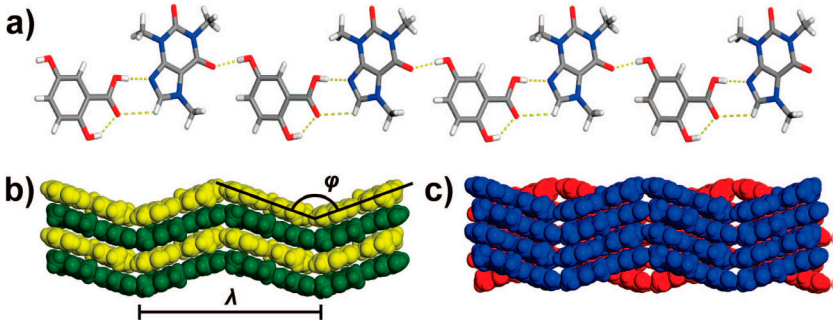


Figure 12. (**a**) Acid-imidazole dimer and hydroxyl–amide dimer between 25DHBA and caffeine resulting a 1D polymeric chain. (**b**,**c**) Stacked packing of the 1D polymer sustained by weak C–H···O hydrogen bond. Adapted with permission from *Cryst. Growth Des.*, 2009, 9 (4), 1932–1943. Copyright 2009, American Chemical Society.

Eddleston et al. reported two 1:1 polymorphic cocrystals of caffeine and theophylline in two separate reports [79,80]. The form II caffeine-theophylline cocrystal was prepared using freeze-drying. They proposed that formation of cocrystal proceed via an amorphous phase that is generated as solvent sublimes during the freeze-drying process. Also, they studied the relative stability of the two polymorphic forms and solid–solution phase obtained during freeze-drying and is in the order Form I > Form II > solid-solution, based on theoretical calculation and thermodynamic study. Local arrangement of hydrogen bonded dimers of caffeine and theophylline in the two polymorphic forms are shown in Figure 13.

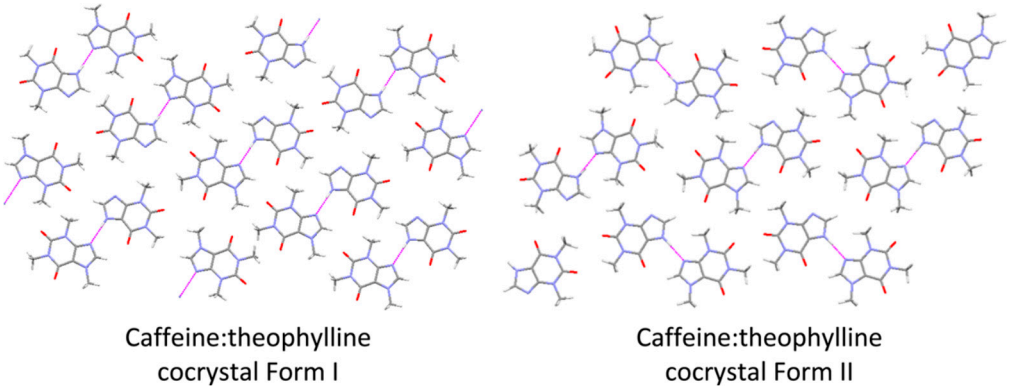


Figure 13. Hydrogen bonded dimer of caffeine and theophylline in two respective caffine-theophylline cocrystal polymorphs. Adapted with permission from *Cryst. Growth Des.*, 2013, **13** (10), 4599–4606. Copyright 2013, American Chemical Society.

Nangia et al. reported [81] two multidrug cocrystals of sulfacetamide with caffeine and theophylline along with a few other coformers. Both the cocrystals crystallized in 1:1 ratio having N–H···O and N–H···N synthon between sulfacetamide and coformer (caffeine and theophylline) molecule as shown in Figure 14. Solubility and intrinsic dissolution profile shows that the cocrystals have lower solubility as well as dissolution compared to the pure drug sulfacetamide (Figure 15).

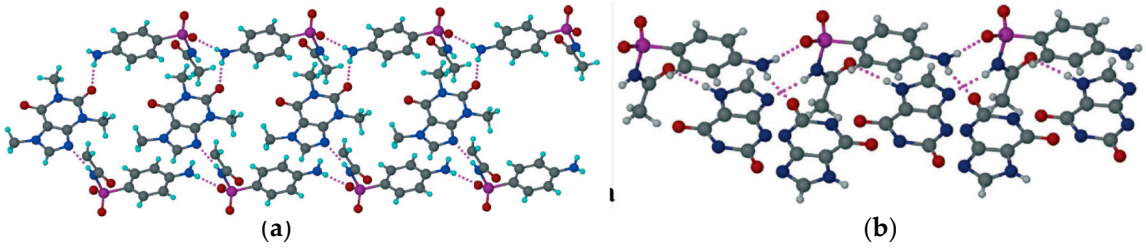


Figure 14. N–H···O and N–H···N hydrogen bond connecting sulfacetamide and coformer (**a**) caffeine and (**b**) theophylline in the respective cocrystals. Adapted with permission from *CrystEngComm*, 2014, *16*, 5859–5869. Copyright 2014, The Royal Society of Chemistry.

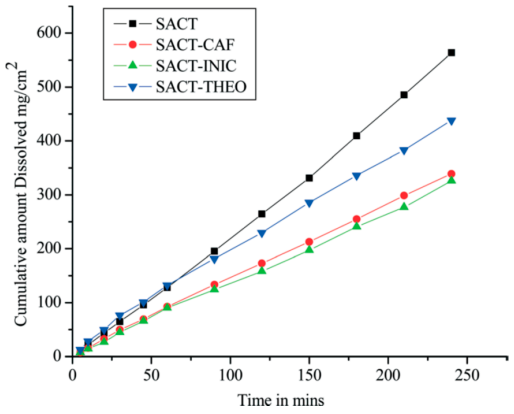
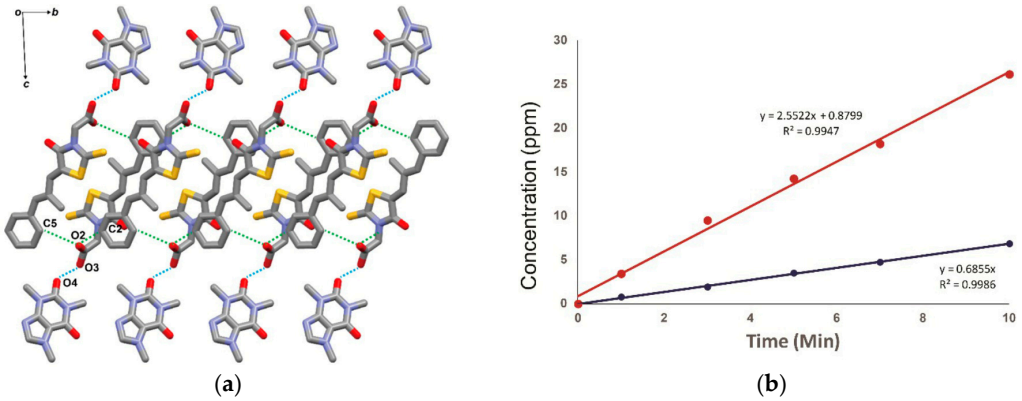


Figure 15. Intrinsic dissolution of sulfacetamide cocrystals in pH = 7 phosphate buffer. Adapted with permission from *CrystEngComm*, 2014, *16*, 5859–5869. Copyright 2014, The Royal Society of Chemistry.

In a very recent report Putra et al. reported [82] a cocrystal of caffeine with epalrestat which is known as an aldose reductase inhibitor for treatment in diabetic neuropathy. The cocrystal showed

layered structure that was predicted to be responsible for the higher solubility and dissolution rate of the resultant cocrystal (Figure 16).



(**a**) (**b**)

Figure 16. (**a**) Layered structure of 1:1 caffeine-epalrestat cocrystal connected through O–H···O hydrogen bond. Hydrogen atoms were removed for clarity. (**b**) Intrinsic dissolution rate of caffeine-epalrestat cocrystal (red) compared with pure epalrestat drug (blue). Adapted with permission from *CrystEngComm*, 2017, 19, 2614–2622. Copyright 2017, The Royal Society of Chemistry.

2.1.5. Carbamazepine Cocrystal System

Majumder et al. reported [83] a carbamazepine–indomethacin cocrystal using the powder X-ray diffraction (PXRD) structure solution. PXRD data shows a clear formation of cocrystal during ball mill grinding. Crystal structure analysis shows a heterodimer formation between the carboxylic acid group of indomethacin and amide group of carbamazepine molecule as shown in Figure 17.

In another report, Perlovich et al. [84] prepared a 1:1 cocrystal of carbamazepine (CBZ) and 4-aminosalicylic acid (PAS) along with two cocrystal solvates in 2:1:1 ratio of CBZ, PAS and solvent (water and methanol) respectively. From structural analysis it was observed that 1:1 cocrystal of CBZ and PAS contain acid–amide heterosynthon; whereas insertion of solvent molecule results trimeric and tetrameric synthon incorporating solvent molecules water and methanol respectively as shown in Figure 18. From dissolution study, it was observed that cocrystallization of CBZ with PAS decreased the rate of hydrate formation, resulting in a 1.5 times increase in solubility of CBZ.

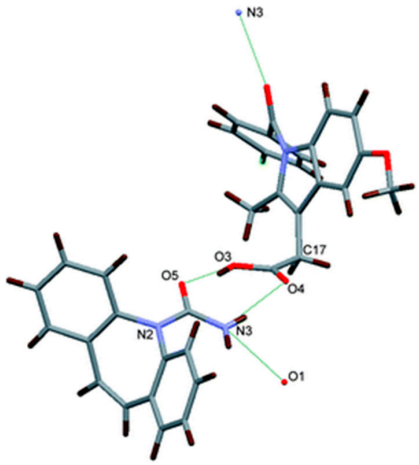


Figure 17. Acid-amide dimer synthon present in carbamazepine-indomethacin cocrystal obtained using PXRD structure solution. Adapted with permission from *CrystEngComm*, 2011, 13, 6327–6328. Copyright 2011, The Royal Society of Chemistry.

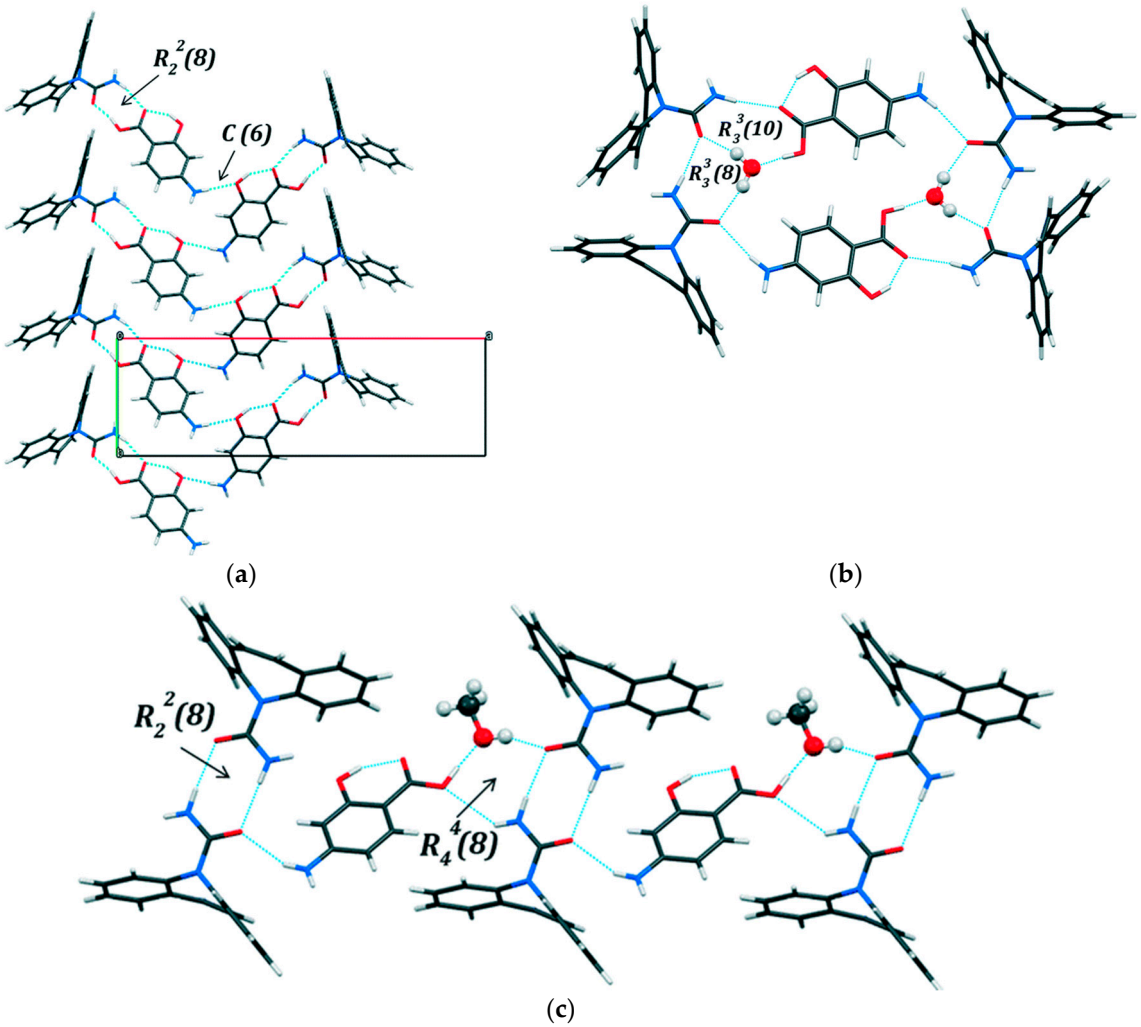
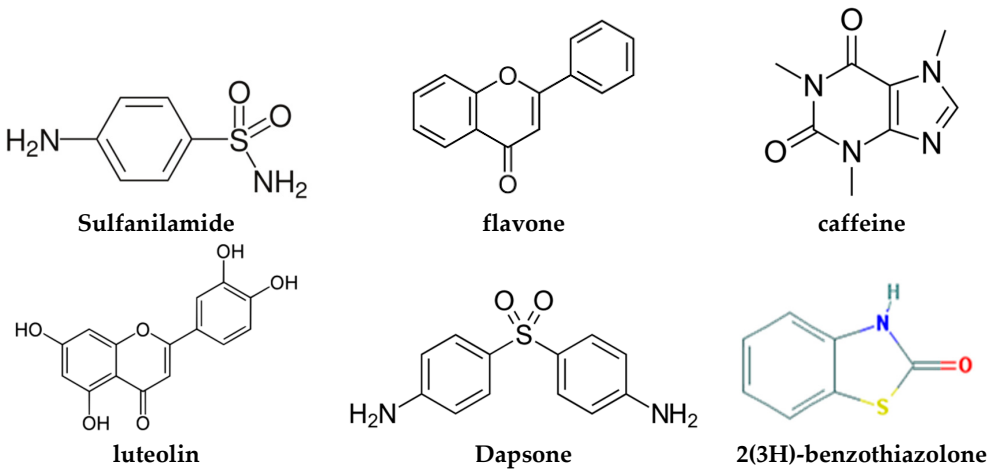


Figure 18. Hydrogen bond interaction present in (**a**) 1:1 CBZ-PAS cocrystal; (**b**) 2:1:1 CBZ-PAS-water and (**c**) 2:1:1 CBZ-PAS-methanol structure. Adapted with permission from *CrystEngComm*, 2017, 19, 4273–4286. Copyright 2017, The Royal Society of Chemistry.

2.1.6. Dapsone-Drug Cocrystals

Xuefeng Mei and coworker in another report [85], prepared a few drug-drug cocrystals of dapsone. Dapsone is a generic drug used for the treatment of tuberculosis, leprosy, malaria, Kaposi's sarcoma, dermatoses, and AIDS-related pneumonia. Due to the presence of $-NH_2$ and $-SO_2-$ groups, it can form intermolecular hydrogen bond with various coformers. They were able to prepare cocrystals with sulfanilamide, flavone, luteolin, caffeine and 2(3H)-benzothiazolone (Scheme 2). With caffeine, dapsone forms two stoichiometric cocrystals (1:1 and 1:2). Hydrogen bond interaction present in dapsone-caffeine 1:1 cocrystal is shown in Figure 19. Solubility and dissolution rate of cocrystals nicely correlate with coformer solubility order.



Scheme 2. Molecular structure of Dapsone and coformers studied.

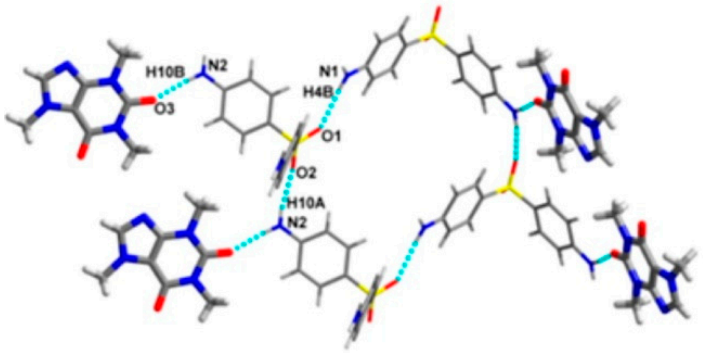


Figure 19. Hydrogen bond interaction present in dapsone-caffeine 1:1 cocrystal. Adapted with permission from *Crystal Growth & Design*, 2014, 14, 4562–4573. Copyright 2017, American Chemical Society.

2.1.7. Ethenzamide-Gentisic Acid Cocrystals

Aitipamula et al. reported [86] a trimorphic cocrystal of ethenzamide and gentisic acid. Ethanzamide (EA) and gentisic acid (GA) both are nonsteroidal anti-inflammatory drug (NSAID) used mainly in combination with other ingredients for the treatment of mild to moderate pain. During cocrystallization, they obtained three polymorphic forms listed in Table 1.

Table 1. Results of various solution crystallization experiments

Polymorph	Solvent of Crystallization
Form I	Acetonitrile
	Formic acid
	Toluene + ethylacetate
	2-Propanol
Form II	Toluene + acetonitrile
	Chloroform + ethylacetate
	Ethylacetate + n-hexane
	Ethylacetate + cyclohexane
Form III	Acetone
	Acetonitrile + acetone
	Methanol + chloroform
	Chloroform + acetonitrile
	Toluene + acetonitrile

Looking into the crystal structure, all the three polymorphic forms contain the most stable acid–amide heterosynthon. In the case of form I, the asymmetric unit contains two molecules of each EA and GA. Only one set of the EA and GA sustained by acid–amide heterosynthon (Figure 20). The second symmetry independent GA molecule connects using O–H···O hydrogen bond between COOH and 5-OH groups resulting a zipper-like structure.

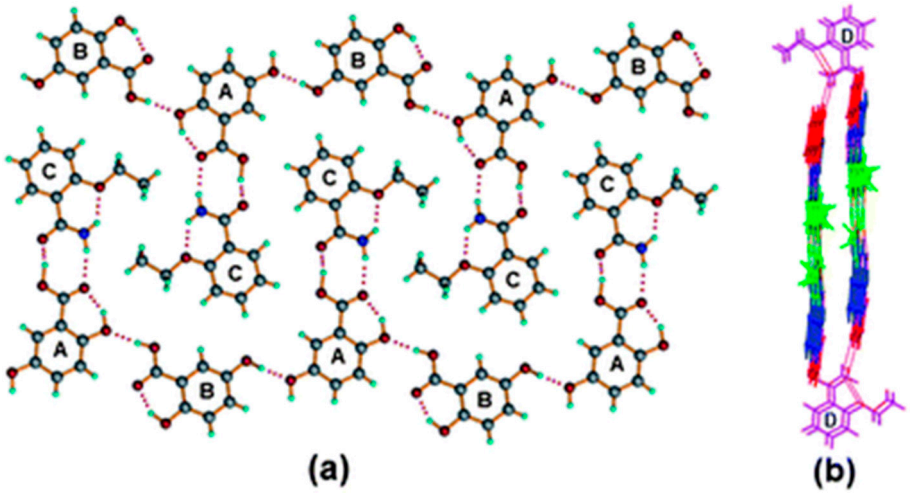


Figure 20. (**a**) A zipper like structure in EA:GA cocrystal Form I. (**b**) 3D crystal packing showing the EA molecule connecting the zipper-like network. Adapted with permission from *CrystEngComm*, 2009, 11, 1823–1827. Copyright 2009, The Royal Society of Chemistry.

Form II and form III structure contains one molecule of each EA and GA in asymmetric units. In form II, the acid–amide heterosynthon is further connected via O–H···O hydrogen bond of GA molecule resulting a linear tape along the crystallographic *b*-axis (Figure 21a). In form III, the acid-amide heterosynthon between the EA and GA molecules are further connected via O–H···O hydrogen bond forming a tetrameric motif as shown in Figure 21b. Dissolution study shows an enhancement in dissolution rate compared to pure drug EA (Figure 22). Among the three polymorphic forms, metastable polymorphs (form II and form III) have better dissolution compared to form I.

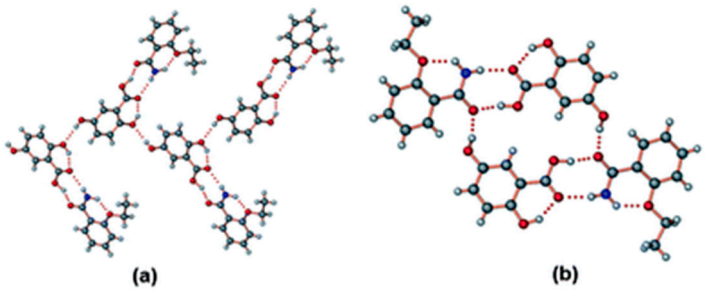


Figure 21. (**a**) A hydrogen bonded linear tape in form II crystal structure. (**b**) A hydrogen bonded tetrameric motif in EA-GA form III crystal structure. Adapted with permission from *CrystEngComm*, 2009, 11, 1823–1827. Copyright 2009, The Royal Society of Chemistry.

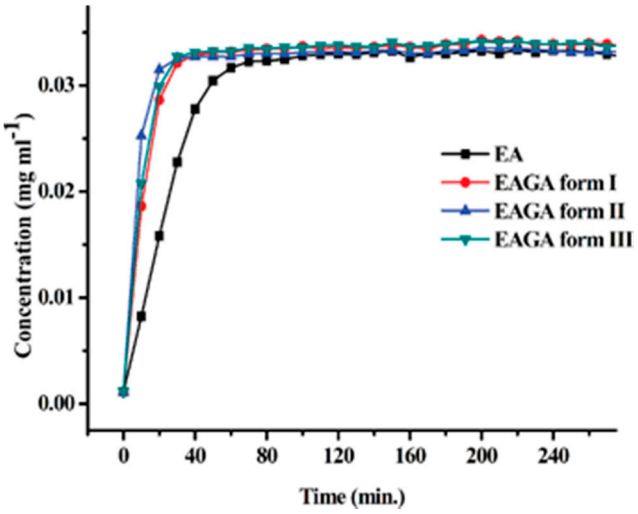


Figure 22. Dissolution profile of EA-GA cocrystal polymorphs I, II, and III compared to pure drug EA. Adapted with permission from *CrystEngComm*, 2009, 11, 1823–1827. Copyright 2009, The Royal Society of Chemistry.

2.1.8. Flufenamic Acid Cocrystals

Trivedi et al. reported [87] two drug-drug cocrystal of flufenamic acid (FFA) with 2-choloro-4-nitrobenzoic acid (CNB) and ethenzamide (EA). Flufenamic acid and EA are non-steroidal anti-inflammatory drugs, whereas CNB is used as a novel potential therapy for immunodeficiency deceases such as an anti-viral and anti-cancer agent. Structural analysis reveals that FFA form acid-acid homosynthon during cocrystallization with CNB, whereas acid-amide heterosynthon was observed in case of FFA–EA cocrystal as shown in Figure 23.

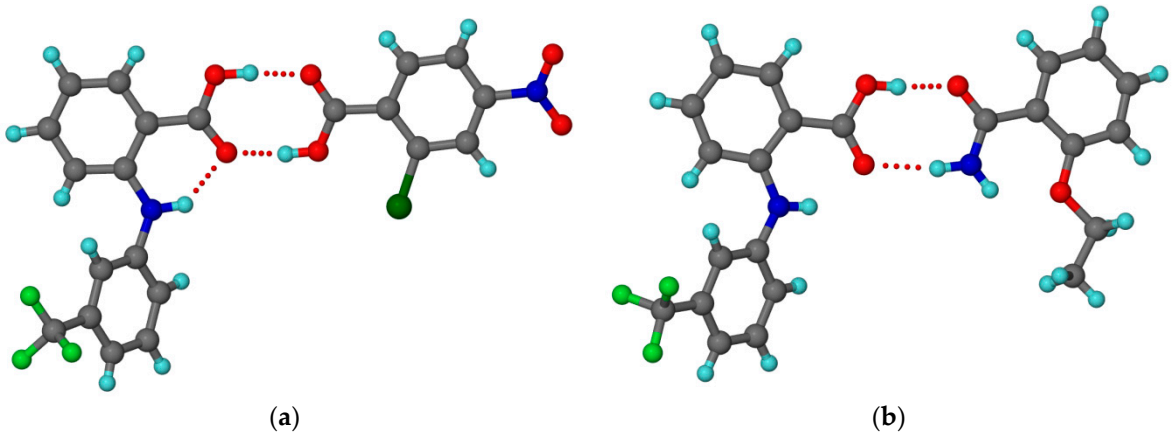
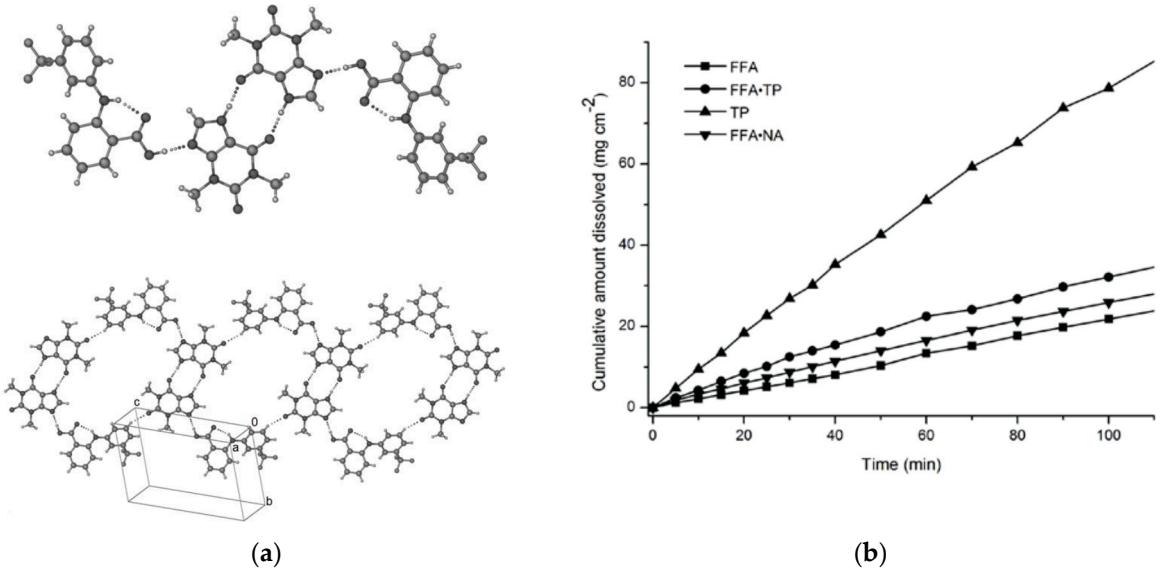


Figure 23. Acid-acid and acid-amide synthon observed in (**a**) FFA-CNB and (**b**) FFA-EA 1:1 cocrystals.

Solubility measurement in 0.1 N HCl (pH = 1) solution shows a five-fold increment in solubility of the cocrystals compared to pure FFA. Also, the synthesized cocrystals were observed to be non-hygroscopic in nature at 75% relative humidity over a period of six months at ambient temperature.

In a different study, Aitipamula and coworker reported [88] a multidrug cocrystal of FFA with theophylline along with two other coformers—namely, 2-pyridone and 4,4′-pyridine. The crystal structure contains theophylline dimer between the saturated N of the imidazole ring and one of the carbonyl group forming N–H···O hydrogen bond. Another O–H···N hydrogen bond involving the carboxylic acid group of FFA and unsaturated N of the imidazole group of theophylline resulting in a

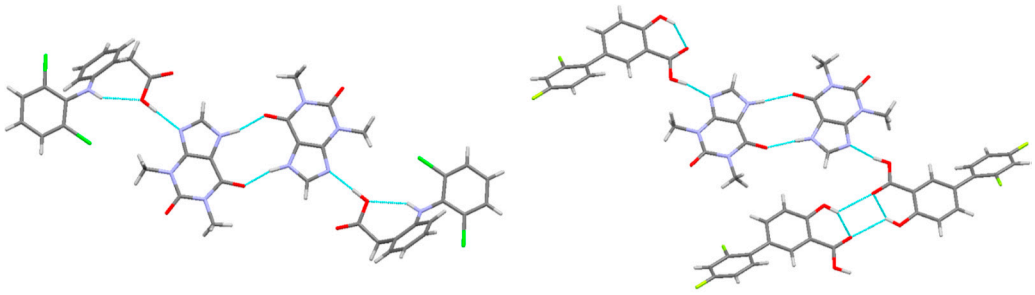
four component supramolecular unit as shown in Figure 24a. The resultant cocrystal shows a better solubility and dissolution rate compared to FFA (Figure 24b). The hygroscopic stability was also found to be improved during cocrystallization.



(**a**) (**b**)

Figure 24. (**a**) Hydrogen bond interaction present in the 1:1 FFA-theophylline cocrystal. (**b**) Intrinsic dissolution rate of FFA and theophylline cocrystals with theophylline and nicotinamide respectively. Adapted with permission from *CrystEngComm*, 2014, *16*, 5793–5801. Copyright 2014, The Royal Society of Chemistry.

Surov et al. [89] prepared two cocrystals of theophylline with halogen containing APIs named diflunisal and diclofenac having similar hydrogen bond synthon present in FFA-theophylline cocrystal (Figure 25).



a **b**

Figure 25. Hydrogen bond synthon present in (**a**) diclofenac–theophylline and (**b**) diflunisal-theophylline cocrystal. Adapted with permission from *Mol. Pharmaceutics*, 2014, *11* (10), 3707–3715. Copyright 2014, American Chemical Society.

The resultant cocrystals showed enhanced apparent solubility; however, intrinsic dissolution rates are comparable to that of the pure drugs.

2.1.9. Furosemide-Caffeine Cocrystals

Goud et al. reported [90] a drug-drug cocrystal of furosemide and caffeine along with few pharmaceutical cocrystals. Furosemide (Lasix) is a loop diuretic drug commonly used for the treatment of hypertension and edema. It is a BCS class IV drug with low solubility (6 mg/L in water) and

low permeability ($logP_{ow}$ 1.4); whereas caffeine is a central nervous system stimulant and one of the most widely consumed psychoactive drugs. On cocrystallizing furosemide-caffeine 1:1 mixture from a MeOH-MeCN solvent mixture resulted cocrystal of the same in 1:1 stoichiometry. The most acidic COOH group of furosemide forms an O–H···N hydrogen bond with imidazole N of caffeine (Figure 26a). The primary sulfonamide NH donor hydrogen bonds to different caffeine C=O acceptor groups (Figure 26b) and the secondary NH is bonded to one of the sulfonyl O acceptors (Figure 26c).

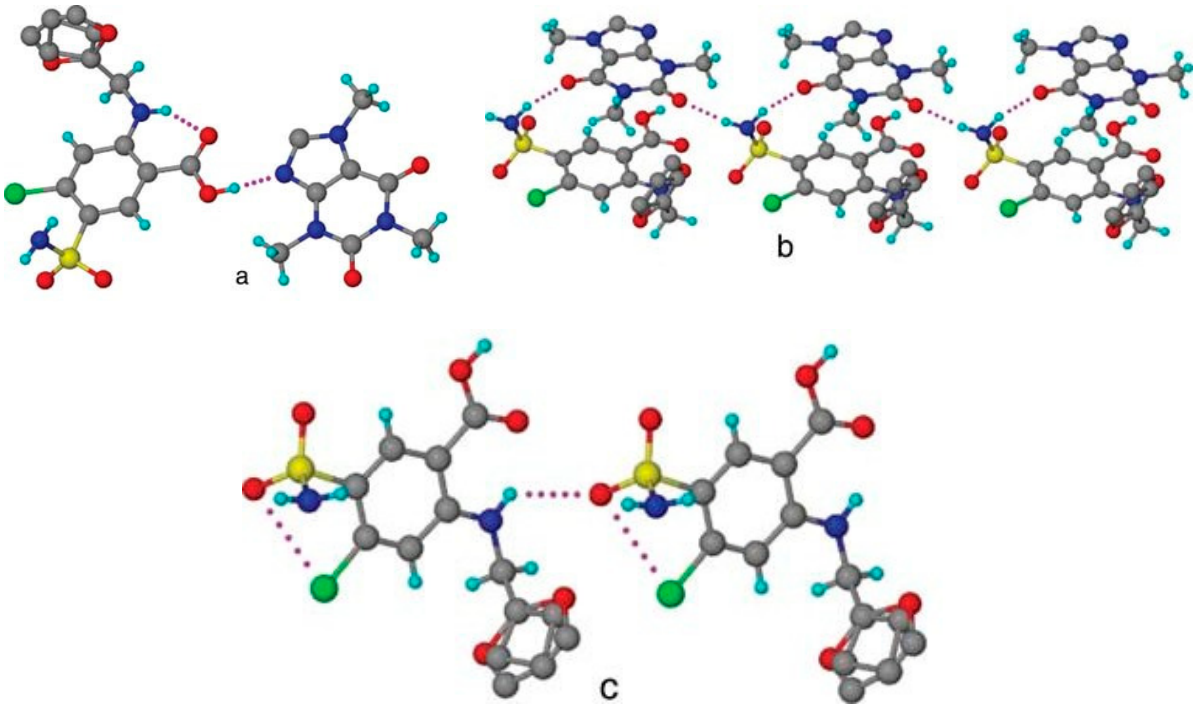


Figure 26. (**a**) O–H···N hydrogen bond between COOH group of furosemide and imidazole N of caffeine. (**b**) Infinite chain of N–H···O hydrogen bond connecting C=O group of caffeine and primary sulfonamide NH. (**c**) Secondary NH bonded to sulfonyl O of another furosemide molecule. Adapted with permission from *Journal of Pharmaceutical Sciences*, 2012, 101, 664–680. Copyright 2012, John Wiley & Sons.

Solubility analysis showed that furosemide-caffeine cocrystal solubility is six times more compared to pure furosemide. Thus, cocrystals could offer a superior strategy to improve the solubility of BCS class IV drug compared to metastable polymorphs and amorphous dispersions of furosemide.

2.1.10. Gefitinib-Furosemide Salt Hydrate

Thorat et al. reported [91] a salt hydrate of an anticancer drug gefitinib with a loop diuretic drug furosemide. Cocrystallizing stoichiometric amount of gefitinib and furosemide from a 1:1 ethanol-water mixture resulted in gefitinib–furosemide salt hydrate. Carboxylic acid proton of furosemide is transferred to the morpholine ring N of gefitinib molecule. Both APIs interact with each other through strong N–H···O hydrogen bond engaging the morpholine group of gefitinib and carboxyl group of furosemide to form API–API dimer (Figure 27). The solubility and dissolution profile shows a solubility order of gefitinib > gefitinib-furosemide salt hydrate > furosemide. Intermediate solubility of molecular salt is due to a stronger hydrogen-bonding synthon, better crystal density, compact crystal packing, and a stable crystal lattice.

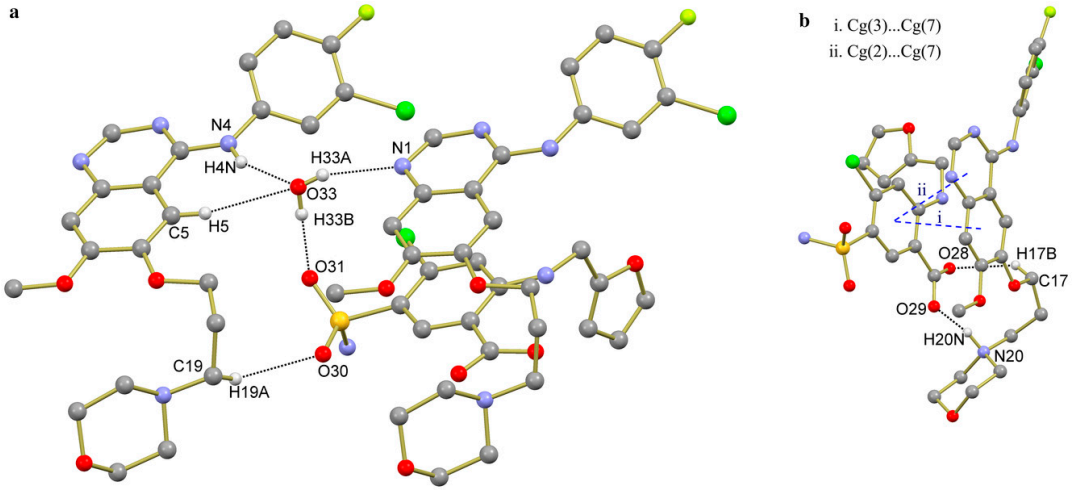


Figure 27. (**a**) Association of water molecule with two molecules of gefitinib through N–H···O, O–H···N and C–H···O interactions and a molecule of furosemide via O–H···O interaction. (**b**) API-API dimer between gefitinib and furosemide connecting carboxylic acid and morpholine group. Adapted with permission from *Journal of Pharmaceutical Sciences*, 2015, 104, 4207–4216. Copyright 2015, John Wiley & Sons.

2.1.11. Gliclazide-Metformin Salt

Putra et al. reported [92] a multidrug crystal of antidiabetic drug gliclazide (GLI) and metformin (MET). Combining these two non-insulin-dependent diabetes mellitus (NIDDM) drug, they have prepared a salt that is more soluble and have higher dissolution rate compared to GLI; and less hygroscopic compared to MET. The crystal structure contains one molecule of each GLI and MET in the asymmetric unit (Figure 28). A proton from the amide group adjacent to sulfur atom of GLI is transfer to the MET resulting a salt structure. The MET molecules formed a centrosymmetric dimer structure through two N−H···N hydrogen bonds. MET also interacted with three molecules of GLI via relatively strong hydrogen bonds, forming a 1D chain along the *a*-axis (Figure 29). The hydrophilic MET molecules are sandwiched by hydrophobic GLI molecules, making the salt structure more stable towards hydration.

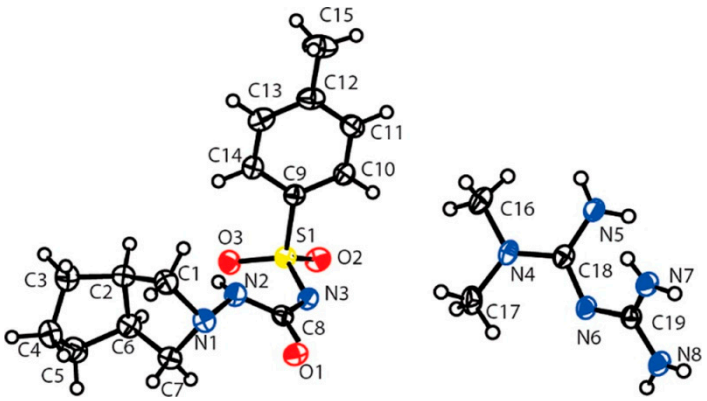


Figure 28. Asymmetric unit containing MET (**right**) and GLI (**left**) molecules drawn at 50% probability level. Adapted with permission from *Crystal Growth & Design*, 2016, **16**, 3577–3581. Copyright 2016, American Chemical Society.

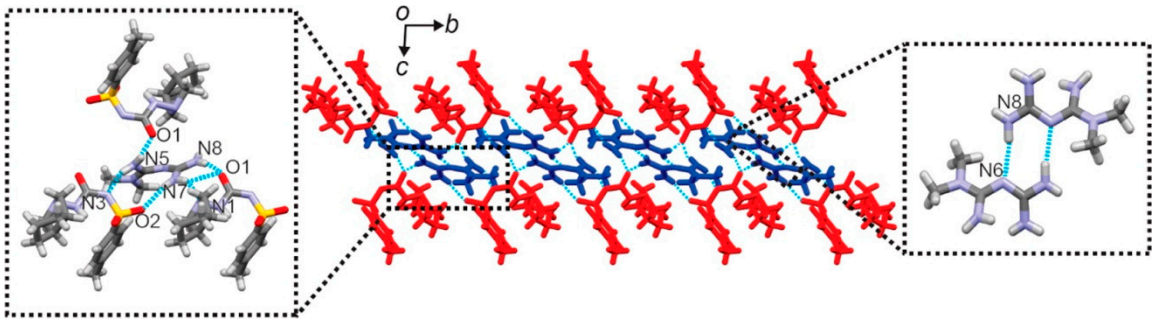


Figure 29. Infinite 1D hydrogen bond chain of MET-GLI crystal along the *a*-axis (blue for MET and red for GLI). Detailed interaction between MET-MET (**right**) and MET-GLI (**left**) presented in default color according to the different elements. Blue-dashed lines indicate hydrogen bonds. Adapted with permission from *Crystal Growth & Design*, 2016, 16, 3577–3581. Copyright 2016, American Chemical Society.

Dynamic vapor sorption (DVS), solubility, and dissolution rate measurement showed (Figure 30) enhanced physicochemical property of the drug-drug salt compared to the pure components GLI and MET.

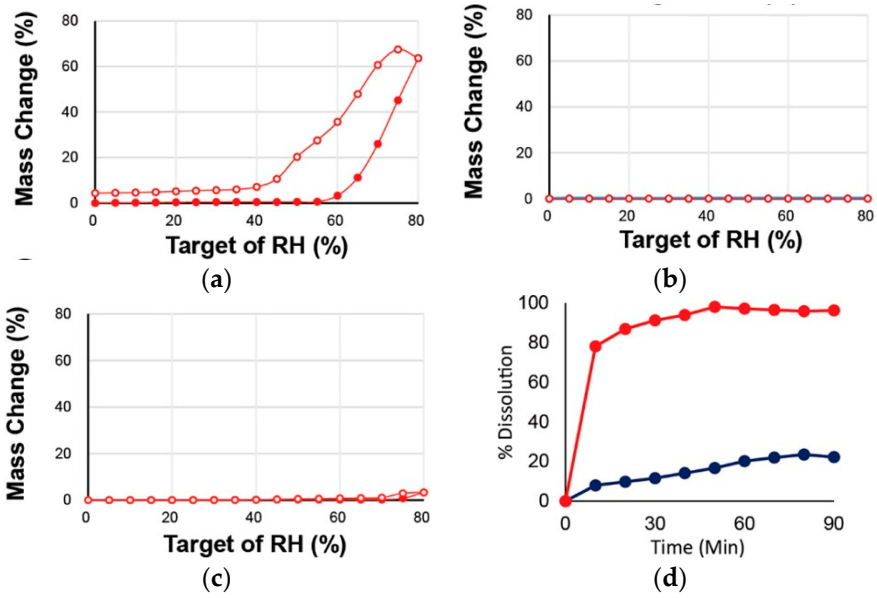
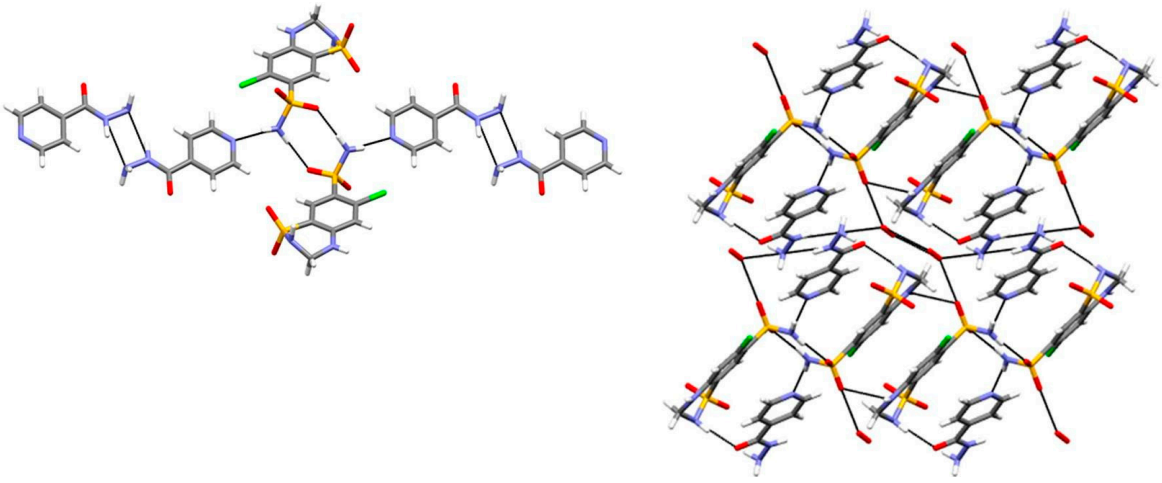


Figure 30. DVS of (**a**) MET, (**b**) GLI, and (**c**) GLI-MET salt showing hydration stability (**left**) and (**d**) higher dissolution rate of GLI-MET salt compared to pure drug GLI (**right**). Adapted with permission from *Crystal Growth & Design*, 2016, 16, 3577–3581. Copyright 2016, American Chemical Society.

2.1.12. Hydrochlorothiazide Cocrystal

Desiraju and coworker reported [93] a few cocrystals of hydrochlorothiazide (HCT) and studied their solubility and membrane diffusivity. During their study, isoniazid an anti-tuberculosis drug was used as a coformer with diuretic drug HCT resulting a cocrystal hydrate in the ratio 1:1:1. Crystal structure contains both sulfonamide dimer as well as amide dimer synthon as shown in Figure 31. In addition the cocrystal structure is stabilized by water with N–H···O and O–H···O hydrogen bond.



(**a**) (**b**)

Figure 31. (**a**) Homodimer synthons of HCT and INZ. (**b**) 3D supramolecular structure of HCT-INZ-H_2O. Adapted with permission from *Crystal Growth & Design*, 2017, 17, 308–316. Copyright 2017, American Chemical Society.

2.1.13. Lamivudine-Zidovudine Cocrystal

Desiraju and coworkers reported [94] a drug-drug cocrystal between two anti-HIV drugs, lamivudine and zidovudine. A combination of these two drugs is marketed as a physical mixture with trade name Combivir. On crystallizing the two drug in 1:1 stoichiometry from ethanol resulted a hydrated cocrystal in space group $P2_1$ containing a trimeric synthon. The crystal structure contains N–H···O and O–H···O hydrogen between lamivudine and zidovudine molecule along with a water of crystallization resulting a 1D chain motif as shown in Figure 32. According to their claim, this cocrystal can be a better drug formulation compared to the exiting physical mixture Combivir.

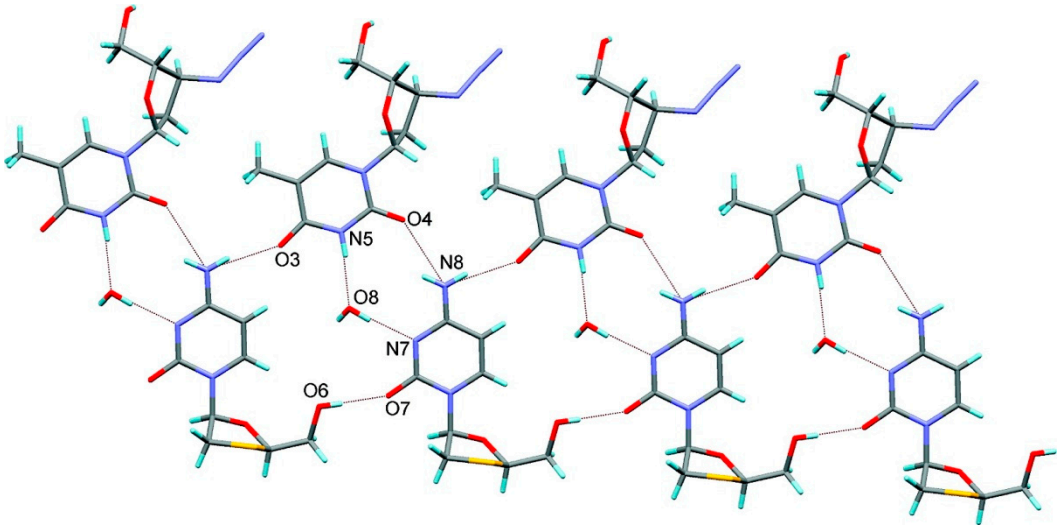


Figure 32. 1D ribbon-type arrangement in lamivudine–zidovudine hydrate cocrystal. Adapted with permission from *Crystal Growth & Design*, 2009, 9, 951–957. Copyright 2009, American Chemical Society.

2.1.14. Myricetin–Piracetam Cocrystal

In a recent report by Sowa et. al. [95] prepared a drug–drug cocrystal between myricetin and piracetam using both solvent drop grinding as well as solution crystallization. They found that the

piracetam adopt an uncommon conformation not obtained earlier in any of the reported cocrystals. The crystal structure contains N–H···O and O–H···O hydrogen bond between the amide group of piracetam and hydroxyl group of myricetin, resulting in an infinite chain as shown in Figure 33. The resulting cocrystal is stable up to 200 °C.

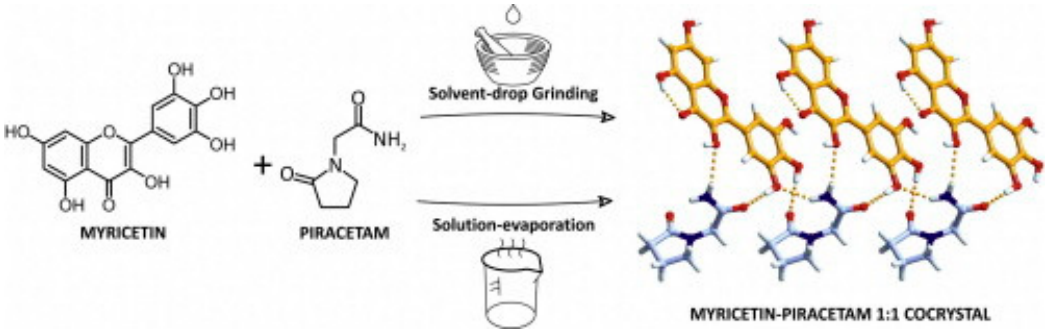
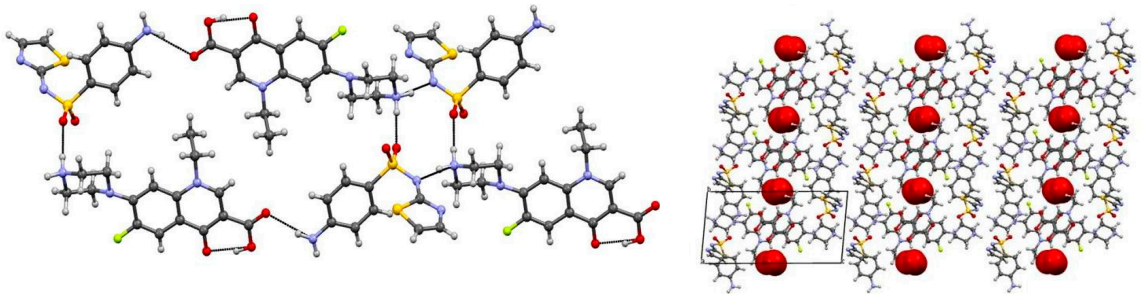


Figure 33. Schematic diagram showing the two drug molecules myricetin and piracetam, resulting in a 1:1 cocrystal structure using both liquid assisted grinding and solution crystallization. Adapted with permission from *Journal of Molecular Structure*, 2014, 1058, 114–121. Copyright 2014, Elsevier.

2.1.15. Norfloxacin–Sulfathiazole Salt Hydrate

In a recent report Desiraju and coworker [96] prepared a new multicomponent solid consisting of antibacterial norfloxacin (NF) and an antimicrobial sulfathiazole (ST) using mechanical grinding. Based on the position of acidic proton of ST the resultant multicomponent solid was confirmed to be a salt hydrate containing a disordered water molecule. From the crystal structure, it was observed that a heterodimer is formed between NF and ST through a proton transfer from the N–H group of ST to the piperazine group of NF. This dimer is further connected via N–H···O hydrogen bond between amino group of ST and carboxyl group of NF resulting a sheet-like structure. Successive sheets make channels occupied by disordered water molecules (sustained by O−H···O and C−H···O interactions) along the *b*-axis (Figure 34). The resultant drug–drug salt hydrate of NF-ST showed enhanced solubility in different pH buffer and improved diffusion rate (Figure 35).



(**a**) (**b**)

Figure 34. (**a**) Hydrogen bond interaction present in NF-ST salt hydrate; (**b**) packing diagram showing water channel present in the salt hydrate. Adapted with permission from *Molecular Pharmaceutics*, 2016, **13**, 3590–3594. Copyright 2016, American Chemical Society.

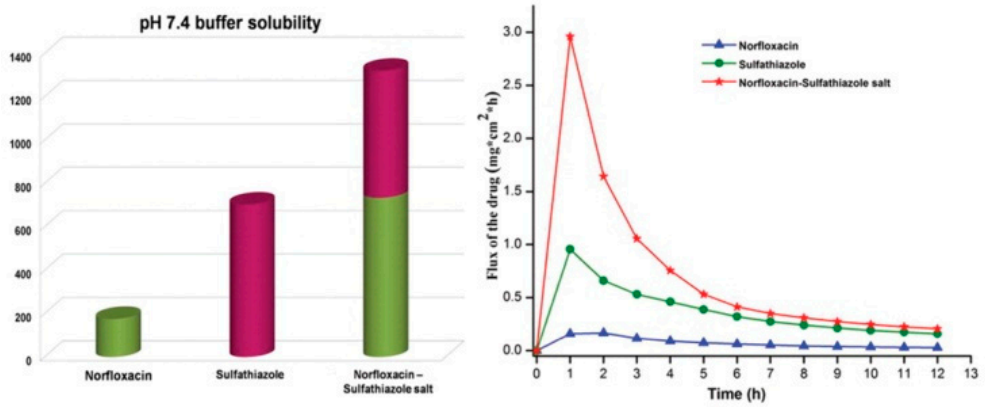


Figure 35. Enhanced solubility and dissolution rate of NF-ST salt hydrate compared to individual drug molecules. Adapted with permission from *Molecular Pharmaceutics*, 2016, 13, 3590–3594. Copyright 2016, American Chemical Society.

Yeh and Lee in a very recent report [97] prepared two drug-drug cocrystals of ST with theophylline and sulfanilamide using non-conventional method described as intensified crystallization process (Figure 36). The cocrystal ST-sulfanilamide has higher solubility, whereas ST-theophylline has comparable solubility with that of ST crystals.

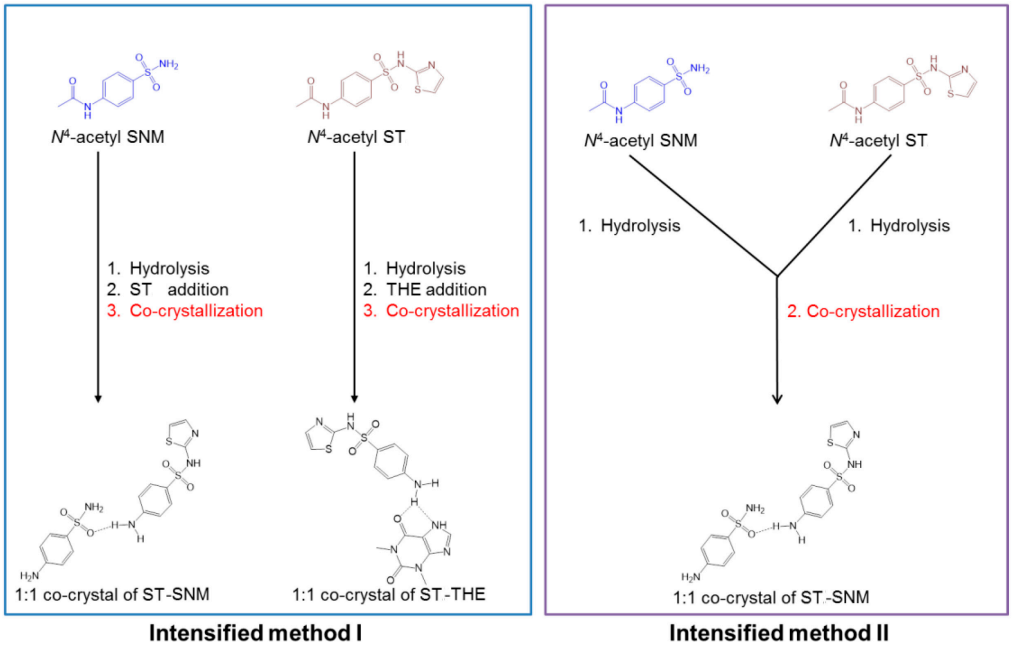


Figure 36. Intensified method for cocrystal preparation. Adapted with permission from *Cryst. Growth Des.*, DOI: 10.1021/acs.cgd.7b01197. Copyright 2018, American Chemical Society.

2.1.16. Oxaprozin-Salbutamol Salt

Aitipamula and coworkers [98] prepared a few multicomponent salts/cocrystals of oxaprozin (OXP) with heteroaromatic compounds—namely piperazine, 4,4′-bipyridine, 1,2-bis(4-pyridyl) ethane along with a drug–drug salt with salbutamol. Oxaprozin (4,5-diphenyl-2-2 oxazole propionic acid) is one of the widely used non-steroidal anti-inflammatory drugs (NSAIDs). OXP has been therapeutically used in inflammatory and painful diseases of rheumatic and nonrheumatic origin, whereas salbutamol (SAL) is an antiasthmatic drug used in the treatment of respiratory disease. In the crystal structure,

carboxylic acid proton of OXP is transferred to the secondary amine group of SAL. A four-component supramolecular unit containing a tetrameric synthon of O–H···O^- and N^+–H···O^- hydrogen bond results a ladder along *b*-axis (Figure 37). These ladders are interconnected to each other via C–H···O and π···π interaction. Surprisingly, this particular salt has a lower solubility and dissolution rate compared to pure SAL and can be a potential formulation for sustained release alternative of pure SAL.

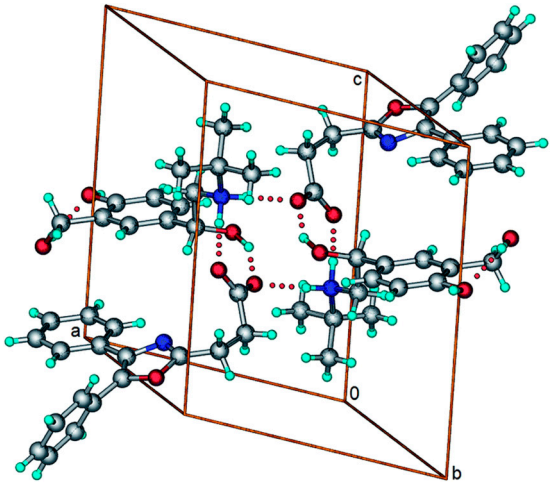


Figure 37. A four-component supramolecular unit in the crystal structure of OXP^--SAL^+-H salt. Adapted with permission from *RSC Advances*, 2016, 6, 34110–34119. Copyright 2016, The Royal Society of Chemistry.

2.1.17. Paracetamol Cocrystal System

Karki et al. [22] carried out mechanical property study of a few cocrystals of acetaminophen—more commonly known as paracetamol (pca)—with various coformers including a few drug molecules namely caffeine, theophylline, theobromine, etc. Cocrystals having layered structures such as paracetamol-theophylline (pca)•(thp) showed better tabletability compared to the existing paracetamol polymorphs (form I and II) (Figure 38). In another report, Lin Lee and Tu Lee [99] prepared caffeine-paracetamol cocrystal by taking p-aminophenol, acetic anhydride, and caffeine on the basis of three component one-pot chemical reaction.

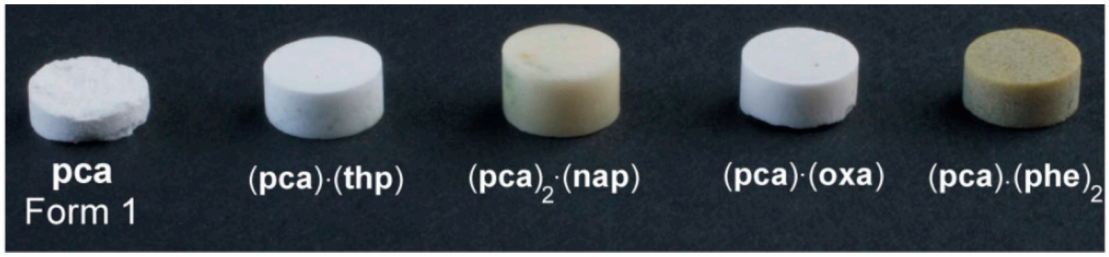


Figure 38. Tablet resulting from compression experiments involving paracetamol (pca form I) and cocrystals with theophylline (thp), naphthalene (nap), oxalic acid (oxa), and phenazine (phe) respectively. Adapted with permission from *Adv. Mater*. 2009, 21, 3905–3909. Copyright 2009, John Wiley & Sons.

2.1.18. Pyrazinamide-Diflunisal Cocrystal

Eusébio et al. [100] prepared a 1:1 cocrystal of pyrazinamide and diflunisal using neat, liquid-assisted grinding and annealing at 80 °C. Although they were unsuccessful to prepare single crystal, however

using spectroscopic and theoretical calculation established the formation of acid-pyridine synthon between diflunisal and pyrazinamide molecule (Figure 39). This particular cocrystal can be used as a combination drug, as pure pyrazinamide has side effects. Moreover, it improves aqueous solubility of diflunisal.

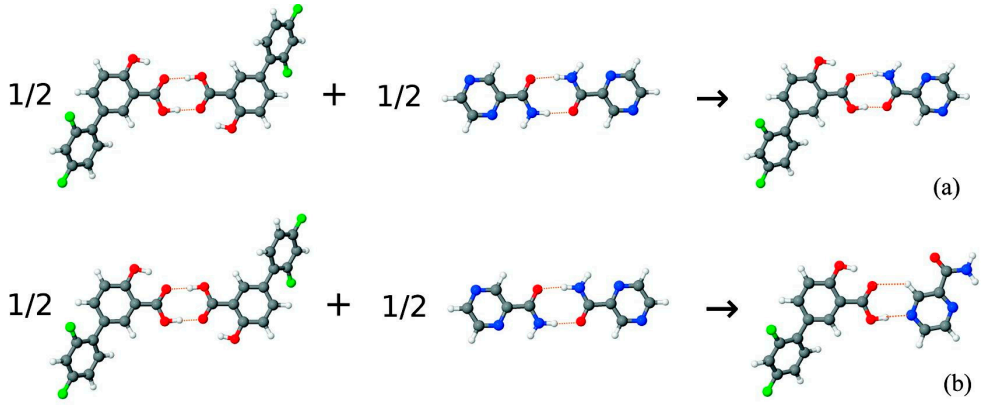
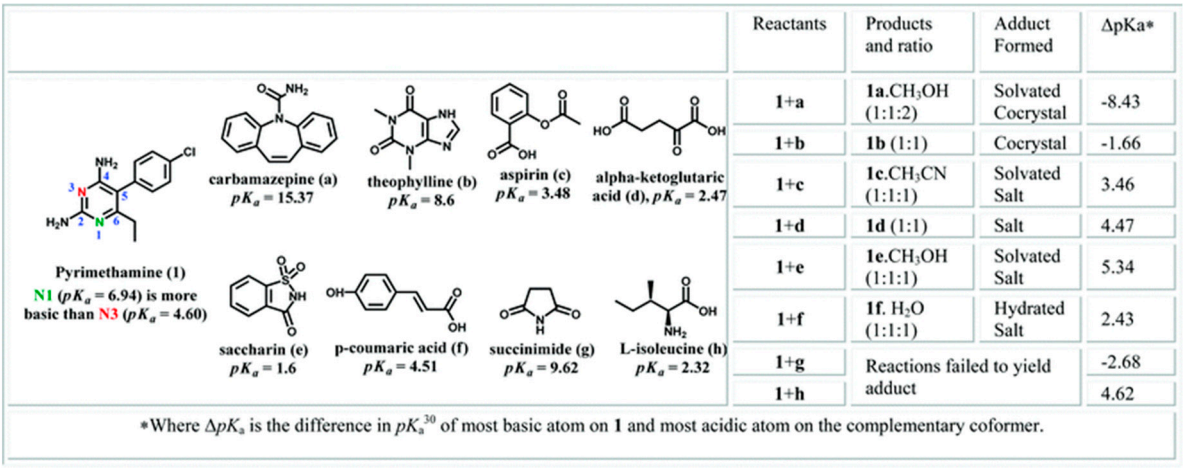


Figure 39. Probable hydrogen bond synthon (**a**) acid-amide and (**b**) acid-pyridine possible between the two drug molecules in 1:1 cocrystal. Adapted with permission from *Crystal Growth & Design*, 2011, 11, 4780–4788. Copyright 2011, American Chemical Society.

2.1.19. Pyrimethamine-Drug Cocrystals

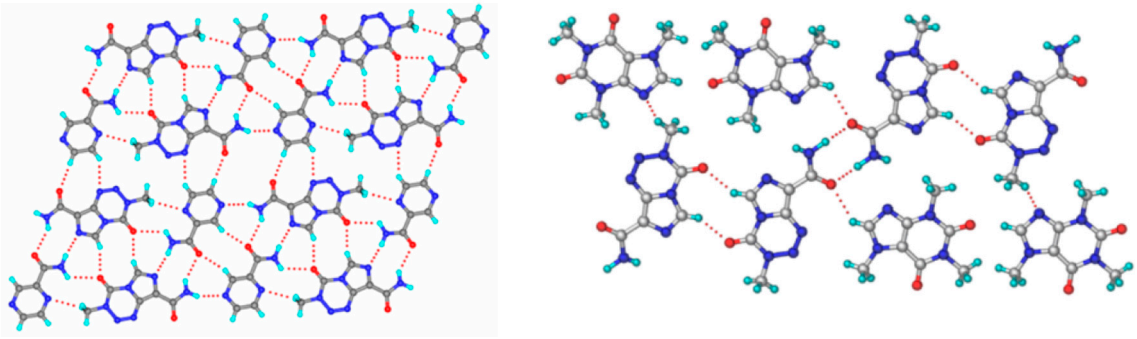
Jones et al. [101] carried out hydrogen bond propensity calculation (HBPC) in order to predict cocrystal/ salt formation considering pyrimethamine as a model compound. They used various drug and GRAS compounds—namely carbamazepine, theophylline, aspirin, α-keotglutaric acid, saccharin, p-coumaric acid, succinimide, and L-isoleucine. HBPC is useful tool which perform a statistical analysis of the occurrence of hydrogen bonds of the relevant structures present in CSD in order to predict cocrystal/ salt formation. The outcome of their analysis can be summarized in Scheme 3 given below.



Scheme 3. Molecular structure of pyrimethamine and coformers used in the study with outcome of cocrystallization studies. Adapted with permission from *CrystEngComm*, 2013, 15, 2916–2928. Copyright 2013, The Royal Society of Chemistry.

2.1.20. Temozolomide Cocrystal System

Nangia et al. reported [102] a few cocrystals of temozolomide, an antitumor prodrug with amide coformers including two pharmaceutically active compounds namely pyrazinamide and caffeine. Hydrogen bond interactions present in the two cocrystal structures are shown in Figure 40.

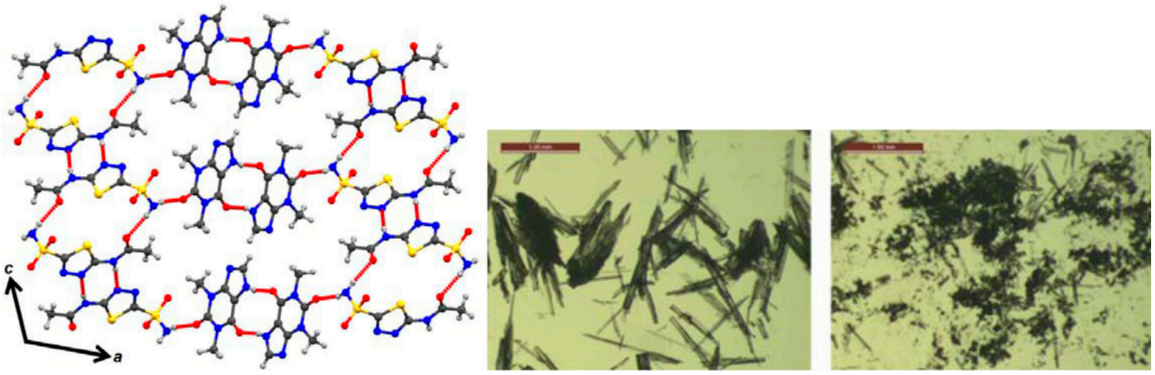


(**a**) (**b**)

Figure 40. Hydrogen bond interaction present in 1:1 temozolomide cocrystal of (**a**) pyrazinamide and (**b**) caffeine. Adapted with permission from *Crystal Growth & Design*, 2013, 13 (5), 2208–2219. Copyright 2013, American Chemical Society.

2.1.21. Theophylline-Acetazolomide Cocrystal

In a very recent report, Kakkar et al. [103] prepared six cocrystal of theophylline and studied their mechanical properties. Among them theophylline-acetazolamide is a drug-drug cocrystal. In the crystal structure, two molecules of each acetazolamide and theophylline form dimers via respective homosynthons. The acetazolamide dimers are further linked with theophylline dimers via N–H···O hydrogen bond forming a tape. They are further connected by N–H···O and C–H···N interactions resulting interlocked 3D network structure (Figure 41a). Due to 3D interlocked structure, theophylline–acetazolamide cocrystal is brittle in nature under mechanical stress (Figure 41b).



(**a**) (**b**)

Figure 41. (**a**) Hydrogen bond interaction present in theophylline–acetazolamide cocrystal structure. (**b**) Plastic deformation in theophylline-acetazolamide cocrystal before (**left**) and after (**right**) application of mechanical stress. Adapted with permission from *CrystEngComm*, DOI: 10.1039/C7CE01915G. Copyright 2018, The Royal Society of Chemistry.

2.1.22. Vitamin D2-Vitamin D3 Cocrystal

Xuefeng Mei and coworker reported [104] two cocrystal polymorphs of vitamin D_2 (VD_2) and D_3 (VD_3) to improve chemical instability using crystal engineering approach. The two polymorphs, form A (column shaped) and B (plate shaped), were obtained from evaporative crystallization using acetonitrile as solvent. Cocrystal was designed based on hydrogen bond donor–acceptor similarity and to accommodate structural complementarities, selecting α-VD_2 and β-VD_3 form as starting materials (Figure 42). From structural analysis, it was observed that both the two polymorphs (A and B) have similar hydrogen bond chain structure connecting VD2 and VD3 alternatively in a head-to-head fashion. The only difference between the two structure is overall 3D crystal packing; in form A adjacent

polymeric chains are slipped parallel to each other, whereas in form B they are columnar in nature (Figure 43). They have further studied the chemical stability of the two polymorphic cocrystals of VD_2 and VD_3 stored at 23 °C with an illuminance of 5000 lx and 40 °C/75% RH, and found that form A shows better stability compared to form B and individual compounds (Figure 44).

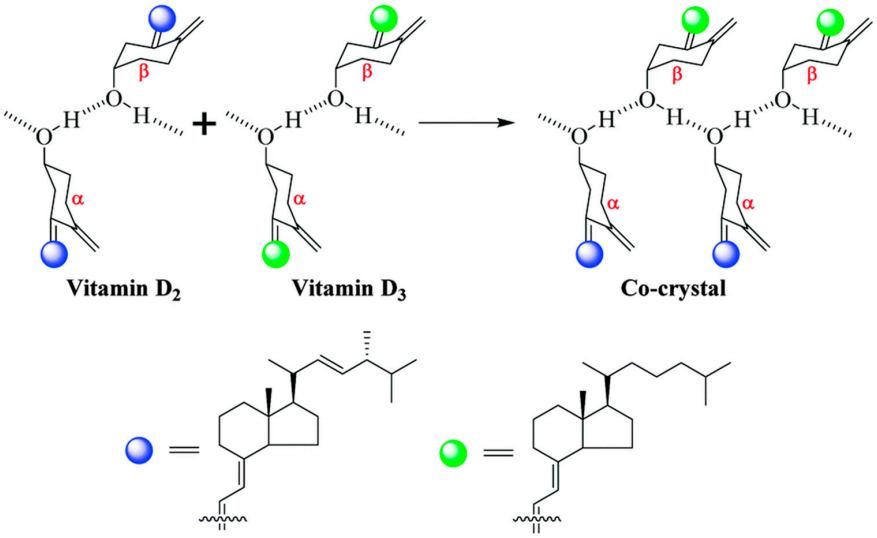


Figure 42. Design and synthesis of VD_2-VD_3 cocrystal. Blue and green ball represent the substituent groups present in VD_2 and VD_3. Adapted with permission from *Chemical Communications*, 2016, 52, 3572–3575. Copyright 2016, The Royal Society of Chemistry.

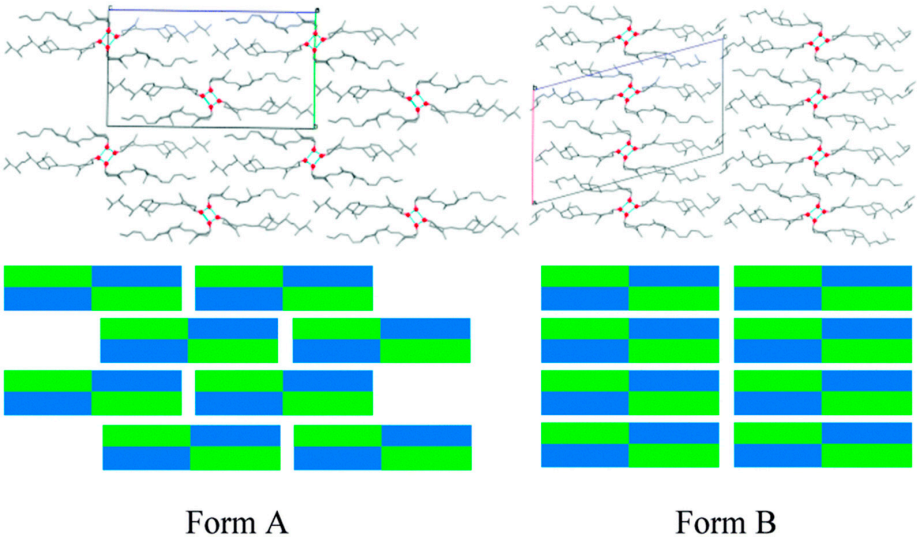


Figure 43. Packing arrangement of cocrystal form A and form B viewed along the helix structure. Adapted with permission from *Chemical Communications*, 2016, 52, 3572–3575. Copyright 2016, The Royal Society of Chemistry.

Zaworotko [105] and Matzger's [106] group reported a few more multi-drug cocrystal systems of piracetam and lamotrigine using supramolecular heterosynthon. Apart from the examples discussed here, numerous pharmaceutical cocrystals and salts were reported in the literature by some renowned groups—namely Braga [107–110], Sun [111–114], Hornedo [9,14,19,34,106,115,116], Myerson [32,33,117], Matzger [106,116,118,119], Bucar [73,78,120–124], and many more [125–131].

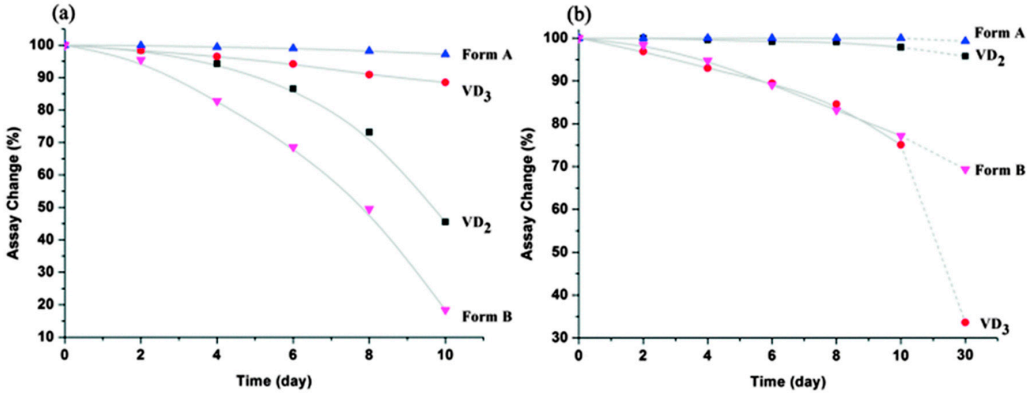


Figure 44. Change in vitamin D_3 assay during storage at (**a**) 23 °C with an illuminance of 5000 lx and (**b**) 40 °C/75%RH for cocrystal A and B compared with starting materials. Adapted with permission from *Chemical Communications*, 2016, 52, 3572–3575. Copyright 2016, The Royal Society of Chemistry.

2.2. Drug-Nutraceutical Cocrystals

Nutraceuticals are a recent addition to the coformer family during cocrystal preparation. A nutraceutical can be defined as "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease and possesses a physiological benefit or reduces the risk of chronic disease" [132]. Nutraceutical includes various polyphenols such as phenolic acids, coumarins, stilbenes, flavonoids, various vitamins such as nicotinic acid, retinal, retinoic acid, pyridoxine, L-ascorbic acid, folic acid, menadione, etc. Hydrogen bonding functional group attached to all these molecules facilitates formation of cocrystal with drug molecules resulting pharmaceutical cocrystal. Lawrence and coworkers in a recent review [133] discuss cocrystallization of nutraceuticals as coformers, taking into account physicochemical property modification during drug development. In another review, Caira [134] discusses sulfa drugs as novel cocrystal former during combination therapy, considering their antibacterial and antimicrobial activity.

Schultheiss and coworker mainly focus their research on preparation of various pharmaceutical cocrystal considering nutraceuticals as coformer. In separate reports, they report on cocrystallization of pterostilbene with caffeine and carbamazepine (Figure 45) [135,136]—p-coumaric acid with caffeine, theophylline [137], etc.—along with their solubility enhancement.

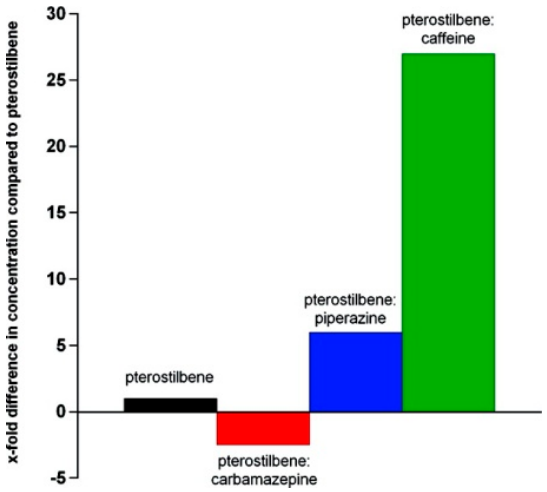
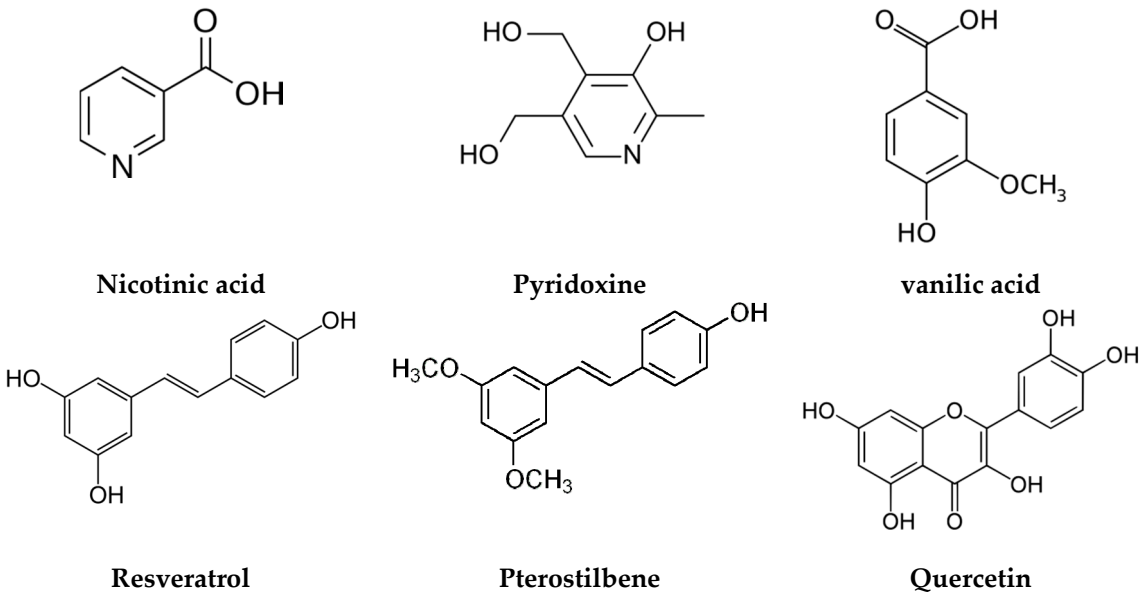


Figure 45. Comparison between the aqueous solubility of pterostilbene and the solution concentration of pterostilbene achieved from three cocrystals with carbamazepine, piperazine and caffeine. Adapted with permission from *Crystal Growth & Design*, 2011, 11, 2817–2823. Copyright 2011, American Chemical Society.

Molecular structures of some of the nutraceuticals are shown in Scheme 4.



Scheme 4. Molecular structure of a few nutraceutical molecules widely used as cocrystal former.

Nangia et al. also reported [138] few case studies considering nutraceuticals like resorcinol, ferulic acid, vanilic acid, and caffeic acid during cocrystallization with isoniazid. The summary of their result is represented in Figure 46.

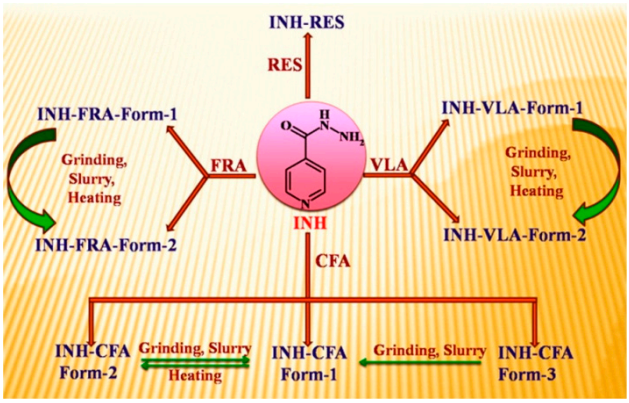


Figure 46. Various cocrystals of isoniazid prepared using nutraceuticals as coformer. Adapted with permission from *Crystal Growth & Design*, 2014, 14, 5991–6005. Copyright 2014, American Chemical Society.

Thakuria et al. studied the solubility of various pharmaceutical cocrystals considering nutraceuticals as coformers and correlated coformer solubility with cocrystal solubility of drug molecules viz. ethenzamide [139] and pyrazinamide (Figure 47) [140].

Smith et al. [141] prepare three different cocrystals of quercetin namely quercetin:caffeine (QUECAF), quercetin:caffeine:methanol (QUECAF•MeOH) and quercetin:theobromine:dihydrate (QUETBR•2H_2O). Solubility of the QUECAF and QUECAF•MeOH are 14 and 8 times greater whereas QUETBR have slightly enhanced solubility compared to quercetin dihydrate. Dissolution profile of all the cocrystals along with quercetin dihydrate are shown in Figure 48.

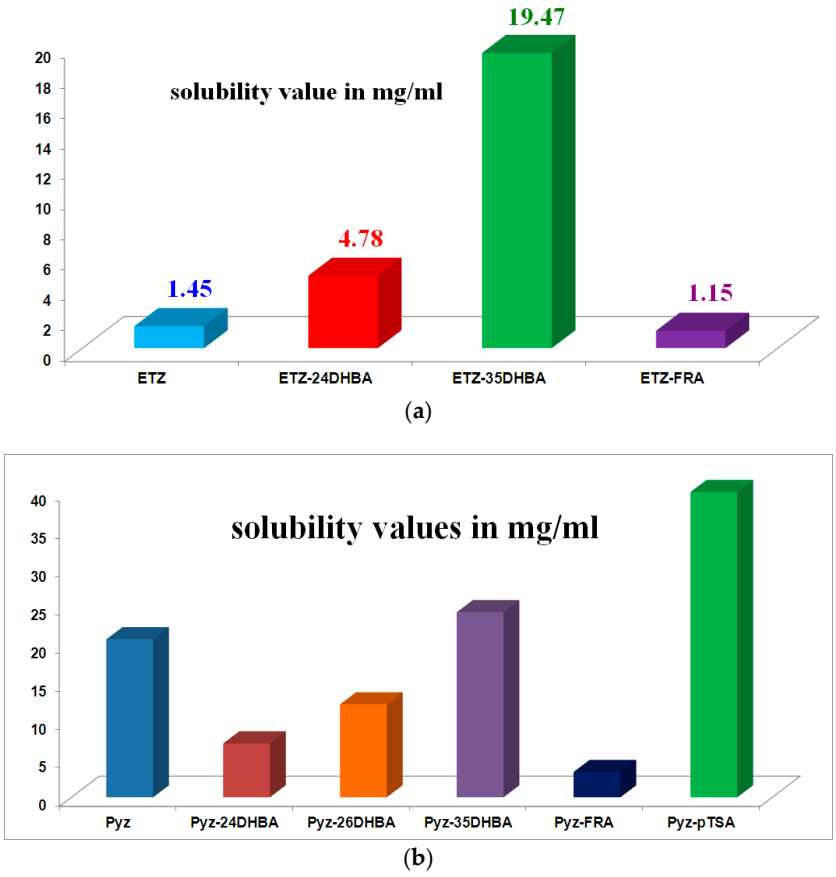


Figure 47. Bar diagram showing solubility profile of (**a**) ethenzamide cocrystals and (**b**) Pyz binary complexes. Ferulic acid is designated as FRA. Adapted with permission from *CrystEngComm*, 2017, 19, 826–833. Copyright 2017, The Royal Society of Chemistry.

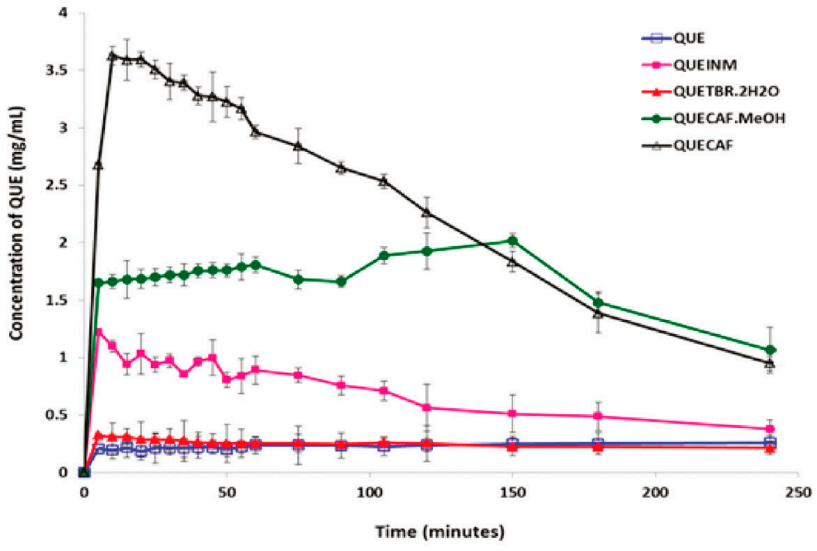


Figure 48. Dissolution profile of quercetin dihydrate and its cocrystals in 1:1 ethanol/water mixture after the first 4 h. Adapted with permission from *Mol. Pharmaceutics*, 2011, 8 (5), 1867–1876. Copyright 2011, American Chemical Society.

3. Future Prospects

From the case studies, it was observed that although multiple reports exist on pharmaceutical cocrystals, drug–drug cocrystals are scarce. The reasons behind the paucity are individual solubility, chemical and physical stability, moisture sensitivity, etc. of APIs. All of these properties can affect the shelf-life of the drugs in multidrug dosage formulation. According to Simon Frantz in his article [142] in *Nat. Rev. Drug Discovery*, 2006, preparation of multidrug formulation is "a cost centred, not a profit centred" process. Also, they can be used only for a specific set of patients with specific sets of multiple disorders but may not be useful for patients having single ailment; therefore, the importance of drug-drug cocrystal is still debatable. It is needless to mention that preparation of salt formation of a drug containing ionisable sites continues with the objective of improving drug properties rather than cocrystal preparation. However, when routine screening efforts fail to provide desirable crystalline free forms or salts, a possible cocrystal formation between API and a coformer may furnish an appropriate dosage provided a crystalline solid form of that API is a preferred formulation. The outlook is the recent approval of a pharmaceutical cocrystals by the FDA which will continue to gain substantial interest from the pharmaceutical industry as materials for drug development. As a result, R&D departments of many pharmaceutical companies have initiated a fairly large investment in plenty of clinical trials to probe the potential benefits of various coformers/nutraceutical/drug in their cocrystals. Therefore drug-drug and drug-nutraceutical cocrystals and/or salt pre-formulations approach is to identify a suitable dosage formulation to treat targeted disease or multiple disorders simultaneously. It is certain that with more research in this field and reviews [143], they will emerge as a viable alternative to traditional drugs in the near future.

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Conflicts of Interest: The authors declare no conflicts of interest.

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