CHAPTER 2

REVIEW OF LITERATURE

2.1 Theophylline in Crystal Engineering:

Theophylline (TP) also known as 1,3-dimethylxanthine, is a methylxanthine drug used in therapy for respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma under a variety of brand names. As a member of the xanthine family, it bears structural and pharmacological similarity to theobromine and caffeine, and is readily found in nature, and is present in tea (Camellia sinensis) and cocoa (Theobroma cacao). A small amount of theophylline is one of the products of caffeine metabolic processing in the liver [1].

Theophylline was first extracted from tea leaves and chemically identified around 1888 by the German biologist [2, 3]. Seven years later, a chemical synthesis starting with 1,3-dimethyluric acid was described by Emil Fischer and Lorenz Ach [4]. The Traube purine synthesis, an alternative method to synthesize theophylline, was introduced in 1900 by another German scientist, Traube [5]. Theophylline's first clinical use came in 1902 as a diuretic [6]. It took an additional 20 years until it was first reported as an asthma drug [7].

Theophylline belongs to a class of medications called bronchodilators, used in treating asthma and other airway diseases. It also strengthens right heart function and diaphragm movement. Theophylline was approved by the FDA in April 1979.

The use of theophylline is complicated by its interaction with various drugs and by the fact that it has a narrow therapeutic window. It can cause nausea, diarrhoea, increase in heart rate, abnormal heart rhythms, and CNS excitation (headaches, insomnia, irritability, dizziness and lightheadedness) [8, 9]. Seizures can also occur in severe cases of toxicity, and are
considered to be a neurological emergency [10]. Its toxicity is increased by erythromycin, cimetidine, and fluoroquinolones, such as ciprofloxacin. It can reach toxic levels when taken with fatty meals, an effect called dose dumping [11]. In addition to seizures, tachyarrhythmias are a major concern [12].

Barnes [13] reported that theophylline (3-methylxanthine) has been used to treat airway diseases for over 70 years. Theophylline is given systemically (orally as slow-release preparations for chronic treatment and intravenously for acute exacerbations of asthma) and blood concentrations are determined mainly by hepatic metabolism, which may be increased or decreased in several diseases and by concomitant drug therapy [14].

Abourahma [15] synthesized the cocrystals of theophylline:p-hydroxybenzoic acid (TP:pHBA) while grinding with additives in the solid state. The TP:pHBA cocystal was found to be robust in the presence of benzoic acid (BA), p-nitrobenzoic acid (pNBA), p-(N,N-dimethylamino)benzoic acid (dMABA), m-hydroxybenzoic acid (mHBA), p-nitrophenol (pNP), hydroquinone (HDQ) and benzamide (BZA), but it disintegrates in the presence of salicylic acid (SA), 3,5-dinitrobenzoic acid (dNBA), acetamide (ACA) and melamine (MLM).

Pharmaceutical cocrystals [15, 16] comprising of at least one active pharmaceutical ingredient (API), have been shown to improve a number of physical properties of the API, including poor solubility,[17–22] poor hydration stability, [23, 24] poor compressibility and poor thermal stability [25, 26]. Since pharmaceutical cocrystals offer great potential to address the limitations of certain APIs, they have gained a lot of interest in recent years [27–29]. Grinding has been shown to effect chemical transformations in the solid state, [30-33]. This study addresses the question by evaluating the robustness of a pharmaceutical
cocrystal containing theophylline, a muscle relaxant used in asthma medications. Over 40 cocrystals of theophylline have been reported in the literature [34-36].

![Chemical structures](image1)

**Fig. 2.1** Chemical structure and abbreviation of coformers employed in evaluating the robustness of TP·pHBA.

![Crystal structure](image2)

**Fig. 2.2** Crystal structure of TP·pHBA (CSD refcode KIGLOC).

The selected competing coformers and abbreviations, shown in Fig. 2.1, are: p-(N,N-dimethylamino)benzoic acid (dMABA), benzoic acid (BA), p-nitrobenzoic acid (pNBA), o-
hydroxybenzoic acid (salicylic acid, SA), m-hydroxybenzoic acid (mHBA), 3,5-dinitrobenzoic acid (dNBA), p-nitrophenol (pNP), hydroquinone (HDQ), benzamide (BZA), acetamide (ACA) and melamine (MLM). Five of the 11 coformers are known to form cocrystals with TP, namely BA, [37] pNBA, dNBA, SA22 and pNP, [38] and the latter two were characterized by single crystal X-ray diffraction (CSD refcodes KIGLES and TOPPNP, respectively). All selected coformers are capable of interacting with theophylline through one of the synthons illustrated in Fig. 2.2, in addition to hydrogen bonding to the second carbonyl functionality in TP. The benzoic acid coformers were selected to have varying competency of hydrogen bonding.

The intermolecular interactions sustaining TP·pHBA, coformers and potential cocrystals were considered since the interplay between homomeric and heteromeric interactions plays a role in cocrystal formation [39-51].

TP·pHBA is robust in the presence of benzamide (BZA), but it disintegrates in the presence of acetamide (ACA). Examination of the crystal structure of BZA (Fig. 2.3) reveals that it is sustained by the centrosymmetric R22(8) amide dimer, which further aggregates into a ladder structure, characteristic of primary amides [52-55]. Breaking the strong homomeric interactions in this case is difficult and unfavourable and therefore no disruption of TP·pHBA cocrystal is observed. The crystal structure of ACA on the other hand is not sustained by the amide dimer, rather each ACA molecule interacts with 4 other molecules via 2 single NH···O hydrogen bonds and a bifurcated O···H-N hydrogen bond.
**Fig. 2.3** Crystal structure of (a) benzamide and (b) acetamide

Wang *et al* [56] reported the novel pharmaceutical cocrystal (THPAH12) of theophylline (TP) with acesulfame (AH). Solid state NMR spectra of the cocrystal indicate that the two AH molecules exist as keto and enol tautomers, which is further confirmed by the refined crystal structure.

Acesulfame (AH) has been used as a guest molecule to prepare novel pharmaceutical crystalline complexes [57-61]. It was found to exist in two polymorphic forms. A 1:1 pharmaceutical cocrystal of Theophylline (TP) with saccharin (SAC) was reported [62] recently, in which an R22(9) synthon formed between of TP, and −NH–C=O group of SAC. Such an R22(9) graph-set motif (or its analogues) has been recognized as a main heterosynthon in cocrystals of theophylline [63-67]. Similar to SAC, the −N5H–C8=O6 group also exists in the keto form of AH.

Lu *et al* [68] synthesized and characterized the co-crystals of nicotinamide with theophylline as an attractive alternative for solid forms of drug products. In this work, nicotinamide (NCT).
Fig. 2.4 Chemical structures of theophylline (a) and nicotinamide (b)

(NCT) was employed as a cocystal former with the active pharmaceutical ingredient theophylline (TP). The TP-NCT cocystal (Fig.2.4) obtained in a 1:1 molar ratio of theophylline and nicotinamide, possesses unique thermal, spectroscopic, and X-ray diffraction properties. In addition, the solubility and hygroscopicity of the TP-NCT cocystal were considerably higher than those of anhydrous theophylline.

Theophylline is apt to hydrate, which gives formulators a challenge of avoiding the interconversion between crystalline anhydrate and monohydrate forms under common processing conditions (Fig.2.5). Theophylline is known to have good potential for cocystal formation due to the presence of O-H and N-H sites in the molecule. Thus, formation of a hydrogen bond with guest molecules is a means of modifying the physicochemical properties of theophylline [69]. In this study, nicotinamide was employed as a cocystal former with theophylline. Nicotinamide was chosen as it is the amide of niacin, one of the vitamin B family (B3), and has been used extensively for human consumption and is largely considered to be safe. Besides, nicotinamide has been reported to have six polymorphs, of which only the
stable form can be obtained from solution, and the other meta stable forms are obtained by super cooling of the melt or by sublimation.

Fulias et al [70] investigated the solvent-assisted slurry grinding combined method with microwave irradiation (MW) to investigate the cocrystal formation between acetylsalicylic acid (ASA) and theophylline (THE). This study indicated that a cocrystal consisting in 1:1 (molar ratio) ASA:THE was characterized by the thermal and spectroscopic techniques. The thermal and spectroscopic analysis carried out on the precursors and cocrystal confirm a different thermal behavior of mixture, and as well a different FTIR spectrum.

Traska et al [71] synthesized and reported the cocrystals of theophylline with oxalic, malonic, maleic, and glutaric acids. Crystal structures were obtained for each cocrystal material, allowing an examination of the hydrogen bonding and crystal packing features.
Fig. 2.5. Packing diagram of: (a) theophylline anhydrate showing hydrogen- bonded ribbons (Ebisuzaki et al., 1997) and (b) theophylline monohydrate, showing theophylline dimers (Sun et al., 2002)

Lu, et al [72] investigated the 4-amino-N-(4,6-dimethylpyrimidin-2-yl) benzenesulfonamide:4-amino-N-(4,6-dimethyl-1,2-dihy-dro-pyrimidin-2-ylidene) benzenesulfonamide–1,3-dimethyl-7H-pur-ine-2,6-dione cocrystals. Each molecule of sulfamethazine forms a hydrogen-bonded ribbon along the b axis crosslinked by further hydrogen bonding. The two sulfamethazine molecules exhibit a hydrogen-shift isomerization so that the crystal structure contains both tautomeric forms. Calculation of their relative energies showed that the tautomer protonated at the chain N atom is considerably more stable than the one where an N atom in the aromatic ring is protonated.

Zhang et al [73] investigated the thermodynamics and crystallization of the theophylline–glutaric acid 1:1 cocrystal. It is found that the cocrystal physically decomposes at 120 °C. The solubility of the cocrystal and pure compounds has been determined in chloroform and acetonitrile. In chloroform, the theophylline concentration of the saturated solution over the cocrystal is clearly higher than that in the saturated solution over pure
theophylline, while for glutaric acid the situation is the opposite. This is depicted in the following diagram.
**Fig. 2.6** The crystal structure of 1:1 theophylline–glutaric acid cocrystal.

Hydrogen bonding between theophylline and glutaric acid is formed between the basic N atom of theophylline and the hydroxyl H of glutaric acid, and two theophylline molecules also form a hydrogenbonded dimer in a cyclic motif [74].
Aitipamula et al. [75] synthesized the co-crystals of theophylline with gentisic acid (1:1). Cocrystals with two-dimensional hydrogen bonded sheets involving N—H...O and O—H...N hydrogen bonds were studied. The overall crystal packing features π-π stacking interactions (Fig. 2.7).

![Theophylline:gentisic acid cocrystal](image)

**Fig. 2.7** Theophylline:gentisic acid cocrystal

Jones and coworkers [76] investigated three cocrystals based on varied supramolecular arrangements, between acetaminophen (APAP):(theophylline), acetaminophen (APAP):(naphthalene), and acetaminophen (APAP):(oxalic acid), with layered topologies (Fig. 2.8).
Fig. 2.8 X-ray crystal structures of (a) (APAP)·(theophylline), (b) 2(APAP)·(naphthalene), and (c) (APAP)·(oxalic acid).

Schultheiss et al [77] studied four cocrystals of p-coumaric acid with caffeine and theophylline and their structural determination by single-crystal X-ray crystallography. The
two theophylline cocrystals displayed synthon polymorphism. However, one polymorph has a hydroxyl–carbonyl synthon (Form I), while in the other a hydroxyl–imidazole synthon (Form II) was observed.

Mukaida et al [78] reported the thermodynamic stability order using acetaminophen (AC) co-crystals of oxalic acid (OX), maleic acid (MA), and theophylline (TP). Vioglio et al [79] reported the crystal structure of theophylline (TP) with pyridoxine·HCl (PyrH+Cl–) by single crystal X-ray diffraction (SCXRD), solid-state NMR (SSNMR), and density functional theory (DFT) calculations and intermolecular forces have been examined. Each structure is characterized by an extensive network of hydrogen bond.

2.2 2-Amino-5-nitropyridine in Crystal Engineering

2-Amino-5-nitropyridine (2A5NP) crystals contain herringbone motifs of chromophores anchored onto inorganic or organic host matrices building noncentrosymmetric frameworks and it’s have been studied very widely and it is found that these exhibit optical and NLO properties [80–82]. 2A5NP has nitro group as an electron acceptor and amino group as an electron donor.

Aakeroy et al [83] reported the crystal structures of 2-amino-5-nitropyrimidine by single-crystal X-ray diffraction. Crystal packing, hydrogen-bond patterns, and intermolecular forces have been examined, and theoretical studies were performed. Each structure is characterized by an extensive network of hydrogen bonds.

Etter et al [84] reported the hydrogen-bond formation of carboxylic acids with 2-aminopyrimidine [85]. Substituted heterocyclic molecules can also have large molecular nonlinear polarizabilities which render them useful for new nonlinear optical (NLO) materials. The favorable orientation of molecules in a crystal lattice emphasizes the
importance of structure and intermolecular forces. 2-Amino-5-nitropyridine has been structurally characterized and the corresponding cation has been used extensively in NLO materials [86]. 2-Amino-5-nitropyrimidine is found to exhibits three polymorphic forms, and the theoretical study provided the strength and weaknesses of crystal structures of organic molecular solids [87-89]. 2-Amino-5-nitropyrimidine is an attractive molecule both from a materials/crystal engineering and from a structural and theoretical perspective: (i) it has a large molecular dipole moment and may be incorporated in new NLO-materials, (ii) it contains several potential donors and acceptors for both weak, C-H…X, and strong, N-H…X, (X = O or N) hydrogen-bond interactions; (iii) it is small enough to make it accessible to ab initio methodologies; (iv) reliable potentials for calculations of lattice energies of such compounds are available; and (v) the molecule has relatively limited conformational flexibility. Previous computational studies include ab initio SCF calculations of the molecular electrostatic potentials around 2-aminopyridine and 2-aminopyrimidine [90] and a study of intermolecular interactions in 2-amino-5-nitropyrimidine (form I) and 2-amino-5-nitropyridine. These structure determinations of three polymorphs of 2-amino-5-nitropyrimidine were accompanied by ab initio and lattice energy calculations to determine the role of the changes in molecular conformation on the crystal structure [91-92]. The effect of the slight conformational variations between the polymorphs was studied by modeling the crystal structures with both the experimental and an idealized molecular structure, obtained by ab initio optimization.

Fur et al [93] reported the cocrystals of 2-amino-5-nitropyridinium and 2-amino-5-nitropyridine. The structures of the 2-amino-5-nitropyridinium trichloroacetate ionic crystal (Fig. 2.9) and 2-amino-5-nitropyridine and chloroacetic acid cocrystals (Fig. 2.10) structures and packings are discussed in terms of steric hindrance and hydrogen bonds. Powder samples
of these materials exhibit second harmonic generation signals comparable to that of 3-methyl-4-nitropyridine N-oxide under Nd\textsuperscript{3+}:YAG laser (1.06 μm) illumination.

Fig. 2.9 Centrosymmetric H-bonded cation-anion clusters stretching along the \textbf{a}+\textbf{c} direction in the 2-amino-5-nitropyridinium trichloroacetate crystal

Fig. 2.10 View along the \textbf{a} direction of the 2-amino-5-nitropyridine/chloroacetic acid cocrystal. The three-dimensional H-bonding scheme is indicated in dotted lines.

Koshima \textit{et al} [94] synthesized and characterized the cocrystals of 2-amino-5-nitropyridine (2A5NP) with achiral benzenesulfonic acids (Ar-SO\textsubscript{2}H), The cocrystal of
2A5NP with 2-nitrobenzenesulfonic acid belongs to acentric space group $\text{Pc}$, in which 2A5NPH$^+$ cation and anion alternately stacked in almost parallel and superimposed manner to form column and layer structures. The cocrystal of 2A5NP with 3-nitrobenzenesulfonic acid is crystallized into chiral space group $\text{P}2_1$. The 2A5NPH$^+$ cation and anion are also alternately stacked with some dihedral angle to form column structures. These organic–organic cocystals are controlled by the aromatic–aromatic interactions as well as multidirectional ionic and hydrogen bondings between the 2A5NPH$^+$ cations and $\text{ArSO}_3$ nions (Fig.2.11).

![Diagram](image)

**Fig. 2.11** Molecular arrangements along (a) the $a$ axis, and (b) the $c$ axis, and on the $bc$ plane of (c) A pairs and (d) B pairs in 1a.
The conformations of species in A and B columns are almost flat because the dihedral angles of pyridine ring and nitro group are only 5.0(6) and 3.7(4)°, and those of pyridine ring and amino group are 12.1(4) and 4.9(4)°, respectively. On the other hand, the phenyl rings and the nitro groups of sulfonic anions are nearly perpendicular, with the dihedral angles of 78.5(4) and 78.4(4)°, respectively. These shapes of cationic and anionic species reflect the parallel stacking arrangement in the crystal.

Zhou et al. [95] synthesized [CuBr(anp)]ₙ (anp=2-amino-5-nitropyridine) from a solvothermal reaction of anp with CuBr·4H₂O, and characterized by single-crystal X-ray diffraction analysis. This complex crystallized in monoclinic space group P2₁/c with a = 3.853(6) Å, b = 7.368(11) Å, c = 29.04(4) Å, and β = 93.19(2)°. The structure of 1 showed a 1-D stair-like chain, which is formed by the interconnection of -[Cu₂Br₂]- step-like units and monodentate anp ligands. Weak hydrogen bonds between amino groups and –NO₂ groups from neighboring chains assemble chains to form a supra-layer along the ab plane.

![ORTEP drawing of [CuBr(anp)]ₙ with 50% thermal ellipsoids with hydrogen atoms being omitted for clarity.](image_url)

As shown in Fig. 2.12, the asymmetrical unit comprises of one neutral anp ligand, one copper atom and one Br⁻ atom. Each copper(I) atom is in a distorted tetrahedral environment coordinated to one nitrogen atom from the pyridine ring of an anp ligand, one Br(1) atom,
and its two symmetry-related atoms. The present Cu-N bond distances being 2.037(6) Å and Cu-Br bonds varying from 2.462(3) to 2.566(4) Å are in the normal ranges and comparative to those found in the literatures. The anp ligand coordinates to one Cu1 atom via its N1 atom of the pyridine ring, acting as a monodentate ligand without its nitro and amino groups participating in the coordination. The Br atom links to three Cu1 atoms as a $\mu_3$-Br bridge. Then two Cu1 atoms and two $\mu_3$-bridging Br atoms form a square -[Cu$_2$Br$_2$]- unit which acts as an “step” of a “stair” polymer, and the step-like units link each other, growing into a stair-like inorganic skeleton [Cu$_2$Br$_2$]$_n$ chain along the $a$-direction (Fig.2.13). The anp ligands coordinate to the Cu centers on both sides of the [Cu$_2$Br$_2$]$_n$ skeleton. All the pyridine rings of the chain are parallel, but the –NO$_2$ groups on one side are pointing antiparallel to the –NO$_2$ groups on the other side.

![Image](image.png)

**Fig. 2.13** A stair-like chain of [CuBr(anp)]$_n$

The minimum distance between the centroids of pyridine rings is about 7.368 Å, indicating no $\pi \cdots \pi$ stacking inter-molecular actions are formed. Weak hydrogen bonds (N
H~O, 3.096(11) Å, 162.1°) exist between amino groups and oxygen atoms of –NO₂ from two neighboring 1-D chains, which further assemble 1-D chains to form a supralayer along the ab plane.

Jovita et al [96] investigated the organic single crystal, 2-amino-5-nitropyridinium trifluoroacetate grown by slow evaporation solution technique at room temperature. The structure of the grown crystal was determined by single crystal X-ray diffraction method. FTIR spectral analysis was carried out to identify the various functional groups present in the crystal. The different types of protons and carbons in the grown crystal were identified by the NMR spectral analysis.

Paredes et al [97] reported the analysis of the molecular structure and the hydrogen-bonding patterns in the crystal structures of 5-methoxy-2-nitroaniline and 5-methoxy-2-nitroaniline with 2-amino-5-nitropyridine (1:1) cocystal. X-ray single crystal diffraction experiments were carried out to analyze the intermolecular forces in terms of geometrical criteria. These intermolecular interactions were also investigated through topological analysis of the electron density (r) employing QTAIM and NCI methods. Additionally, Raman spectroscopy was employed to analyse the vibrational characteristics of the entitled materials. The supramolecular structure of it is produced by crosslinked chains, which are primarily dominated by N-H…O hydrogen bonds. However, C-H…O interactions reinforce this connectivity. Furthermore, the molecules in are connected through two-centre instead of the three-centre hydrogen-bonding interactions between the -NH₂ and -NO₂ groups commonly observed in nitroanilines.

Manivannan et al [98] investigated the engineered host-guest hydrogen-bonded 2-amino-5-nitropyridinium tetrafluoroborate (2A5NPFB) salt following a strategy applied to the 2-
amino-5-nitopyridinium salts. The crystal structure of organic-inorganic 2A5NPFB has been determined, and it belongs to the noncentrosymmetric space group Fdd2 (Fig. 2.14).

Fig. 2.14  Packing of 2A5NPFB illustrating the hydrogen bonding scheme

Kamalesu et al. [99] synthesized the cocrystal of 2-amino-5-nitropyridine with 2-naphthoxy acetic acid which have been characterized by single crystal XRD analysis. This complex is crystallized in monoclinic crystal system with space group P2(1)/c.

2.3. Barbituric Acid in Crystal Engineering:

Barbituric acid or malonylurea or 6-hydroxyuracil is based on a pyrimidine heterocyclic skeleton. It is an odorless powder soluble in water. Barbituric acid is the parent compound of barbiturate drugs, although barbituric acid itself is not pharmacologically active. Barbituric acid is one of four ingredients used to make riboflavin (vitamin B2).
Nichol et al [100] synthesized the cocrystals of 4,4'-bipyridine (4,4'-bipy) with barbituric (BAH), and orotic acid (ORH) and uracil-5-carboxylic acids (U5CAH) which have been characterized by single-crystal X-ray diffraction. The products include a co-crystal of neutral species with $Z'$ 2(4,4'-bipy/BAH), an organic complex ion pair (4,4'-bipy/ORH) and a compound containing both ionic and hydrogen-bonded neutral species (4,4'-bipy/U5CAH). Partial proton transfer is observed in both of the ionic cases, and in all three structures the crystal packing arrangement is such that weak hydrogen bonding, $\pi \cdots \pi$ and molecular dipole interactions are optimized

![Diagram](image)

**Fig. 2.15.** 4,4'-Bipyridine (4,4'-bipy) with barbituric (BAH) acid

Four crystal structures of organic complexes formed by reacting 1,8-bis(dimethylamino)naphthalene with barbituric (BAH), violuric (VIH), cyanuric (CYH), and orotic (ORH) acids, are reported and investigated [101] the extent of weak intermolecular interactions were investigated. (principally C-H $\cdots$ X hydrogen bonding and $\pi \cdots \pi$ stacking) between acid and base when classical hydrogen bonding is not possible. Much of the recent literature on this topic is conveniently summarized by Steed and co-workers [102].
Braga *et al* [103] reported the ICCs formed between solid barbituric acid, BA, and alkali salts (KBr, RbBr, CsBr). Depending on the alkali metal, the anhydrous or the hydrated product could be obtained, or both. All ionic cocrystals are characterized by higher thermal stability and dissolution rates with respect to pure barbituric acid. The structure of (BA)·(KBr)·(H₂O)₂ is shown in figure 2.16.

![Figure 2.16](image)

**Fig. 2.16** Crystalline (BA)·(KBr)·(H₂O)₂ (top) and the hydrogen bonded chain made of alternating BA molecules and Br⁻ anions (potassium in violet, bromide in gold).

Griesser *et al.* had observed that the IR-spectrum of the anhydrous form II of barbituric acid in KBr showed an additional absorption band at 3500 cm⁻¹, which could only be explained by assuming that some solid state transformation had occurred [104]. It was then shown that upon grinding, with or without the help of MeOH, a solid was obtained that presented the same IR band, and corresponding to the structure of the dihydrated ionic cocrystal (BA)·(KBr)·(H₂O)₂. The same cocrystal could also be obtained if barbituric acid in its anhydrous form III or dihydrated form was employed as starting reagent. In all these ionic cocrystals, barbituric acid is present as a neutral molecule.

These ionic co-crystals have different thermal stability with respect to the pure components. Although all crystals show incongruent melting followed by decomposition of
the organic moiety, for the solid forms containing sodium and potassium, decomposition is observed at a temperature close to the melting point of pure barbituric acid (onset values 255 and 249 °C, respectively, versus 245 °C), while for the co-crystals containing RbBr, CsBr and CsI the value is much higher (307, 298 and 308 °C, respectively).

Furthermore, the co-crystals show dissolution rates that are higher than that of pure barbituric acid [dissolution rates for BA and its anhydrous co-crystals are 21(2), 22(3), 27(1) and 29.1(0.3) mol L⁻¹ min⁻¹ for BA, BA·RbBr, BA·CsBr and BA·CsI, respectively], thus confirming that co-crystallization can represent a strategy to alter the dissolution properties of an organic molecule [105].

In yet another recent example, mechanical treatment of piracetam with the lithium salts LiCl and LiBr has also generated new ICCs [106-110]. Ionic cocrystals were also obtained from solution and kneading (Fig. 2.17) of barbituric acid, diacetamide, malonamide, nicotinamide and piracetam with the inorganic salt CaCl₂, which is known for its non-toxicity. The structures of ICCs were determined either from single crystal diffraction data or from powder diffraction data, using simulated annealing procedures. Crystalline products were analyzed by DSC, TGA and variable temperature XRPD. Intrinsic dissolution rate measurements were also performed on nicotinamide and piracetam ICCs.
Fig. 2.17 Screening for ICC formation: kneading of barbituric acid, diacetamide, malonamide, nicotinamide and piracetam with the inorganic salt CaCl$_2$.

Mahmudov et al [111] reported the role of barbituric acid H$_3$BA (pyrimidine-2,4,6 (1H,3H,5H)-trione) in coordination, organometallic, and supramolecular chemistry.

Singh et al reported the structures of the co-crystals of indole with barbituric acid. Evaluations of these molecules over 60 cell line panel of human cancer cells have identified two molecules with significant anticancer activities. Dockings of two active molecules in the active sites of COX-2, thymidylate synthase and ribonucleotide reductase indicate their strong interactions with these enzymes [Fig.2.18].

![Fig. 2.18 Indol: barbituric acid cocystal](image_url)

Molokeev et al [112] reported the cocystal of ciprofloxacin (CfH, C$_{17}$H$_{18}$FN$_3$O$_3$) crystallized with 2-thiobarbituric (H$_2$tsba) and barbituric acid (H$_2$ba) in the aqueous solution to
yield salt CfH₂(Htba)·3H₂O (1), salt cocrystal CfH₂(Hba)(H₂ba)·3H₂O (2), and salt CfH₂(Hba)·H₂O (3). These compounds were analyzed through X-ray single-crystal diffraction. The numerous intermolecular hydrogen bonds N–H···O and O–H···O formed by water molecules, Htba⁻/Hba⁻ and CfH2⁺ ions, and H₂ba molecules stabilize the crystal structures.

2.4. 2, 4-Diamino-6-phenyl-1,3,5-triazine in Crystal Engineering:

Jali et al [113] reported the structures of the cocrystals of 2,4-diamino-6-phenyl-1,3,5-triazine (dpt) with oxalic acid (Oxa), succinic acid (Suc), adipic acid (Adp), fumaric acid (Fum) and maleic acid (Mal) abbreviated as Oxa·2dpt, Suc·2dpt, Adp·2dpt, Fum·2dpt and Mal·2dpt respectively have been carried out. The packing patterns of these cocrystals are of end capped dicarboxylic acids with lengths varying from 23 to 28 Å. In the cocrystal 1 the oxalic acid molecules are involved in R₂²(9) and R₂²(6) type hydrogen bonds. The oxalic acid molecules have lateral orientation with respect to dpt, which reduces the length of the end-capped structure from a possible longitudinal orientation. It also makes difference from the longitudinal orientations of the dicarboxylic acids observed in the cocrystals. The structures of the cocrystals are guided by conventional R₂²(8) type of interactions between a nitrogen and amine group of heterocycle with carboxylic acid groups.

The structure of the cocrystals of 2,4-diamino-6-phenyl-1,3,5-triazine (dpt) with oxalic acid, succinic acid, adipic acid, fumaric acid are comprised of end capped subunits of length in the range of 23–28 Å, which are comprised of one acid and two dpt molecules whereas cocrystal of dpt with maleic acid has assemblies of infinite zipper like structure.
Fig. 2.19 (a) ORTEP diagram of asymmetric unit of cocrystal 1 with thermal ellipsoids (50%).

Fig. 2.19 (b) Hydrogen bond interactions of cocrystal 1 (Symmetry of $' = 2 - x, 1 - y, 1 - z$)

The crystallographic asymmetric unit of each compound has half of the carboxylic acid with one molecule of dpt Fig. 2.19 (a). The Oxad2dpt (1) has a packing pattern as shown in Fig. 2.19 (b). There are neither assemblies between the amine part or oxalic part independently, but each oxalic acid acts as bridge to form end capped structures formed by holding a carboxylic acid molecule by two trazine molecules. Such units when measured from the two para-hydrogen atoms of the benzene rings on trazine as terminal end have length 23.043 Å.

Bubulak and coworkers [114] have investigated the synthesis of 2,4-diamino-6-biphenyl-4-yl-1,3,5-triazines carrying either one semi perfluorinated or two lipophilic alkoxy
chains at the terminal position of the biphenyl moiety in binary mixtures with two-chain and three-chain partially fluorinated benzoic acids. Equimolar compositions of the triazines with the complementary two-chain benzoic acid form discrete hydrogen-bonded heterodimers. The dimeric supermolecules organize to rectangular columnar phases in the C$_2$ plane group. H-bonded associates of the fluorinated triazine with three equivalents of the two-chain acid form a rectangular columnar phase. Replacing the one fluorinated chain of the triazine by two alkoxy groups leads to a columnar phase on a two-dimensional square lattice in a 1:3 mixture with the two-chain benzoic acid. The 1:3 mixed systems of the triazines with the three-chain aromatic acid display micellar cubic phases.

Wang et al [115] synthesized and characterized the structure of the cocrystal of tetrafluoroterephthalic acid, (H2tfBDC), with a series of N-containing heterocycles: 2,3-dimethylpyrazine (2,3-Pyr), 2,6-dimethylpyrazine (2,6-Pyr), 2,4-diamino-6-methyl-1,3,5-triazine (dmt), benzoguanamine (bga), 2-methylbenzimidazole (2-MeBzlM), 1,4-bis(imidazol)butane (bimb), 2-amino-4-hydroxy-6-methylpyrimidine (ahmp), 1,2-bis[(2-methylimidazol-1-yl)methyl]benzene, and 1,4-bis[(2-methylimidazol-1-yl)methyl]benzene (L5). These crystal structures including salts/co-crystals/hydrates were analyzed and characterized by single crystal X-ray diffraction, IR, and TGA. Single crystal X-ray diffraction studies show that the huge numbers of hydrogen bonds play a significant part in assembling individual molecules into larger architectures, especially the strong N–H···O, O–H···O hydrogen bonds, and weak but highly directional C–H···O and C–H···F interactions exist commonly in all nine novel crystals. Crystal structure analysis shows that the F atom of the H2tfBDC participates in C–H···F hydrogen bond formation, producing different supramolecular synths. More importantly, the N–H···O, O–H···O, and C–H···O hydrogen bonds are mainly involved in the supramolecular assembly of these molecules, but C–H···F hydrogen bonds convert two-dimensional networks into three dimensional, hence, the C–
H···F interactions have a crucial role in the formation of higher-order supramolecular structures.

Kohlmeier et al [116] synthesized and studied the crystal structure of two 2,4-diamino-6-phenyl-1,3,5-triazines carrying either one or two alkoxy chains at the phenyl substituents in binary mixtures with two-chain partially fluorinated benzoic acids. Equimolar compositions of the complementary molecular species form discrete hydrogen-bonded dimeric supermolecules. The dimers organize to infinite ribbons of parallel aligned H-bonded polar aromatic cores that are separated by mixed aliphatic/fluorinated regions. The cross-sectional shape of the ribbon aggregates and, therefore, the two-dimensional lattice symmetries of the ribbon phases, rectangular or oblique, are defined by the number of alkoxy chains of the triazine component. Docking of 2 or 3 equiv of the semiperfluorinated benzoic acids to the diaminotriazine core leads to H-bonded aggregates with a circular cross-sectional shape and, consequently, to the formation of columnar phases on a two-dimensional hexagonal lattice.

Manzano et al [117] reported a few coordination polymers obtained by the self-assembly of silver salts AgX (X = BF₄, PF₆, CF₃SO₃) and 2,4-diamino-6-R-1,3,5-triazines.

2-Amino-4,6-dimethoxypyrimidine-4-aminobenzoic acid [1/1], 2-amino-4,6-dimethoxypyrimidine-anthranilic acid [1/1], 2-amino 4,6- dimethoxypyrimidine-phthalic acid [1/1], 2-amino-4,6- dimethoxypyrimidine-2,4-dichlorobenzoic acid (1/1) and 2- amino-4,6- dimethylpyrimidine-fumaric acid (0.5/0.5) cocrystals were prepared and characterized by Muthiah et al. [118]. The carboxylic acid group interacts with the corresponding 2-aminopyrimidine moiety through N-H···O and O-H···N hydrogen bonds to form an R₂⁺(8) ring motif.
Xiao et al (119) reported a number of co-crystals, salts, polymorphs, hydrates, and solvates containing both inorganic and organic acids. 3,5-Dihydroxybenzoic acid was crystallized with 6-methyl-1,3,5-triazine-2,4-diamine in a 4:3 ratio of ethanol and water by adding a few drops of nitric acid upon slow evaporation in ambient conditions, 6-methyl-1,3,5-triazine-2,4-diamine and 3,5-dihydroxybenzoic acid with the nitric acid form of 1:1:1, an inorganic-organic salt formulated as \( [(C_6H_5N_3)^+ (NO_3^-) (C_7H_4O_4)^-] \). The supramolecular architecture, which is quite elegant and simple, appeared as stacking of a 3D network in adduct. Proton transfer from the \( \text{HNO}_3 \) to 6-methyl-1,3,5-triazine-2,4-diamine \( \text{N} \) acceptor (triazine \( \text{N} \)) occurred in the organic salt and led to the ionic heterosynthon in the structure. Cooperation among the \( –\text{COOH}, –\text{OH}, \text{NO}_3^- \), and \( –\text{NH}– \) functional groups for the observed hydrogen bond synthon was examined in the structure. In addition, recognition among the constituents is established through \( \text{N}–\text{H}⋯\text{O}, \text{O}–\text{H}⋯\text{N}, \) and \( \text{O}–\text{H}⋯\text{O} \) hydrogen bonds. The agglomerated molecules are linked through the intermolecular hydrogen bonding interactions (O–H⋯O) to form a 1D chain. The nitric acid anions and base cations act as donors and acceptors of hydrogen bonds and interlink, almost to co-planarity, the hydrogen-bonded chains through interchain \( \text{N}–\text{H}⋯\text{O}, \text{O}–\text{H}⋯\text{N}, \) as well as \( \text{O}–\text{H}⋯\text{O} \) interactions into a 2D sheet structure. Persistent \( \text{N}–\text{H}⋯\text{O} \) interactions were found to play an important role in the formation of the final 3D array. The salt was characterized by elemental analysis, IR, thermogravimetric analysis, and single crystal X-ray diffraction.

2.5. Carboxylic Acids in Crystal Designing:

Organic molecules containing carboxylic acids have been used as building blocks in crystal engineering [120, 121]. Carboxyl groups are among the best-investigated hydrogen bond functionalities since they possess a hydrogen bond donor as well as acceptor sites. Carboxyl groups can readily form hydrogen bonds between each other as cyclic dimers or
open arrays. The roles of hydrogen bonding carboxyl groups in crystal packing have been analyzed in depth [122, 123] and they have become a popular building block in deliberate crystal design [124, 125].

Polycarboxylic acids, which are ubiquitous in organic chemistry play key roles in cell metabolism. They are also good organic supramolecular synthons due to the ability of the carboxylic acid groups to form moderate to strong hydrogen bonds. The organic aromatic polycarboxylic ligands, especially 1,4-benzenedicarboxylate, 1,3,5-benzenetricarboxylate, and 1,2,4,5- benzenetetracarboxylate have been extensively applied in the construction of a rich variety of infinite high dimensional structures because of their diverse coordinate modes and high structural stability [126].

It is well-known that carboxylate ligands play an important role to construct novel metal organic framework in coordination chemistry. They usually adopt binding modes diverse as terminal monodentate, chelating to one metal center, bridging bidentate in a syn-syn, syn-anti, and anti-anti configuration to two metal centers. Within the class of polycarboxylic compounds, benzene, pyridine, and polyazine derivatives are of special interest, because they represent a unique example where a high level of predictability of potential supramolecular arrangements is achieved [127].

5-Fluoro-1,3-dihydropyrimidine-2,4-dione with 5-fluorouracil–5-bromothiophene-2-carboxylic acid (1/1), C₅H₃BrO₂S.C₄H₅FN₂O₂, and 5-fluorouracilthiophene-2-carboxylic acid (1/1), C₄H₅FN₂O₂.C₃H₄O₂S, cocrystal were prepared and characterized by Muthiah et al [128]. The carboxylic acid molecules are linked through an acid–acid R₂²(8) homosynthon (O—H…O) to form a carboxylic acid dimer and 5-fluouracil (5FU) molecules are connected through two types of base pairs homosynthon, R₂²(8) motif via a pair of N—H…O hydrogen bonds.
Phenylthioacetic acid (PTAA) is a colourless compound, soluble in alcohols. It can be prepared by the subsitution reaction of sodium chloroacetate with thiophenol or by the treatment of bromoacetic acid with thallium (I) benzothiolate. Derivatives of PTAA (o-hydroxyphenylthio)acetic- and benzal-bis-(beta-thiopionic) acid show anti-tuberculotic activity [129-131]. Ph-S-CH₂-COOH is used as a free radical quencher in laser flash photolysis experiments [132]. Ph-S-CH₂-COOH in its triplet excited state undergoes intermolecular electron transfer allowed by hydrogen abstraction and decarboxylation producing alkyl radicals, which are the active initiator radicals in photo induced polymerization as given below Fig.2.20.

![Chemical Reaction Image]

Fig. 2.20 Alkyl radicals

Bacterial infections are commonly treated with antibiotic chemotherapy. The biological targets of these antibiotics are at the origin of appearance of resistant bacterial strains. Recently, the development of new approaches, such as the ‘antivirulence strategy’ leads the medicinal chemist to describe novel targets with a reduced probability of resistance development. Virulence factors, such as enzymes involved in the biosynthesis of amino acids, have been validated as such targets [133]. Compounds containing S-aryl ketones are a new class of histidinol dehydrogenase inhibitors [134] (Fig.2.21).

![Chemical Structure Image]

Fig. 2.21 An S- aryl ketone derivative
Phenylthioacetic acid (PTAA) is a synthetic precursor for a variety of Ph-S-containing compounds such as PhSCH$_2$=C=O [135], PhSCH$_2$CON=CH=S [136], PhSCH$_2$CO$_2$Me [136], PhSCH$_2$NO$_2$ [137] MeCH=CH(NO$_2$)SPh [138], PhSCHCICO$_2$H, PhSCH$_2$C [139], and 2-(phenylthio)methyl-1-oxazolidine derivatives [140].

PTAA has two reactive sites, the carboxylic acid group and the active methylene group, providing a useful method for constructing various cyclic compounds [141]. PTAA generates a dianion by the action of equiv of butyl-lithium or lithium isopropylamide (LDA). The C-anion site of the PTAA dianion is more reactive than the C-anion of methylphenylthioacetate. Treatment of the dianion with alkyl halide gives a monoalkylated product [142, 143]. Reaction of the dianion with a carboxylic ester accompanied by decarboxylation provides a useful method for the introduction of the PhSCH$_2$ moiety. Introduction of PTAA into a furan ring has also been achieved [144,145] by means of [3,3]-sigmatropic rearrangement as depicted below.

![Fig. 2.22 [3,3]-PTAA sigmatropic rearrangement](image)

β-Phenylthiopropionic acid:caffeine cocrystal was prepared and characterized by Kumaresan et al [146]. The asymmetric unit of the cocrystal consists of one β-phenylthiopropionic acid and one caffeine units. The phenylthiopropionic acid and caffeine moieties are linked by O–H⋯N and C–H⋯O interactions. The β-phenylthiopropionic acid
present in each side of the caffeine makes one dimensional chains parallel to the chain constructed by caffeine moieties. Hence both the chains are alternately packed and interlinked by C-H···O [C(14)–H(14)···O(4) ; and C(17)–H(17)···O(1); interactions which make a two dimensional sheet like structure (Figure 2.24) parallel to the ac plane. The two dimensional sheet is constituted by $R^3_4$ (20) and $R^4_4$ (25) rings. Parallel stacking of adjacent sheets formed in the cocrystal makes the structure as a three dimensional framework (Fig. 2.23 and 2.24).

Fig. 2.23 Perspective view of 2D sheet formed in β-phenylthiopropionic acid: caffeine parallel to the ac-plane

![Perspective view of 2D sheet formed in β-phenylthiopropionic acid: caffeine parallel to the ac-plane](image)

Fig. 2.24 Packing diagram of β-phenylthiopropionic acid: caffeine

Remenar et al [147] synthesized the cocrystals of cis-itraconazole with 1,4-dicarboxylic acids. The crystal structure of the succinic acid cocrystal was determined to be a trimer by single-crystal X-ray. The trimer is comprised of two molecules of 1,4-dicarboxylic
acids and triazole oriented in antiparallel fashion to form a pocket with a triazole at either end. The extended succinic acid molecule fills the pocket, bridging the triazole groups through hydrogen-bonding interactions rather than interacting with the more basic piperazine nitrogens. The solubility and dissolution rate of some of the cocrystals are approximately the same as those of the amorphous drug in the commercial formulation and are much higher than those for the crystalline free base.

Childs et al [148] reported the crystal engineering method used to investigate cocrystal formation of piroxicam with pharmaceutically acceptable carboxylic acids. Forming cocrystals of piroxicam can potentially result in solid forms with increased bioavailability. A total of 50 unique cocrystals containing piroxicam and a guest carboxylic acid were identified in screening experiments. Each of the 23 guest molecules tested formed at least one cocrystal with piroxicam. In addition, the three known polymorphs of piroxicam were observed. Raman data for the piroxicam cocrystals can be sorted into three distinct groups based on spectral similarity. These groups are differentiated by the piroxicam tautomer present in the cocrystal and the presence or absence of a strong hydrogen bond donor interacting with piroxicam's amide carbonyl group. X-ray powder diffraction data revealed six isostructural piroxicam cocrystals. Single-crystal structure determination revealed that this isostructural series is a host–guest system in which the piroxicam forms a well-ordered host containing disordered guest compounds. Crystal structures of eight piroxicam cocrystals and a dioxane solvate of piroxicam are reported. All carboxylic acid guest compounds are non-ionized in the cocrystals, and piroxicam is present as the non-ionized or zwitterionic tautomer. Of special interest are two 1:1 piroxicam/4-hydroxybenzoic acid cocrystal polymorphs. While the unit cell contents are identical, one polymorph contains the non-ionized piroxicam tautomer plus the guest, while the other contains the zwitterionic tautomer plus the guest. In a related phenomenon, a 4:1 piroxicam/fumaric acid cocrystal is reported that contains one
zwitterionic tautomer, one non-ionized tautomer, and one-half of a non-ionized fumaric acid in the asymmetric unit Fig. 2.25.

![Image](image1.png)

**Fig. 2.25 ORTEP of biroxicam-carboxylic acid cocrystal**

Bucar *et al* [149] synthesized and studied the crystal structure of cocrystals of caffeine with hydroxy-2-naphthoic acids. The compounds were analyzed through single-crystal X-ray diffraction and IR analysis Fig. 2.26.

![Image](image2.png)

**Fig. 2.26 Crystal structures of caffeine with different carboxylic acids**
The imidazole–carboxylic acid synthon was observed in co-crystals involving 1-hydroxy-2-naphtoic and 3-hydroxy-2-naphtoic acid. In the case of 6-hydroxy-2-naphtoic acid, the co-crystal exhibits a hydrogen-bonded carboxylic acid dimer in the presence of a hydroxyl–caffeine heterosynthon.
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