Crystal Engineering of Pharmaceutical Cocrystals

Sreya Mukherjee

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Crystal Engineering of Pharmaceutical Cocrystals

By

Sreya Mukherjee

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science
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DEDICATION

To my parents, husband and brother.
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LIST OF ABBREVIATIONS

DNA – Deoxyribonucleic acid
API- Active Pharmaceutical Ingredient
CBZ- Carbamezepine.
CSD- Cambridge Structural Database.
BCS- Biopharmaceutics Classification System
GI- Gastrointestinal
AD- Alzheimer’s disease
Aβ- β-Amyloid
DMF- Dimethyl Formamide.
GRAS- Generally Regarded as Safe
EAFUS- Every Added to Food in United States
I.V. –Intravenous
ABSTRACT

Pharmaceutical cocrystals use principles of crystal engineering for the design of crystalline forms of drugs and can improve their solubility, bioavailability, stability and other important properties without changing the efficacy of the drug. Herein reported are pharmaceutical cocrystals of two API’s, caffeine and Pentoxifylline.

Research has indicated that caffeine has the ability to reverse Aβ plaque deposition in the brain (believed to be the primary cause of Alzheimer’s pathogenesis) and thus revert memory and improve cognitive impairment. But owing to the fast absorption rate and short half life, a controlled release formulation of caffeine would be clinically beneficial. Thus, novel cocrystals of caffeine are presented with varying solubilities with respect to caffeine. The pharmaceutical cocrystals of caffeine used herein include: caffeine-cyanuric acid monohydrate, caffeine-syringic acid tetrahydrate, caffeine-chlorogenic acid and caffeine-catechin hydrate. Three caffeine cocrystals were prepared in our lab previously which include caffeine-ferulic acid, caffeine-ethyl gallate dihydrate and caffeine-caffeic acid. In addition, six caffeine cocrystal forms were reproduced from the literature and included in the solubility study: caffeine· quercetin, caffeine-salicylic acid, caffeine-1-hydroxy-2-napthoic acid, caffeine-gallic acid hemihydrate, caffeine-ellagic acid monohydrate and caffeine· coumaric acid. Dissolution studies were performed in aqueous media at room temperature. All of the cocrystals decreased the solubility of caffeine with the highest being a 278 fold decrease in the solubility of caffeine. Analysis of melting point, crystal packing efficiency and solubility of cocrystal former with solubility was
also done to determine if they influenced the solubility. Presented herein are the results of the analyses. It was seen that solubility of the cocrystal former had no effect on the decrease in cocrystal solubility. Moreover melting point and solubility of the cocrystal could not be correlated probably due to the variability in the cocrystal formers. Crystal packing efficiency though did not show a high correlation with solubility but it was seen that highest solubility achieved by pure caffeine achieved the lowest crystal packing efficiency and vice versa suggesting its role in cocrystal solubility.

Pentoxifylline is contraindicated for its use in autism. But owing to high solubility of the drug, a less soluble form of the drug would help in decreasing the half life and thereby help in forming a sustained form of the drug by modifying the inherent solubility of the API. Here, novel cocrystals of Pentoxifylline are presented with varying solubilities with respect to the API. The pharmaceutical cocrystals used herein include: pentoxifylline-benzoic acid, pentoxifylline-1-hydroxy-2-napthoic acid, pentoxifylline-salicylic acid, pentoxifylline-gallic acid, pentoxifylline-salicylamide, pentoxifylline-coumaric acid, pentoxifylline-caffeic acid and pentoxifylline-catechin hydrate. Dissolution studies were also performed in aqueous media at room temperature. All of the cocrystals decreased the solubility of Pentoxifylline with the highest being a 99 fold decrease in the solubility with pentoxifylline-coumaric acid. On analyzing melting point, crystal packing efficiency and relation of solubility of cocrystal former with solubility of cocrystal, as was done in the case of caffeine, the parameters showed no effect on solubility of the cocrystal.
1. CHAPTER 1: INTRODUCTION

1.1. Crystal Engineering

Crystal Engineering, a part of organic solid state chemistry was introduced in 1955 by Pepinsky and established by Schmidt through the topochemical reactions on cinnamic acid. Though Schmidt and his contemporaries worked on this newly formed field to discover structures with reference to assembly of molecules and thereby stability in structures with the help of X-ray crystallography, this field gained prominence from the 1900’s with the advent of metal organics, organometallics and organic solids and since then the field of crystal engineering has advanced resulting in greater understanding of how to design viable crystalline forms. Gautam Desiraju, a pioneer in the field, defined crystal engineering as “the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties”. Intermolecular forces play a vital role in crystal engineering and the most important being non covalent interactions which includes hydrogen bonding, Van der Waals forces, hydrophobic forces, electrostatic forces and π-π interactions , which further help in crystal packing and self assembly. Crystal engineering is also based on the principle of understanding motifs present in a molecule, leading to the formation of “synthons” using non covalent interactions. The term “synthons” as defined by Corey are “structural units within
molecules which can be formed and/or assembled by known or conceivable synthetic operations”. Desiraju further utilized this concept to define “supramolecular synthons” which are defined as “structural units within supermolecules which can be formed and/or assembled by known or conceivable intermolecular interactions”, in the context of a set of compounds known as “Cocrystals”. Supramolecular synthons are categorized further into 2 classes (a) supramolecular homosynthons: composed of identical self-complementary functionalities (b) supramolecular heterosynthons: composed of different but complementary functionalities. Figure 1.1(a) illustrates a supramolecular homosynthon, usually formed between similar types of functional groups and in this case between two carboxylic acid molecules to form a dimer and 1.1(b) illustrates a supramolecular heterosynthon, usually formed between competing and complementary functional groups, and in this case between a carboxylic acid and amide.

![Figure 1.1](image)

**Figure 1.1.** (a) A supramolecular homosynthon is formed between identical functional groups, in this case between two carboxylic acid moieties to form a dimer.

(b) A supramolecular heterosynthon is formed between complementary but different functional groups, in this case between carboxylic acid and amide moieties.
1.2. Cocrystals

Cocrystals, a class of compounds for which the principles of crystal engineering are utilized, have gained a lot of recent attention owing to their amenability to design and their ability to tailor physiochemical properties. They represent a class of compounds with huge potential and play an important part in chemistry and pharmaceuticals especially in the field of non linear optics, purification, polymorphism, chiral separation, discovery of persistent synthons and also modifying physicochemical properties of API’s.

As the properties of a compound depends on the arrangement of the atoms in the crystal structure, designing “crystals with a purpose” and thereby modifying its properties has resulted in the development of cocrystals. They are a “long known but little studied” set of compounds which constitute only c.a. 0.5% of the Cambridge Structural Database. This class of compounds was popularized by Etter. The first cocrystal synthesized was quinhydrone which is a 1:1 cocrystal between benzoquinone and hydroquinone as illustrated in Figure 1.2 and was made by Wohler in 1844.
The first cocrystal, Quinhydrone was reported in 1844. It is a 1:1 cocrystal between benzoquinone and hydroquinone (CSD Refcode: QUIDON). Following this, Hoogsten in 1963 synthesized a complex between 1-methyl thymine and 1-methyl adenine as seen in DNA base pairing and used the term “cocrystal “for the first time. Figure 1.3 illustrates Hoogsten’s base pairing in the complex.

Hoogsten’s “cocrystal” between 1-methyl adenine and 1-methyl thymine forms a supramolecular heterosynthon (CSD Refcode: MTHMAD).

Probably the most prominent biological example of a cocrystal is the base pairing observed in DNA which shows a strong hydrogen bonding between the purines and pyrimidines.
Cocrystals have been defined in various ways by various people and have been named as “Addition Compounds” (early 1900’s), “Organic Molecular Compounds” (1937), “Complexes” (1960’s) or “Heteromolecular Crystals” (2005) from time to time. Accordingly cocrystals defined in our lab states that they are “a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components or cocrystal formers coexist as a stoichiometric ratio of a target molecule or ion and a neutral molecular cocrystal former(s)”.

This definition excludes clathrates, solvates and hydrates. As seen from the definition above, cocrystals contain two or more components which are held together by supramolecular synthons. In order to achieve that, complementary or similar functional groups in each molecule capable of forming supramolecular hetero or homosynthons help in the design of a crystal. Thus the radical in developing a cocrystals lies in the following 1) Choosing the target molecule 2) Finding the complementary functional groups which is capable of forming a hydrogen bond. 3) Methods of Preparation. This is known as the supramolecular synthons approach which in conjunction with analysis of the current structural data from the Cambridge Structural Database helps in the discovery of cocrystals.

1.3. Pharmaceutical Cocrystals

Crystal form screening of APIs has become an integral part of the pharmaceutical industry. This is due to the inherent nature of crystalline forms maintaining stability
compared to amorphous forms. Different crystal forms that can be discovered include salts, \(^{28}\) hydrates, \(^{29}\) solvates, and cocrystals. \(^{9}\)

Pharmaceutical cocrystals, \(^{20, 21}\) a highly studied subset of cocrystals, afford new crystal forms of APIs and can be defined as, “a multiple component crystal in which at least one component is molecular and a solid at room temperature and forms a supramolecular synthons with a molecular or ionic API.” \(^{20(a)}\) Over the years pharmaceutical cocrystals have been studied in the context of improving physicochemical properties including modifying the solubility of the parent API. \(^{22}\) Herein reported is a study on the solubility of caffeine and Pentoxifylline, two molecules amenable to crystal engineering due to their hydrogen bond acceptors, and discuss the use of cocrystallization to tailor its solubility.

Crystalline forms of API are sought as they provide stability and also helps in the formation of pure products. But these are also subjected to various complications arising from polymorphism \(^{26}\), low aqueous solubility, amorphous nature. The existence of polymorphism for an API creates lots of problems arising from instability during drug formulation.

Crystal engineering has created a paradigm to improve these problems. \(^{20(a)}\) Usually when a new API comes into discovery, and has limited physical properties, it is converted to a salt form of the drug based on the ionizable functional groups in it. \(^{28}\) Salt formation has been shown to be an effective tool for bettering properties without affecting the biological activity. But the FDA recognizes some 90 acids and 30 bases for salt formation and the presence of ionisable group makes it again a limited approach for neutral molecules. \(^{28}\) Cocrystals have come in to cross the barrier due to the large group of
pharmaceutically accepted compounds which can be used in its design without changing any properties. Pharmaceutical cocrystals opens door for multiple functional groups (including weakly or nonionizable) and molecules that possess a broader range of hydrogen bonding moieties. There are various pharmaceutical cocrystals that have been made in this context and examples to show how they can improve physicochemical properties also exist. Other factors which make this such a versatile class of compound include 1) Intellectual property rights – it is considered to be a new compound, so can be patented. 2) It has new physical properties 3) It can be designed and does not need difficult steps for synthesis.

To exemplify this, Fluoxetine Hydrochloride, also known as Prozac® is a good example. It a popular antidepressant which is used to treat depression and bipolar disorder. The salt form of the drug was cocrystallized with carboxylic acids like benzoic, succinic and fumaric acid. On performing powder dissolution studies in water on the API and its cocrystals for 120 minutes the dissolution profile generated was as seen as in Figure 1.4 (a) below.
Figure 1.4. (a) The powder dissolution profile of cocrystals of Prozac® measured over 120 minutes shows higher solubility, lower solubility and dissociation for fumaric acid, benzoic acid and succinic acid cocrystals respectively. (b) Chemical structure of Prozac®.

As seen in the profile, the cocrystal with succinic acid is seen to dissociate quickly in solution, and finally recrystallizing out as the API. The cocrystal with fumaric acid shows solubility higher than the parent API suggesting higher bioavailability and with benzoic acid, a decrease in the solubility is observed.

This clearly exemplifies that cocrystals have the capacity to modify the intrinsic solubility of a molecule/API by either increasing or decreasing the solubility.

To exemplify how pharmaceutical cocrystals can modify bioavailability, a good example would be that of Carbamezepine (CBZ), popularly known as Tegretol® which has limited solubility. The cocrystal of CBZ with saccharin is more soluble than the pure API and its dehydrate form. The bioavailability when tested in vivo on dog plasma showed that the cocrystal had improved bioavailability as compared to the pure API. Figure 1.5(a)
illustrates the in vivo bioavailability studies performed on CBZ (b) depicts the crystal structure of the Carbamezepine-Saccharin cocrystal. 21(a)

Figure 1.5. (a) In vivo studies conducted on Tegretol® cocrystal upon dogs showed that the cocrystal (red) had improved bioavailability as compared to the pure API (blue). (b) Crystal structure of the Carbamezepine-Saccharin cocrystal. Pharmaceutical cocrystals also have shown enhanced stability as for the case of Caffeine·Oxalic acid cocrystal as illustrated in Figure 1.6, which exhibited higher stability to moisture as compared to other cocrystals of caffeine and also pure caffeine itself. 31

Figure 1.6. The Caffeine Oxalic acid cocrystal (CSD Refcode : GANXUP) that is sustained by hydrogen bonding between an aromatic nitrogen of caffeine and carboxylic acid moieties exhibited higher stability to hydration than pure caffeine.
Thus as illustrated pharmaceutical cocrystals have wide range of benefits and play a important role in the field of pharmaceuticals and in the following chapters, pharmaceutical cocrystals of two API's caffeine and Pentoxifylline are discussed along with solubility studies performed on them and finally analysis of melting point, crystal packing efficiency and solubility of cocrystal former with measured cocrystal solubility was also done to determine if they influenced the overall solubility. Presented herein are also the results of the analyses.

1.4. Cambridge Structural Database

Cambridge Structural Database (CSD) as mentioned above is an essential tool in the field of crystal engineering. Data collected from this software helps in understanding the supramolecular synthons that could be formed between functional groups. With those statistics it is easier to understand what complementary functional groups would be promising for the functional groups in a target molecule and thus the cocrystal formers can be selected.

The CSD was developed in 1965 in Cambridge University by Kennard. It contains results of X-ray and neutron diffraction studies of organics, organometallics and complexes of metals. The database stores bibliographic information, crystallographic data and chemical connectivity information for each entry which is named as a refcode. The CSD consists of 4 components a) ConQuest: allows searching information and retrieving it. b) Mercury: helps in visually looking at a structure. c) Vista: provides numerical analysis and d) PreQuest: helps in database creation.
The CSD has grown over time with a huge number of structures being deposited every year and as of 2011, the total number of structures in the system has gone up to 562,000. And thus this has become a versatile tool and a prerequisite before any crystal engineering experiment.

1.5. Biopharmaceutics Classification System

The Biopharmaceutics Classification System (BCS) was developed in 1995 by Amidon and coworkers which correlates in vitro drug dissolution and in vivo drug bioavailability. For orally delivered drugs, drug dissolution and permeability in the G.I tract are now understood as mandatory requisites. This formed the basis of the correlation developed. The BCS system classified drugs into 4 categories, based on aqueous solubility and permeability as shown in Figure 1.7 below. 32(a)

![Figure 1.7](image)

**Figure 1.7. The Biopharmaceutics Classification System is based on aqueous solubility and permeability.**

- a) Class I: Represents drugs with high permeability and high solubility.
- b) Class II: Represents drugs with high permeability and low solubility.
- c) Class III: Represents drugs with low permeability and high solubility.
d) Class IV: Represents drugs with low permeability and low solubility.

Cocrystallization is a very good technique to increase the bulk solubility for drugs with low solubility which belongs to BCS Class II and IV. As discussed above, for example with CBZ which has limited solubility and cocrystallization helped to increase the solubility of the drug.

The FDA guidance of BCS which was brought about in 2000, classifies a substance to be highly soluble when the highest dosage is soluble in 250 mL or less aqueous media over pH range of 1-7.5. It classifies a substance to be highly permeable when the extent of absorption in humans is determined to be > 90% of an administered dose based on mass-balance or in comparison to an intravenous reference dose.\(^{32(b)}\)

Caffeine and Pentoxifylline the two API investigated here are both BCS class I drugs and in this case the solubility of the API’s were decreased by cocrystallization.

### 1.6. REFERENCES


2. CHAPTER 2: PHARMACEUTICAL COCRYSTALS OF CAFFEINE

2.1. Introduction

Caffeine (1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione)\(^\text{12}\) is a natural alkaloid, methyl xanthine, found in various plants. It is a bitter white solid, BCS class I\(^\text{26}\) API, whose solubility in water is 22 mg/mL at 25 °C. It is the active ingredient in coffee and tea\(^\text{13}\) and is the most consumed central nervous system stimulant by man. Caffeine is present in medications for asthma, apnea in newborns,\(^\text{14}\) and also some over-the-counter medications for headaches.

![Figure 2.1. The molecular structure of Caffeine (CSD Refcode: NIWFEE02)]
2.2. Caffeine Metabolism and Pharmacokinetics

Caffeine is metabolized in the liver with the help of cytochrome P450 oxidase enzymes to form monomethyl xanthenes, dimethyl xanthenes, monomethyl uric acids, trimethyl and dimethyl allantoin and also uracil derivatives. The principle dimethyl xanthenes formed after metabolism are paraxanthine, theophylline and theobromine which are potent compounds themselves.\textsuperscript{17(a)}

After consumption it gets absorbed from the gastrointestinal (GI) tract rapidly and almost completely in humans in around 30 to 45 minutes.\textsuperscript{15} The half-life of caffeine has a wide range (2.7-9.9.hours) primarily due to intra-subject variability.\textsuperscript{15, 16} Caffeine has shown to be effective against various diseases including Type II diabetes\textsuperscript{17} and Alzheimer’s.\textsuperscript{19}

2.3. Caffeine and Alzheimer’s disease

Alzheimer’s Disease (AD) is a neurodegenerative, incurable disease which usually affects people of age 65 and up.\textsuperscript{17(c)} Current AD drugs can ameliorate the cognitive deficits to a certain degree to provide relief but not reverse the effects of AD. Deposition and further aggregation of the protein β-Amyloid (Aβ) in the brain is believed to be the cause of AD pathogenesis\textsuperscript{18, 19, 20(c)}. In lieu of that, research to prevent deposition of Aβ, production or removal of Aβ is being conducted. Decreasing Aβ deposition through inhibition of β or γ-secretase or promoting the non-amyloidogenic processing of the amyloid precursor protein (APP) through promotion of α-secretase activity are other arenas of research for the treatment of AD.\textsuperscript{20(a)} Direct removal of monomeric Aβ on the other hand has benefits but can also lead to erroneous consequences since it also has
normal cognitive functions in the brain. Caffeine has been shown to suppress Aβ deposition by reduction of β-secretase and γ-secretase, two enzymes responsible for Aβ production in the brain and thus revert the progression of AD pathogenesis.

With caffeine having a rapid absorption rate and variable-to-short half-life, creation of a sustained dosage form of caffeine for AD patients could aid in dispensing the drug to AD patients over a considerable time period. The proposal is the eventual use of caffeine cocrystals for this purpose. The existing sustained release formulations of caffeine, in the form of chewing gums or microparticulate caffeine slow down its dissolution using formulation changes but do not tailor caffeine’s thermodynamic solubility. Since pharmaceutical cocrystals have been successfully used to modify the solubility of many APIs and caffeine’s therapeutic potential is high, there is sufficient motivation to clinically develop and study alternate caffeine crystal forms.

2.4. Caffeine cocrystals in CSD

Caffeine has been well studied and various crystal forms of the drug have been isolated and published. A more detailed analysis of the structures reported in the CSD showed that caffeine has been cocrystallized with carboxylic acids, polyphenols and other APIs like sulfaproxilne and sulfaacetamide. Therefore, using the supramolecular synthon approach and statistics from CSD, cocrystal synthesis through crystal engineering was achieved. It is shown here that caffeine can be cocrystallized with nutraceuticals and pharmaceutically acceptable or approved compounds. Solubility studies were performed on novel as well as a selected set of
previously reported cocrystals. Further analyses were done on the data collected to study the impact physicochemical properties and crystal packing had upon solubility.

2.5. Experimental Section

2.5.1 Synthesis of Cocrystals

Caffeine was cocrystallized with four compounds, namely cyanuric acid, syringic acid, catechin hydrate and chlorogenic acid. The other cocrystal formers used in this study were 1-hydroxy-2-napthoic acid, quercetin, salicylic acid coumaric acid, ellagic acid, ferulic acid, gallic acid, ethyl gallate, caffeic acid and the cocrystals were prepared as previously reported in the literature 27,28,29,30 or prepared previously in our lab. Figure 2.2 shows the chemical structures of caffeine and the cocystal formers which were used in this study. They have all been given a 3 lettered refcode which will be used hence forth. All the cocrystal formers used were either Generally Regarded as Safe compounds (GRAS) 47 or included in the Every Added to Food in United States (EAFUS) 48 list. Cocrystallization with the cocrystal formers mentioned resulted in successful cocrystal formation of caffeine via multiple synthetic methods such as slow evaporation, solvent drop and neat grinding 57 and also slurring techniques 28. Single crystals suitable for X-ray diffraction studies were also made for some cocrystals.
2.5.2. Caffeine·Cyanuric acid monohydrate, CAFCYA.H₂O (2:1:1)

The cocrystal was made via multiple methods (a) Solvent drop grinding: 0.038g (0.000195mmol) of caffeine and 0.013g (0.0001 mmol) cyanuric acid were ground with 50 µL of ethanol for fifteen minutes in a ball mill with two balls and it gave rise to CAFCYA with approximately 100% conversion. Solvent drop grinding with water and dimethyl formamide (DMF) also resulted in CAFCYA. (b) Dry grinding: 0.038g (0.000195mmol) of caffeine and 0.013g (0.0001 mmol) cyanuric acid were ground without any solvent and also resulted in CAFCYA with approximately 100% conversion. (c) Slurry: 0.38 g (0.00195 mmol) of caffeine and 0.13 g (0.001 mmol) of cyanuric acid was slurried at ca. 125 rpm in 4 mL of acetonitrile overnight under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid shows 100% conversion to CAFCYA. The filtrate from the slurry was left for slow evaporation and afforded block shaped crystals with 60% yield after seven days which were used for single crystals X ray diffraction.
2.5.3. Caffeine·Ferulic acid, CAFFER

The cocrystal was made via the following method in our lab (a) Slurry: 0.19 g (0.000097 mmol) of caffeine and 0.19g of ferulic acid (0.000097 mmol) was slurried at ca. 125 rpm in 4 mL of methanol overnight under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid from the experiment gave 100% yield of CAFFER.

2.5.4. Caffeine·Syringic acid tetrahydrate ,CAFSYR.4H2O (1:1:4)

This cocrystal was also made via multiple methods (a) Solvent drop grinding: 0.038 g (0.000195mmol) of caffeine and 0.040g (0.0002 mmol) of syringic acid were ground
with 50 μL of ethanol, water and DMF for fifteen minutes in a ball mill with two balls resulting in CAFSYR with around 100 % yield.(b) Dry grinding: 0.038 g (0.000195mmol) of caffeine and 0.040g (0.0002 mmol) of syringic acid was ground without any solvent but resulted in total conversion to CAFSYR. (c) Slurry: 0.19 g (0.00097 mmol) of caffeine and 0.20g of syringic acid (0.001 mmol) was slurried at ca. 125 rpm in 5 mL of water overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid gave 100% conversion to CAFSYR. The filtrate from the slurry was left for slow evaporation and gave rise to needle shaped crystals with 85 % yield after 10 days which was used for single crystal analysis.

2.5.5. Caffeine-Ethyl gallate dihydrate, CAFETG.2H2O (1:1:2)

This cocrystal was also made via the slurring technique in our lab (a) Slurry: 0.19 g (0.00097 mmol) of caffeine and 0.20g of ethyl gallate (0.001 mmol) was slurried at ca. 125 rpm 3 mL of a 50:50 mixture of ethanol: water, overnight under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The solid resulted in total conversion to CAFETG.

2.5.6. Caffeine-Caffeic acid, CAFCFA

This cocrystal was prepared via the following method in our lab. (a) Slurry: 0.19 g (0.00097 mmol) of caffeine and 0.18 g of caffeic acid (0.001 mmol) was slurried at ca.
125 rpm in 5 mL of water overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid gave 100% conversion to CAFCFA.

### 2.5.7. Caffeine-Chlorogenic acid, CAFCGA

0.38 g (0.00097 mmol) of caffeine and 0.354 g of chlorogenic acid (0.001 mmol) was slurried at ca. 125 rpm in 1 mL of water overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid showed 100% conversion to CAFCGA. Suitable single crystals for X-ray diffraction studies could not be grown for this cocrystal.

### 2.5.8. Caffeine-Quercetin methanol solvate, CAFQUE.MeOH (1:1:1)

This cocrystal was prepared by in our lab by taking 0.19 g (0.00097 mmol) of caffeine and 0.34 g (0.001 mmol) of quercetin was slurried at ca. 125 rpm 5 mL of methanol, overnight under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The solid resulted in 100% cocrystal CAFQUE.

### 2.5.9. Caffeine-Salicylic acid, CAFSAL (1:1)

The cocrystal was prepared as outlined in the paper by Bucar et al. 27
2.5.10. Caffeine-1-hydroxy-2-napthoic acid, CAF1HY (1:1)

The cocrystal was prepared as outlined in the paper by Bucar et al. 28

2.5.11. Caffeine-Ellagic acid Monohydrate, CAFELA.H₂O (1:1:1)

The cocrystal was prepared as outlined in the paper by Clarke et al. 29

2.5.12. Caffeine-Gallic acid Hemihydrate, CAFGAL.0.5H₂O (1:1:0.5)

The cocrystal was prepared as outlined in the paper by Clarke et al. 29

2.5.13. Caffeine-Coumaric acid, CAFCOU (2:1)

The cocrystal was prepared as outlined in the paper by Schultheiss et al. 30

2.5.14. Caffeine-Catechin Hydrate, CAFCAT

This cocrystal was prepared by in our lab by taking 0.19 g (0.00097 mmol) of caffeine and 0.29 g (0.001 mmol) of catechin hydrate was slurried at ca. 125 rpm five ml of ethyl acetate, overnight under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The solid resulted in 100% cocrystal CAFCAT. Single crystals could not be grown for this cocrystal but the cell parameters and space group were retrieved.
2.5.15. Dissolution studies on cocrystals

Powder dissolution studies were performed on all cocrystals and pure caffeine. The study was performed in deionized water at room temperature. All the crystal forms were sieved to get consistent particle sizes between 53 -75µm as the dissolution rate is affected by particle size. Supersaturated slurries were stirred with magnetic stir bars at a rate of 125 rpm. Dissolution rate was determined by drawing fixed aliquots with a syringe and filtering through 0.45µm filters after 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 120, 150, 180, 240, and 2400 minutes. The solutions were analyzed to determine the concentration of caffeine using HPLC with UV/Vis detection. The experiment was done in triplicate to allow for statistical analysis. The leftover solid was characterized at the end of the study to identify the solid phase post dissolution.38

2.6. Results And Discussion

2.6.1. Cocrystals of Caffeine

Caffeine has been a molecule of choice in the field of crystal engineering owing to its capacity to readily form hydrogen bonds with complementary functional groups such as carboxylic acids, polyphenols and amides and these types supramolecular heterosynthons formation are exemplified by structures deposited in the CSD.25 A survey of the CSD (version 5.32, May 2011 update) was carried out using ConQuest (version 1.13) and the search was limited to organic molecules with determined 3D coordinates determined and
This survey revealed 44 entries of caffeine including solvates. A caffeine molecule has three hydrogen bond acceptors including an aromatic nitrogen in the imidazole ring (N_{arom}) and two carbonyl groups. Carboxylic acids, alcohols, phenols and amides have hydrogen bond donors which readily participate in hydrogen bonding and the CSD survey mentioned above contained these types of hydrogen bond donors interacting with caffeine. On performing a CSD analysis with these acceptor centers in an earlier study, it has been seen that the N_{arom}···COOH supramolecular heterosynthon has a 98% occurrence, the N_{arom}···OH has a 78% occurrence incidence and N_{arom}···CONH$_2$ has a 33% incidence of occurrence; in the absence of competing functional group and homosynthons. A similar statistical analysis conducted for the carbonyl group determined that the carbonyl group specific to the structure has lower incidences of bonding with carboxylic acids, alcohols, phenols and amides.

In the study, caffeine cocrystals with 1-hydroxy-2-napthoic acid (KIGKIV), salicylic acid (XOBCAT), coumaric acid, gallic acid, ellagic acid and quercetin have been included from the literature. Cocrystals of caffeine with gallic acid, ellagic acid and quercetin were made in our lab and published earlier. It has been remade and used for the purpose of this study.

The statistics concretely shows that the radical for using the three complementary groups are promising and logical choices for cocrystallization.

The cocrystal formers that were targeted for the study are illustrated in Table 2.1, 2.2 and 2.3 below.
### Table 2.1. Cocrystal formers- carboxylic acids

<table>
<thead>
<tr>
<th>Name</th>
<th>M.W</th>
<th>M.P</th>
<th>pka</th>
<th>LD 50(mg/kg)</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolic acid</td>
<td>76.05</td>
<td>75-80</td>
<td>3.82</td>
<td>1950, oral rat</td>
<td>soluble</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>138</td>
<td>158</td>
<td>2.97</td>
<td>891, oral rat</td>
<td>2</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>122.12</td>
<td>122.4</td>
<td>4.21</td>
<td>oral, rat 1700</td>
<td>3.4</td>
</tr>
</tbody>
</table>

### Table 2.2. Cocrystal formers – polyphenols and flavanoids

<table>
<thead>
<tr>
<th>Name</th>
<th>pka</th>
<th>LD 50(mg/kg)</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeic acid</td>
<td>4.4</td>
<td>721</td>
<td>0.7</td>
</tr>
<tr>
<td>Gallic acid</td>
<td>4.5,10</td>
<td>5000</td>
<td>11</td>
</tr>
<tr>
<td>Catechin Hydrate</td>
<td>7.8</td>
<td>3890</td>
<td>1.6</td>
</tr>
<tr>
<td>Syringic acid</td>
<td>4.33, 7.5</td>
<td>2000</td>
<td>0.57</td>
</tr>
<tr>
<td>Chlorogenic acid</td>
<td>3.34</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Coumaric acid</td>
<td>4.4,9.35</td>
<td>2850</td>
<td>0.8</td>
</tr>
<tr>
<td>Ferulic acid</td>
<td>4.8,9.4</td>
<td>3890</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Table 2.3. Cocrystal formers- amides

<table>
<thead>
<tr>
<th>Name</th>
<th>M.W</th>
<th>pka</th>
<th>Solubility (mg/ml)</th>
<th>LD 50(mg/kg)</th>
<th>M.P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanuric acid</td>
<td>129.07</td>
<td>6.9</td>
<td>2.7</td>
<td>7700 Rat oral.</td>
<td>320-360</td>
</tr>
<tr>
<td>Iso nicotinamide</td>
<td>122.12</td>
<td>3.67</td>
<td>191.7</td>
<td>78 rat oral</td>
<td>155-158</td>
</tr>
<tr>
<td>Salicylamide</td>
<td>137.136</td>
<td>8.32</td>
<td>soluble</td>
<td>980 , rat oral</td>
<td>140</td>
</tr>
</tbody>
</table>

2.6.2. Crystal Structure Discussion: Caffeine Cyanuric acid monohydrate 2:1:1

Caffeine. Cyanuric acid, CAFCYA crystallizes in the space group $P2_1/n$. The asymmetric unit contains two caffeine molecules, one cyanuric acid and one water molecule. Figure 2.3 demonstrates hydrogen bonding between the molecules which are arranged in tapes, in one sheet. Each cyanuric acid molecule acts as a donor to two caffeine molecules through interaction with the imidazole nitrogens, N···N. 2.913(5) Å, 2.953(5) Å, and one water molecule with an N···O distance of 2.712(4) Å. The water molecule also hydrogen bonds to a carbonyl of another cyanuric acid molecule with an O···O distance of 2.753(4) Å thereby connecting the cyanuric acid molecules in a chain. The water molecule which connects the cyanuric acids, is also seen to participate in hydrogen bonding with one carbonyl (adjacent to the imidazole ring) of caffeine in the sheet below it with an O···O distance of 2.791(5) Å as depicted in Figure 2.4. This finally results in the bilayer sheets
supported by $\pi$-$\pi$ interactions, depicted for clarity in two colors and designated as AABBAABB in Figure 2.5. Data were collected on single crystals of CAFCYA and CAFSYR on a Bruker-AXS SMART APEX 2 CCD diffractometer with monochromatized Cu Kα radiation ($\lambda = 1.54178$ Å). The diffractometer was connected to a KRYO-FLEX low temperature device. Data for CAFCYA was collected at 105 K and CAFSYR at 293 K. Indexing was performed using SMART v5.625 \(^{31(a)}\) or using APEX 2008v1-0. \(^{31(b)}\) Frames were integrated with SaintPlus 7.51 \(^{32}\) software package. Absorption corrections were performed by multi-scan method implemented in SADABS. \(^{33}\) The structures were solved using SHELXS-97 and refined using SHELXL-97 (Matrix Non-Linear Least-Squares) contained in SHELXTL v6.10 \(^{34}\) and WinGX v1.70.01 \(^{35,36,37}\) program packages.

A search for cyanuric acid in the CSD revealed 12 cocrystals of the compound. Out of them, in cyanuric-urea (PANVUV), the NH of cyanuric acid forms a supramolecular heterosynthon with the amide group of urea, cyanuric acid-phenazine (YIZXID) shows cyanuric acid molecules forming dimers with each other and the phenazine molecules stacked by $\pi$-$\pi$ interactions. BADCUR, cocrystal between cyanuric acid and 8-bromo 9-ethylene adenine is a monohydrate where water bridges the compounds together in the lattice. Other than these, all the other 9 cocrystals reported, HADCU, ZIHEE, MOPYAR, VEDFAM, YIZXAH, VEXQUE and VEXQUK show supramolecular heterosynthon between aromatic nitrogen and NH of cyanuric acid.
Figure 2.3. Hydrogen bonding observed in CAFCYA.H₂O reveals that the aromatic nitrogen of caffeine forms a supramolecular heterosynthon with the NH group on cyanuric acid molecules. Cyanuric acid molecules are connected by water molecule thereby affording a tape like structure.

Figure 2.4. Stacking of CAFCYA.H₂O sheets viewed along b-axis. Water molecules bridge the layers.
2.6.3. Caffeine·Syringic acid tetrahydrate 1:1:4

The cocrystal caffeine-syringic acid, CAFSYR crystallizes in Fdd2. Each asymmetric unit contains one caffeine molecule, one syringic acid molecule and four water molecules. The interactions between the molecules are shown in Figure 2.6. The carbonyl moiety in the carboxylic acid in syringic acid engages in hydrogen bonding with one water molecule at an O···O distance of 2.8(4) Å. This water molecule in turn engages in hydrogen bonding with two additional water molecules, to form an O···O hydrogen bonded chain, O···O, 2.7(5) Å, 2.8(6) Å. The hydroxyl moiety of the carboxylic acid on syringic acid hydrogen bonds to a third water molecule, via O···O interactions at distances of 2.6 (4) Å which is in turn hydrogen bonds to the aromatic nitrogen of caffeine on one side through an O···N interaction, O···N at a distance of 2.8(5) Å and another water molecule above, OH···O at a distance of 2.9(5) Å. This water engages in hydrogen bond
with the carbonyl group adjacent to the imidazole ring of caffeine, O···O at a distance of 2.6(5) Å. The hydroxy group on syringic acid and one methoxy group bonds with the fourth water molecule O···O at a distance of 2.8 (4) Å. This water molecule now is found to bond with the first water molecule and another syringic acid molecule to form a terameric structure as shown in Figure 2.7. Intramolecular hydrogen bonding is also seen to occur between the hydroxyl group of syringic acid and methoxy group, O···O at a distance of 2.7 (4) Å. The water molecule which points downward forms the bridge, O···O at a distance of 2.8(5) Å.

A CSD analysis of syringic acid shows that there are no reported crystal forms of this compound, thereby making caffeine-syringic acid the first cocrystal ever reported.

Figure 2.6. Hydrogen bonding in CAFSYR.4H₂O reveal that carboxylic acid moieties and aromatic nitrogen atoms of caffeine form a heterosynthon with water.
2.6.4. Caffeine Chlorgenic acid, Caffeine Catechin Hydrate

These cocrystals were prepared via various methods in a 1:1 ratio as mentioned in the experimental section and characterized via PXRD, TGA, DSC and FT-IR. Efforts to prepare single crystals however did not yield any results as of yet. For caffeine-catechin hydrate though the crystal structure was not resolved but the cocrystal was indexed to P2₁2₁2₁.

A search of chlorogenic acid in the CSD yields 2 salt ⁴⁹ entries with caffeine, no cocrystals are reported. In case of catechin hydrate, only the crystal structure of catechin hydrate (LUXWOR) is reported, no cocrystals of catechin hydrate are reported making this one with caffeine the first reported cocrystal.
2.6.5. Dissolution and Solubility Studies

Powder dissolution studies were done on I-XII in aqueous media to determine the dissolution profile for each cocrystal. Caffeine’s dissolution profile was also determined over twenty-four hours to show the change of caffeine to caffeine monohydrate. For purposes of clarity, the time point for the 24th hour reading was changed to 480 minutes. This is made evident after the solubility of the anhydrous material reduces to 22.09 mg/mL which is in agreement with literature reported solubility of caffeine.50
Figure 2.8. Dissolution profiles in water for caffeine and CAFCYA.H₂O, CAFQUE.MeOH and CAFSAL.
Figure 2.9. Dissolution profiles in water for CAFFER, CAFETG.2 H₂O, CAFCOU, CAF1HY and CAFELA.H₂O.

The dissolution profiles have been divided into 2 figures for clarity. Figure 2.8 shows the kinetic solubility profiles of caffeine and caffeine cocrystals CAFCYA.H₂O, CAFQUE.MeOH and CAFSAL with solubility in the range of 3-22 mg/mL. Figure 2.9, shows the kinetic solubility profiles for cocrystals CAFFER, CAFETG.2H₂O, CAFCOU, CAF1HY and CAFELA.0.5H₂O with solubility ranging between 0.1-2.9
mg/mL. For cocrystals **CAFCGA, CAFGAL.0.5H₂O, CAFSYR.4H₂O** and **CAFCGA** the profiles generated are similar to those shown above.

From Noyes-Whitney’s initial experiments on dissolution, thermodynamic solubility of a crystal form is a fixed property upon which the rate of dissolution is dependant. With the change in thermodynamic solubility of the caffeine in the cocrystals, the dissolution rate is also modified and the smooth curves exemplify the constant dissolution rates achieved for the cocrystals. A comparative graph showing the thermodynamic solubility of each cocrystal and caffeine measured over twenty-four hours has been shown in the Figure 2.10. The figure demonstrates the wide range of solubility that has been achieved by different cocrystals.

![Figure 2.10. A comparison of the thermodynamic solubility of caffeine and its cocrystals.](image)
From the dissolution study it can be seen that $\text{CAFCYA.H}_2\text{O}$ showed maximum concentration of ca 12.6 mg/mL till 3 hours and then lowers down to ca 10 mg/mL over 24 hours. $\text{CAFQUE.MeOH}$ shows maximum concentration of ca 8.55 mg/mL by the end of 24 hours. $\text{CAFSAL}$’s dissolution profile shows a smooth plateau after reaching a maximum concentration of ca 3.5 mg/mL. $\text{CAFETG.2H}_2\text{O}$, $\text{CAF1HY}$, $\text{CAFELA.H}_2\text{O}$ and $\text{CAFCOU}$ also show smooth plateau like profiles with maximum concentration of ca 0.5 mg/mL ca 0.23 mg/mL, and ca 0.08 mg/mL, and ca 1.1 mg/mL respectively. On the other hand $\text{CAFER}$ shows a profile which shows maximum concentration at ca 3.3 mg/mL and then reducing to ca 2.85 mg/mL over 24 hours. The profile suggests that the crystal form shows signs of forming a hydrate after dissolving in water, which is less soluble than the anhydrous form $^{41, 42}$ but has the same powder pattern as seen before the study possibly implying formation of an isostructural hydrate of the crystal form.

The thermodynamic solubility data of $\text{CAFSYR.4H}_2\text{O}$ was found to be ca 1.17 mg/mL. The maximum concentrations of $\text{CAFCFA}$, $\text{CAFCGA}$ and $\text{CAFGAL.0.5H}_2\text{O}$ were recorded as follows ca. 0.6 mg/mL, 11.9 mg/mL and 5.7 mg/mL respectively. This solubility data clearly indicates that a lower solubility crystal form for caffeine can be achieved at different magnitudes depending on the cocrystal former employed which are thermodynamically stable over 8 hours. The PXRD and DSC’s of the residual solids were done after the study at the end of twenty four hours and it was found that the all the cocrystals were stable till that time period.
2.6.6. Caffeine as a drug

Amidon’s solubility studies tell us that for a drug to be freely soluble and permeable in the body the ideal solubility of the drug should be greater than or equal to 1 mg/mL. As seen from the data CAFCYA.H₂O, CAFER, CAFSYR.4H₂O, CAFCGA, CAFQUE.MeOH, CAFSAL, CAFGAL.0.5H₂O and CAFCOU achieve solubility above 1 mg/mL showcasing their suitability as drugs. As mentioned before, a slow release, sustained dosage form of caffeine is desirable for AD. The solubility data of these crystal forms exhibit a wide range of solubility and showcases their possible utility for a sustained dosage form of caffeine. Thus crystal engineering affords a wide range of solubility for an API through cocrystallization and this study clearly shows that the above mentioned cocrystals of caffeine can be used as suitable alternate forms for oral delivery as.

2.6.7. Correlation between Solubility and Melting Point

For thermodynamically stable cocrystals this correlation is important. It could help to know if solubility of an API could be tailored on the basis of melting point. Various studies have been done but this relation still remains elusive. Attempts to correlate the log of the solubility and the onset of the melting point of the cocrystal for this dataset were unsuccessful most probably due to the variability in the cocrystal formers used. (Shown in Figure 2.11 below). This result is consistent with Bak et al’s recent data. Table 2.4 below shows the comparison of melting points of cocrystal and cocrystal former.
Figure 2.11. Solubility of cocrystals shows no relationship with melting point probably due to the variability of coformers used.

Table 2.4. Melting points of the cocrystal formers and the cocrystals

<table>
<thead>
<tr>
<th>COCRYSTAL/COMPOUND</th>
<th>M.P. of compound/cocrystal (°C)</th>
<th>M.P of CCF (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAF</td>
<td>238</td>
<td></td>
</tr>
<tr>
<td>CAFCYA.H₂O</td>
<td>228</td>
<td>360 (decom)</td>
</tr>
<tr>
<td>CAFFER</td>
<td>147</td>
<td>168</td>
</tr>
<tr>
<td>CAFSYR.4H₂O</td>
<td>180</td>
<td>205</td>
</tr>
<tr>
<td>CAFETG.2H₂O</td>
<td>145</td>
<td>149</td>
</tr>
<tr>
<td>CAFCFA</td>
<td>200</td>
<td>211</td>
</tr>
<tr>
<td>CAFCGA</td>
<td>131</td>
<td>210</td>
</tr>
<tr>
<td>CAFQUE.MeOH</td>
<td>244</td>
<td>310</td>
</tr>
<tr>
<td>CAFSAL</td>
<td>147</td>
<td>158</td>
</tr>
<tr>
<td>CAFIHY</td>
<td>190</td>
<td>195</td>
</tr>
<tr>
<td>CAFELA.H₂O</td>
<td>304</td>
<td>360 (decom)</td>
</tr>
<tr>
<td>CAFGAL.0.5H₂O</td>
<td>244</td>
<td>268</td>
</tr>
<tr>
<td>CAFCOU</td>
<td>178</td>
<td>214</td>
</tr>
</tbody>
</table>

(* Melting points were taken from scifinder.org)
On trying to correlate these two parameters between specific classes of compounds, some correlations were observed. On comparing melting point onsets of cocrystals of caffeine with cinnamic and hydroxy cinnamic acids (ferulic acid, caffeic acid, coumaric acid and chlorogenic acid) a correlation of 85% was observed, as shown in Figure 2.12. It was seen that with increase in melting point of the cocrystal, a decrease in solubility occurred.

![Figure 2.12. Solubility of cocrystals shows a high correlation with melting point within the specific group of cinnamic and hydroxycinnamic acids.](image)

This study shows that compounds belonging to individual classes do show that solubility and melting point are related in some ways. To come to a consensus of how different classes of compounds might vary in solubility and if melting point is a versatile cocrystal design parameter, more systematic studies like need to be done amongst various classes of compounds for multicomponent cocrystals.
2.6.8. Correlation between solubility of cocrystal former to solubility of cocrystal

The collected data shows that there has been a decrease in the solubility of caffeine through cocrystallization as compared to the original API and in this context the above parameters were correlated to determine any relationship between them as shown in Figure 2.13 similar to analysis conducted by Nair et al where it was shown that with the increase in the solubility of the cocrystal former there is an increase in the solubility of cocrystal. \(^{44}\) It has been seen that in this case all the cocrystal formers are of solubility lower than and comparable to caffeine, the cocrystals are thermodynamically stable over 24 hours, and there is a general trend of decrease in caffeine solubility in the cocrystals. But there is no correlation observed that could help in prediction of solubility.

![Graph showing correlation between log([CCF]/[API]) and log([CC]/[API])](image)

Figure 2.13. On correlating cocrystal former solubility and cocrystal solubility no correlation other than the general decrease is observed in cocrystal solubility.
2.6.9. Correlation between solubility and crystal structure

All the cocrystals were classified according to their solubility following Amidon’s solubility classification. No trends could be seen when the study encompassed cocrystal formers of wide range of solubility as shown in Table 2.5. On then trying to see if the crystal structures themselves had an impact upon solubility. Amongst all the cocrystals CAFSAL, CAF1HY and CAFCOU are anhydrous structures, whereas others are hydrates or solvates. In lieu of that there is no structure specific property observed that could be distinguishing between the structures. Considering that N\textsubscript{arom} of caffeine is the principle hydrogen bond acceptor with phenols and carboxylic acids as compared to the other bond acceptors in caffeine, it has been seen that the principle synthons noticed involving the aromatic nitrogen do not render any conclusive result or relationship.

Table 2.5. Solubility classification of cocrystal formers according to Amidon

<table>
<thead>
<tr>
<th>Practically insoluble(&lt;0.1mg/mL) CCF</th>
<th>Very slightly soluble(0.1-1mg/mL) CCF</th>
<th>Slightly soluble(1-10mg/mL) CCF</th>
<th>Sparingly soluble(10-33mg/mL) CCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUERCETIN</td>
<td>COUMARIC ACID</td>
<td>CYANURIC ACID</td>
<td>GALLIC ACID</td>
</tr>
<tr>
<td>ELLAGIC ACID</td>
<td>FERULIC ACID</td>
<td>SALICYLIC ACID</td>
<td>CHLOROGENIC ACID</td>
</tr>
<tr>
<td>1-HYDROXY-2 NAPTHOIC ACID</td>
<td></td>
<td>ETHYL GALLATE</td>
<td></td>
</tr>
<tr>
<td>CAFFEIC ACID</td>
<td></td>
<td>SYRINGIC ACID</td>
<td></td>
</tr>
</tbody>
</table>
2.6.10. Relationship between Solubility and Crystal packing efficiency

Polymorphic compounds are known to have different crystal packing and that is one factor that contributes to different physicochemical properties between them. Since it is known that molecules arrange themselves in different ways, crystal packing efficiency is an important calculable parameter that could showcase and shed some light on the observed solubility. With new forms showing different physicochemical properties, it is envisaged that crystal packing plays a critical role. Crystal packing efficiency was calculated for the cocrystals of caffeine (using the software Platon) and correlated as a function of solubility. To define the regularities of formation of molecular crystals, Kitaigorodskii established the principle of close packing which is based on the understanding of the tendency of molecules to fill available space in the most efficient way with the greatest number of energetically favorable intermolecular van der Waals contacts. Crystal packing efficiency helps to calculate the efficiency of the molecules to pack closely. For organic molecules, efficiency is typically found to be in the range of 65%-77%. The following, Table 2.6, depicts solubility of the cocrystal/compound with single crystal data and its corresponding packing efficiency. Caffeine monohydrate’s packing efficiency was determined here as it is the thermodynamically stable form during dissolution and was thus a more appropriate compound to compare to than anhydrous caffeine.
Table 2.6. Crystal packing efficiency and solubility of caffeine monohydrate and crystal forms

<table>
<thead>
<tr>
<th>Compound/Cocrystal</th>
<th>Crystal packing efficiency(%)</th>
<th>Solubility(mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine Monohydrate</td>
<td>65</td>
<td>22.09</td>
</tr>
<tr>
<td>CAFCYA.H₂O</td>
<td>75</td>
<td>10.01</td>
</tr>
<tr>
<td>CAFSYR.4H₂O</td>
<td>72</td>
<td>1.17</td>
</tr>
<tr>
<td>CAFETG.2H₂O</td>
<td>70.1</td>
<td>0.56</td>
</tr>
<tr>
<td>CAFQUE.MeOH</td>
<td>72.9</td>
<td>8.55</td>
</tr>
<tr>
<td>CAFSAL</td>
<td>73.8</td>
<td>3.5</td>
</tr>
<tr>
<td>CAF1HY</td>
<td>71.8</td>
<td>0.23</td>
</tr>
<tr>
<td>CAFELA.H₂O</td>
<td>75.6</td>
<td>0.08</td>
</tr>
<tr>
<td>CAFGAL.0.5H₂O</td>
<td>74.9</td>
<td>5.7</td>
</tr>
</tbody>
</table>

As shown in Figure 2.14 below, there is a 41% correlation between crystal packing efficiency and solubility, which indeed provides the impression that crystal packing might play a role in the solubility of crystal forms. For example, caffeine monohydrate has the highest solubility and the lowest packing efficiency whereas CAFELA (X) has the highest packing efficiency and the lowest solubility, thus the crystal packing can have a vital effect upon the solubility of the crystal form.
Figure 2.14. On correlating crystal packing efficiency with solubility shows that highest packing efficiency is achieved by lowest solubility cocrystal and vice versa.

2.6.11. Determination of solubility of cocrystal former from solubility of cocrystal

It is definite that with change in solubility of API or principle cocrystal former in the cocrystal, there is also a change in the solubility of the other cocrystal former. In our cocrystals, the cocrystal formers are mostly nutraceuticals. Nutraceuticals \(^{55}\) are a class of compounds which benefits human health and is defined as a medicinal or nutritional component that includes a food, plant or naturally occurring material, which may have been purified or concentrated, and that is used for the improvement of health by preventing or treating a disease \(^{55(c)}\). They can be used as pharmaceuticals, dietary
supplements etc. Dietary polyphenols are also considered nutraceuticals. They are the principle antioxidants in food. 52,55(c).

The cocrystal formers cyanuric acid and 1-hydroxy-2-napthoic acid too are safe compounds. And as mentioned before, changes occur in both the formers during cocrystallization thereby helping in tailoring the solubility of both of the components in the cocrystal.

The experimental solubility of both caffeine and the cocrystal former’s were compared to the measured solubility of caffeine and literature values for the other cocrystal formers. The results are shown in the Table 2.7 below.

Notably, amongst all the cocrystal formers the two least soluble compounds, quercetin 59 and ellagic acid 60 have shown massive increase in solubility, approximately 5000 and 12-fold, respectively.

Table 2.7. Solubility modification (increase or decrease) of caffeine and other cocrystal former in caffeine crystal forms

<table>
<thead>
<tr>
<th>Cocrystal</th>
<th>With respect to CCF (Increase (inc)/Decrease (dec))</th>
<th>With respect to caffeine (decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAFCYA.H₂O</td>
<td>1.2 fold (inc)</td>
<td>-2 fold</td>
</tr>
<tr>
<td>CAFFER</td>
<td></td>
<td>-8 fold</td>
</tr>
<tr>
<td>CAFSYR.4H₂O</td>
<td>-0.209 fold (dec)</td>
<td>-19 fold</td>
</tr>
<tr>
<td>CAFETG.2H₂O</td>
<td>-0.1428 fold (dec)</td>
<td>-39 fold</td>
</tr>
<tr>
<td>CAFQUE.MeOH</td>
<td>5354 fold (inc)</td>
<td>-3 fold</td>
</tr>
<tr>
<td>API</td>
<td>Change</td>
<td>Solubility</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>CAFCFE</td>
<td>-33 fold</td>
<td></td>
</tr>
<tr>
<td>CAFCGA</td>
<td>-2 fold</td>
<td></td>
</tr>
<tr>
<td>CAFSAL</td>
<td>1.24 fold(inc)</td>
<td>-6 fold</td>
</tr>
<tr>
<td>CAFH1HY</td>
<td>-0.45 fold(dec)</td>
<td>-96 fold</td>
</tr>
<tr>
<td>CAFELA.H₂O</td>
<td>12.8 fold(inc)</td>
<td>-278 fold</td>
</tr>
<tr>
<td>CAFGAL.0.5H₂O</td>
<td>-0.45 fold(dec)</td>
<td>-4 fold</td>
</tr>
<tr>
<td>CAFCOU</td>
<td>-0.844 fold(dec)</td>
<td>-20 fold</td>
</tr>
</tbody>
</table>

Thereby, formation of cocrystals of API or compounds with the other component or cocrystal formers can be chosen in such a way during co crystallization such that the solubility of both the components altered can be beneficial to us.

2.7. Conclusion

In summary, pharmaceutical cocrystals posses the ability to tailor the aqueous solubility of an API. This statement is exemplified by the case study presented here where the cocrystals of caffeine lowered the solubility of caffeine, allowing for the potential of a slow release drug for the treatment of AD. 12 cocrystals of caffeine were studied and their solubility in water analyzed.
All the crystal forms were tested to determine the aqueous solubility and dissolution profile. All of them were found to be thermodynamically stable till after twenty-four hours. The dissolution profiles showed that CAFELA.H₂O had achieved the lowest concentration of 0.08 mg/mL. On looking at the profiles some have achieved solubilities above 1 mg/mL showcasing their suitability as a drug for AD which will be a slow release form of caffeine as visible from the smooth plateau’s of their dissolution profiles.

The effects of melting point, solubility of cocrystal former and crystal packing efficiency upon solubility were also studied. It was seen that, in general, melting point could not be correlated as a function of solubility probably due to the variability in cocrystal formers, but when correlated amongst specific class of compounds like the hydroxycinnamic acids, high correlations amongst these two parameters could be seen, suggesting that amongst specific classes even multicomponent cocrystals can show this correlation and can be used to tailor solubility based on the melting point that one would want.

Further studies were performed considering solubility as a function of crystal packing efficiency. Crystal packing is an important parameter for crystalline compounds. It was found from the data, that a 41% correlation occurs between solubility and packing efficiency; with the highest packing efficiency having the lowest solubility and vice versa. Caffeine monohydrate with the highest solubility had the lowest packing efficiency and all the cocrystals of varying solubility showed higher packing efficiency. This shows that this property could be important and will help in future understanding of cocrystal solubility.
Influence of supramolecular synthons could not be established as a function of solubility. In case of relation between the cocrystal former and cocrystal solubility, a general trend was observed, where coformers used herein with solubility lower than caffeine, an overall decrease in the solubility of the pure API occurred, but no specific relationship between them could be established showing that predicting solubility is not a possibility.

It was determined that solubility of the cocrystal formers alters the solubility of the target API or compound. More specifically, it was shown here that some cocrystal formers can have a huge impact upon solubility such as Quercetin. Quercetin is an insoluble flavonoid has shown an approx. 5000 fold increase in solubility as a cocrystal with caffeine. Ellagic acid another insoluble flavonoid showed a 12 fold increase in its solubility.

Caffeine’s solubility was thus successfully lowered through cocrystallization with nutraceutical or pharmaceutically acceptable compounds. Predictability of the resultant solubility through melting point or coformer solubility correlation was not successful but it was shown that cocrystals with packing efficiencies greater than caffeine hydrate maintained lower aqueous solubility’s over the time studied.

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38. The dissolution studies performed do not make use of the standard USP apparatus. This is due to the limitations of our in lab facilities. But the results produced are comparable reasonably to standards. As future development this study will be done with the help of contract research organization using the standard USP apparatus.


48. *Everything Added to Food Stuff in United States*,


50. Caffeine solubility, was determined gravimetrically in the lab and also found at http://www.pharmainfo.net/reviews/extraction-caffeine-tea-leaves.


3. CHAPTER 3: PHARMACEUTICAL COCRYSTALS OF PENTOXIFYLLINE

3.1. Introduction

Pentoxifylline popularly known as TRENTAL®, a drug sold by Aventis, is a methylxanthine derivative drug and belongs to the same class like caffeine, theophylline and theobromine. It is available as tablet, film-coated tablet and sugar-coated tablet formulations containing dosage of 100, 200 and 400 mg respectively. It is also administered intravenously.¹

It is a white, crystalline powder which has a bitter taste with slight odor, with a reported solubility of 77mg/mL at 25°C in water and pka is reported as 0.28.²

Pentoxifylline is essentially used for treatment of intermittent claudication, ischemia of heart, Reynolds syndrome, diabetes, cerebrovascular diseases and also uremia.³,⁴,⁵ All these disorders have red blood cell deformity which is improved by the API by increasing membrane ATP.³ Pentoxifylline also blocks platelet aggregation, stimulates fibrinolysis and decreases plasma fibrinolysis levels, thereby showing its effects as a hemorrhheologic drug.³
3.2. Pharmacokinetics and Metabolism

Pentoxifylline is absorbed from the GI tract readily but undergoes extensive first pass metabolism. On giving the drug via I.V. route the half life of the drug is $1.63 \pm 0.8$ hours. In case of oral delivery of the drug, the $t_{\text{max}}$ is around 0.29-0.41 hours with the half life ranging in between 0.39-0.84 hours. Since it undergoes metabolism, the bioavailability of the sustained release form of the drug is around 20% and 30% for capsules.

Pentoxifylline gets metabolized in the liver and red blood cells and forms 7 metabolites. Excretion of the metabolites occurs via urine.

3.3. Pentoxifylline and Autism

Pentoxifylline is a phosphodiesterase inhibitor and has been contraindicated for use in autism. Autism is a disorder in which there are developmental problems in the central
nervous system and affects children and the signs are visible from the age of 2. Though there are pharmacological therapies targeting symptoms and behavioral therapies, no specific treatment for the disease is available yet. Antipsychotic drugs like Risperidone and Haloperidol are mostly used and Risperidone is shown to be well tolerated and efficacious in treating behavioral symptoms in patients but not cure the disease. It has been found that autism is linked not only to hemorrhheologic property but also has inhibitory effects on tumor necrosis factor-α which is a vital cytokine in vivo and in vitro and is found to be in higher levels in autistic patients than in controls. TNF-α (Tumor Necrosis factor) affects the neuroendocrine system, causes death of oligodendrocites and demyelation and is suggested to play a vital role in neurologic disorders like multiple sclerosis AIDS. Autistic patients have been treated from time to time with Pentoxifylline and these studies have shown promising results. Pentoxifylline was also studied in a double blinded placebo test with Risperidone and the results showed that with it, the symptoms, both immunological and behavioral were reduced within 10 weeks as compared to that of the placebo. 7

Though there are sustained release forms of the drug 8 and various formulations are made for sustained dosage of the highly soluble drug, none of them cater to reducing the solubility of the drug such that the dissolution rate is reduced giving rise to a longer half life of the drug. Thus, with a drug with such great potential and pharmaceutical cocrystals actively helping in tailoring solubility of an API, cocrystals of the API were made which could be used clinically in the future.

Using the supramolecular synthon approach 9, 10 and statistics from CSD, 20 cocrystal synthesis through crystal engineering was achieved. It is shown here that Pentoxifylline
can be cocrystallized with nutraceuticals and pharmaceutically acceptable or approved compounds. Solubility studies were performed on the novel set of cocrystals. Further analyses were done on the data collected to study the impact physicochemical properties and crystal packing had upon solubility.

3.4 Experimental Section

3.4.1. Cocrystal synthesis

Pentoxifylline was cocrystallized with benzoic acid, salicylic acid, 1- hydroxy-2-napthoic acid, caffeic acid, coumaric acid, gallic acid, salicylamide and catechin hydrate. Chemical structures of all the compounds along with the 3 letter refcodes are illustrated in Figure 3.2. These refcodes will be used to designate cocrystals henceforth. The cocrystal formers used in this study are broadly carboxylic acids, amides, polyphenols and flavonoids. Some of the cocrystal formers used have health benefits associated with them.

Caffeic acid, coumaric acid, gallic acid, salicylic acid and catechin hydrate are nutraceutical compounds with antioxidant properties. Salicylamide, a non prescription drug is used as an over the counter pill with other API’s like caffeine and aspirin. It has anti inflammatory, mild analgesic and antipyretic properties. Benzoic acid and 1-hydroxy-2-napthoic acid are GRAS (Generally regarded as Safe) listed carboxylic acids. Cococrystallization with the above mentioned conformers resulted in successful
cocrystal formation with Pentoxifylline via multiple methods such as slow evaporation, solvent drop grinding\textsuperscript{15} and also slurring\textsuperscript{16} techniques. Single crystals suitable for X ray diffraction studies were also made for most of the cocrystals.

Figure 3.2. The chemical structures of Pentoxifylline and cocrystal formers used in the study.

3.4.2. Pentoxifylline-Benzoi acid, PENBEN (1:1)

This cocrystal was made via multiple methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.012g (0.0001 mmol) of benzoic acid were ground with 50µL of ethanol for fifteen minutes in a ball mill with two balls resulting in PENBEN
with 100 % yield. Solvent drop grinding with water and DMF also resulted in PENBEN. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.012 g (0.0001 mmol) of benzoic acid was ground without any solvent but resulted in total conversion to PENBEN. (c) Slurry: 0.28 g (0.0001 mmol) of Pentoxifylline and 0.12 g of benzoic acid (0.001 mmol) was slurried at ca. 125 rpm in 5 mL of ethanol overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The solid shows 100% conversion to PENBEN. The filtrate from the slurry was left for slow evaporation and gave rise to tiny needle shaped crystals with 65% yield after 10 days which was used for single crystal analysis.

3.4.3. Pentoxifylline-1-hydroxy-2-napthoic acid, PEN1HY (1:1)

This cocrystal was made via the following methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.019g (0.0001 mmol) of 1-hydroxy-2-napthoic acid were ground with 50 µL of ethanol for fifteen minutes in a ball mill with two balls resulting in PEN1HY with approximately 100 % yield. Solvent drop grinding with water and DMF also resulted in PEN1HY. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.019 g (0.0001 mmol) of 1-hydroxy-2-napthoic acid was ground without any solvent but resulted in conversion to PEN1HY. (c) Slurry: 0.28 g (0.0001 mmol) of Pentoxifylline and 0.12 g (0.001 mmol) of 1-hydroxy-2-napthoic acid was slurried at ca. 125 rpm in 4 mL of acetonitrile overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation which yielded single crystals. The residual solid showed 100% conversion to PEN1HY.
3.4.4. Pentoxifylline-Salicylic acid, PENSAL (1:1)

This cocrystal was also made via multiple methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.014g (0.0001 mmol) of salicylic acid were ground with 50µL of ethanol, water and DMF for fifteen minutes in a ball mill with two balls resulting in total conversion to PENSAL. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.014 g (0.0001 mmol) of salicylic acid was ground without any solvent but resulted in total conversion to PENSAL. (c) Slurry: 0.28 g (0.0001 mmol) of pentoxifylline and 0.14 g of salicylic acid (0.001 mmol) was slurried at ca. 125 rpm in 5 mL of acetonitrile overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid showed 100% conversion to PENSAL. The filtrate from the slurry was gave rise to needle shaped crystals after 5 days which was used for single crystal analysis.

3.4.5. Pentoxifylline-Gallic acid monohydrate, PENGAL.H₂O (1:1:1)

This cocrystal was made via multiple methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.017g (0.0001 mmol) of gallic acid were ground with 50µL of ethanol, water and DMF for fifteen minutes in a ball mill with two balls resulting in total conversion to PENGAL. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.017 g (0.0001 mmol) of gallic acid was ground without any solvent but resulted in total conversion to PENGAL. (c) Slurry: 0.28 g (0.0001 mmol) of Pentoxifylline and 0.17 g of gallic acid (0.001 mmol) was slurried at ca. 125 rpm in 7 mL of water overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for
slow evaporation. The residual solid gave 100% conversion to PEN G4L. The filtrate from the slurry was left for slow evaporation and gave rise to tiny needle shaped crystals after 10 days which was used for single crystal analysis.

3.4.6. Pentoxifylline-Salicylamide, PENS4C (1:1)

This cocrystal was also made via multiple methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.014g (0.0001 mmol) of salicylamide were ground with 50µL of ethanol, water and DMF for fifteen minutes in a ball mill with two balls resulting in PENS4C with 100% yield. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.014 g (0.0001 mmol) of salicylamide was ground without any solvent but resulted in total conversion to PENS4C. (c) Slurry: 0.28 g (0.0001 mmol) of Pentoxifylline and 0.14 g of salicylamide (0.001 mmol) was slurried at ca. 125 rpm in 5 mL of water overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid gave 100% conversion to PENS4C. The filtrate from the slurry was left for slow evaporation and gave rise to tiny needle shaped crystals after a week which was used for single crystal analysis.

3.4.7. Pentoxifylline-Coumaric acid, PENC4OU

This cocrystal was made via multiple methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.016g (0.0001 mmol) of coumaric acid were ground with 50µL of ethanol, water and DMF for fifteen minutes in a ball mill with two balls resulting
in PENCOU with total conversion. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.016 g (0.0001 mmol) of coumaric acid was ground without any solvent but resulted in total conversion to PENCOU. (c) Slurry: 0.28 g (0.0001 mmol) of Pentoxifylline and 0.16 g of coumaric acid (0.001 mmol) was slurried at ca. 125 rpm in 5 mL of water overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid showed 100% conversion to PENCOU. The filtrate from the slurry was left for slow evaporation and gave rise to needle shaped crystals after 6 days which was used for single crystal analysis.

3.4.8. Pentoxifylline-Caffeic acid, PENCFA

This cocrystal was made via multiple methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.018g (0.0001 mmol) of caffeic acid were ground with 50µL of ethanol, DMF and water for fifteen minutes in a ball mill with two balls resulting in PENCFA with approximately 100 % yield. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.018 g (0.0001 mmol) of caffeic acid was ground without any solvent but resulted in total conversion to PENCFA. (c) Slurry: 0.28 g (0.0001 mmol) of Pentoxifylline and 0.18 g of caffeic acid (0.001 mmol) was slurried at ca. 125 rpm in 5 mL of ethanol overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid showed 100% conversion to PENCFA. The filtrate from the slurry gave rise to needle shaped crystals after 10 days which was used for single crystal analysis.
3.4.9. Pentoxifylline-Catechin Hydrate, PENCAT

This cocrystal was also made via multiple methods (a) Solvent drop grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.015g (0.00005 mmol) of catechin hydrate were ground with 50µL of ethanol for fifteen minutes in a ball mill with two balls resulting in PENCAT with 100 % yield. (b) Dry grinding: 0.028 g (0.0001 mmol) of Pentoxifylline and 0.015 g (0.00005 mmol) of catechin hydrate was ground without any solvent but resulted in total conversion to PENCAT. (c) Slurry: 0.28 g (0.0001 mmol) of Pentoxifylline and 0.15 g of catechin hydrate (0.0005 mmol) was slurried at ca. 125 rpm in 5 mL of ethanol overnight, under ambient conditions. The resulting solid was filtered and the filtrate was left for slow evaporation. The residual solid showed 100% conversion to PENCAT.

3.4.10. Dissolution studies on cocrystals

Powder dissolution studies were performed on all cocrystals and pure Pentoxifylline. The study was performed in deionized water at room temperature. All the crystal forms were sieved to get consistent particle sizes between 53 -75µm as dissolution rate is affected by particle size. Supersaturated slurries were stirred with magnetic stir bars at a rate of 125 rpm. Dissolution rate was determined by drawing fixed aliquots with a syringe and filtering through 0.45µm filters after 5, 10, 15, 20, 25, 30, 60, 120, 180, 240, and 2400 minutes. The solutions were analyzed to determine the concentration of Pentoxifylline using Gas Chromatography and Mass spectrophotometer detector. The experiment was
done in triplicate to allow for statistical analysis. The leftover solid was characterized at the end of the study identify the solid phase post dissolution. 19

3.5. Results and Discussion

3.5.1. Cocrystals of Pentoxifylline

Pentoxifylline belongs to derived class of methyl xanthenes, as mentioned before and has the same functional groups as them except for the side chain attachment which contains an extra carbonyl group. Due to the similar hydrogen bonding moieties present in it, and owing to the inherent capacity of methyl xanthenes to readily form hydrogen bonds with complementary functional groups such as carboxylic acids, flavonoids and amides as has been reported in the CSD for caffeine, aided in understanding supramolecular heterosynthons that could be formed and thus cocrystals of the API was achieved readily.

A survey of the Cambridge Structural Database (version 5.31, update of May 2011) was carried out using ConQuest (version 1.12) and limited to organic molecules with determined 3D-coordinates and $R \leq 0.075$. The survey revealed that there is just one entry for Pentoxifylline, JAKGEH, depicting its crystal structure shown in Figure 3.1. There are no other reported cocrystals of the API.

A CSD analysis performed on the functional groups of the API has already been shown in the previous chapter and was used in this case too. The cocrystal formers used in this case study are depicted in Table 2.1, 2.2 and 2.3.
3.5.2. Crystal Structure Discussion: Pentoxifylline·Benzoic acid 1:1

Pentoxifylline·Benzoic acid, PENBEN crystallizes in the space group P-1. Each asymmetric unit contains one Pentoxifylline and one benzoic acid molecule. Figure 3.3 depicts the hydrogen bonding between the molecules. The molecules are discretely arranged in the sheet.

![Figure 3.3. The arrangement of Pentoxifylline and benzoic acid molecules in PENBEN reveals that it is sustained by a supramolecular heterosynthon between aromatic nitrogen and carboxylic acid.](image)

The aromatic nitrogen in imidazole ring of Pentoxifylline is seen to participate in hydrogen bonding with the carboxylic acid moiety of benzoic acid with a N····O distance of 2.751 (3) Å. This is the only synthon observed in this cocrystal. The sheets are stacked with the help of π-π interactions and follow the herringbone pattern as shown in Figure 3.4.
Figure 3.4. Herringbone pattern observed between the sheets in PENBEN sustained by π-π interactions.

3.5.3. Pentoxifylline·1-hydroxy-2-napthoic acid 1:1

Pentoxifylline·1-hydroxy-2-napthoic acid, PEN1HY crystallizes in the space group P-1. Each asymmetric unit contains one molecule each of Pentoxifylline and 1-hydroxy-2-napthoic acid. The molecules are arranged discretely. Figure 3.5 illustrates the hydrogen bonding between the two molecules. The aromatic nitrogen is participates in hydrogen bonding with carboxylic acid moiety, O···N, at a distance of 2.597 Å. Intramolecular hydrogen bonding is also seen to occur between the hydroxyl group of 1-hydroxy-2-napthoic acid and carbonyl group, O···O at a distance of 2.521 Å. The stacking of molecules arranged via π-π interactions are shown in Figure 3.6. A CSD search of 1-hydroxy-2-napthoic acid cocrystals revealed that there are 3 cocrystals listed out of which KIGKIV and KIGLIW, cocrystals with caffeine and theophylline respectively show similar hydrogen bonding between the aromatic nitrogen and carboxylic acid as seen in PEN1HY. The third cocrystal, between carbamazepine and 1-hydroxy-2-napthoic acid (MOXWEC) show hydrogen bonding between carboxylic acid and amide group.
Figure 3.5. Hydrogen bonding between Pentoxifylline and 1-hydroxy-2-napthoic acid reveals that it is sustained by a supramolecular heterosynthon between aromatic nitrogen and carboxylic acid. Intramolecular hydrogen bonding is also observed between hydroxyl and carbonyl group in 1-hydroxy-2-napthoic acid.

Figure 3.6. The stacking of PEN1HY sustained by π-π interactions.

3.5.4. Pentoxifylline-Salicylic acid 1:1

Pentoxifylline-Salicylic acid, PENSAL also crystallizes in P-1 space group. The asymmetric unit contains one molecule each of Pentoxifylline and salicylic acid. Hydrogen bonding between the molecules can be observed as shown in Figure 3.7.
Figure 3.7. Hydrogen bonding between Pentoxifylline and Salicylic acid sustained by supramolecular heterosynthon between aromatic nitrogen and carboxylic acid.

The molecules are arranged in discrete tapes in the sheet. Aromatic nitrogen of the is seen to participate in hydrogen bonding with the carboxylic acid moiety of salicylic acid, O···N at a distance of 2.648(4) Å. Salicylic acid also is involved in intramolecular hydrogen bonding between the carbonyl group and hydroxyl group, O···O, at a distance of 2.579(3) Å. Tapes of the molecules arranged and sustained by π-π interactions as seen in Figure 3.8. A CSD search of salicylic acid reveals 8 cocrystals sustained by the same heterosynthon (aromatic nitrogen and carboxylic acid) as seen in case of PENSAL.

Figure 3.8. The arrangement of PENSAL in the crystal lattice. Stacking of the cocystal is achieved with the help of π-π interactions.
3.5.5. Pentoxifylline. Gallic acid monohydrate 1:1:1

Pentoxifylline-Gallic acid, PENGAL.H₂O crystallizes in monoclinic space group P21/n. Each asymmetric unit contains one molecule each of Pentoxifylline, gallic acid and water. Aromatic nitrogen of Pentoxifylline engages in supramolecular heterosynthon with the carboxylic acid moiety of gallic acid, O···N, at a distance of 2.705(4) Å. The carbonyl group on the side chain of Pentoxifylline engages in hydrogen bonding with hydroxyl groups in the meta and para position of gallic acid, O···O at distances of 2.785(3) Å and 2.716(3) Å respectively. These interactions are illustrated in Figure 3.9 with the hydroxyl group in the para position of gallic acid also hydrogen bonds to the carbonyl group adjacent to the methyl group in the benzene ring in Pentoxifylline, O···O at a distance of 2.672(3) Å.

![Figure 3.9](image-url)

**Figure 3.9. Interactions between Pentoxifylline and gallic acid molecules in PENGAL.H₂O reveals supramolecular heterosynthon between aromatic nitrogen and carboxylic acid.**

The hydroxyl group on the ortho position of gallic acid is seen to participate in hydrogen bonding with the water molecule as can be seen in Figure 3.10 below. The hydrogen
bond distances observed in this tetramer are, O···O, 2.668(3) Å and 2.741(3) Å. Another tetrameric structure formed between water and carbonyl group next to the imidazole ring of Pentoxifylline is shown in Figure 3.11 below with bond distance of, O···O at 2.818(3) Å.

There are 7 cocrystals of gallic acid reported in the CSD. It has been seen that in case of caffeine-gallic acid hemihydrates cocrystal (MUPNOB) the hydrogen bonding occurs between the acid and aromatic nitrogen moiety as seen in IV but in case of gallic acid-theobromine dihydrate cocrystal aromatic nitrogen hydrogen bonds to the water molecule. Other cocrystals involve bonding between other functional groups and are seen to form the acid···amide dimer (MUPPAP) or acid···acid dimer (RUWFOF, RUWGUM).

Figure 3.10. The tetramer observed between water and gallic acid molecule in PENGAL.H₂O formed between hydroxyl group of the gallic acid molecule and water.
Figure 3.11. The tetramer observed between water and Pentoxifylline molecule in PENGAL. H$_2$O formed between carbonyl group of Pentoxifylline and water.

3.5.6. Pentoxifylline-Salicylamide 1:1

Pentoxifylline.Salicylamide, PENSLC (V) also crystallizes in P-1 space group. Each asymmetric unit contains one Pentoxifylline and one salicylamide molecule. The hydrogen bonding observed between the molecules is shown in Figure 3.12. The molecules are discretely arranged in the sheet.

Figure 3.12. The hydrogen bonding between Pentoxifylline and Salicylamide reveals the formation of an amide amide dimer(supramolecular homosynthon) as opposed to a heterosynthon.
In this cocrystal the amide moiety of the salicylamide molecule is seen to participate in a homosynthon by forming the amide amide dimer with another salicylamide molecule, N···O at a distance of 2.831(2) Å and 2.915(2) Å instead of forming the acid-amide heterosynthon. Salicylamide also is seen to participate in intramolecular hydrogen bonding between its carbonyl and hydroxyl group, O···O at a distance of 2.538(1) Å. Figure 3.13 depicts the stacking of each sheet of the cocrystal sustained by π-π interactions.

There is just one reported cocrystal of salicylamide in the CSD and also involves formation of an amide···amide dimer as seen in this case.

3.13. The stacking of PENS|C is sustained by π-π interactions.

3.5.7. Pentoxifylline-Catechin Hydrate

This cocrystal was prepared via various methods in a 1:1 ratio as has been mentioned in the experimental section and characterized via PXRD. But efforts to prepare single
crystals did not yield any results as of yet. The powder of the cocrystal was used for crystal data analysis and though the structure has not been solved yet, it has been indexed to P21.

In case of catechin hydrate, only the crystal structure of catechin hydrate (LUXWOR) is reported as mentioned before, no cocrystals of catechin hydrate are reported making this one the second reported cocrystal after the one with caffeine.

3.5.8. Pentoxifylline-Coumaric acid, Pentoxifylline-Caffeic acid

These cocrystals was prepared via various methods in a 1:1 ratio as has been mentioned in the experimental section and characterized via PXRD. But efforts to prepare single crystals did not yield any results as of yet.

3.5.9. Dissolution and Solubility Studies

Dissolution studies were performed on the API and all the cocrystals. Following dissolution studies, the concentration vs. time graph was generated for a time period of 24 hours. For purposes of clarity, the time point for the 24th hour reading was changed to 480 minutes. Pentoxifylline’s solubility was found to be 76 mg/mL which is in agreement with the literature reported solubility value. The dissolution profiles have been divided into two figures for clarity. Figure 3.14 illustrates the solubility profiles for Pentoxifylline and all its cocrystals; Figure 3.15 illustrates the solubility profile for cocrystals in the solubility range of 1-10 mg/mL.
3.14 Dissolution profiles in water for 24 hours for Pentoxifylline and its cocrystals.

From the graph it can be seen that PENBEN showed maximum concentration of 8.2 mg/mL. PEN1HY achieved maximum concentration of 1 mg/mL by the end of 24 hours. PENSAL’s dissolution profile also shows a smooth plateau in the curve with maximum concentration at 9 mg/mL. PENGAL shows a maximum concentration of 2.5 mg/mL also show smooth plateau like profile. PENSLC, PENCOU, PENCFA, and PENCAT reach concentration of 20 mg/mL, 4.7 mg/mL, 1.25 mg/mL and 0.8 mg/mL respectively by the end of 24 hours.
This solubility data is critical in pointing that an API with very high solubility can be manipulated with cocrystallization with novel crystal forms.

The PXRD and DSC’s of the residual solids were done after the study at the end of twenty four hours and it was found that the all the cocrystals were stable till that the time period.

3.15. Dissolution profiles in water for cocrystals PENCOU, PENSAL, PENCFE, PENGAL.H₂O, PENBEN, PEN1HY and PENCAT (solubility range 1-10 mg/mL).

These results show that all the cocrystals, can be used as an alternative form of the API as the solubility of API in the cocrystals have decreased, and thus using these forms for sustained release dosage is promising.
3.5.10. Correlation between Solubility and Melting Point

The cocrystal formers used in the study can be classified into the following classes as shown in Table 3.1.

**Table 3.1. Classification of cocrystal formers**

<table>
<thead>
<tr>
<th>Hydroxycinnamic acid</th>
<th>Carboxylic acid</th>
<th>Phenolic acid</th>
<th>Flavonoid</th>
<th>Amide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumaric acid</td>
<td>1-hydroxy-2 napthoic acid</td>
<td>Gallic acid</td>
<td>Catechin hydrate</td>
<td>Salicylamide</td>
</tr>
<tr>
<td>Caffeic acid</td>
<td>Benzoic acid</td>
<td>Salicylic acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As shown with caffeine in the previous chapter, the correlation between solubility and melting point is a vital analysis in terms of correlating calculable physicochemical property with solubility for thermodynamically stable cocrystals. Generally higher the melting point lower is the solubility and vice versa. Here again on correlating log of solubility (to make the points appear closer) and onset of melting point of cocrystal illustrated in Figure 3.16, shows that there is no concrete relationship between these two parameters (22%), which is in consensus with Bak et al’s conclusion 9(d) and also what was observed with caffeine’s cocrystals.
Figure 3.16. Solubility of cocrystals shows no relationship with melting point probably due to the variability in coformers used.

When looked within specific classes of compounds, in case of caffeine cocrystals a very high correlation was observed (85 %) with the hydroxycinnamic acids but since the data set here is smaller, that area was not investigated here as the data would be inconclusive.

Table 3.2 below lists the melting points of the cocrystal and the cocrystal formers in this study.

Table 3.2. Melting points of the cocrystal formers and the cocrystals

<table>
<thead>
<tr>
<th>COCRYSTAL /COMPOUND</th>
<th>M.P. of compound/cocrystal (° C)</th>
<th>M.P of CCF (° C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>PENBEN</td>
<td>91</td>
<td>121</td>
</tr>
<tr>
<td>PEN1HY</td>
<td>124</td>
<td>195</td>
</tr>
<tr>
<td>PENSAL</td>
<td>98</td>
<td>158</td>
</tr>
<tr>
<td>PENGAL.H₂O</td>
<td>188</td>
<td>268</td>
</tr>
<tr>
<td>PENSIC</td>
<td>103</td>
<td>140</td>
</tr>
<tr>
<td>PENCOU</td>
<td>128</td>
<td>214</td>
</tr>
<tr>
<td>PENCHE</td>
<td>150</td>
<td>211</td>
</tr>
<tr>
<td>PENCAT</td>
<td>169</td>
<td>214</td>
</tr>
</tbody>
</table>

(* Melting points were taken from scifinder.org)
3.5.11. Relationship between solubility and crystal packing efficiency

Crystal packing as discussed previously is an important parameter for crystalline compounds. The way a molecule packs in a crystal, allows for different properties of compounds to be expressed. For organic molecules packing efficiency is found to be in the range of 0.65-0.77. Though a small range, it was seen in the previous chapter that it can be critical in demonstrating solubility patterns. The software Platon \(^{22}\) was used to calculate the Kitaigorodskii \(^{21}\) packing efficiency. Table 3.3 lists the crystal packing efficiency and solubility of cocrystals with crystal structures solved. We found that for caffeine cocrystals, highest solubility was related to the lowest efficiency and vice versa thereby showing that crystal packing does have a role to play in cocrystal solubility. For this data set however we explored this arena again and found no correlation (7%) as seen in Figure 3.17. Thus though, crystal packing efficiency is an important parameter, for this dataset, a conclusion cannot be made.

Table 3.3. Crystal packing efficiency and solubility of Pentoxifylline and its cocrystals

<table>
<thead>
<tr>
<th>Compound/Cocrystal</th>
<th>Crystal packing efficiency (%)</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>70.7</td>
<td>76.1</td>
</tr>
<tr>
<td>PENBEN</td>
<td>71.7</td>
<td>8.18</td>
</tr>
<tr>
<td>PEN1HY</td>
<td>68.8</td>
<td>1.03</td>
</tr>
<tr>
<td>PENSAL</td>
<td>69.9</td>
<td>9.03</td>
</tr>
<tr>
<td>PENGAL.H(2)O</td>
<td>72.1</td>
<td>2.46</td>
</tr>
<tr>
<td>PENSLC</td>
<td>71</td>
<td>19.88</td>
</tr>
</tbody>
</table>
Figure 3.17. Crystal packing efficiency on correlation with cocrystal solubility shows no correlation.

3.5.12. Correlation between solubility of cocrystal former to solubility of cocrystal

As seen for caffeine, the collected data here also shows that there has been a decrease in the solubility of the API through cocrystallization and in this context the above parameters were correlated to determine any relationship between them as shown in Figure 3.18. It is seen that there is a general trend of decrease in Pentoxifylline solubility in the cocrystals as seen with caffeine cocrystals. But still there is no correlation observed that could help in prediction of solubility, thereby suggesting that solubility of cocrystal former is not directly proportional to cocrystal solubility.
3.5.13. Modification of solubility of Pentoxifylline following cocrystallization

The experimental solubility of API in its cocrystals was compared to the measured solubility of the API. The results are shown in the Table 3.4 below.

Table 3.4. Solubility modification of Pentoxifylline in its cocrystals

<table>
<thead>
<tr>
<th>Cocrystal</th>
<th>With respect to Pentoxifylline (decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PENBEN</td>
<td>-9 fold</td>
</tr>
<tr>
<td>PEN1HY</td>
<td>-74 fold</td>
</tr>
<tr>
<td>PENSAL</td>
<td>-8 fold</td>
</tr>
<tr>
<td>PENGAL.H₂O</td>
<td>-31 fold</td>
</tr>
</tbody>
</table>

Figure 3.18. On correlation cocrystal former solubility and cocrystal solubility no correlation other than a general decrease is observed in cocrystal solubility.
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PENSLC</td>
<td>-4 fold</td>
</tr>
<tr>
<td>PENCOU</td>
<td>-99 fold</td>
</tr>
<tr>
<td>PENCFE</td>
<td>-61 fold</td>
</tr>
<tr>
<td>PENCAT</td>
<td>-16 fold</td>
</tr>
</tbody>
</table>

As seen from the table, the maximum decrease of solubility of the API is around 99 folds and is achieved by **PENCOU**.

### 3.6. Conclusion

In summary, as shown earlier with caffeine and other examples from the literature, pharmaceutical cocrystals can modify physicochemical properties of an API. This statement is exemplified again by the case study presented here where the cocrystals of Pentoxifylline lowered the solubility of the API, allowing for the potential of a slow release form of the drug. Eight new cocrystals of were made and their solubility in water was analyzed.

All of them were found to be thermodynamically stable after twenty-four hours. The dissolution profiles showed that **PENCOU** had achieved the lowest concentration of 0.7 mg/mL and **PENSLC** the highest. The effects of melting point, solubility of cocrystal former and crystal packing efficiency upon solubility were also investigated as was done for caffeine cocrystals. It was seen that, in general, melting point could not be correlated
as a function of solubility, and due to the small dataset, correlations amongst specific class of compounds were not made as that would render inconclusive analysis.

As done previously, solubility as a function of crystal packing efficiency was analyzed and it was found, that no correlation occurs between solubility and packing efficiency; This shows that though property could be important and help in future understanding of cocrystal solubility, at least in this case its role was not evident.

For relation between the cocrystal former and cocrystal solubility, a general trend was observed, where for coformers used herein with solubility lower than Pentoxifylline, gave an overall decrease in the solubility of the pure API with the maximum being a 99 fold decrease but like caffeine cocrystals no specific relationship between them could be established.

Pentoxifylline’s solubility was thus successfully lowered through cocrystallization with nutraceutical or pharmaceutically acceptable compounds. Predictability of the resultant solubility through melting point or coformer solubility correlation or crystal packing efficiency was not successful.

3.7. REFERENCES


19. The dissolution studies performed do not make use of the standard USP apparatus. This is due to the limitations of our in lab facilities. But the results produced are comparable reasonably to standards. As future development this study will be done with the help of contract research organization using the standard USP apparatus.


4. CHAPTER 4: CONCLUSIONS AND FUTURE DIRECTIONS

Pharmaceutical cocrystals, an emerging class of compounds have the capacity to modify physicochemical properties of a compound without affecting its biological activity and in turn afford crystalline compounds. Herein two API’s, caffeine and Pentoxifylline were targeted as case studies.

Caffeine was targeted for cocrystallization for its possible clinical use for Alzheimer’s disease. In the case, caffeine was cocrystallized with cyanuric acid, chlorogenic acid, syringic acid and catechin hydrate using statistics from the CSD. Following synthesis, dissolution studies were performed on a set of 12 cocrystals which included reported forms from the literature and the ones which were newly synthesized, for a period of 24 hours in deionized water at room temperature. Particle size was controlled by sieving. All the cocystal formers had solubility lower than that of caffeine. Dissolution studies showed a marked decrease in caffeine solubility in its cocrystals. Powder XRD done at the end of 24 hours on the leftover solid confirmed that all the cocrystals were thermodynamically stable. This data is critical in pointing out that solubility can be decreased using cocrystals. The smooth plateau like curves achieved by the cocrystals showcase constant dissolution rate and hence potential for a sustained dosage. Future directions would involve in vivo studies to make this an achievable objective. Various
analyses were also made between cocrystal solubility and melting point, crystal packing efficiency and cocrystal former solubility.

Pentoxifylline, a drug which contraindicated for use in autism has a low half life. This drug was targeted for cocristallization to see if cocrystals can achieve lower solubility and a dissolution rate such that the half life can be modified to get a sustained dosage form. The coformers used in the study were benzoic acid, salicylic acid, 1-hydroxy-2-napthoic acid, gallic acid, coumaric acid, caffeic acid, catechin hydrate and salicylamide. The dissolution study conditions were similar to that of caffeine and powder XRD done at the end of the study confirmed stability of the cocrystals. The smooth plateau like curves achieved by these cocrystals also, showcase constant dissolution rate and hence potential for a sustained dosage form.

In both the cases, the cocrystals had achieved lower solubility as compared to the respective API’s and the conformers too were of solubility lower than that of each, thus cocrystal former solubility was correlated with cocrystal solubility to see if any correlation exists in this regard. It was seen that no correlation exists between these parameters in both the cases suggesting that solubility prediction is not possible. Solubility of cocrystals in both cases was correlated with melting point and it was seen that no correlation could be established in either case. Thus tailoring solubility by prediction of melting point before synthesis is still an elusive situation and more studies would be required to make a conclusion.

Crystal packing efficiency was correlated with solubility of cocrystal and in case of caffeine cocrystals it was seen that a 41% correlation existed and the highest crystal
packing efficiency was achieved by CAFELA which had the lowest solubility and vice versa. In case of Pentoxifylline though this correlation did not exist suggesting that though crystal packing efficiency seems to be an important parameter but a conclusion in this case cannot be made.

Thus in conclusion, CAFELA.H₂O achieved a 278 fold decrease in caffeine solubility and PENCOU a 99 fold decrease in Pentoxifylline solubility. It is hence understandable that pharmaceutical cocrystals are versatile and can help modifying properties and successfully shows the significance of making “crystals with a purpose”.
APPENDICES
APPENDIX A: EXPERIMENTAL DATA

The experimental data was collected using DSC (TA instrument 2920), FT-IR (Nicolet Avatar 320 FTIR, solid state), Powder X-ray diffraction (Bruker AXS D8, Cu radiation), TGA (STM6000).

1.1. Experimental data for Caffeine·Cyanuric acid monohydrate, CAFCYA.H₂O 2:1:1

Data includes DSC thermogram for caffeine-cyanuric acid monohydrate, DSC thermogram for caffeine-cyanuric acid anhydrate got after heating the monohydrate for 1 day, FT-IR spectrum of the cocrystal, comparison between calculated (from single crystal data) and experimental powder patterns (from bulk sample) and TGA data for the cocrystal monohydrate.

Figure A1. DSC thermogram of CAFCYA.H₂O
APPENDIX A (Continued)

Figure A2. DSC thermogram of CAFCYA anhydrate.

Figure A3. FT-IR of CAFCYA.H₂O.
APPENDIX A (Continued)

Figure A4. PXRD comparison of CAFCYA.H₂O.

Figure A5. TGA Data of CAFCYA.H₂O.
APPENDIX A (Continued)

1.2. Experimental data for Caffeine-Syringic tetrahydrate, CAFSYR.4H₂O 1:1:4

Data includes DSC thermogram for caffeine-syringic acid tetrahydrate, FT-IR spectrum of the cocrystal, comparison between calculated (from single crystal data) and experimental powder patterns (from bulk sample) and TGA data for the cocrystal.

Figure A6. DSC thermogram of CAFSYR.4H₂O.

Figure A7. FT-IR of CAFSYR.4H₂O.
Figure A8. PXRD comparison of CAFSYR.4H₂O.

Figure A9. TGA Data of CAFSYR.4H₂O.
APPENDIX A (Continued)

1.3. **Experimental data for Caffeine-Chlorogenic Acid, CAFCGA**

Data includes DSC thermogram for caffeine-chlorogenic acid, FT-IR spectrum of the cocrystal, comparison between powder patterns of the starting materials and the cocrystal and TGA data for the cocrystal.

**Figure A10.** DSC thermogram of CAFCGA.

**Figure A11.** FT-IR of CAFCGA.
Figure A12. PXRD Comparison of CAFCGA.

Figure A13. TGA Data of CAFCGA.
APPENDIX A (Continued)

1.4. Experimental data for Caffeine·Catechin Hydrate, CAFCAT

Data includes DSC thermogram for caffeine-catechin hydrate, FT-IR spectrum of the cocrystal, comparison between powder patterns of the starting materials and the cocrystal.

Figure A14. DSC thermogram of cocrystal of CAFCAT.

Figure A15. FT-IR of CAFCAT.
Figure A16. PXRD Comparison of CAFCAT.
1.6. Experimental data for Pentoxifylline·Benzoic acid, PENBEN 1:1

Data includes DSC thermogram for pentoxifylline·benzoic acid, FT-IR spectrum of the cocrystal, comparison between calculated (from single crystal data) and experimental powder patterns (from bulk sample) and TGA data for the cocrystal.

![DSC thermogram of PENBEN](image1.png)

Figure A17. DSC thermogram of PENBEN.

![FT-IR of PENBEN](image2.png)

Figure A18. FT-IR of PENBEN.
APPENDIX A (Continued)

Figure A19. TGA Data of PENBEN.

Figure A20. PXRD Comparison of PENBEN.
1.7. **Experimental data for Pentoxifylline·1-hydroxy-2-napthoic acid, PEN1HY 1:1**

Data includes DSC thermogram for pentoxifylline·1-hydroxy-2-napthoic acid, FT-IR spectrum of the cocrystal, comparison between calculated (from single crystal data) and experimental powder patterns (from bulk sample) and TGA data for the cocrystal.

![DSC thermogram of PEN1HY.](image)

**Figure A21. DSC thermogram of PEN1HY.**

![FT-IR of PEN1HY.](image)

**Figure A22. FT-IR of PEN1HY.**
Figure A23. TGA Data of PEN1HY.

Figure A24. PXRD Comparison of PEN1HY.
1.8. Experimental data for Pentoxifylline-Salicylic acid, PENSAL 1:1

Data includes DSC thermogram for pentoxifylline-salicylic acid, FT-IR spectrum of the cocrystal, comparison between calculated (from single crystal data) and experimental powder patterns (from bulk sample) and TGA data for the cocrystal.

![DSC thermogram of PENSAL.](image)

Figure A25. DSC thermogram of PENSAL.

![FT-IR of PENSAL.](image)

Figure A26. FT-IR of PENSAL.
Figure A27. TGA Data of PENSAL.

Figure A28. PXRD Comparison of PENSAL.
APPENDIX A (Continued)

1.9. **Experimental data for Pentoxifylline·Gallic acid, PENGAL.H₂O 1:1:1**

Data includes DSC thermogram for pentoxifylline·gallic acid, DSC of the anhydrate of the cocrystal, comparison between calculated (from single crystal data) and experimental powder patterns (from bulk sample) and TGA data for the cocrystal.

**Figure A29. DSC thermogram of PENGAL.H₂O.**

**Figure A30. DSC thermogram of cocrystal anhydrate.**
Figure A31. PXRD Comparison of PENGAL.H$_2$O.

Figure A32. TGA Data of PENGAL.H$_2$O.
APPENDIX A (Continued)

1.10. **Experimental data for Pentoxifylline·Salicylamide, PENSLC 1:1**

Data includes DSC thermogram for pentoxifylline·salicylamide, FT-IR spectrum of the cocrystal, comparison between calculated (from single crystal data) and experimental powder patterns (from bulk sample) and TGA data for the cocrystal.

![Figure A33. DSC thermogram of cocrystal of PENSLC.](image)

![Figure A34. FT-IR of PENSLC.](image)
Figure A35. PXRD Comparison of PENSLC.

Figure A36. TGA Data of PENSLC.
APPENDIX A (Continued)

1.11. Experimental data for Pentoxifylline-Coumaric acid, PENCOU

Data includes DSC thermogram for pentoxifylline-coumaric acid, FT-IR spectrum of the cocrystal, comparison between powder patterns of the starting materials and the cocrystal and TGA data for the cocrystal.

Figure A37. DSC Thermogram of PENCOU.
Figure A38. FT-IR of PENCOU.

Figure A39. PXRD Comparison of PENCOU.
Figure A40. TGA Data of PENCOU.
APPENDIX A (Continued)

1.12. **Experimental data for Pentoxifylline-Caffeic acid, PENCFA**

Data includes DSC thermogram for pentoxifylline-coumaric acid, FT-IR spectrum of the cocrystal, comparison between powder patterns of the starting materials and the cocrystal and TGA data for the cocrystal.

![DSC Thermogram of PENCFA](image1.png)

**Figure A41.** DSC Thermogram of PENCFA.

![FT-IR Spectrum of PENCFA](image2.png)

**Figure A42.** FT-IR of PENCFA.
Figure A43. TGA Data of PENCFA.

Figure A44. PXRD comparison of PENCFA.
1.13. Experimental data for Pentoxifylline·Catechin hydrate, PENCAT

Data includes DSC thermogram for pentoxifylline·catechin hydrate, FT-IR spectrum of the cocrystal, comparison between powder patterns of the starting materials and the cocrystal and TGA data for the cocrystal.

Figure A45. DSC Thermogram of PENCAT.

Figure A46. FT-IR of PENCAT.
Figure A47. PXRD comparison of PENCAT.

Figure A48. TGA Data of PENCAT.
### APPENDIX B: CRYSTALLOGRAPHIC DATA

Table B1. Hydrogen bond distances and parameters for the novel cocrystals of caffeine presented herein

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hydrogen Bond</th>
<th>(d) (H⋯A)/Å</th>
<th>(D) (D⋯A)/Å</th>
<th>(\theta)°</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAFCYA. H₂O</strong></td>
<td>N-H⋯N</td>
<td>1.98</td>
<td>2.913(5)</td>
<td>160.5</td>
</tr>
<tr>
<td></td>
<td>N-H⋯N</td>
<td>2.07</td>
<td>2.953(5)</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>N-H⋯O</td>
<td>1.71</td>
<td>2.712(4)</td>
<td>168.4</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>1.84</td>
<td>2.791(5)</td>
<td>162.3</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>2.07</td>
<td>2.753(4)</td>
<td>146.9</td>
</tr>
<tr>
<td><strong>CAFSYR. 4H₂O</strong></td>
<td>O-H⋯O</td>
<td>2.02</td>
<td>2.8(4)</td>
<td>155.1</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>2.21</td>
<td>2.7(4)</td>
<td>114.6</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>1.76</td>
<td>2.6(4)</td>
<td>164.8</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>2(3)</td>
<td>2.8(6)</td>
<td>148</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>2(3)</td>
<td>2.8(4)</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>O-H⋯N</td>
<td>1.9(15)</td>
<td>2.8(5)</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>2(3)</td>
<td>2.9(5)</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>1.88</td>
<td>2.7(5)</td>
<td>163.6</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>1.8(13)</td>
<td>2.6(5)</td>
<td>170</td>
</tr>
<tr>
<td></td>
<td>O-H⋯O</td>
<td>2(4)</td>
<td>2.8(5)</td>
<td>142</td>
</tr>
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</table>

The space group and cell parameters of caffeine-catechin hydrate were determined but the crystal structure of could not determined.
APPENDIX B (Continued)

Table B2. Crystallographic data and structure refinement parameters for the caffeine cocrystals reported herein

<table>
<thead>
<tr>
<th></th>
<th>CAFCYA.H2O</th>
<th>CAFSYR.4H2O</th>
<th>CAFCAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C_{19} H_{25} N_{11} O_{8}</td>
<td>C_{17} H_{28} N_{4} O_{11}</td>
<td></td>
</tr>
<tr>
<td>MW</td>
<td>535.50</td>
<td>464.43</td>
<td></td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
<td>Orthorhombic</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>( P2_1/n )</td>
<td>( Fdd2 )</td>
<td>( P2_12_1_2_1 )</td>
</tr>
<tr>
<td>( a ) (Å)</td>
<td>9.174(2)</td>
<td>30.278(5)</td>
<td>5.03</td>
</tr>
<tr>
<td>( b ) (Å)</td>
<td>12.991(4)</td>
<td>41.759(7)</td>
<td>12.56</td>
</tr>
<tr>
<td>( c ) (Å)</td>
<td>19.286(6)</td>
<td>6.7523(12)</td>
<td>34.13</td>
</tr>
<tr>
<td>( \alpha ) (deg)</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>( \beta ) (deg)</td>
<td>103.237(13)</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>( \gamma ) (deg)</td>
<td>90</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>( V / \text{Å}^3 )</td>
<td>2237.5(12)</td>
<td>8537(3)</td>
<td></td>
</tr>
<tr>
<td>( D_c / \text{g cm}^{-3} )</td>
<td>1.590</td>
<td>1.445</td>
<td></td>
</tr>
<tr>
<td>( Z )</td>
<td>4</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>2θ range</td>
<td>4.14 to 67.72°</td>
<td>3.61 to 66.80°</td>
<td></td>
</tr>
<tr>
<td>( N_{\text{ref.}}/N_{\text{para}} )</td>
<td>3834/354</td>
<td>3322/313</td>
<td></td>
</tr>
<tr>
<td>( T / \text{K} )</td>
<td>105(2)</td>
<td>0.0336</td>
<td></td>
</tr>
<tr>
<td>( R_1 ) [I&gt;2( \sigma (I) )]</td>
<td>0.0756</td>
<td>0.0878</td>
<td></td>
</tr>
<tr>
<td>( wR_2 )</td>
<td>0.1895</td>
<td>1.026</td>
<td></td>
</tr>
<tr>
<td>GOF</td>
<td>1.080</td>
<td>1.046</td>
<td></td>
</tr>
<tr>
<td>Abs coef</td>
<td>1.083</td>
<td>0.923</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX B (Continued)

Table B3. Crystallographic data and structure refinement parameters for the Pentoxifylline cocrystals reported herein

<table>
<thead>
<tr>
<th></th>
<th>PENBEN</th>
<th>PENSAL</th>
<th>PENAL.H₂O</th>
<th>PENSLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formula</strong></td>
<td>C₂₀H₂₄N₄O₅</td>
<td>C₂₀H₂₄N₄O₆</td>
<td>C₂₀H₂₆N₄O₉</td>
<td>C₂₀H₂₅N₅O₅</td>
</tr>
<tr>
<td><strong>MW</strong></td>
<td>400.43</td>
<td>416.43</td>
<td>466.45</td>
<td>415.45</td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
<td>Triclinic</td>
<td>Triclinic</td>
<td>Monoclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td><strong>Space group</strong></td>
<td>P-1</td>
<td>P-1</td>
<td>P2₁/n</td>
<td>P-1</td>
</tr>
<tr>
<td><strong>a (Å)</strong></td>
<td>13.3080(4)</td>
<td>6.6579(12)</td>
<td>6.728(1)</td>
<td>7.7991(6)</td>
</tr>
<tr>
<td><strong>b (Å)</strong></td>
<td>13.3931(4)</td>
<td>8.4161(16)</td>
<td>12.649(2)</td>
<td>11.1913(8)</td>
</tr>
<tr>
<td><strong>c (Å)</strong></td>
<td>13.8838(4)</td>
<td>19.325(4)</td>
<td>25.192(3)</td>
<td>12.6449(9)</td>
</tr>
<tr>
<td><strong>α (deg)</strong></td>
<td>64.4(2)</td>
<td>83.603(12)</td>
<td>90</td>
<td>69.051(4)</td>
</tr>
<tr>
<td><strong>β (deg)</strong></td>
<td>81.171(2)</td>
<td>82.659(12)</td>
<td>96.811(5)</td>
<td>79.322(4)</td>
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<tr>
<td><strong>γ (deg)</strong></td>
<td>60.425(2)</td>
<td>70.944(11)</td>
<td>90</td>
<td>78.760(5)</td>
</tr>
<tr>
<td><strong>V / A³</strong></td>
<td>1935.25(11)</td>
<td>1012.3(3)</td>
<td>2128.9(5)</td>
<td>1002.87(13)</td>
</tr>
<tr>
<td><strong>Dc/g cm⁻³</strong></td>
<td>1.374</td>
<td>1.366</td>
<td>1.455</td>
<td>1.376</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>2θ range</strong></td>
<td>3.54 to 65.82°</td>
<td>2.31 to 65.37°</td>
<td>3.53 to 65.95°</td>
<td>3.77 to 65.91°</td>
</tr>
<tr>
<td><strong>Nref./Npara</strong></td>
<td>6383/531</td>
<td>3280/276</td>
<td>3615/311</td>
<td>3338/281</td>
</tr>
<tr>
<td><strong>T /K</strong></td>
<td>100(2)</td>
<td>100(2)</td>
<td>100(2)</td>
<td>100(2)</td>
</tr>
<tr>
<td><strong>R₁ [I&gt;2σ (I)]</strong></td>
<td>0.0588</td>
<td>0.0582</td>
<td>0.0553</td>
<td>0.0368</td>
</tr>
<tr>
<td><strong>wR₂</strong></td>
<td>0.1414</td>
<td>0.1361</td>
<td>0.1345</td>
<td>0.0965</td>
</tr>
<tr>
<td><strong>GOF</strong></td>
<td>1.025</td>
<td>0.983</td>
<td>1.009</td>
<td>1.034</td>
</tr>
<tr>
<td><strong>Abs coef</strong></td>
<td>0.832</td>
<td>0.855</td>
<td>0.985</td>
<td>0.837</td>
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