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REVIEW ARTICLE

Polymorphs and Cocrystals: A Comparative Analysis

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Abstract | Controlling polymorphism has been the subject of vigorous research in the recent past in the pharmaceutical industry due to the distinct physicochemical properties associated with each solid form. Developing cocrystals/salts of active pharmaceutical ingredients (APIs) has gained tremendous research interest in recent years owing to their potential to improve pharmaceutically relevant properties without affecting therapeutic efficacy. It is observed that compounds that exhibit polymorphism and also contain several H bond donor/acceptor groups have a tendency to form cocrystals and sometime even display cocrystal polymorphism, although this tendency cannot be generalized. The aim of this contribution is to correlate crystal structures of some polymorphic APIs and their respective cocrystals to understand the rationale behind a polymorphic compound generating cocrystals. Here, we make an attempt to compare how the conformation of the molecule observed in its polymorphs support the generation of cocrystals/salts. We understand that it is impossible to cover all the polymorphs and their cocrystals/salts available in the CSD; the comparative study has been carried out with a few case studies, wherein APIs displayed polymorphism (conformation) and also formed cocrystals/salts.

1 Introduction

Polymorphs are among the most intensively researched areas in crystal engineering in the present times because of the tremendous basic and commercial interest in pharmaceutical solids, high-energy materials, dyes, and pigments.[1] According to W. L. McCrone,[2] "every compound has different polymorphic forms, and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound". Polymorphism is the result of the competition between the energetically similar interactions which exist during crystal growth that generates different supramolecular synthons.[3] The existence of polymorphs provides a unique opportunity to study crystal structure–property relationships of the same compound in different crystalline forms. In recent years, investigation on polymorphic behaviour of APIs and novel drug intermediates has become the significant part of the drug development program of pharmaceutical companies.[1] This is because polymorphs not only alter and tune the physicochemical properties of API that include stability, solubility, bioavailability, hygroscopicity, and compatibility, but also there is a gain of intellectual property on novel solid forms with improved physicochemical properties.[4–7] However, because of the different pharmaceutical properties associated with each polymorph, studies on controlling polymorphism have gained a significant importance in recent years. Without proper control, polymorphism can cause structural impurity in the final product that will affect its performance/functionality and may cause difficulties in processability of materials due to dissimilar morphology. One of the strategies to control polymorphism is to prepare cocrystals or molecular salts of the API[8] with the suitable cocrystal former selected from the FDA list of generally recognized as safe (GRAS) compounds.[9] Therefore, cocrystals

Polymorphic API: The correlation of the crystal structures of polymorphic APIs and their respective cocrystals has been carried out to understand the rationale behind a polymorphic compound generating cocrystals. The case studies clearly show a definite trend in grossly retaining of the conformations of flexible molecules in polymorphs and their respective cocrystals. The understanding of the flexible conformers and their preferred orientation in polymorphs and cocrystals will be valuable in designing desired cocrystals.

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and molecular salts of APIs have deliberately been synthesized to control polymorphism of the native material.[8] In addition, cocrystals/salts of APIs show great promise in improving pharmaceutically relevant properties, such as solubility,[11–15] bioavailability,[16–19] compressibility,[20, 21] stability,[22–27] hygroscopicity,[28, 29] crystallinity,[30] etc. without altering their therapeutic efficiency. This has prompted pharmaceutical companies to engage in developmental aspects of cocrystals that not only include physicochemical characterization,[31–33] but also its scale up,[34, 35] processing and formulations of these novel materials.[36, 37] Although cocrystals have been known since the 19th century,[38] they, however, have gained tremendous interest in recent times because of their ability to modify the material properties for pharmaceutical and material science applications. Therefore, cocrystals are also considered as promising and patentable novel solid forms of the API.[39] Despite its widespread popularity, there is a considerable debate surrounding its definition and different authors have used different parameters to define what cocrystal is. However, most agree with the general statement, "A cocrystal is a crystalline solid containing at least two different neutral molecular components that are solids under ambient conditions and present in definite stoichiometric ratio".[40] Although the molecular salts and cocrystals are considered as multicomponent crystals, wherein components (atom, ion, or molecule) are held together by non-covalent interactions, such as hydrogen bond, halogen bond, and π-stacking, but cocrystal is different than salt. One can differentiate cocrystals and salts based on whether a proton transfer has taken place from an acid to a base.[41] In general, if the difference between p*K*a of base and acid (ΔpK_a) is greater than 3, cocrystallization will result in salt formation,[42] whereas ΔpK_a value less than 0 will exclusively produce cocrystal.[43] Formation of cocrystals A·B (A·B does not define stoichiometry) comprising of two components A and B could be due to the relatively strong affinity between heteromolecules (A···B) yielding thermodynamically stable crystal lattice than between homomolecules (A···A or B···B). Components within the cocrystal associate via predictable or known intermolecular interactions (hydrogen bond, halogen bond, π-stacking, etc.) termed supramolecular synthon which are further categorized as supramolecular homosynthon (composed of identical self-complementary functionalities, such as acid···acid, amide···amide, etc.) or supramolecular heterosynthon (composed of different, but complementary functionalities, such as acid···amide, acid···pyridine, alcohol···amide, etc.).[10, 44, 45] For the development of cocrystal, selection of the suitable coformer is crucial. The coformer should comprise of suitable hydrogen bond donor and acceptor groups to form robust supramolecular heterosynthon by breaking the supramolecular homosynthon formed between the native molecules. Although the strong hydrogen bonds dictate the supramolecular assembly and molecular aggregation during nucleation, but the weak interaction, such as C–H···O, C–H···π, C–H···N, and C–H···halogen, hydrophobic forces give fine tuning to the assembly process, and sometimes, the cumulative effect of these interactions plays a structure directing role and perturbs the favourable assembly even in the presence of strong interactions.

Increasing interest in the development of cocrystals in recent time has resulted in the reporting of large number of polymorphic cocrystals.[46, 47] While it might be proposed that cocrystal formation may restrict polymorphism,[8, 10], our previous encounter showed that molecules which have a tendency to display polymorphism can reveal polymorphism in their cocrystals too.[48] Systematic investigations pertaining to the formation of cocrystals or attempts at the correlation of the structure of their constituent molecules in polymorphs with their ability to form cocrystals are more or less non-existent. The aim of this contribution is to provide a correlation between the conformation of the constituent molecule in its polymorphs and cocrystals. Here, we make an attempt to compare how the conformation of the molecule observed in its polymorphs support the generation of cocrystals/salts. We understand that it is practically impossible to cover all cases of polymorphs and their cocrystals/salts available in the Cambridge Structural Database (CSD), and the comparative study has been carried out by selecting few APIs which exhibit conformational polymorphism and formed cocrystals/salts. It is of the interest to examine how different conformations of these molecules present in their polymorphs help in producing cocrystals/salts. The polymorphs and cocrystals discussed in this article were retrieved from the CSD (Version 5.38, November 2016, without imposing restriction on the R-factor, disordered, polymeric, powder, and error structures)[49] and from the major crystallographic and pharmaceutical journals. CSD search was carried out on APIs which are known to exhibit conformational polymorphism and yielded cocrystal too. The polymorphs and cocrystals/salts (including solvates) of some of the APIs retrieved from the CSD are listed in Table 1. The APIs chosen for carrying out a comparative

Table 1: CSD survey on number of polymorphs and cocrystals of active pharmaceutical ingredients

Sr. no.	APIs	CSD analysis	
		Polymorphs	Cocrystal/ salts/solvates
1.	Aripiprazole	8	19
2.	Flufenamic acid	8	5
3.	Chlorpropamide	8	No hits found
4.	Rac-Tazofelone	6	No hits found
5.	Carbamzepine	5	61
6.	Piroxicam	5	39
7.	Piracetam	5	17
8.	Sulfanilamide	5	17
9.	Sulfathiazole	5	13
10.	Felodipine	5	12
11.	Tolfenamic acid	5	12
12.	Phenobarbital	5	11
13.	Fluconazole	5	7
14.	Sulfapyridine	5	3
15.	Tolbutamide	5	2
16.	Axitinib	5	No hits found
17.	Pyrazinamide	4	26
18.	Efivirenz	4	7
19.	Donepezil	4	4
20.	Sulfamethoxazole	4	4
21.	Epalrestat	4	3
22.	Chlorothalonil	4	2
23.	Nembutal	4	1
24.	Furosemide	3	33
25.	Paracetamol	3	32
26.	Diclofenac	3	27
27.	Temozolomide	3	27
28.	Diflunisal	3	22
29.	Gabapentin	3	19
30.	Mefenamic Acid	3	14
31.	Sulfamerazine	3	9
32.	Benperidol	3	7
33.	Sulfamethoxydiazine	3	5
34.	Tegafur	3	5
35.	Modafinil	3	3
36.	Carvedilol	3	1
37.	Chlorthalidone	3	1
38.	D-mannitol	3	1
39.	Stavudine	3	1
40.	Abecarnil	3	No hits found
41	Ambroxol	3	No hits found
42.	Clevudine	3	No hits found
43.	Fenofibrate	3	No hits found
44.	R-Tamsulosin	3	No hits found
45.	Temazepam	3	No hits found

investigation are furosemide, flufenamic acid, fluconazole, piroxicam, piracetam, sulfamerazine, difunisal, mefenamic acid, sulfathiazole, and diclofenac. APIs, such as carbamazepine, paracetamol, pyrazinamide, gabapentin, and temozolomide which displayed polymorphism and also produced a number of cocrystals/salts, have not been considered in this analysis because of their conformation rigidity. The CSD refcodes of all the selected APIs polymorphs and cocrystals are listed in Table 2. We might miss some of the polymorphs or cocrystals/salts of these selected APIs due to an oversight, we sincerely offer our apologies to the inventors and the authors of those articles.

2 Case Study: Furosemide

Furosemide, a diuretic drug commonly used for the treatment of hypertension and edema[50, 51], displayed polymorphism not only in its pure form, but also in cocrystals. Nangia et al.[52] reported three polymorphic forms of furosemide, of which one is thermodynamically stable (form 1) and other two forms (forms 2 and 3) are metastable. The thermal stability of form 1 crystals was attributed to the more efficient crystal packing and higher crystal density as compared to other two metastable forms. In all the polymorphs, the anthranilic acid moiety of furosemide is locked in an intramolecular N–H···O hydrogen bond (Fig. 1a), thereby restricting its conformational freedom. However, different orientations adopted by conformationally flexible groups, sulfonamide and furan (torsions τ_1, τ_2, and τ_3), in the crystal structure are found to be the main cause of conformational polymorphism

Table 2: CSD refcodes of the selected APIs polymorphs and cocrystals

S. No.	Crystals forms	REFCODE entry
Furosemide		
Polymorphs		
1.	Form 1	FURSEM 01, 03, 13, 17, 18
2.	Form 2	FURSEM 14, 15
3.	Form 3	FURSEM 16
Cocrystals/salts/solvates/hydrates		
4.	Anthranilamide	ESAVIF
5.	Piperazine	ESAVOL
6.	Hemikis(piperazine)	ESAXAZ
7.	2-picolinamide hydrate	ESAVUR
8.	2,3,5,6-tetramethylpyrazine	ESAWAY
9.	4-toluamide ethanol solvate	ESAWEC
10.	4-toluamide nitromethane solvate	ESAWIG
11.	4-toluamide methanol solvate	ESAWOM
12.	Toluene solvate	ESAWUS
13.	4,4′-bipyridine	BOKHAM, BOKHAM01, BOKHAM02
14.	4,4′-bipyridine DMSO solvate	BOKHEQ
15.	4,4′-bipyridine methanol solvate	BOKHIU
16.	4,4′-bipyridine ethylene glycol	BOKHOA
17.	4,4′-bipyridine hemikis(hydroquinone)	BOKHUG
18.	4,4′-bipyridine 1,4-butanediol solvate	BOKJAO
19.	Pentoxifylline	FEFYAS
20.	Pentoxifylline monohydrate	FEFYEW
21.	Pentoxifylline acetone solvate	FEFYIA
22.	2,2′-bipyridine	HUQWAT
23.	4-aminopyridine	HUQWEX
24.	Gefitinib monohydrate	JUYTUU
25.	Caffeine	XAVTEV
26.	Cytosine	XAVTIZ
27.	Piroxicam acetone solvate	XIFRAH
28.	Nicotinamide	YASGOQ, YASGOQ01, YASGOQ02, YASGOQ03
29.	Nicotinamide dihydrate	YASHIL
30.	Sodium trihydrate	YODTOC
31.	Potassuium monohydrate	YODTUI
Flufenamic acid		
Polymorphs		
1.	Form 1	FPAMCA11, FPAMCA18
2.	Form 2	FPAMCA17
3.	Form 3	FPAMCA, FPAMCA19
4.	Form 4	FPAMCA15
5.	Form 5	FPAMCA16
6.	Form 6	FPAMCA14
7.	Form 7	FPAMCA12
8.	Form 8	FPAMCA13

Table 2: (Continued).

S. No.	Crystals forms	REFCODE entry
Cocrystals/salts/solvates/hydrates		
9.	Nicotinamide	EXAQAW
10.	Adamantan-1-amine	SOZGAR
11.	Theophylline	ZIQDUA
12.	2-pyridon	ZIQFAI
13.	4,4′-bipyridine	ZIQFEM, ZIQFEM01, ZIQFEM02
Fluconazole		
Polymorphs		
1.	Form 2 (as mentioned in CSD Nov.2016)	IVUQOF
2.	Form 4	IVUQOF01
3.	Form 5	IVUQOF02
4.	Form 6	IVUQOF03
5.	Form 7	IVUQOF04
Cocrystals/salts/solvates/hydrates		
6.	2-hydroxybenzoic acid	EZEGIA
7.	Ethyl acetate solvate	IVUQEV
8.	Monohydrate	IVUQIZ, IVUQIZ01, IVUQIZ02, IVUQIZ03, IVUQIZ04, IVUQIZ05
9.	Malonic acid	MEWTAL
10.	Maleic acid	UPOQAS
11.	Fumaric acid	UPOQEW
12.	Glutaric acid	UPOQIA
Piroxicam		
Polymorphs		
1.	Form 1—β-monoclinic I	BIYSEH, BIYSEH01, BIYSEH03, BIYSEH04, BIYSEH10, BIYSEH13, BIYSEH14
2.	Form 2—α1 or -orthorhombic	BIYSEH02, BIYSEH08
3.	Form 2—α2 or β-monoclinic II	BIYSEH05, BIYSEH06, BIYSEH09
4.	Form 3	BIYSEH07, BIYSEH11
5.	Form 4	BIYSEH12
Cocrystals/salts/solvates/hydrates		
6.	Monohydrate	CIDYAP, CIDYAP01, CIDYAP02, CIDYAP05
7.	Saccharin	YANNEH, YANNEH01
8.	Methanol solvate	AKITAR
9.	2-fluorobenzoic acid	CEKLAH, CEKNAJ
10.	2-methylbenzoic acid	CEKLEL
11.	3-bromobenzoic acid	CEKLIP
12.	3-chlorobenzoic acid	CEKLOV
13.	3-fluorobenzoic acid	CEKLUB, CEKNOX
14.	3-nitrobenzoic acid	CEKMAI
15.	4-fluorobenzoic acid	CEKMEM, CEKPIT
16.	2-aminobenzoic acid	CEKMIQ
17.	2-bromobenzoic acid	CEKMOW
18.	2-chlorobenzoic acid	CEKMUC

Table 2: (Continued).

S. No.	Crystals forms	REFCODE entry
19.	Salicylic acid	CEKNEN
20.	2-nitrobenzoic acid	CEKNIR
21.	3-hydroxybenzoic acid monohydrate	CEKNUD
22.	3-methylbenzoic acid acetonitrile solvate	CEKPAL
23.	3-methylbenzoic acid	CEKPEP
24.	4-methylbenzoic acid	CEKPOZ
25.	Succinic acid	DIKCIK
26.	1-hydroxy-2-naphthoic acid	DIKCOQ
27.	Caprylic acid	DIKCUW
28.	Malonic acid	DIKDAD
29.	4-hydroxybenzoic acid	DIKDEH, NIFKIX
30.	Fumaric acid	DIKDIL
31.	Benzoic acid	DIKDOR
32.	*p*-dioxane solvate	DIKDUX
33.	Bromanilic acid	SOHVOC
34.	Triazole	SOHWUJ
35.	Benzotriazole	SOHXAQ
36.	Pyrazine	SOHXEU
37.	Chloranilic acid	SOHXIY
38.	Chloranilic acid acetonitrile solvate	SOHXUK
39.	Hydrochloride	TIGNAA
40.	Acetate	TIGNEE
41	Gentisic acid	TUFNUF
42.	Gentisic acid acetone	TUFPAN
43.	Furosemide acetone solvate	XIFRAH
44.	Isobutyric acid solvate	XIFREL
Piracetam		
Polymorphs		
1.	Form 1	BISMEV03, BISMEV05
2.	Form 2	BISMEV, BISMEV06, BISMEV11
3.	Form 3	BISMEV01, BISMEV02, BISMEV12, BISMEV13
4.	Form 4	BISMEV04
5.	Form 5	BISMEV07, BISMEV08, BISMEV09, BISMEV10
Cocrystals/salts/solvates/hydrates		
6.	Benzene-1,4-diol	ABORAM
7.	Gallic acid	AKISEU
8.	Gentisic acid	DAVPAS
9.	P-hydroxybenzoic acid	DAVPEW
10.	Myricetin	FIXROV
11.	4-hydroxybenzoic acid monohydrate	LATBOZ
12.	Monohydrate	YAKWAJ
13.	Dihydrate	LIFNOE
14.	L-tartaric acid	RUCDUP
15.	Citric acid	RUCFAX, RUCFEB

Table 2: (Continued).

S. No.	Crystals forms	REFCODE entry
16.	Rac-mandelic acid	RUCFIF
17.	L-mandelic acid	XOZSOV
Sulfamerazine		
Polymorphs		
1.	Form 1 (*Pbca*)	SLFNMA01
2.	Form 2 ($Pna2_1$)	SLFNMA02, SLFNMA04
3.	Form 3 ($P2_1/c$)	SLFNMA03
Cocrystals/salts/solvates/hydrates		
4.	Tetrahydrofuran solvate	AKOBUZ
5.	1,4-dioxane solvate	FALSES, FALSIW
6.	Dimethylformamide solvate	FALSOC
7.	Dimethylacetamide solvate	FALSUI
8.	Cyclopentanone solvate	FALTAP
9.	3-picoline solvate	FALTET
10.	(18-crown-6) Diacetonitrile clathrate	HADNAB
11.	2-methyl-1,4-naphthoquinone	RUYZAO
Diflunisal		
Polymorphs		
1.	Form V	FAFWIS
2.	Form I	FAFWIS01
3.	Form III	FAFWIS02
Cocrystals/salts/solvates/hydrates		
4.	1,2-bis(Pyridinium-4-yl)ethane acetonitrile solvate	UWOKEY
5.	Pyrazine	UWOKIC
6.	1,3-bis(Pyridinium-4-yl)propane	UWOKOI
7.	1,3-dihydroxy-2-methylpropan-2-aminium	CUXZOM
8.	2-(4-hydroxyphenyl)ethanaminium	CUXZUS
9.	1,3-dihydroxy-2-(hydroxymethyl)propan-2-aminium	CUYBIJ
10.	2-phenylethanaminium	CUYBOP
11.	Ciprofloxacin	KOFFAO
12.	Triphenyl-bismuth	NOJJED
13.	THF inclusion complex	NUZGUM
14.	Caprolactone inclusion complex	NUZHAT
15.	Theophylline	OPOGAD
16.	Monohydrate clathrate	QOQXAV
17.	Chloroform solvate	RUXRUX
18.	Acetic acid solvate	RUXSAE
19.	Hexane solvate	YEJWEP
Mefenamic acid		
Polymorphs		
1.	Form I	XYANAC
2.	Form II	XYANAC02,04,05
3.	Form III	XYANAC03

Table 2: (Continued).

S. No.	Crystals forms	REFCODE entry
Cocrystals/salts/solvates/hydrates		
4.	Nicotinamide	EXAQOK
5.	β-cyclodextrin clathrate	MUPNEQ, MUPNEQ01
6.	Di-sodium dihydrate	NUSSUQ
7.	Potassium	NUSTAX
8.	Diaqua-calcium monohydrate	NUSTEB
9.	Adamantan-1-aminium	PUHVAR
10.	2-amino-1,3-dihydroxy-2-(hydroxymethyl) propane monohydrate	RUVNEC
11.	1,4,7,10-tetra-azacyclododecane	RUVNIG
12.	Piperazine	RUVNOM
13.	Meso-5,7,7,12,14,14-hexamethyl-1,4,8,11-tetra-azacyclotetradecane	RUVNUS
14.	4,4′-bipyridine	XOWKEB, XOWKEB01
15.	*N*,*N*-dimethylformamide solvate	ZAZGAK
16.	4-aminopyrimidinone	ZAZGEO
Sulfathiazole		
Polymorphs		
1.	Form I	SUTHAZ, 03,09,10,18,24,30,31,32
2.	Form II	SUTHAZ01,07,08,16,28,29,43
3.	Form III	SUTHAZ02,11,12,17,25,33,34,35,44
4.	Form IV	SUTHAZ04,13,14,19,26,36,37,38,45
5.	Form V	SUTHAZ05,06,27
Cocrystals/salts/solvates/hydrates		
6.	Pyridine solvate	ADEDIX, ADEDIX01, ADEDIX02
7.	Acetonitrile clathrate	BABYIN
8.	*N*-pormylpiperidine	BABYOT
9.	4-nitrobenzoic acid	FIZFUR
10.	1,4-dioxane solvate	FURDIF
11.	(18-crown-6) Acetonitrile clathrate	HADMUU
12.	4-aminobenzamide	KUFWOZ
13.	Pentanedioic acid	LOFLUP
14.	*N*,*N*-dimethylpropanamide solvate	SOGSEO
15.	Sulfanilamide	STHSAM01
16.	Theophylline	SULTHE01
17.	2,4,6-tris(pyridin-2-yl)-1,3,5-triazine	WIYLAT
Diclofenac		
Polymorphs		
1.	Form I	SIKLIH,01,03,05,06,07,10
2.	Form II	SIKLIH02,08,09
3.	Form III	SIKLIH04
Cocrystals/salts/solvates/hydrates		
4.	Sodium pentahydrate	AKOTAV
5.	Hexa-aqua-magnesium dihydrate	GOLPIG
6.	β-cyclodextrin sodium undecahydrate clathrate	HEHJEJ

Table 2: (Continued).

S. No.	Crystals forms	REFCODE entry
7.	2-ammonioethyl amine	IJOQUT, IKIDIP
8.	Sodium hydrate	LIQFUN
9.	Bis(Ethylenediamine)-dinitro-cobalt(iii)	NEWQUC
10.	Piperazine	NIFGIS
11.	Theophylline	OPOFUW
12.	Adamantane	PUHTIX
13.	Diethylammonium	QIJZUE, RORQEU, RORQEU01
14.	2-hydroxyethyl ammonium	TEKVAG
15.	Pyrrolidinium	TIJHUP
16.	2-hydroxymethyl methylammonium	TUDPIR
17.	Isonicotinamide	UMUZAE
18.	1-phenylethylammonium	VAKVIO
19.	*N*-(2-hydroxyethyl)piperidine	WIRREU
20.	*N*-(2-hydroxyethyl)morpholine	WIRRIY
21.	*N*-(2-hydroxyethyl)piperazine	WIRROE
22.	2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazole	XUVQUB
23.	2-(4-methoxyphenyl)-6-methylimidazo[2,1-b][1,3,4]thiadiazole	XUVSIR
24.	2-aminopyridine	XUVYAP

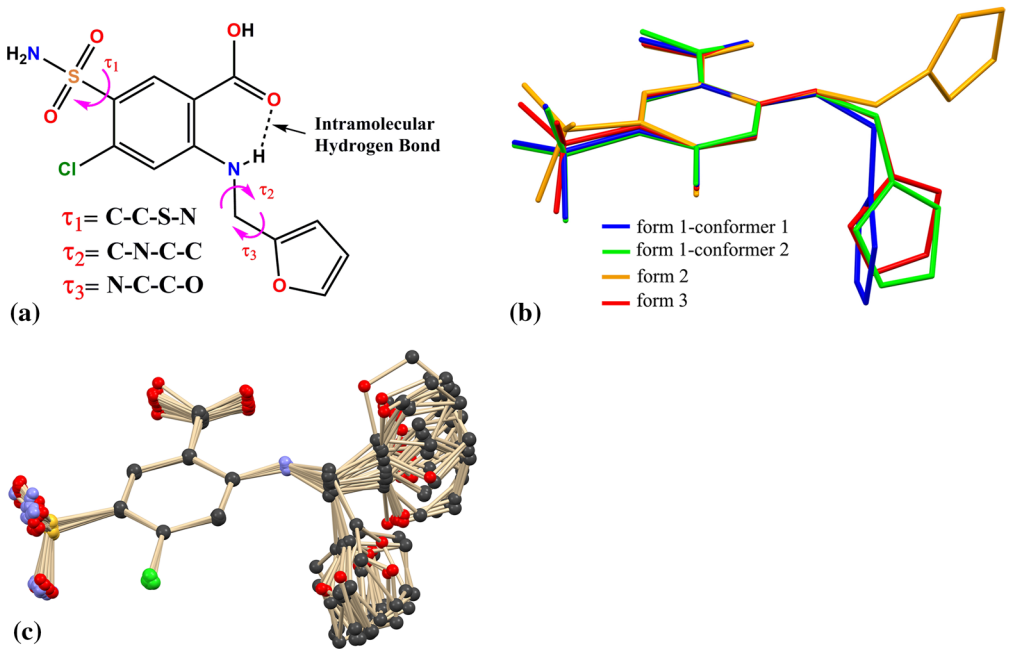

Figure. 1: **a** Three torsion angles in furosemide showed a significant conformation change in polymorphs and cocrystals. The anthranilic acid moiety is locked in an intramolecular N–H···O hydrogen bond in all the conformational isomers of furosemide; **b**, **c** molecular overlay of furosemide in its polymorphs and cocrystals, respectively.

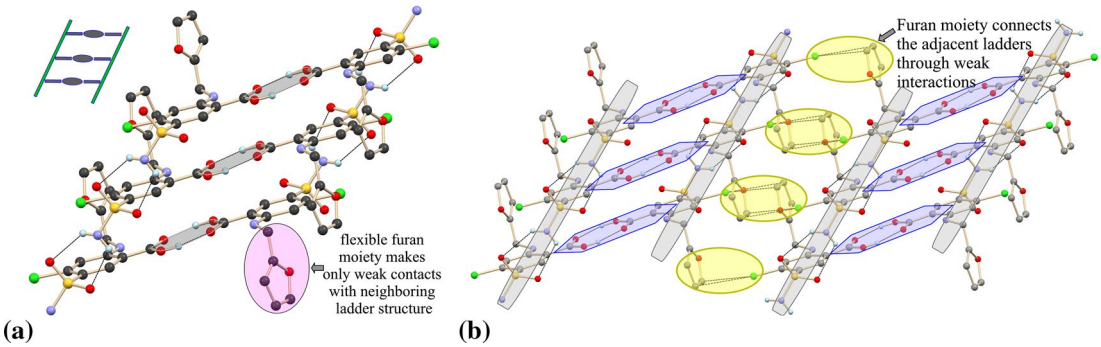

Figure 2: **a** Common ladder structure formed by furosemide molecules in all the polymorphs engaging sulfonamide and carboxyl groups leaving only the furan moiety to adapt different orientations and **b** adjacent ladders are bridged through furan moiety using weak interactions.

(Fig. 1a). Among these, furan moiety exhibited a significant conformational difference in the polymorphs. The sulfonamide moiety showed the orientation difference of ~125° (torsion τ_1), whereas the furan ring displays two different orientations (torsions τ_2 and τ_3). The torsion τ_2 acquires two different major conformations (61°–91°; folded conformation) and (155°–178°; extended conformation) with respect to the basal anthranilic acid moiety. Similarly, torsion τ_3 also shows two different conformations, namely, folded (60°–93°) and extended (156°–176°) (Fig. 1b).

In all the polymorphs, the acid moiety is engaged through dimeric O–H···O hydrogen bond to generate a ladder structure, wherein the acidic moieties fulfil the role of the rungs and the rest of the molecule as a rail. The role of sulfonamide moiety in all the three polymorphs is to engage the neighbouring molecules to generate the ladder structure (monolayer) through N–H···O hydrogen bond (Fig. 2a), while the furan moiety plays a role in associating the adjacent monolayers (Fig. 2b). The absence of free strong hydrogen bond forming groups that can engage furan moiety to freeze its conformation enables furan group to take different orientations in three polymorphs. Therefore, only weak interactions, such as C–H···O, C–H···N, C–H···Cl, and C–H···π, get an opportunity to interact with furan moiety and thus stabilize the crystal structure. Careful assessment of the weak interactions which hold the furan moiety revealed that in form 1 crystals, furan group is involved in total four–five weak interactions resulting in the compact and stable molecular packing compared to other polymorphs, wherein the furan group is making only one or two interactions. This could be one of the reasons for the higher stability of form 1 crystals over other two forms and its preferential formation during crystallization as well.

Furosemide belongs to Class IV according to the BCS (biopharmaceutics classification system)[53] and suffers from both poor aqueous solubility (solubility 0.006 mg mL^{-1}).[52] The low solubility of furosemide has been attributed to strong intermolecular hydrogen bonding in its crystal structure that prevents its ready dissolution/solvation. This necessitated the enhancement of its solubility as its bioavailability solely dependent on in vivo dissolution profile. Therefore, furosemide has been investigated largely for generating various novel solid forms (cocrystals and salts) to augment its solubility. CSD survey revealed ~28 cocrystals and salts of furosemide mostly with nitrogen containing coformers because of the presence of anthranilic acid moiety. Furosemide readily forms cocrystals as it comprised of potential hydrogen bond forming groups, such as sulfonamide, amine, and carboxyl that makes the conventional O–H···N or N–H···O hydrogen bond. The polymorphic behaviour of FS was restricted in several of its cocrystals with cocrystal formers that could lock the conformations of flexible groups (sulfonamide and furan) except with coformer (iso)nicotinamide[54, 55] and 4,4′-bipyridine,[48] which produced cocrystal polymorphs. In these cocrystal polymorphs, both conformations (extended and folded) of furan moiety have been preserved and could be the main reason for cocrystal polymorphism. This suggests that furosemide has the ability to show conformational tuning (similar to its polymorphic crystals) even in cocrystals that is eventually manifested into cocrystal polymorphism. Figure 1b, c shows the structure overlay of furosemide in its polymorphs and cocrystal, respectively. Both sulfonamide and furan ring take orientations similar to that observed in polymorphs, the sulfonamide group orientations differed by c.a. ~132° and furan ring adopts two major conformations either in plane

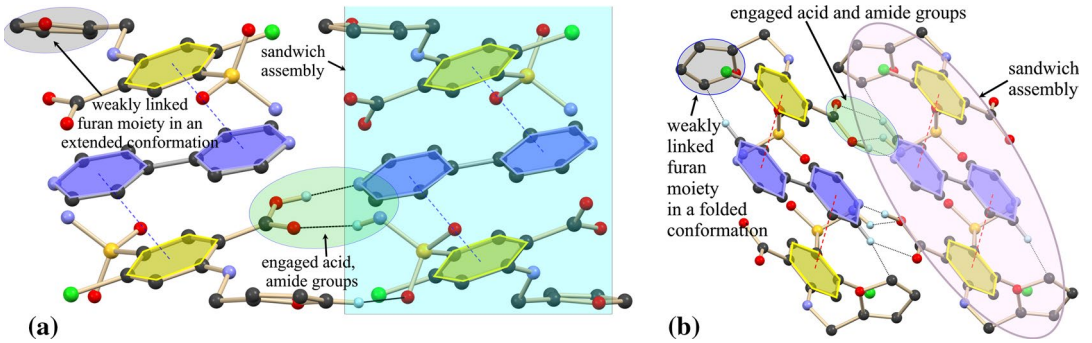

Figure 3: Common structural features in furosemide cocrystals/salts with pyridines showing different conformations of furan moiety: **a** extended and **b** folded.

(extended conformation, 156°–176° and) or takes almost perpendicular orientations (folded confirmation 61°–91°) with respect to the basal plane of the central benzene ring.

The common structural features observed in cocrystals/salts of furosemide with pyridines (except in structural isomers of nicotinamide) are the formation of sandwich motifs comprising furosemide and pyridines through π-stacking interactions between the benzene ring of furosemide and the pyridine rings (Fig. 3).[48] Both carboxyl and sulfonamide groups are engaged in associating the sandwich motifs through hydrogen bonding. Carboxyl group makes O–H···N interactions with pyridine N atoms and sulfonamide moiety either involved in linking furosemide molecules or engaged with pyridines through hydrogen bonds. This spares the flexible furan moiety, which is involved in weak hydrogen boning to adapt the orientation that suits close packing. However, in all cocrystals/salts, furan moiety has adapted only two orientations, extended or folded depending on the orientations of anthranilic acid and pyridine within the sandwich assemblies. It is observed and involvement of furan ring in C–H···O and C–H···π contacts resulted in its acquiring the folded conformation (Fig. 3b), whereas its engagement only via C–H···O interactions led to extended conformation (Fig. 3a).

In cocrystals, polymorphs of furosemide with (iso)nicotinamides, both anthranilic acid and

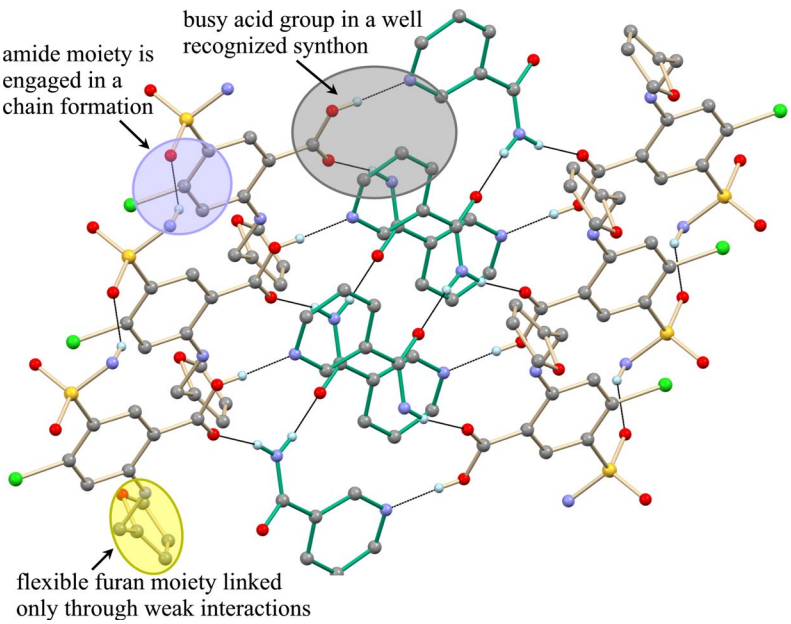

Figure 4: Association of furosemide and nicotinamide molecules in one of their cocrystal polymorphs (CSD refcode: YASGOQ01).

sulfonamide groups, are engaged in the formation of linear assembly through the conventional O–H···N and N–H···O hydrogen bonds with (iso)nicotinamides (Fig. 4), which are also the common structural features. However, the different orientations of the furan moiety which is not involved in making any strong interactions (except in refcode YASGOQ) in the molecular packing seem to have led to cocrystal polymorphism. The absence of sandwich assemblies in these cocrystal polymorphs with nicotinamide could be because of the presence of the hetero atom (N) in the nicotiamide which directly interacts with anthranilic acid COOH groups through O–H···N hydrogen bond. In addition, repulsion between the two electron deficient rings, furosemide benzene and nicotinamide pyridine as well as the presence of other hydrogen bonding sites in nicotinamide moiety could have prevented its parallel alignment (π-stacking assembly) with the furosemide benzene.

3 Case Study 2: Flufenamic Acid (FFA)

Flufenamic acid is non-steroidal anti-inflammatory drug (NSAID).[56] FFA belongs to Class II drugs according to the BCS that shows low aqueous solubility (9.09 mg L^{-1}) and high permeability (log $P = 5.25$).[56] FFA exists in total nine polymorphic forms of which eight of them were characterized by single-crystal X-ray crystallography and the crystal structure of the ninth form still remain elusive, although it has been characterized using Raman and PXRD analysis.[57] Therefore, FFA is considered as one of the most polymorphism exhibiting system at ambient temperature and atmospheric pressure. The existence of two polymorphs of FFA has been known since long time. The crystal structure of its most stable form (form III) was determined in 1973,[58] while the structure of form I was reported in 1982.[59] The marketed solid dosage forms of FFA mostly contain these two forms and form I crystals convert to form III crystals around 42 °C, whereas form III crystals are stable at room temperature. The remaining seven crystalline polymorphs of FFA were reported by Matzger et al.[57] All the polymorphs of flufenamic acids are conformation polymorphs. Amongst eight crystallographically characterized polymorphs, forms I, II, and III contained a molecule in the asymmetric unit, whereas the asymmetric unit of forms IV, V, VI, VII, and VIII contained 3, 4, 6, 2, and 9.5 molecules, respectively.[57] Form VI is a low-temperature polymorph of form IV, although it is stable at room temperature. In all the polymorphs (including all 27 conformational isomers), the anthranilic acid moiety of flufenamic acid molecule is locked in an intramolecular N–H···O hydrogen bond that restricts its conformations freedom (Fig. 5a). However, free rotation along the C–N–C–C (τ_1) torsion is found to be the main cause of conformational polymorphism. In some of the polymorphs, the CF_3 group also displayed umbrella-type orientational disorder. The structural overlay of all 27 conformational isomers of all the polymorphs of flufenamic acid shows two major orientations of a benzene ring with respect to the amine and acid moieties (Fig. 5b). In most of the conformational isomers (except form VIII and form III), the CF_3 group is orientated along the side of amine

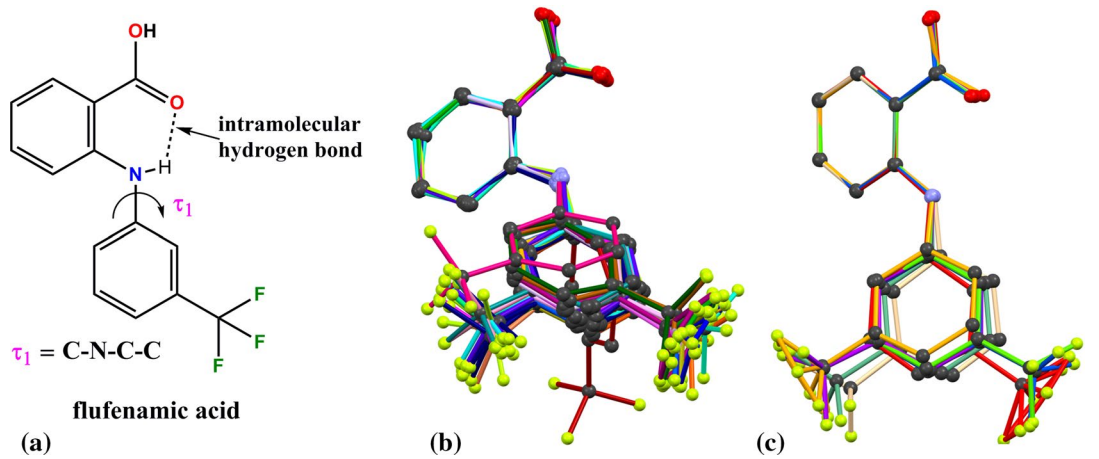

Figure 5: **a** Structure of FFA showing involvement of anthranilic acid in intramolecular N–H···O hydrogen bond; **b**, **c** structure overlay of 27 conformational isomers of eight polymorphs of FFA and FFA molecules in its cocrystals/salts, respectively, showing two distinct orientations of the trifluoromethyl benzene ring.

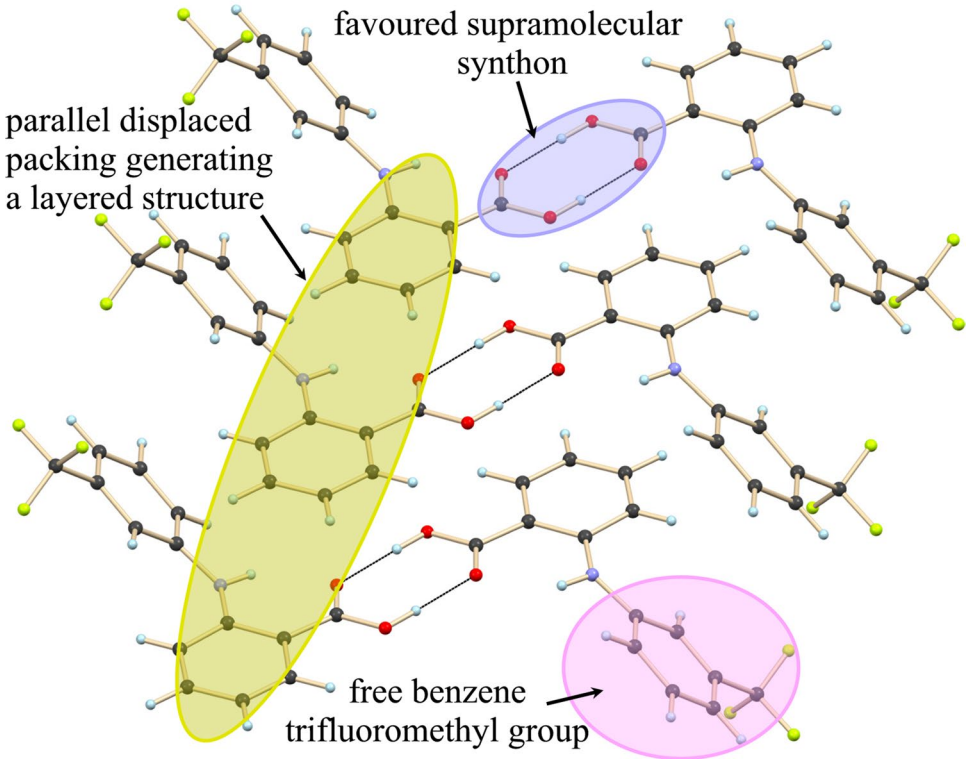

Figure 6: View of molecular packing in thermodynamically stable form III crystals of FFA showing parallel alignment of O–H···O hydrogen bond linked dimeric supramolecular synthon.

and acid moieties (τ_1 = 130–155°), whereas in the remaining conformers, the CF_3 group takes almost opposite orientation with respect to the amine and acid moieties (τ_1 = 24°–42°). In addition, in form III, trifluoromethyl benzene ring is roughly coplanar with the anathranilic acid group (τ_1 = ~−8.72°).

In all the polymorphs, the acid moiety is engaged through the dimeric O–H···O hydrogen bond to generate the well-known zero-dimensional supramolecular synthon (Fig. 6). The involvement of acid and amine moieties in intramolecular and intermolecular hydrogen bonds gives rigidity to the anathranilic acid and its dimeric association. Furthermore, the conformation of the flexible trifluoromethyl benzene group has been frozen by its association with neighbouring molecules solely via weak intermolecular interactions, such as C–H···F, C–H···π, F···F, etc. The competition between these energetically similar weak interactions (exist in equilibrium during crystal growth) tunes the conformation of the trifluoromethyl benzene ring. The common structural features observed in most of the polymorphs of FFA are the face-to-face alignment of zero-dimensional dimeric motif through parallel displaced π-stacking interactions between the benzene rings of anthranilic acid generating the layered structure (Fig. 6). However, this association sets trifluoromethyl benzene ring free to adapt orientations in the crystal lattice that favours close packing of layered structure.

Total five cocrystals of FFA were retrieved from CSD with coformer nicotinamide (refcode: EXAQAW), theophylline (refcode: ZIQDUA), 2-pyridone (refcode: ZIQFAI), 4, 4′ bipyridine (refcode: ZIQFEM02), and adamantan-1-aminium (SOZGAR). The availability of very few cocrystals in the database could be because of the dominance of preferred dimeric motif in nucleation favouring homosynthons over heterosynthons or not many efforts have been put to cocrystallize FFA. The conformation of FFA molecule which was observed in its cocrystal structure was found to be similar to polymorphs, i.e., the anthranilic acid moiety is locked in an intramolecular N–H···O hydrogen bond with amine N–H, thereby restricting its orientation freedom leaving the flexible trifluoromethyl benzene moiety to adjust its conformation that offers stability to the crystal lattice. In concurrence to the polymorphs, the benzene trifluoromethyl group also reveals two major orientations (τ_1 = 37–54° and 135°–153°, Fig. 5c). This shows that the

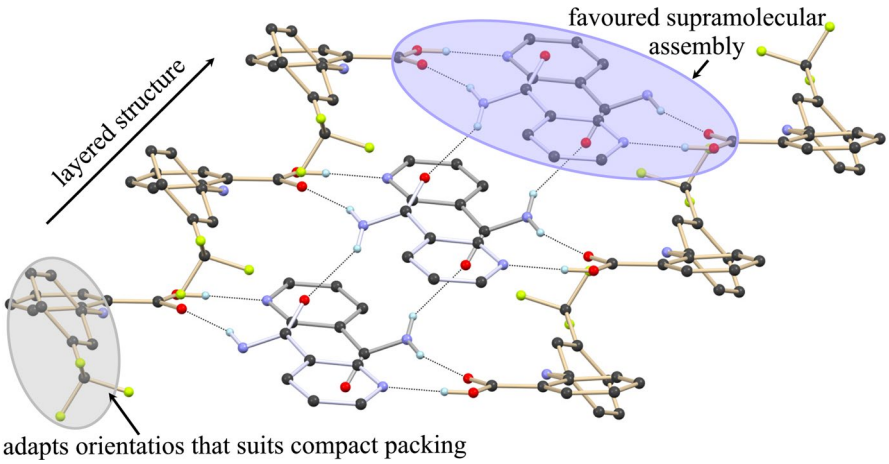

Figure 7: View of molecular packing in cocrystal of FFA with nicotinamide showing the engagement of the acid group with nicotinamide proton donor and acceptor groups.

conformation of the trifluoromethyl benzene ring is preserved in its cocrystals. Furthermore, the molecular packing in cocrystals is similar to the polymorphs of FFA, except that the acid···acid dimeric association of the FFA molecules through O–H···O hydrogen bond is replaced by O–H···N and N–H···O hydrogen bonds between the acid and the coformer molecule. In cocrystals with nicotinamide, two molecules of FFA engage two molecules of nicotinamide through O–H···N and N–H···O hydrogen bonds to form a zero-dimensional supramolecular assembly, the subsequent alignment of which generate the layered arrangement (Fig. 7). Similar FFA-coformer association was found in other cocrystals, leaving the trifluoromethyl benzene ring to fine-tune its orientations utilizing available weak interactions that favours the aggregation of the layered structure to attain stable packing.

4 Case Study 3: Fluconazole

Fluconazole (2-(2,4-difluorophenyl)-1,3-di(1H-1,2,4-triazol-1-yl)propan-2-ol) is an orally active bis-triazole derivative used for the prophylaxis and treatment of superficial and systemic fungal infections.[60] Fluconazole belongs to BCS Class I drugs, which shows high aqueous solubility and high permeability.[61] After its launch in the United States and 15 additional countries by Pfizer in 1994, a larger number of research groups are engaged in its polymorph screening to enhance its pharmaceutical and physicochemical properties. Fluconazole exists in total nine polymorphic forms, of which five of them were characterized by single-crystal X-ray crystallography and crystal structure of four other forms remains mysterious, although they have been characterized using PXRD.[62] All the single-crystal XRD characterized polymorphs (polymorphs 1, 4, 5, 6, and 7) of fluconazole are conformation polymorphs caused by the orientational freedom of two triazole groups which are attached to the main difluorobenzene ring via CH_2 spacer. Polymorphs 4 (refcode: IVUQOF01), 6 (refcode: IVUQOF03) and 7 (refcode: IVUQOF04) contained two molecules in the asymmetric unit, whereas other two forms [polymorphs 1 (IVUQOF) and 5(IVUQOF02)] contained a single molecule in the asymmetric unit. The conformational flexibility of the triazole moiety facilitated by the CH_2 spacer helps the molecule to have different conformers depending on its association with neighbouring molecules. The presence of only one strong hydrogen bond donor (OH) and several hydrogen bond acceptor groups (triazole N atoms) in the molecule generates several possibilities of association owing to the flexible nature of molecule. The triazole 1 and triazole 2 labelled in the molecular structure of fluconazole are used to distinguish the identical groups (Fig. 8a). Structure overlay of the conformational isomers of all the polymorphs shows two major orientations of the triazole groups: triazole 1 adapted folded conformation (torsion τ_2 = C–C–C–N, 52°–69°) in all the polymorphs, while triazole 2 takes extended conformation (torsion τ_1 = C–C–C–N, 165°–178°) except in polymorph 4, wherein triazole 2 displays folded conformation (torsion τ_1 = C–C–C–N, 64°–65°). The torsion τ_3 (C–C–N–N, 76°–101°) and torsion τ_4 (C–C–N–N, 80°–99°) also show

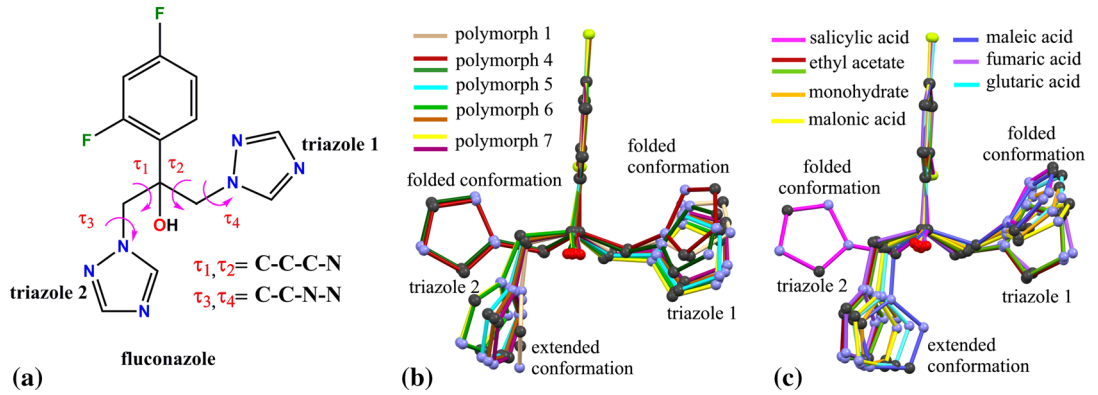

Figure 8: **a** Structure of fluconazole; **b**, **c** structure overlay of conformational isomers of polymorphs and cocrystals, respectively.

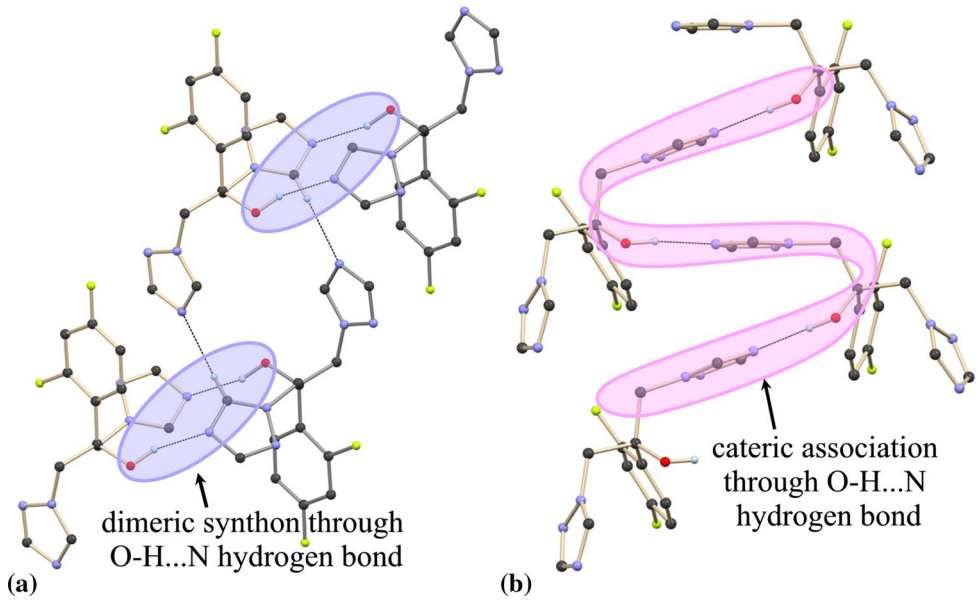

Figure 9: **a** Dimeric (polymorph 1) and **b** catemeric (polymorph 4) associations of fluconazole molecules in polymorphs of fluconazole.

noticeable variation in the conformation (Fig. 8a, b). Both triazole moieties not adapting extended conformation could be because of the steric hindrance. The folded conformation adapted by triazole 1 could be because of its involvement in the intermolecular O–H···N hydrogen bond with the hydroxyl group generating either dimeric synthon or catemeric structure depending on the crystallization conditions. Conversely, triazole 2 adapts two different orientations, extended and folding (only polymorph 4), without taking part in strong hydrogen bond formation. Fluconazole molecule in polymorphs 1, 6, and 7 generates the dimeric synthon (Fig. 9a), whereas in polymorphs 4 and 5, it forms catemeric assembly through O–H···N hydrogen bond (Fig. 9b). The engagement of triazole 2 in bifurcated C–H···O interactions with hydroxyl oxygen in polymorph 4, which connects the adjacent helical chains, seems to the reason for its folded conformation.

About 7 cocrystals including one hydrate (refcode: IVUQIZ) and one ethyl acetate solvate (refcode: IVUQEV) of fluconazole were retrieved from CSD. In all these forms, both triazole molecules adapt conformations similar to that observed in its polymorphs. The triazole 1 takes folded conformation (torsion τ_2 = C–C–C–N, 47°–67°), while the triazole 2 acquires extended conformation (torsion τ_1 = C–C–C–N, 168°–180°) except in cocrystal with salicylic acid it

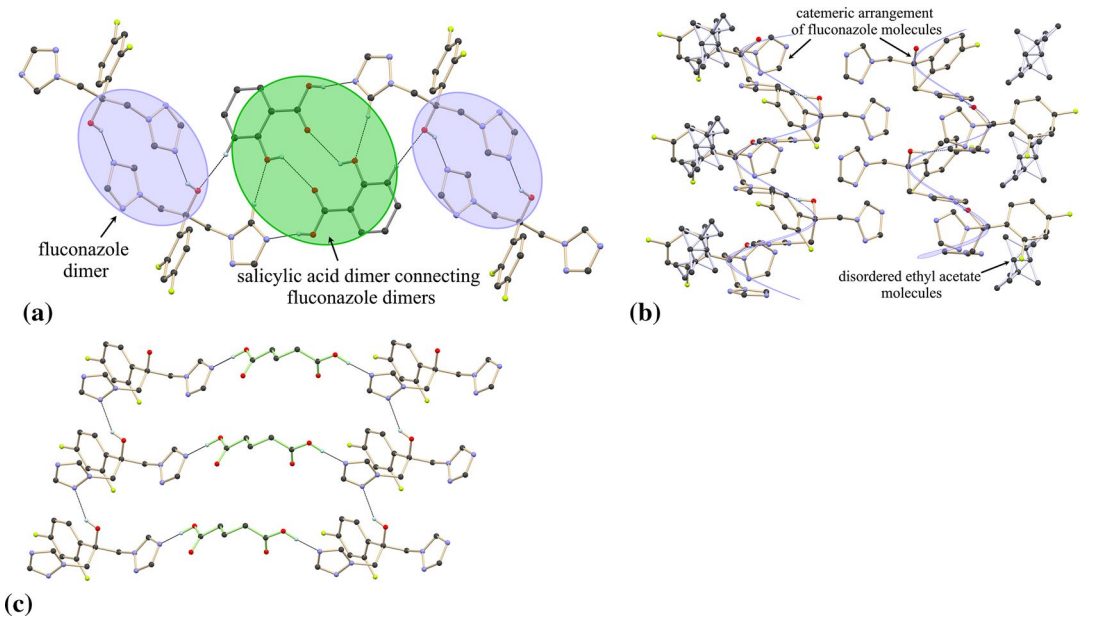

Figure 10: Structure of fluconazole with **a** salicylic acid and **b** ethyl acetate solvate and **c** glutaric acid showing different motifs.

adapts folded conformation (torsion τ_1 = C–C–C–N, 63°) (Fig. 8c). The other two torsions also show significant variations (τ_3 = C–C–N–N, 77°–101° and τ_4 = C–C–N–N, 70°–116°). The presence of several proton accepting N atoms makes fluconazole a good candidate for the cocrystal development. Like in polymorphs, in cocrystal too, the fluconazole molecule forms two different motifs, dimer and helical, in addition to the chain structure. In salicylic acid (SA, refcode: EZEGIA) and fumaric acid (FA, refcode: EPOQEW) cocrystals, the fluconazole molecule forms a dimeric motif through O–H···N hydrogen bond engaging hydroxyl and N atom of the triazole. The neighbouring dimers are connected through coformer using hydrogen bond between acid O–H and triazole N (Fig. 10a). In fluconazole hydrate, two water molecules connect the two fluconazole molecules in dimeric fashion through O–H···O hydrogen bonds and subsequent aggregation of which generate the compact packing. In ethyl acetate (EA) solvate, the fluconazole molecules form the catemeric structure (helical) similar to polymorph 4 and EA molecules are linked to the helix through weak interactions (Fig. 10b). In glutaric acid (GA, refcode: UPOQIA) and maleic acid (refcode: UPOQAS) cocrystals, the coformer molecules connect the linear chains of fluconazole molecules through N–H···O and O–H···N hydrogen bonds (Fig. 10c). Although the architecture of the cocrystals structure is different than that of the polymorph structures, the conformation of the fluconazole molecules is preserved.

5 Case Study 4: Piroxicam

Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) belonging to the class of oxicam. Piroxicam belongs to BCS Class II drugs, which shows low aqueous solubility and high permeability, and thus, its oral absorption considered to be dissolution rate limited.[63] To enhance its solubility, piroxicam has been studied extensively in the solid state to explore different polymorphs. Crystalline piroxicam exists in total five polymorphic forms; however, the literature on piroxicam polymorphism is largely conflicting in terms of the number and nomenclature of polymorphs. Form I (β form) was the first structure to be determined (CSD: BIYSEH).[64] Form III crystal was obtained by Vrečer et al.[65] The crystal structure of form III was determined from powder X-ray diffraction (PXRD) data in 2012 (BIYSEH07),[66] whereas its single-crystal structure has been successfully determined by Wilson et al. (CSD: BIYSEH11).[67] The single-crystal structures of α_1 form (Orthorhombic, $Pca2_1$, refcode: BIYSEH02) and α_2 form (form II, monoclinic space group, $P2_1/c$, refcode: BIYSEH06) were determined by Reck et al. [68] and Vrečer et al. [65], respectively. Both these forms are polytypes[69] and considered as form II. Another new solid form of piroxicam, form IV, was recently reported by Wilson et al.

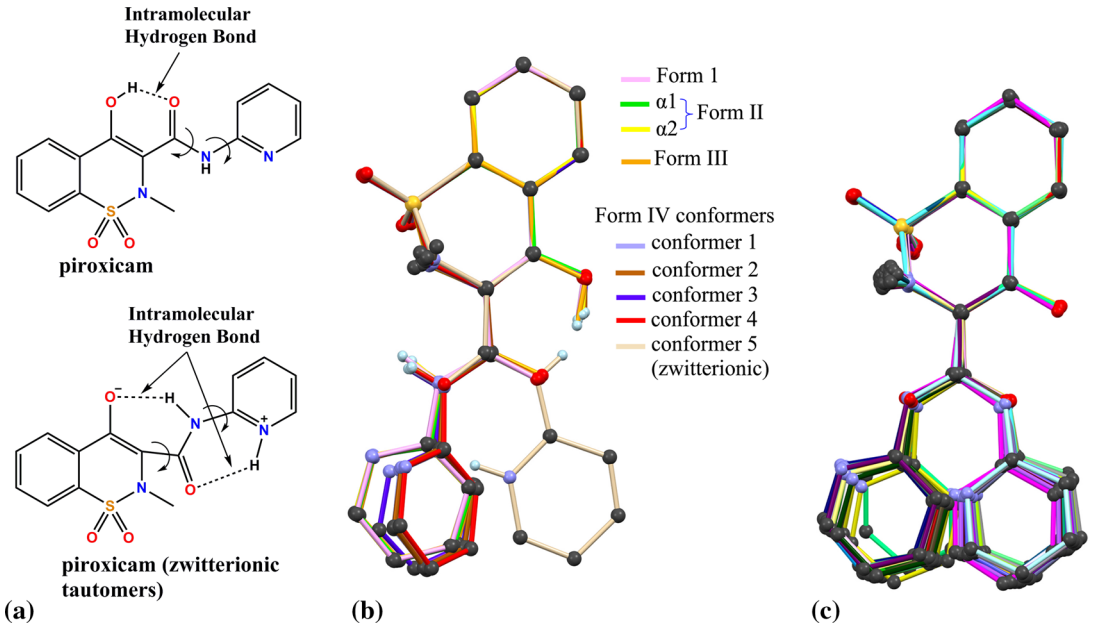

Figure 11: **a** Structure of piroxicam showing intramolecular O–H···O hydrogen bonding in its neutral (top) and two N–H···O hydrogen bond in zwitterionic (bottom) molecules; **b**, **c** structure overlay of conformational isomers of polymorphs and cocrystals of piroxicam, respectively.

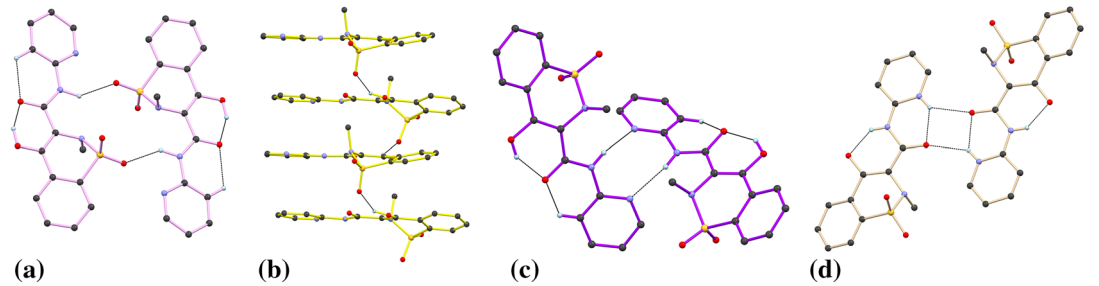

Figure 12: Different hydrogen bond motifs in polymorphs of piroxicam, **a** dimer motif through N–H···O (sulphonyl) hydrogen bond present in forms I and III, **b** catemer synthon through non-linear O–H···O hydrogen bond exists in form II (α_1 and α_2), **c** dimer synthon using N–H···N hydrogen bond present in neutral molecules of form IV, and **d** dimer synthon using N–H···O (carbonyl) hydrogen bond present in zwitterionic molecule of form IV.

(refcode: BIYSEH12).[67] In form IV, the piroxicam molecules are present in both the neutral and zwitterionic forms. Polymorphs I, II, and III contained only a single molecule in the asymmetric unit, whereas the asymmetric unit of form IV contained five molecules, four of them are neutral and the fifth one is zwitterionic. In all the polymorphs (including all conformational isomers, except the zwitterionic molecule), the conformation of the pyroxicam molecule is locked by an intramolecular O–H···O hydrogen bond between the hydroxy and the carbonyl oxygen (Fig. 11a, b). In zwitterionic structure, because of the transfer of a hydroxyl proton to pyridine nitrogen, two intramolecular N–H···O hydrogen bonds restrict its conformation one between amine hydrogen and hydroxyl oxygen and the other one between pyridine N–H and carbonyl oxygen (Fig. 11a, b).

In form I and form III polymorphs, molecules assemble to generate the dimeric motif through N–H···O hydrogen bond between amine N–H and sulphonyl oxygen (Fig. 12a). The neighbouring dimers are stitched differently via weak C–H···O interactions to generate the different molecular architecture. In form II (α_1 and α_2), molecule assembles helically rather through a non-linear O–H···O hydrogen bond between hydroxyl O–H and sulphonyl oxygen (Fig. 12b). The non-reproducibility of this form could be due to this unfavourable supramolecular motif.

The neighbouring helices are joined through weak C–H···O interactions. In form IV, the neutral molecules are involved in dimer formation through N–H···N hydrogen bond between amine N–H and pyridine N atom (Fig. 12c). Conversely, the zwitterionic molecule forms a dimeric structure using N–H···O hydrogen bond between the amine N–H and the carbonyl oxygen (Fig. 12d). All these dimeric motifs are assembled through weak C–H···O contacts to create the compact molecular architecture. Although the conformation of the piroxicam molecule has been frozen due to the intramolecular hydrogen bond, the existence of its four crystalline forms is because of the availability of energetically similar several hydrogen bond donors and acceptor groups.

About 39 cocrystals of piroxicam with several acidic and basic cocrystal formers are retrieved from CSD that excludes hydrate and solvates (methanol, dioxane, acetone, isobutyric acid, acetonitrile, etc.). Piroxicam formed cocrystals with several *ortho*, *meta,* and *para* substituted benzoic acid, including—halo (fluoro, chloro, and bromo), hydroxy, and methyl groups in addition to *ortho*, *meta*-nitro, and *ortho*-amino benzoic acids. It also formed cocrystals with succinic acid, fumaric acid, gentisic acid, 1-hydroxy-2-naphthoic acid, saccharin, chloranilic acid, and bromonilic acid along with triazole, benzotriazole, pyrizine, etc. (Table 2). Piroxicam formed dimorphic cocrystals with F-benzoic acid (*ortho*, *meta* and *para*), 4-hydroxy benzoic acid, and chloronilic acid. In all the cocrystals, the piroxicam molecule exists in either neutral or zwitterionic form (Fig. 11a). Two different conformations of piroxicam, in neutral and zwitterionic forms, were seen in cocrystal too (Fig. 11c). In fact, the zwitterionic form is more favoured in cocrystals compared to non-ionic form. In addition, the presence of various hydrogen bond donor and acceptor groups opened up several avenues for development of cocrystals and cocrystal polymorphism through the formation of different hydrogen bonding synthons.

Close inspection of the synthon formation in these cocrystals reveals three different associations of piroxicam with the coformers. The most preferred synthon observed amongst most of the cocrystals is the formation of flat dimeric structure between the piroxicam molecule either through the non-linear O–H···O hydrogen bond and short O···O contacts (neutral molecule and fewer hits) or through N–H···O hydrogen bonds (Fig. 13a, zwitterionic molecule and more hits). The second favoured dimeric association between the piroxicam molecules is their parallel displace overlapping through non-linear O–H···O (sulphonyl) hydrogen bonds (Fig. 13b) and the third

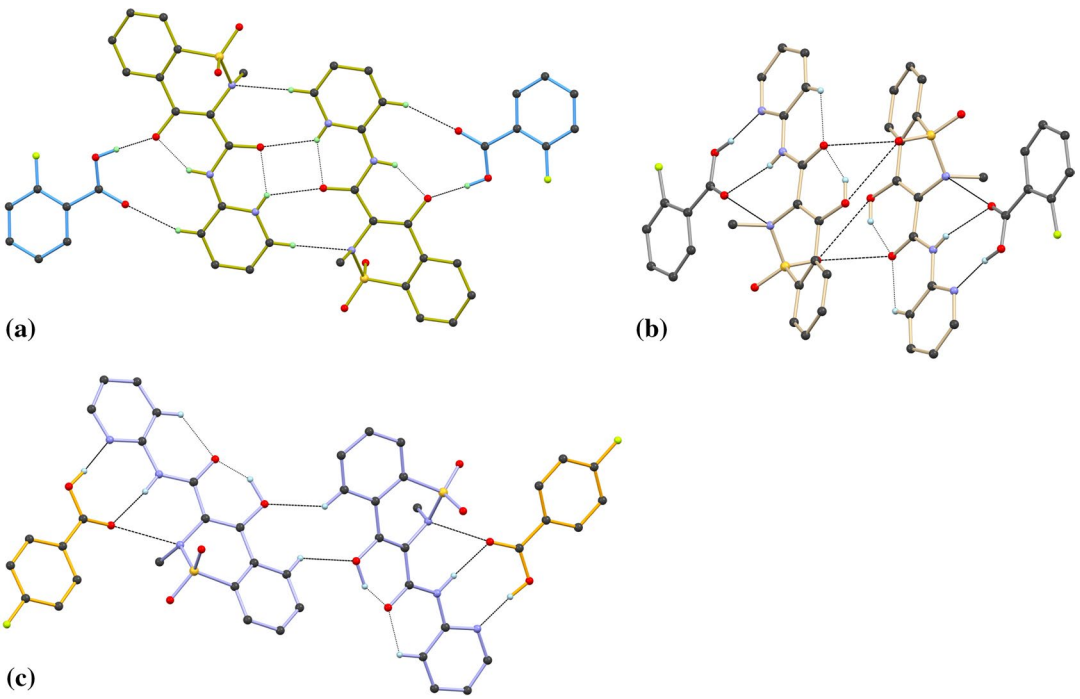

Figure 13: Different dimeric synthons formed by piroxicam molecules in its cocrystals, **a** the most favoured flat dimeric synthon through N–H···O hydrogen bond; **b** parallel displaced dimeric synthon through O–H···O and short O···O contact and **c** dimeric synthon through C–H···O contacts.

and least preferred dimric synthons through C–H···O interactions (Fig. 13c). It is to be mentioned here that the most preferred dimeric motif of piroxicam (Fig. 13a) was also present in its form IV crystals (Fig. 12d). The common structural feature observed in most of these cocrystals is the attachment of coformers to the either side of the dimeric synthons through O–H···O, N–H···O, O–H···N, and C–H···O hydrogen bonds. The polymorphic modifications of cocrystals of *ortho*, *meta,* and *para* fluoro benzoic acid, 4-hydroxy benzoic, and chloronilic acid could be because of different neutral and zwitterionic natures of piroxicam molecules.

6 Case Study 5: Piracetam

Piracetam, (2-oxo-1-pyrrolidinyl)acetamide,[70] is a nootropic drug that works to boost intelligence by stimulating the central nervous system. Total five polymorphs of piracetam have been structurally characterized.[71, 72] Forms II and III are characterized using single-crystal XRD studies,[73, 74] whereas the crystal structure of the form I was determined using X-ray powder diffraction in combination with minimisation of the crystal lattice potential energy.[75] Form I (high-temperature phase, refcode: BISMEV03) converted to form II (refcode: BISMEV) at the ambient temperature, while both forms II and III (refcode: BISMEV01) are transformed to form I at high temperature (399 K). Differential scanning calorimetry and hot stage microscopy analysis[76] as well as lattice energy calculations[75] indicated stability order form III > form II > form I. Form IV (refcode: BISMEV04)[72] and form V (refcode: BISMEV07)[71] are high-pressure forms. The conformational flexibility of the piracetam is due to the different orientations (torsions τ_1 = C–N–C–C and τ_2 = N–C–C–N) adapted by a primary amide group because of the flexible CH_2 spacer that connects it to 2-pyrrolidone (Fig. 14a). The conformation of amide moiety (τ_1 = 90°–92° and τ_2 = 155°–159°) is similar in forms II, III, and V, while it slightly differs in form I (τ_1 = 103° and τ_2 = 178°), but it varies significantly in the high pressure form IV (τ_1 = 115° and τ_2 = 31°) (Fig. 14b).

Molecules in forms II, III, and V make identical zero-dimensional centrosymmetric amide···amide supramolecular homosynthon through N–H···O hydrogen bond, a motif commonly found in primary amide.[77] The neighbouring piracetam molecules also form a chain structure through N–H···O hydrogen bond engaging amide N–H and pyrrolidone carbonyl oxygen. Both the chain and dimers constitute the infinite ribbons (Fig. 15a). The slight change in the conformation of the amide moiety of piracetam in form I altered the entire arrangement of molecules. Molecules in form I generate a chain structure connecting amide moieties using N–H···O hydrogen bond. Neighbouring parallel chains are connected via another set of N–H···O hydrogen bond formed between amide N–H and pyrrolidone carbonyl oxygen (Fig. 15b). The significant difference in the conformation of amide moiety in form IV results in the helical arrangement of molecules through N–H···O hydrogen bond between the amide groups along crystallographic 2_1 screw axis (Fig. 15c). The adjacent antiparallel helices stitched across the inversion centre through another N–H···O hydrogen bond between amide N–H and pyrrolidone carbonyl oxygen.

CSD survey revealed that piracetam readily formed cocrystals with acid and alcohol containing molecules. About 12 cocrystals of piracetam were retrieved from CSD (metal complexes excluded). Cocrystals of piracetam are mostly formed with coformers containing hydroxyl and carboxyl groups, such as dihydroxy benzene, mono, di and tri-hydroxy benzoic acids, tartaric acid, *rac*- and L-mandelic acid, citric acids, etc. In cocrystals too, the conformation of amide moiety

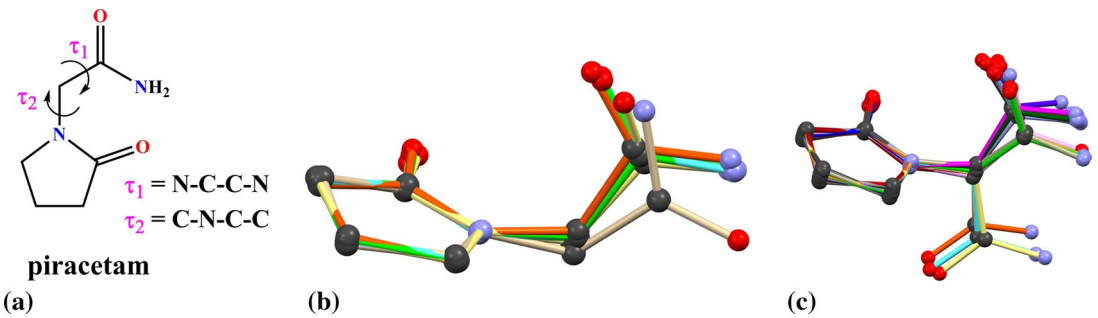

Figure 14: **a** Structure of piracetam showing conformtionally flexibility; **b**, **c** structure overlay of conformational isomers of piracetam in polymorphs and cocrystals, respectively.

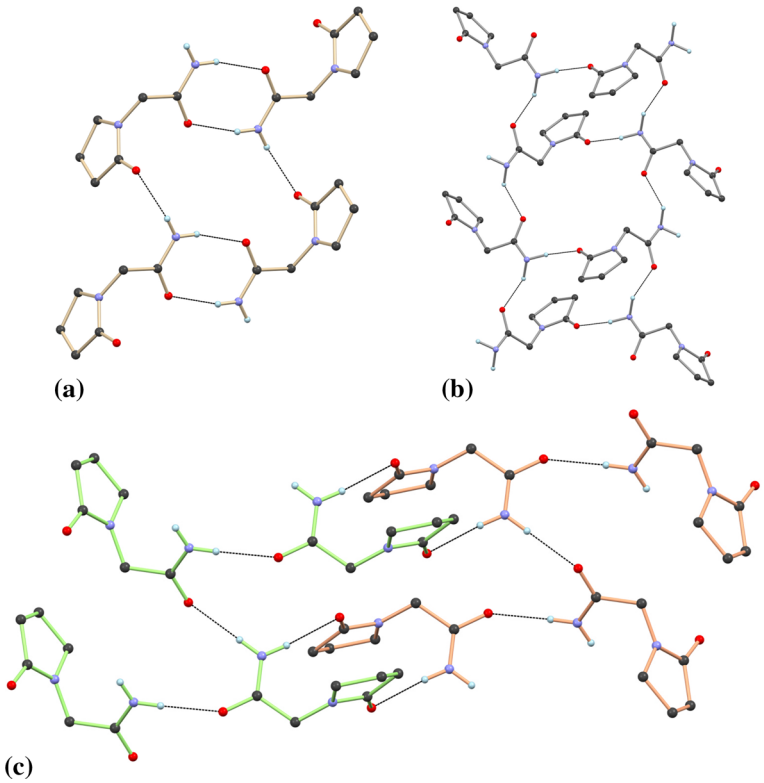

Figure 15: Different associations of piracetam molecules in their polymorphs **a** forms II, III, and V—dimeric motif, **b** form I—infinite chain, and **c** form IV—helical chain along the crystallographic 2_1 screw axis.

showed orientational variations. Majority of the conformation displayed by amide moiety in cocrystals matched with that observed in polymorphs, except in cocrystals with chiral coformers, such as L-tartaric acid (refcode: RUCDUP) and L-mandelic acid (refcode: XOZSOV). In cocrystal, the torsions τ_1 and τ_2 showed orientation variations in the range 72°–114° and 152°–176°, respectively (Fig. 14c).

The ribbon structure observed in polymorphs II, III, and V is retained in cocrystals with dihydroxy benzene (refcode: ABORAM) and *p*-hydroxy benzoic acid (refcode: LATBOZ). The adjacent ribbons are stitched with coformer molecules using weak interactions (Fig. 16a). In cocrystal with *rac*-mandelic acid (refcode: RUCFIF), the dimeric association is retained; however, the neighbouring dimers are linked through mandelic acid molecules via N–H···O hydrogen bonds (Fig. 16b). Conversely, in cocrystals with dihydroxy benzoic (refcode: DAVPAS, gentisic acid) and tri-hydroxy benzoic acid (refcode: AKISEU), the dimeric homosynthon is replaced by heterosynthon. The coformers linked the piracetam molecules thorough N–H···O and O–H···O hydrogen bonds (Fig. 16c). In other cocrystals (citric acid, tartaric acid, etc.), the molecular packing is more complex because of several hydrogen bond donors and acceptor groups.

Although the molecular architecture is vastly different in polymorphs and cocrystals of piracetam, the conformation of the amide moiety is grossly similar. This suggests that the flexible amide moiety preserves its orientations in polymorphs and cocrystals. The distinctly different orientations acquired by the amide moiety in cocrystals with chiral coformers (Fig. 14c) could be because of the chirality driven self-assembly.

7 Case Study 6: Sulphamerazine

Sulfamerazine is a sulfonamide class of antibacterial drug that seems to have exhibited polymorphism because of the presence of various hydrogen bonding donor and acceptor groups in its molecular structure that leads to variability in its hydrogen bonding patterns. Total three polymorphs of sulfamerazine (SMZ) are reported, of which two polymorphs forms I (refcode: SLFNMA01) and II (refcode: SLFNMA02) were reported in 1982[78] and 1992[79], whereas the third polymorph form III (refcode: SLFNMA03) was recently reported.[80]

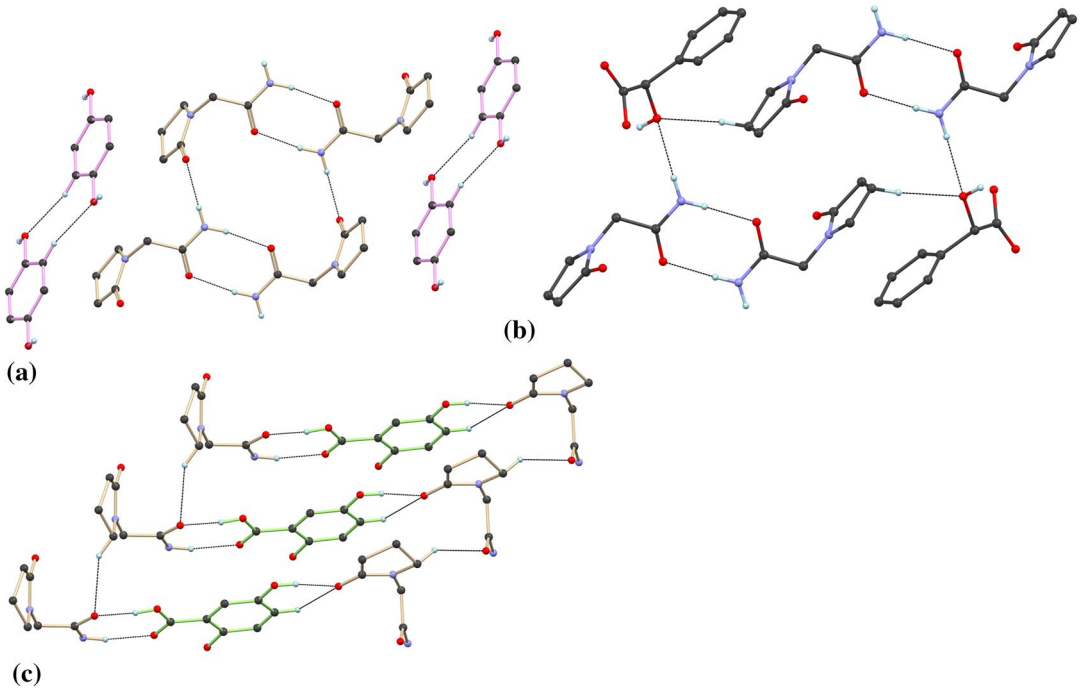

Figure 16: Association of piracetam molecules in its cocrystals with **a** dihydroxy benzene, **b** rac-mandelic acid, and **c** gentisic acid.

Forms I, II, and III crystallized in orthorhombic *Pbca*, $Pna2_1$, and monoclinic $P2_1/c$ space groups, respectively. Forms I and III contained a molecule in the asymmetric unit, whereas the asymmetric unit of form III comprised two molecules. All the three polymorphs of SMZ are conformational polymorph due to the confirmation flexibility offered by sulphonamide moiety along C–N–S–C torsion (Fig. 17a). Structure overlay of the conformational isomers of all the polymorphs revealed similar orientations of sulphonamide moiety in forms II and III crystals having C–N–S–C torsion values in the range 56°–64°, while in form I crystals, the torsion C–N–S–C showed slight deviation with value 71° (Fig. 17b). The common structural motif observed in all the polymorphs is the formation of self-complementary dimeric motif through N–H···N hydrogen bond involving amide N–H and pyrimidine N atom. Two complementary C–H···O=S(sulfonyl) hydrogen bonds also supplement the dimeric association (Fig. 17d). However, this association sets the sulphonamide moiety free to adapt different hydrogen bonding patterns with NH_2 and one of the sulfonyl oxygens leading to polymorphism (Fig. 18).

About seven solvates with THF (refcode: AKOBUZ), dioxane, DMF, cyclopentanone (refcode: FALTAP), 3-picoline (refcode: FALTET), and one cocrystal with menadione (vitamin K3, refcode: RUYZAO) were retrieved from CSD. Solvates with dioxane (refcodes: FALSES and FALSIW) and DMF (refcodes: FALSOC and FALSUI) showed solvatomorphism. Structural overlay of all the conformers of SMZ in solvates and a cocrystal shows the trend similar to polymorphs (Fig. 17b, c). SMZ molecules in these crystals also generate the self-complementary dimeric motif through N–H···N hydrogen bond (Fig. 17d). Two different modes of associations of the dimeric motifs have been observed in dioxane solvates. In one, the linking of the closely related dimers through π-stacking interactions facilitated by the face-to-face alignment of pyrimidine moieties to generate the columnar structure (refcode: FALSIW; Fig. 19a). This is the most common structural motif seen in most of the solvates (expect THF solvate) and a cocrystal. The adjacent columns are bridged through solvent/coformer molecules. In the other dioxane solvate (refcode: FALSES), the dimeric motifs make the linear chain and the neighbouring chains are held together by dioxane molecules (Fig. 19b).

8 Case Study 7: Diflunisal

Diflunisal (DIF) a non-steroidal anti-inflammatory drug (NSAID) belongs to BCS class II drug with low solubility and high permeability. It is mainly used for the treatment of rheumatoid arthritis[81] and chronic lower back

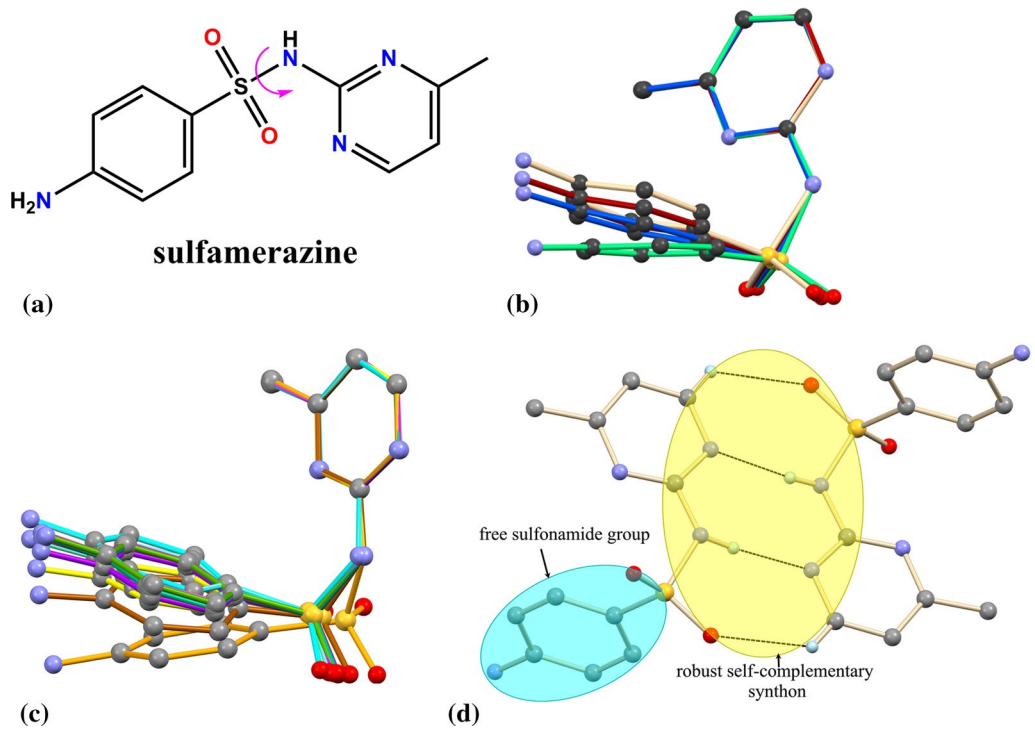

Figure 17: **a** Structure of sulfamerazine, **b**, **c** structure overlay of conformers of sulfamerazine in polymorphs and cocrystals, respectively, and **d** common dimeric motif formed by sulfamerazine in all the polymorphs.

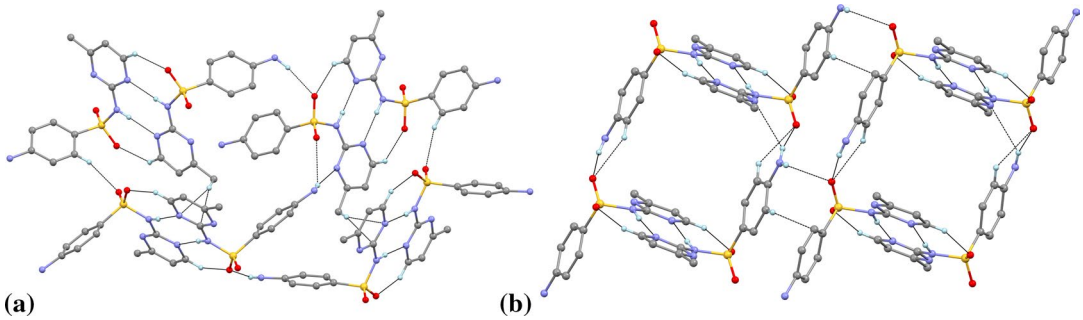

Figure 18: Different association of dimeric motifs in **a** form I and **b** form II polymorphs through N–H···O, N–H···N, and C–H···O interactions.

pain.[82]Although DIF exists in four polymorphic forms,[83] only three polymorphs (designated as form V, form I, and form III) were retrieved from CSD. The crystals of form V (refcode: FAFWIS) belong to the monoclinic space group, *C*2/*c*, while form I (refcode; FAFWIS01) crystallized in the triclinic space group, *P*-1 each containing a molecule in the asymmetric unit. Crystal structure of form III (refcode: FAFWIS02) which was solved from X-ray powder diffraction data belongs to orthorhombic $P2_12_12_1$ chiral space group having two molecules in the asymmetric unit. In forms I and V polymorphs, F atom at the *ortho* position showed statistical disorder over two positions. In all the polymorphs, the 2-hydroxybenzoic acid moiety of the DIF is locked in an intramolecular O–H···O hydrogen bond that restricts its conformations freedom (Fig. 20a) and, however, that leaves diflurobenzne moiety to adapt different orientations due to the conformational flexibility offered by C–C single bond (τ). Interestingly, the structural overlay of four conformational isomers

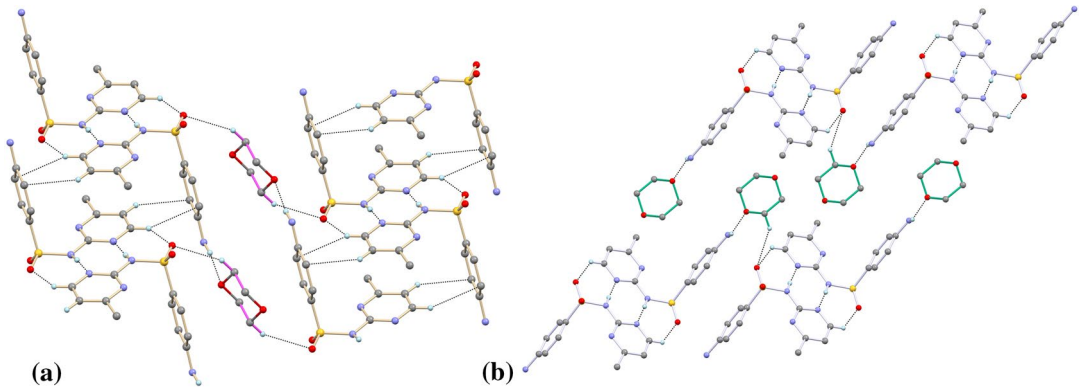

Figure 19: Two different modes of associations of sulfamerazine molecules in dioxane solvate, **a** refcode: FALSIW and **b** refcode: FALSES.

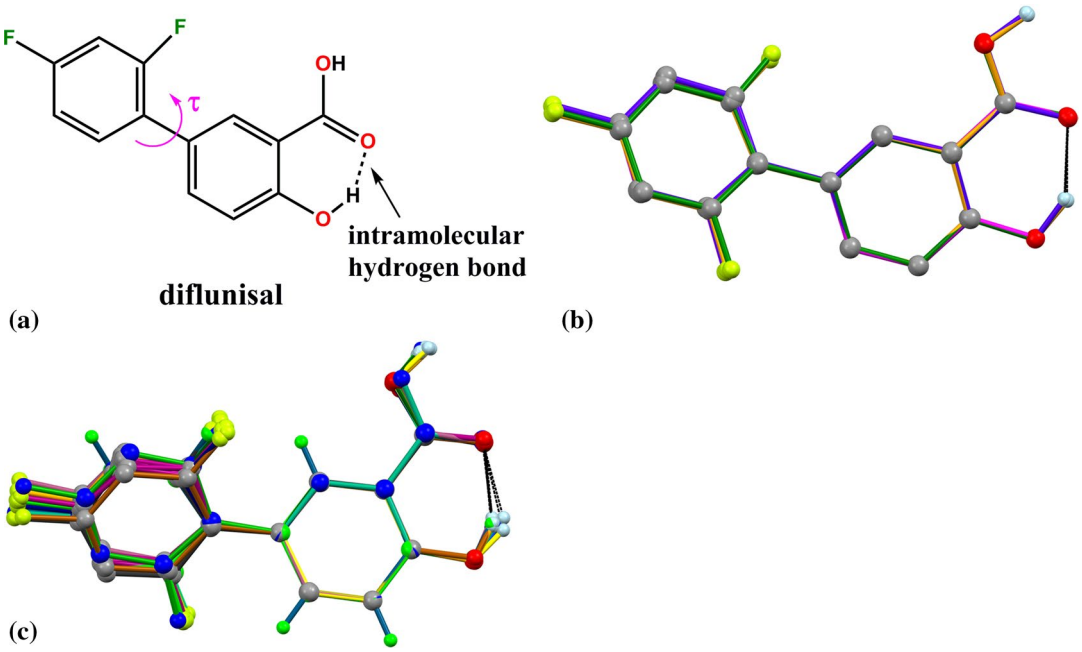

Figure 20: **a** Structure of the diflunisal showing intramolecular O–H···O hydrogen bond between an acid and hydroxy groups and conformational flexibility displayed by fluorobenzene moiety; **b**, **c** structure overlay of conformers of diflunisal in polymorphs and cocrystals, respectively.

of all the three polymorphs showed similar orientations for difluorobenzene moieties (Fig. 20b), revealing polymorphs to be the packing polymorphs. In all the four conformational isomers, the value of torsion (τ) C–C–C–C(F) was found to be in the range 135°–140°.

In all the polymorphs, the acid moiety forms a zero-dimensional dimeric synthon through the conventional O–H···O hydrogen bond. In addition, the involvement of acid and hydroxyl groups in intramolecular O–H···O hydrogen bond formation gives rigidity to this synthon. The common structural features observed in the polymorphs of the DIF are the parallel alignment of zero-dimensional dimeric motifs through parallel displaced π-stacking interactions between the benzene rings resulting in the formation of layered structure (Fig. 21). The involvement of difluorobenzene ring in π-stacking interactions could be the cause of its inability to exhibit conformational flexibility. The adjacent layers are linked through peripheral F and benzene C–H groups using weak C–H···O, C–H···F, and F···F interactions. The competition between these energetically similar weak interactions generates different packing patterns of layered structure depending on the crystallization conditions resulted in the occurrence of polymorphs.

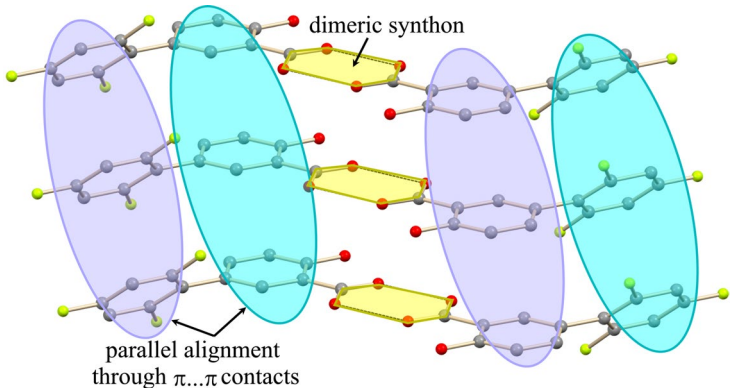

Figure 21: Association of dimeric motifs through face-to-face π-stacking interactions in form V polymorph of diflunisal.

About 16 cocrystals/salts of DIF, including hydrate (refcode: QOQXAW), chloroform (refcode: RUXRUX), acetic acid (refcode: RUXSAE), and hexane (refcode: YEZWEP) solvates, were retrieved from CSD. The structural overlay of conformation isomers of DIF in these crystals also revealed similar orientations of difluorobenzene moiety as observed in its polymorphic systems, although free rotation along the C–C single bond is allowed. The torsion (τ) along C–C–C–C(F) was found to be in the range 132°–143°. This indicates that the conformation of fluorobenzene ring is locked in the molecular packing. The arrangement of diflunisal molecules in solvates resembles to that of polymorphs, forming a parallel chain of O–H···O-linked dimeric synthon through face-to-face π-stacking interactions, thus leaving the peripheral F and C–H atoms to interact with neighbouring molecules via weak C–H···O, C–H···F, and F···F interactions (Fig. 22a). The parallel alignment of the DIF molecules through face-to-face π-stacking interactions was also observed in most of the cocrystal\salt structures resulting in the generation of the layered structure (Fig. 22b). These adjacent layers are bridged through coformer molecules via N–H···O, O–H···O, O–H···N, and C–H···O hydrogen bonds.

9 Case Study 8: Mefenamic Acid

Mefenamic acid (MA) is a non-steroidal anti-inflammatory drug commonly used as an analgesic–antipyretic agent.[84] As per the Biopharmaceutics Classification System (BCS), MA belongs to Class II type with low solubility and high permeability. Coordinates of three polymorphs of MA were retrieved from CSD. Amongst these, form I (refcode: XYANAC) was reported in 1976[85] and crystal structures of the other two forms, form II (refcode: XYANAC04) and metastable phase form III (refcode: XYANAC03), were recently reported.[86] All the trimorphs belong to the triclinic space group, *P*-1 containing a molecule in the asymmetric unit. In all the polymorphs, the amino benzoic acid moiety of MA is locked in an intramolecular N–H···O hydrogen bond that restricts its conformations freedom (Fig. 23a). However, free rotation along the C–N–C–C (τ_1) torsion is found to be the main cause of conformational polymorphism. The structural overlay of conformational isomers shows two major orientations of *ortho*-xylene moiety with respect to the amine and acid moieties (Fig. 23b). In forms I and II, the methyl groups are approximately on the same side of the amine and acid moieties ($\tau_1 = -119°$ and $-80°$ for forms I and II, respectively), whereas in form III, they take roughly opposite orientations with respect to the amine and acid moieties ($\tau_1 = 75°$). In addition, *ortho*-xylene ring is almost orthogonal to the amino benzoic acid ($\tau_1 = \sim 75°–80°$) in forms II and III, while it slightly deviates from orthogonal approach in the form I phase ($\tau_1 = \sim 62°$).

In all the polymorphs, the acid moiety is engaged through the dimeric O–H···O hydrogen bond to generate the zero-dimensional dimeric supramolecular synthon (Fig. 24). The involvement of acid and amine moieties in intramolecular and intermolecular hydrogen bonds gives firmness to the dimeric association. This suggests that the polymorphic modification of MA is due to the different conformations of *ortho*-xylene group (Fig. 23b). The neighbouring dimers are associated through xylene moiety using weak interactions, such as C–H···O, C–H···π, π···π, etc. The competition between these energetically

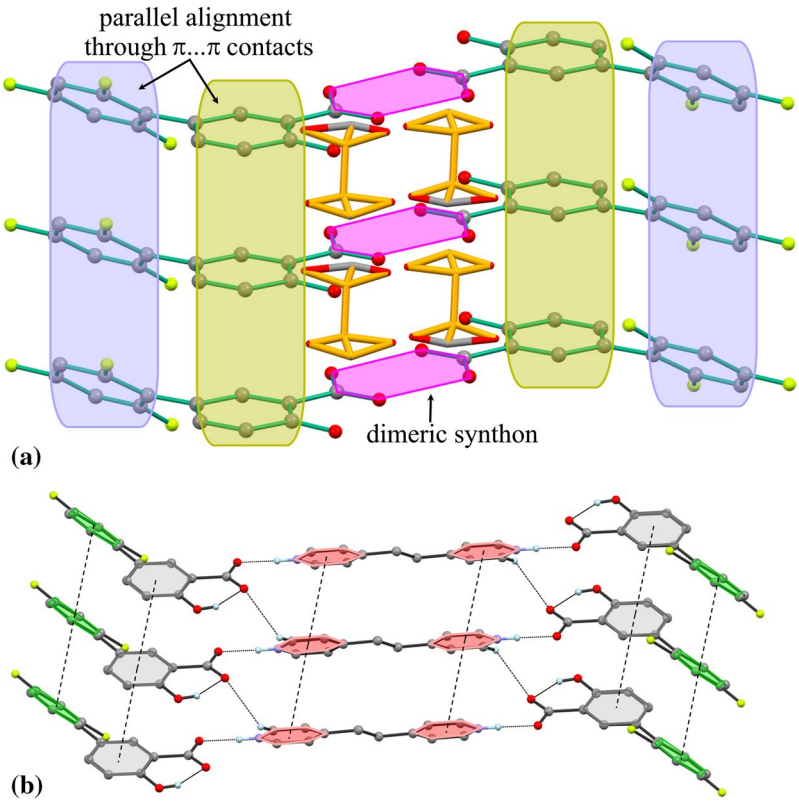

Figure 22: Packing of diflunisal molecules in **a** acetic acid solvate (refcode: RUXSAE) and **b** 1,2-bis,4-pyridyl-ethylene cocrystal (refcode: UWOKEY).

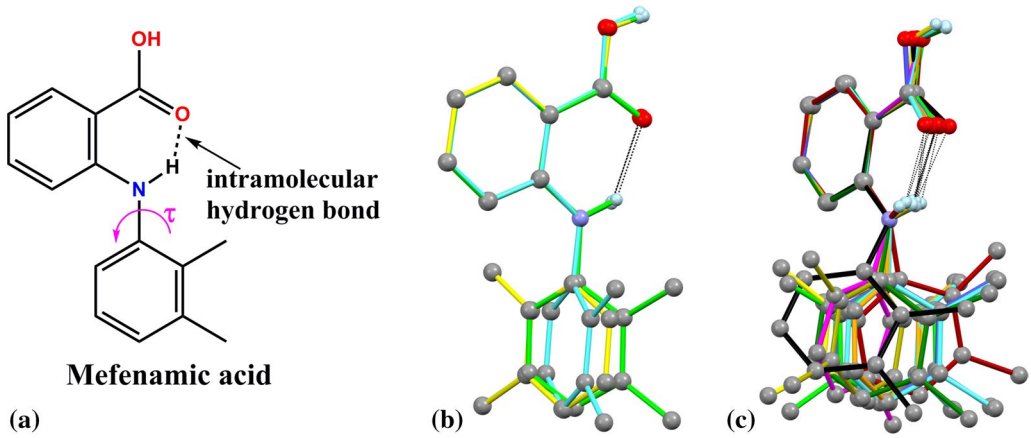

Figure 23: **a** Structure of mefanamic acid showing intramolecular N–H···O hydrogen bond between amine and acid groups and conformational flexibility displayed by xylene moiety; **b**, **c** structure overlay of conformers of mefanamic acid in polymorphs and cocrystals, respectively.

similar weak interactions optimizes the confirmation of *ortho*-xylene ring. Adjacent dimers create a layered (forms I and II) (Fig. 24a, b) and sheet (forms III) structures through face-to-face arrangement of *ortho*-xylene rings (Fig. 24c).

About 13 cocrystals/salts of MA, including DMF solvate (refcode: ZAZGAK), were retrieved from CSD. The structural overlay of conformers of MA in these crystals also revealed two major orientations of *ortho*-xylene moiety with respect

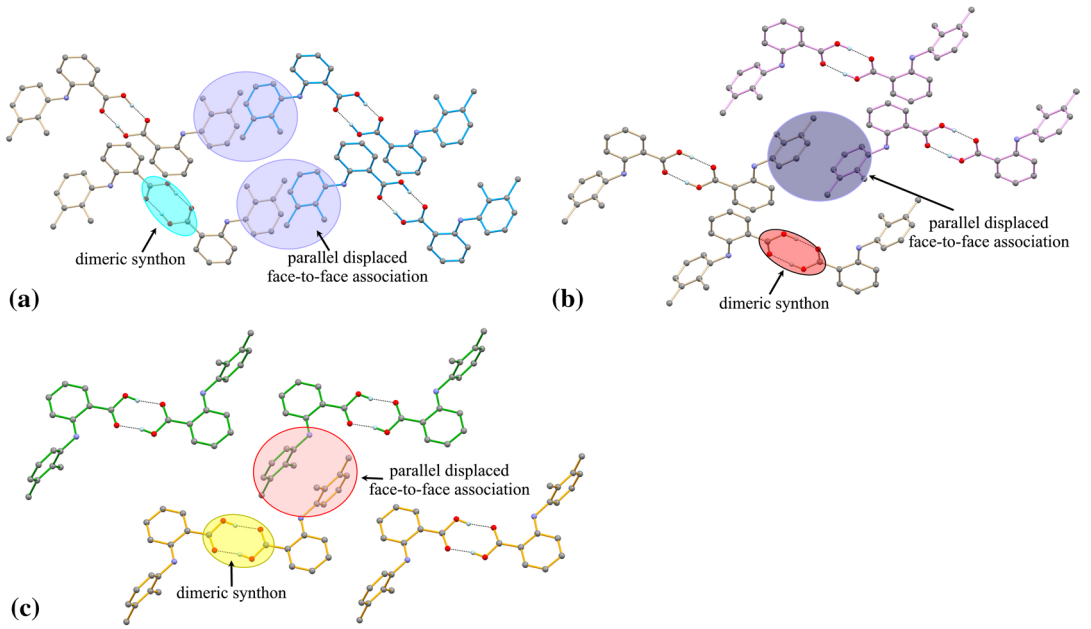

Figure 24: Association of dimeric motifs through face-to-face π-stacking interactions in **a** form I, **b** form II, and **c** form III crystals.

to the amine and acid moieties (Fig. 23c) similar to its polymorphs with torsion angle (C–N–C–C); τ_1 and τ_2 values lay in the range 72°–137° and 77°–100°, respectively. Although the dimeric association between the MA molecules has been replaced by MA-coformer relationship through N–H···O and O–H···O hydrogen bonds in most of the cocrystals/salts structures, the flexible *ortho*-xylene moieties are held through π-stacking contacts, similar to the polymorphic structure. This indicates that the flexible *ortho*-xylene group strives to achieve face-to-face alignment in polymorphs as well as in the cocrytals/salts structures (Fig. 25).

10 Case Study 9: Sulfathiazole

Sulfathiazole (STZ) is a well-known sulphonamide drug used as an antimicrobial agent.[87] It is also given in combination with sulfabenzamide and sulfacetamide. It is known to have at least five polymorphic forms and a several cocrystals and solvates.[88] The CIFs of its polymorphs and cocrystals/solvates were retrieved from CSD. All the polymorphs have been designated as forms I–V. Forms I (refcode: SUTHAZ01), II (refcode: SUTHAZ), and III (refcode: SUTHAZ02) crystallized in the monoclinic space group, $P2_1/c$, whereas forms IV (refcode: SUTHAZ04) and V (refcode: SUTHAZ06) belong to space group, $P2_1/n$. The asymmetric unit of forms II and IV contained a molecule, whereas other three forms comprised two molecules. The stability of all these forms depends on the temperature, in the lower temperature range of 10–50 °C, the stability order is form I < form V < form IV < form II < form III, whereas at temperatures above 100 °C, the stability order is form II < form III < form IV < form V < form I. The structural overlay of all the conformations of STZ (Fig. 26a) revealed an orientation difference of about 10°–11° along the torsion angle τ_1 (C-S–N-C, torsion value = 77°–89°), whereas the conformational variation along torsion τ_2 (C–C-S–N, torsion value = 40°–81°) was found to be very significant (40°–41°) (Fig. 26b).

The presence of several hydrogen bonding donor and acceptor groups in STZ led to the formation of different hydrogen bonding patterns and their successive arrangement resulted in the polymorphism. The common structural pattern which observed in forms II, III, IV, and V is the generation of zig-zag chain through N–H···O=S and N–H···N hydrogen bonds. Amine N–H and sulfonyl oxygen interact via N–H···O=S hydrogen bond, whereas the N–H···N hydrogen bond is generated between thiazole N–H and amine N atoms. The adjacent chains are stitched through (amine)N–H···O (Sulfonyl) and (amine)N–H···N(amide N) hydrogen bonds (Fig. 27a). In contrast, molecules in form I make dimeric synthon through N–H···N hydrogen bonds between triazole N–H and amide N. The adjacent dimers are connected through (amine) N–H···O(sulfonyl) hydrogen bond and

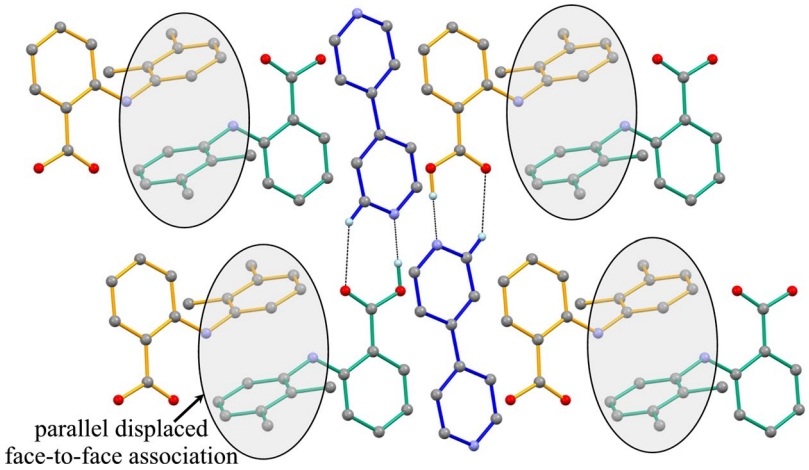

Figure 25: Association of mefanamic acid molecules in cocrystal with 4,4′-bipyridine (refcode: XOWKEB).

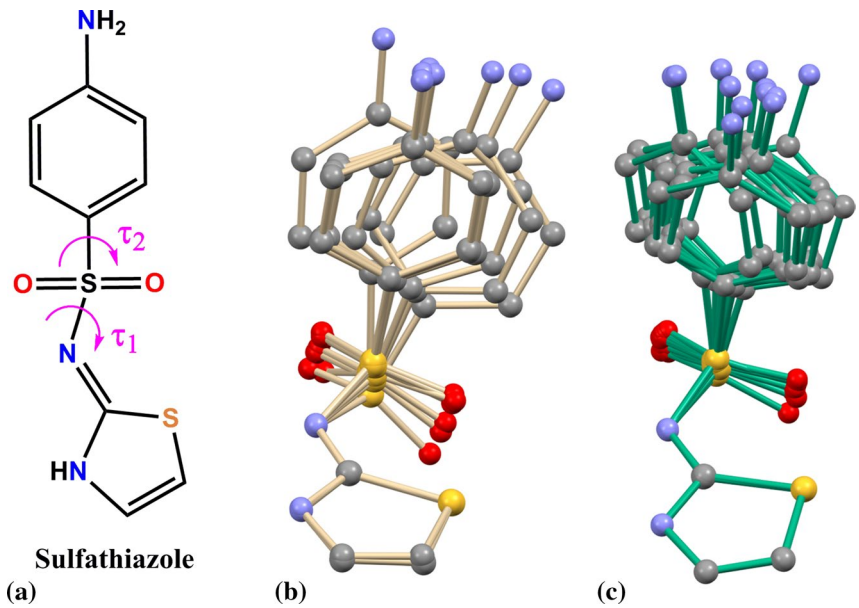

Figure 26: **a** Structure of sulfathiazole; **b**, **c** structure overlay of conformers of sulfathiazole in polymorphs and cocrystals, respectively.

C–H···π interactions to generate the 2D packing (Fig. 27b). In all these structures, C–H···O contact between the benzene C–H and sulfonyl oxygen associates the 2D packing in the third dimensions. This indicates that although the conformation of molecules showed considerable variation in their polymorphs, the molecular arrangement is grossly similar except in form I polymorph.

About 12 cocrystals/solvates of STZ were retrieved from CSD. The structural overlay of all the conformers of STZ indicates variation in the orientations of sulphonamide moiety along torsions τ_1 and τ_2 similar to its polymorph (Fig. 26c). The torsions' values lay in the range of 75°–93° and 51°–100°, respectively. The common structural feature observed in several of these crystals is the dimeric association of STZ molecules through N–H···N hydrogen bond similar to form I polymorph. The adjacent dimeric units associate through various interactions to generate the overall packing depending on the hydrogen bonding features of coformers/solvents (Fig. 28).

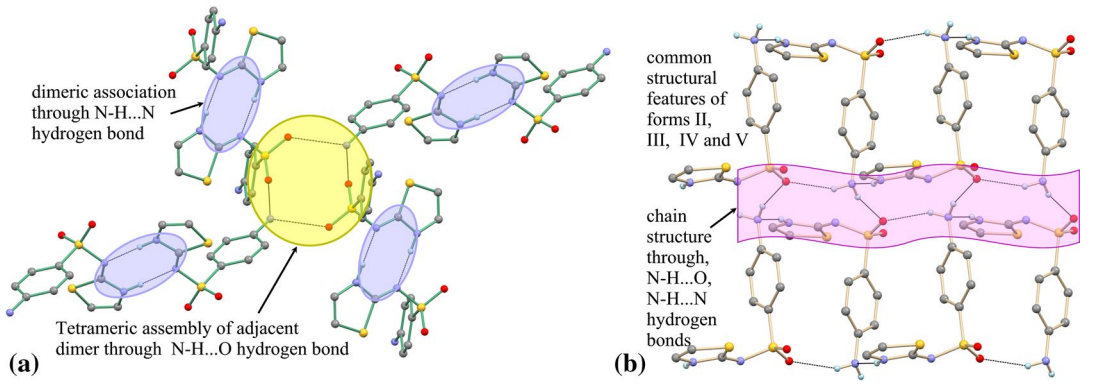

Figure 27: Association of sulfathiazole molecules in **a** form I (dimeric motif) and **b** form III crystals (catemeric motif).

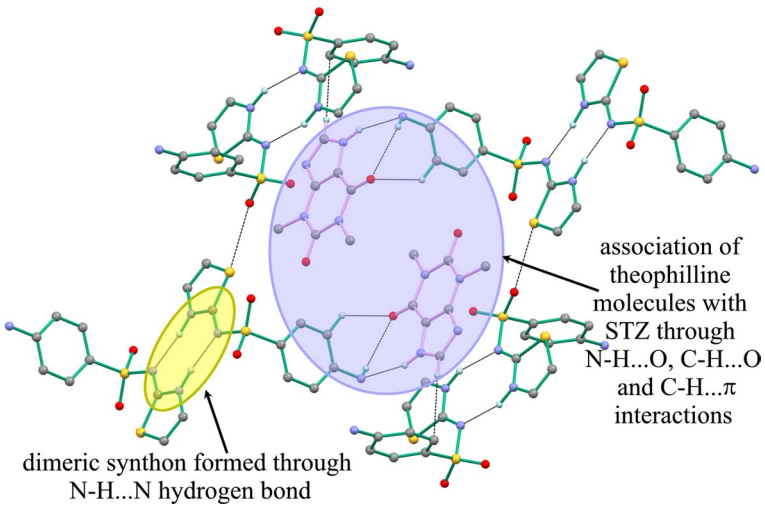

Figure 28: View of molecular packing in cocrystal of STZ with theophylline (refcode: SULTHE01) showing the association of dimers through N–H···O and C–H···O hydrogen bonds.

11 Case Study 10: Diclofenac

Diclofenac is a potent NSAID (non-steroidal anti-inflammatory drug) frequently used in inflammatory and rheumatic disease, in many cases in the form of its sodium, potassium, or other salts.[89] As per the Biopharmaceutics Classification System (BCS), diclofenac belongs to Class II type with low solubility and high permeability. Three polymorphs of diclofenac were retrieved from CSD of which three belong to monoclinic space groups, *C*2/*c* (form I, refcodes: SIKLIH,[90] SIKLIH03[91]), $P2_1/c$ (form II, refcode: SIKLIH02[91]), and orthorhombic space group, *Pcan* (form III, refcode: SIKLIH04[92]) each containing a molecule in the asymmetric unit. In all the polymorphs, the phenyl acetic acid moiety is conformationally locked due to the intramolecular N–H···O hydrogen bond between secondary amine N–H and the carbonyl oxygen of the carboxyl moiety (Fig. 29a). Therefore, the dichlorobenzne moiety which is not involved in any intramolecular locking is all set to adapt different orientations due to the allowed rotation along the C–C single bond. Interestingly, the structural overlay of all the four conformers revealed similar conformation of diclofenac molecules (Fig. 29b) including dichlorobenzene ring, suggesting its involvement in intermolecular interactions.

In all the polymorphs, molecules form a dimeric homosynthon through O–H···O hydrogen bond involving acid groups. However, linking of these dimeric units in all the three dimensions is exclusively governed by weak interactions, such as C–H···O, C–H···Cl, Cl···π, π···π, etc., thereby generating different packing patterns indicating their important role in the polymorphic modification

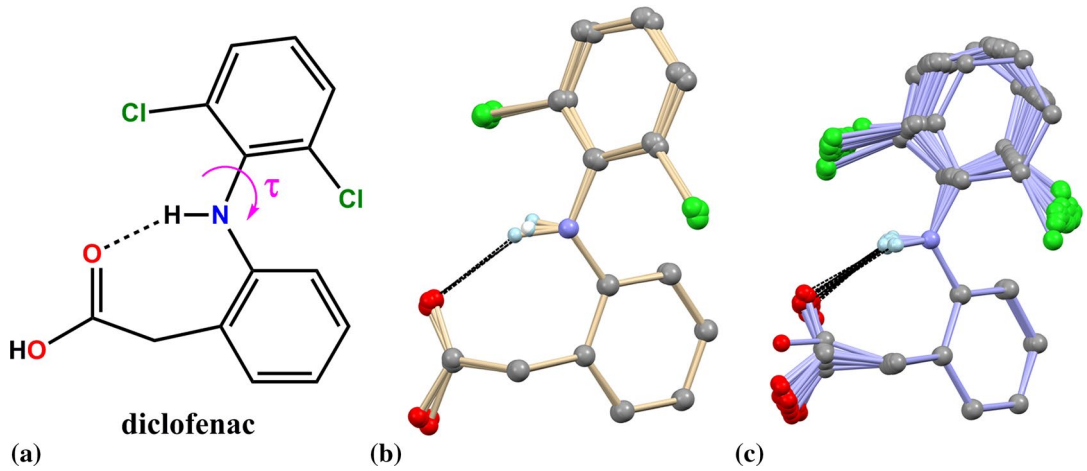

Figure 29: **a** Structure of diclofenac showing intramolecular N–H···O hydrogen bond between amine and acid groups and conformational flexibility displayed by dichlorobenzene moiety; **b**, **c** structure overlay of conformers of diclofenac in polymorphs and cocrystals, respectively.

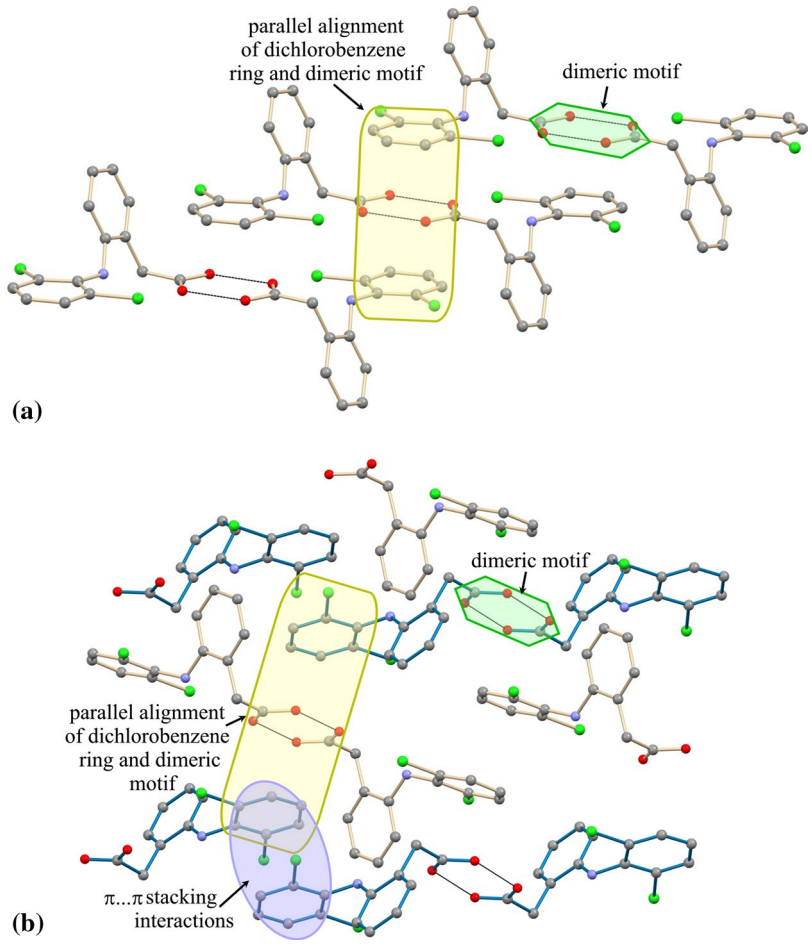

Figure 30: Different associations of O–H···O hydrogen bonded dimeric units in **a** form I (refcode: SIKLIH03) and **b** form II (refcode: SIKLIH020 polymorphs. The common structural feature observed in all the polymorphs is the parallel alignment of the dichlorobenzene ring and hydrogen bonded dimeric unit, shown by yellow shaded portion.

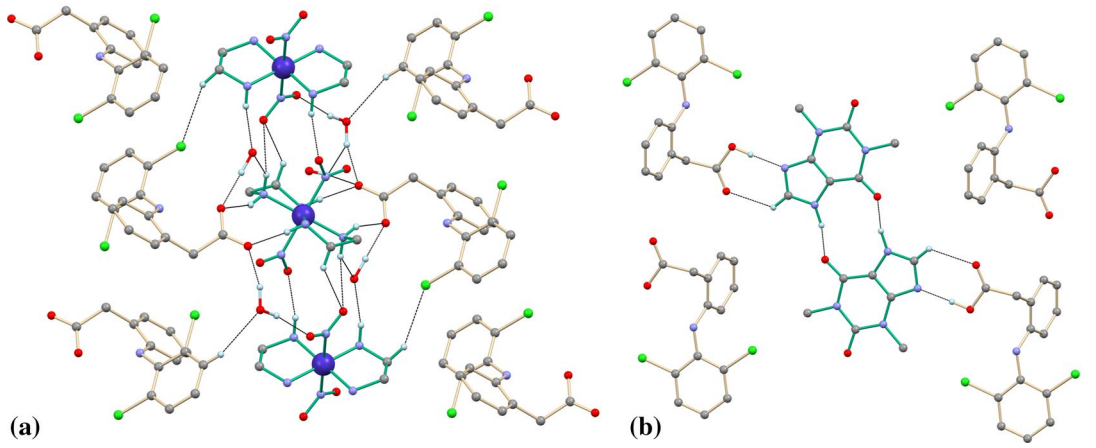

Figure 31: Association of diclofenac molecules with **a** cobalt (III) complex (refcode: NEWQUC) and **b** theophylline (refcode: OPOFUW) in their cocrystals/salts that prevent its dimeric assembly using O–H···O hydrogen bond.

of diclofenac. However, similar conformations of dichlorobenzene moiety in all the trimorphs could be because of the its parallel alignment with dimeric motif at the hydrogen bonding junction, which is a common structural feature (Fig. 30). In addition, dichlorobenzene ring is supported by weak interactions, such as π···π, C–H···π, and Cl···π.

About 21 cocrystals/salts of diclofenac including solvates and hydrates were retrieved from CSD. Structural overlay of all the conformers of diclofenac in these crystals revealed slight variation ~20° (τ = 113–133°) in the conformation of dichlorobenzene moiety (Fig. 29c). In all these crystals, the dimeric association of diclofenac molecules through O–H···O hydrogen bond is replaced by O–H···O, N–H···O, and O–H···N hydrogen bonds between diclofenac and coformer molecules (Fig. 31). The variation in the conformation of dichlorobenzene moiety could be because of the absence of the face-to-face positioning of O–H···O hydrogen bonded dimeric units and dichlorobenzene moiety.

A compilation of the case studies here reveals that the polymorphic behaviour of molecule depends on the conformations of the flexible substituents and their association in the crystal lattice and crystallization conditions. Although the presence of complementary strong hydrogen bonds (either homo or hetero synthons) dictates the molecular assembly, weaker interactions play a significant role in freezing the conformation of flexible groups to produce stability to the overall molecular architecture, e.g., diflunisal and diclofenac. The only difference between the polymorphs and the cocrystal is that the supramolecular homo/hetero synthons (homomolecules) in polymorphs are replaced by more robust supramolecular heterosynthons that self-assembles the heteromolecules. However, this self-assembly seems to provide rigidity only to the supramolecular synthon to which hydrogen bonding functional groups are linked, thus leaving the flexible moieties to adapt orientations that suits close packing. Grossly retaining of the orientations of flexible moieties in polymorphs and cocrystals clearly shows a definite trend in their preferred conformation that it achieves by coaxing using weak interactions in the lattice. This indicates that conformationally flexible molecules comprising hydrogen bond donor and acceptor groups could have more tendencies to adapt different orientations, and hence, it has more chances of forming multicomponent systems.

12 Conclusions

Polymorph and cocrystals are an outcome of the balance between molecular conformational flexibility, the complementary supramolecular synthons that associate the molecules and the conditions of crystallization. Although they are familiar to the chemist, and more particular to the crystallographers, its potential is realized in pharmaceutical industry[93, 94] and high-energy material research.[95–98] The importance of these in optimizing the material properties necessitated the systematic investigation with regard to understating polymorphism and utilization of the suitable coformers to build the desired cocrystal. One can predict the supramolecular synthon based on the hydrogen bonding forming functional groups, but the conformational flexibility of the molecules takes the final call on the outcome of the crystallization results. Therefore,

the understanding of the flexible conformers and their preferred orientation in polymorphs and cocrystals will be valuable in designing desired cocrystals. The inference drawn here is only based on a few case studies discussed here and may or may not be true in other cases. We feel that this comparative study may aid in the selection of the suitable coformer not only based on the complementary hydrogen bonds but also on preferred orientations of the conformationally flexible groups. Generalization may be possible with more examples.

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References

1. Bernstein J (2002) Polymorphism in molecular crystals. Clarendon, Oxford
2. McCrone WC (1965) Physics and chemistry of the organic solid state, vol 2. In: Fox D, Labes MM, Weissberger A (eds) Wiley Interscience Publishers, New York, pp 725–767
3. Kitaigorodskii AI (1970) Advances in structure research by diffraction methods, vol 3. In: Brill R, Mason R (eds) Pergamon Press, Oxford, pp 173–247
4. Brittain HG (1999) Polymorphism in pharmaceutical solids. Marcel Dekker, New York
5. Hilfiker R (2006) Polymorphism in the pharmaceutical industry. Wiley, Weinheim
6. Berstein J (1987) Organic solid state chemistry. Elsevier, Amsterdam, pp 471–518
7. Byrn SR, Pfeiffer RR, Stowell JG (1999) Solid-state chemistry of drugs, 2nd edn. SSCI, West Lafayette
8. Vishweshwar P, McMahon JA, Peterson ML, Hickey MB, Shattock TR, Zaworotko MJ (2005) Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. J Chem Commun 4601–4603
9. US Food and Drug Administration. FDA approves new drug to treat heart failure. Press release—July 7, 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453845.htm
10. Reddy LS, Babu NJ, Nangia A (2006) Carboxamide–pyridine N-oxide heterosynthon for crystal engineering and pharmaceutical cocrystals. Chem Commun 1369–1371
11. Sarkar A, Rohani S (2014) Cocrystals of acyclovir with promising physicochemical properties. J Pharm Sci 104:98–105
12. Aitipamula S, Vangala VR, Chow PS, Tan RBH (2012) Cocrystal hydrate of an antifungal drug, griseofulvin, with promising physicochemical properties. Cryst Growth Des 2:5858–5863
13. Good D, Rodriguez-Hornedo N (2009) Solubility advantage of pharmaceutical cocrystals. Cryst Growth Des 9:2252–2264
14. Remenar JF, Morissette SL, Peterson ML, Moulton B, MacPhee JM, Guzman HR, Almarsson O (2003) Crystal engineering of novel cocrystals of a triazole drug with 1,4-dicarboxylic acids. J Am Chem Soc 125:8456–8457
15. Gonnade RG (2015) Pharmaceutical cocrystals of gefitinib. WO2015170345 A1
16. Duggirala NK, Smith AJ, Wojtas L, Shytle RD, Zaworotko MJ (2014) Physical stability enhancement and pharmacokinetics of a lithium ionic cocrystal with glucose. Cryst Growth Des 14:6135–6142
17. Jung MS, Kim JS, Kim MS, Alhalaweh A, Cho W, Hwang SJ, Velaga SP (2010) Bioavailability of indomethacin-saccharin cocrystals. J Pharm Pharmacol 62:1560–1568
18. Variankaval N, Wenslow R, Murry J, Hartman R, Helmy R, Kwong E, Clas SD, Dalton C, Santos I (2006) Preparation and solid-state characterization of nonstoichiometric cocrystals of a phosphodiesterase-IV inhibitor and L-tartaric acid. Cryst Growth Des 6:690–700
19. McNamara DP, Childs SL, Giordano J, Iarriccio A, Cassidy J, Shet MS, Mannion R, O'Donnell E, Park A (2006) Use of a glutaric acid cocrystal to improve oral bioavailability of a low solubility API. Pharm Res 23:1888–1897
20. Sun C (2013) Cocrystallization for successful drug delivery. Expert Opin Drug Deliv 10:201–213
21. Karki S, Friščić T, Fabian L, Laity PR, Day GM, Jones W (2009) Improving mechanical properties of crystalline solids by cocrystal formation: new compressible forms of paracetamol. Adv Mater 21:3905–3909
22. Vangala VR, Chow PS, Tan RBH (2012) Co-crystals and co-crystal hydrates of the antibiotic nitrofurantoin: structural studies and physicochemical properties. Cryst Growth Des 12:5925–5938
23. Azizi A, Ebrahimi A, Habibi-Khorassani M, Rezazade S, Behazain R (2014) The effects of interactions of dicarboxylic acids on the stability of the caffeine molecule: a theoretical study. Bull Chem Soc Jpn 87:1116–1123
24. Cassidy A, Gardner C, Jones W (2009) Following the surface response of caffeine cocrystals to controlled humidity storage by atomic force microscopy. Int J Pharm 379:59–66
25. Trask AV, Motherwell WDS, Jones W (2006) Physical stability enhancement of theophylline via cocrystallization. Int J Pharm 320:114–123
26. Trask AV, Motherwell WD, Jones W (2005) Pharmaceutical cocrystallization: engineering a remedy for caffeine hydration. Cryst Growth Des 5:1013–1021
27. Vangala VR, Chow PS, Tan RBH (2011) Characterization, physicochemical and photo-stability of a co-crystal involving an antibiotic drug, nitrofurantoin, and 4-hydroxybenzoic acid. CrystEngComm 13:759–762
28. Sanphui P, Bolla G, Nangia A, Chernyshev V (2014) Acemetacin cocrystals and salts: structure solution from

powder X-ray data and form selection of the piperazine salt. IUCrJ 1:136–150
29. Mittapalli S, Bolla G, Perumalla S, Nangia A (2016) Can we exchange water in a hydrate structure: a case study of etoricoxib. CrystEngComm 18:2825–2829
30. McKellar SC, Kennedy AR, McCloy NC, McBride E, Florence AJ (2014) Formulation of liquid propofol as a cocrystalline solid. Cryst Growth Des 14:2422–2430
31. Hong C, Xie Y, Yao Y, Li G, Yuan X, Shen H (2015) A novel strategy for pharmaceutical cocrystal generation without knowledge of stoichiometric ratio: myricetin cocrystals and a ternary phase diagram. Pharm Res 32:47–60
32. Chow S, Shi L, Ng WW, Leung K, Nagapudi K, Sun C, Chow A (2014) Kinetic entrapment of a hidden curcumin cocrystal with phloroglucinol. Cryst Growth Des 14:5079–5089
33. Maeno Y, Fukami T, Kawahata M, Yamaguchi K, Tagami T, Ozeki T, Suzuki T, Tomono K (2014) Novel pharmaceutical cocrystal consisting of paracetamol and trimethylglycine, a new promising cocrystal former. Int J Pharm 473:179–186
34. Dhumal RS, Kelly AL, York P, Coates PD, Paradkar A (2010) Cocrystalization and simultaneous agglomeration using hot melt extrusion. Pharm Res 27:2725–2733
35. Sheikh AY, Rahim SA, Hammond RB, Roberts KJ (2009) Scalable solution cocrystallization: case of carbamazepine-nicotinamide I. CrystEngComm 11:501–509
36. Qiu S, Li M (2015) Effects of coformers on phase transformation and release profiles of carbamazepine cocrystals in hydroxypropyl methylcellulose based matrix tablets. Int J Pharm 479:118–128
37. Li M, Qiu S, Lu Y, Wang K, Lai X, Rehan M (2014) Investigation of the effect of hydroxypropyl methylcellulose on the phase transformation and release profiles of carbamazepine-nicotinamide cocrystal. Pharm Res 31:2312–2325
38. Stahly GP (2009) A survey of cocrystals reported prior to 2000. Cryst Growth Des 9:4212–4229
39. Trask AV (2007) An overview of pharmaceutical cocrystals as intellectual property. Mol Pharm 4:301–309
40. Aitipamula S, Banerjee R, Bansal AK, Biradha K, Cheney ML, Choudhury AR, Desiraju GR, Dikundwar AG, Dubey R, Duggirala N, Ghogale PP, Ghosh S, Goswami PK, Goud NR, Jetti RRKR, Karpinski P, Kaushik P, Kumar D, Kumar V, Moulton B, Mukherjee A, Mukherjee G, Myerson AS, Puri V, Ramanan A, Rajamannar T, Reddy CM, Rodriguez-Hornedo N, Rogers RD, Row TNG, Sanphui P, Shan N, Shete G, Singh A, Sun CC, Swift JA, Thaimattam R, Thakur TS, Thaper RK, Thomas SP, Tothadi S, Vangala VR, Variankaval N, Vishweshwar P, Weyna DR, Zaworotko MJ (2012) Polymorphs, salts, and cocrystals: what's in a name? Cryst Growth Des 12:2147–2152
41. Lide DR (2000) CRC handbook of chemistry and physics, 81st edn. CRC Press, Boca Raton, pp 2–55
42. Childs SL, Stahly GP, Park A (2007) The salt−cocrystal continuum: the influence of crystal structure on ionization state. Mol Pharm 4:323–338
43. Bhogala BR, Basavoju S, Nangia A (2005) Tape and layer structures in cocrystals of some di- and tricarboxylic acids with 4,4′-bipyridines and isonicotinamide. From binary to ternary cocrystals. CrystEngComm 7:551–562
44. Desiraju GR (1989) Crystal engineering: the design of organic solids. Elsevier, Amsterdam
45. Desiraju GR, Vittal JJ, Ramanan A (2011) Crystal engineering. A textbook. World Scientific, Singapore
46. Aitipamula S, Chow PS, Tan RBH (2014) Polymorphism in cocrystals: a review and assessment of its significance. CrystEngComm 16:3451–3465
47. Aitipamula S, Chow PS, Tan RBH (2010) Polymorphs and solvates of a cocrystal involving an analgesic drug, ethenzamide, and 3, 5-dinitrobenzoic acid. Cryst Growth Des 10:2229–2238
48. Sangtani E, Sahu SK, Thorat SH, Gawade RL, Jha KK, Munshi P, Gonnade RG (2015) Furosemide cocrystals with pyridines: an interesting case of color cocrystal polymorphism. Cryst Growth Des 15:5858–5872
49. Allen FH (2002) The Cambridge structural database: a quarter of a million crystal structures and rising. Acta Cryst B58:380–388
50. The American Society of Health-System Pharmacists. Retrieved 3 Apr 2011
51. DrugBank. http://www.drugbank.ca/drugs/DB00695
52. Babu NJ, Cherukuvada S, Thakuria R, Nangia A (2010) Conformational and synthon polymorphism in furosemide (Lasix). Cryst Growth Des 10:1979–1989
53. BCS Classification. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm128219.htm
54. Ueto T, Takata N, Muroyama N, Nedu A, Sasaki A, Tanida S, Terada K (2012) Polymorphs and a hydrate of furosemide–nicotinamide 1:1 cocrystal. Cryst Growth Des 12:485–495
55. Harriss BI, Vella-Zarb L, Wilson C, Evans IR (2014) Furosemide cocrystals: structures, hydrogen bonding, and implications for properties. Cryst Growth Des 12:783–791
56. https://www.drugbank.ca/drugs/DB02266
57. López-Mejías V, Kampf JW, Matzger AJ (2012) Nonamorphism in flufenamic acid and a new record for a polymorphic compound with solved structures. J Am Chem Soc 134:9872–9875
58. McConnell JF (1973) 3'-Trifluoromethyldiphenylamine-2-carboxylic acid, $C_{14}H_{10}F_3NO_2$ flufenamic acid. Cryst Struct Commun 3:459–461
59. Kirshna Murthy HM, Bhat TN, Vijayan M (1982) Structure of a new crystal form of 2-{[3-(trifluoromethyl) phenyl]amino}benzoic acid (flufenamic acid). Acta Cryst B38:315–317
60. Sugar AM (1990) Treatment of fungal infections in patients infected with the human immunodeficiency virus. Pharmacotherapy 10:154S–158S
61. Proposal to waive In vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. http://www.who.

int/medicines/services/expertcommittees/pharmprep/QAS04_109Rev1_Waive_invivo_bioequiv.pdf
62. Karanam M, Dev S, Choudhury AR (2012) New polymorphs of fluconazole: results from cocrystallization experiments. Cryst Growth Des 12:240–252
63. Mirza S, Miroshnyk I, Habib MJ, Brausch JF, Hussain MD (2010) Enhanced dissolution and oral bioavailability of piroxicam formulations: modulating effect of phospholipids. Pharmaceutics 2:339–350
64. Kojić-Prodić B, Ružić-Toroš Ž (1982) Structure of the anti-inflammatory drug 4-hydroxy-2-methyl-N-2-pyridyl-2H-1λ6, 2-benzothiazine-3-carboxamide 1, 1-dioxide (piroxicam). Acta Cryst B38:2948–2951
65. Vrečer F, Vrbinc M, Meden A (2003) Characterization of piroxicam crystal modifications. Int J Pharm 256:3–15
66. Naelapää K, van de Streek J, Rantanen J, Bond AD (2012) Complementing high-throughput X-ray powder diffraction data with quantum–chemical calculations: application to piroxicam form III. J Pharm Sci 101:4214–4219
67. Thomas LH, Walesa C, Wilson CC (2016) Selective preparation of elusive and alternative single component polymorphic solid forms through multi-component crystallization routes. Chem Commun 52:7372–7375
68. Reck G, Dietz G, Laban G, Günther W, Bannier G, Höhne E (1988) X-ray studies on piroxicam modifications. Pharmazie 43:477–481
69. International Union of Crystallography, Online Dictionary of Crystallography. http://reference.iucr.org/dictionary/Polytypism
70. Scheuer K, Rostock A, Bartsch R, Müller WE (1999) Piracetam improves cognitive performance by restoring neurochemical deficits of the aged rat brain. Pharmacopsychiatry 32:10–16
71. Fabbiani FPA, Allan DR, David WIF, Davidson AJ, Lennie AR, Parsons S, Pulham CR, Warren JE (2007) High-pressure studies of pharmaceuticals: an exploration of the behavior of piracetam. Cryst Growth Des 7:1115–1124
72. Fabbiani FPA, Allan DR, Parsons S, Pulham CR (2005) An exploration of the polymorphism of piracetam using high pressure. CrystEngComm 7:179–186
73. Bandoli G, Clemente DA, Grassi A, Pappalardo GC (1981) Molecular determinants for drug-receptor interactions. Mol Pharmcol 20:558–564
74. Admiraal G, Eikelenboom JC, Vos A (1982) Structures of the triclinic and monoclinic modifications of (2-oxo-1-pyrrolidinyl) acetamide. Acta Cryst B38:2600–2605
75. Louër D, Louër M, Dzyabchenko VA, Agafonov V, Céolin R (1995) Structure of a metastable phase of piracetami from X-ray powder diffraction using the atom–atom potential method. Acta Cryst B51:182–187
76. Kühnert-Brandstätter M, Bürger A, Völlenkee R (1994) Stability behaviour of piracetam polymorphs. Sci Pharm 62:307–316
77. Hagles AT, Leiserowitz L (1978) The amide hydrogen bond and the anomalous packing of adipamide. J Am Chem Soc 100:5879–5887
78. Acharya KR, Kuchela KN, Kartha G (1982) Crystal structure of sulfamerazine. J Crystallogr Spectrosc Res 12:369
79. Caira MR, Mohamed R (1992) Positive identification of two orthorhombic polymorphs of sulfamerazine ($C_{11}H_{12}N_4O_2S$), their thermal analyses and structural comparison. Acta Cryst B48:492–498
80. Hossain GMG (2006) A new polymorph of sulfamerazine. Acta Cryst E62:o2166–o2167
81. Brogden RN, Heel RC, Pakes GE, Speight TM, Avery GS (1980) Diflunisal: a review of its pharmacological properties and therapeutic use in pain and musculoskeletal strains and sprains and pain in osteoarthritis. Drugs 19:84–106
82. Berry H, Bloom B, Hamilton EB, Swinson DR (1982) Naproxen sodium, diflunisal, and placebo in the treatment of chronic back pain. Ann Rheum Dis 41:129–132
83. Cross WI, Blagden N, Davey RJ (2003) A whole output strategy for polymorph screening: combining crystal structure prediction, graph set analysis, and targeted crystallization experiments in the case of diflunisal. Cryst Growth Des 2:151–158
84. Flower RJ (1974) Drugs which inhibit prostaglandin biosynthesis. Pharmacol Rev 26:33–67
85. McConnell JF, Company FZ (1976) N-(2, 3-Xylyl) anthranilic acid, $C_{15}H_{15}NO_2$. Mefenamic acid. Cryst Struct Commun 5:861–864
86. SeethaLekshmi S, Guru Row TN (2012) Conformational polymorphism in a non-steroidal anti-inflammatory drug, mefenamic acid. Cryst Growth Des 12:4283–4289
87. Munroe A, Rasmuson AC, Hodnett BK, Croker DM (2012) Relative stabilities of the five polymorphs of sulfathiazole. Growth Des 12:2825–2835
88. Hu Y, Erxleben A, Hodnett BK, Li B, McArdle P, Rasmuson AC, Ryder AG (2013) Solid-state transformations of sulfathiazole polymorphs: the effects of milling and humidity. Cryst Growth Des 13:3404–3413
89. Perlovich GL, Surov AO, Hansen LK, Bauer-Brandl A (2007) Energetic aspects of diclofenac acid in crystal modifications and in solutions—mechanism of solvation, partitioning and distribution. J Pharm Sci 96:1031–1042
90. Moser P, Sallmann A, Wiesenberg I (1990) Synthesis and quantitative structure-activity relationships of diclofenac analogs. J Med Chem 33:2358–2368
91. Castellari C, Ottani S (1997) Two monoclinic forms of diclofenac acid. Acta Cryst C53:794–797
92. Jaiboon N, Yos-in K, Ruangchaithaweesuk S, Chaichit N, Thutivoranath R, Siritaedmukul K, Hannongbua S (2001) New orthorhombic form of 2-[(2, 6-dichlorophenyl) amino] benzeneacetic acid (diclofenac acid). Anal Sci 17:1465–1466
93. Jones W, Motherwell WDS, Trask AV (2009) Pharmaceutical cocrystals: an emerging approach to physical property enhancement. MRS Bull 31:875–879
94. Bolla G, Nangia A (2016) Pharmaceutical cocrystals: walking the talk. Chem Commun 52:8342–8360

95. Bolton O, Simke LR, Pagoria PF, Matzger AJ (2012) High power explosive with good sensitivity: a 2: 1 cocrystal of CL-20: HMX. Growth Des 12:4311–4314
96. Millar DIA, Maynard-Casely HE, Allan DR, Cumming AS, Lennie AR, Mackay AJ, Oswald IDH, Tang CC, Pulham CR (2012) Crystal engineering of energetic materials: co-crystals of CL-20. CrystEngComm 14:3742–3749
97. Bolton O, Matzger A (2011) Improved stability and smart-material functionality realized in an energetic cocrystal. J Angew Chem Int Ed 50:8960–8963
98. Zhangab J, Shreeve JM (2016) Time for pairing: cocrystals as advanced energetic materials. CrystEngComm 18:6124–6133

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