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Review Article

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HARNESSING HYDROGEN-BONDING: ADVANCEMENTS AND APPLICATIONS IN PHARMACEUTICAL CO-CRYSTALLIZATION

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ABSTRACT

Background: In the context of supramolecular chemistry, the formation of solid-state structures that exhibit predictable form and function through the use of intermolecular interactions is known as crystal engineering. In crystal engineering, the hydrogen bonds provide a directional and strong interaction between co-formers, helping to create a stable and well-defined crystalline lattice. The formation of hydrogen bonds can modify key properties of a co-crystal, such as solubility, melting point, and mechanical properties, which are valuable in pharmaceutical applications to improve drug efficacy. Fexofenadine co-crystals have been shown to significantly enhance solubility, achieving an 11-fold increase in water and a 2.47-fold increase in hydrochloric acid solutions. **Objective:** The review primarily focuses on the process of recognizing molecules and forming complex assemblies that are controlled via non-covalent interactions. **Methodology:** Various strategies, including hydrogen bond-based co-crystal design, are discussed and elaborated upon in this review. **Result and Discussion:** Reliable tools for developing supramolecular architectures can be obtained by complementarily combining hydrogen bonds with the understanding of robust supramolecular synthons. In addition to bringing different molecules together, these strong supramolecular synthons play a significant role in co-crystallization by adding dimensionality and a degree of directionality to the three-dimensional solid structures. **Conclusion:** Accurately predicting co-crystal synthesis requires a deep understanding of supramolecular interactions and a carefully selected library of co-formers with functional groups that complement those of the target compound.

INTRODUCTION

The study of non-covalent interactions is known as supramolecular chemistry. Hydrogen-binding, Van der Waals forces, coordination bonding, π-π stacking, and electrostatic interactions are a few examples of these interactions. These forces are weaker than covalent bonds, abundant in nature, and highly reversible. These interactions involve many recognition processes, including protein structure maintenance and enzyme-substrate binding. Supramolecular chemistry, in particular, is concerned with using non-covalent interactions to create

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complex chemical systems. The hydrogen bond (a type of non-covalent interaction) maintains the structure of the DNA double helix by connecting base pairs [1]. Although supramolecular chemistry has made significant advances, there are still challenges to completely understanding and handling these non-covalent interactions to develop molecules, drug delivery systems, and functional materials. Establishing the exact mechanisms governing the stability and self-assembly of supramolecular structures, especially in complex environments, is a significant research gap. Furthermore, research is ongoing to develop robust supramolecular frameworks with predictable characteristics for applications in pharmaceuticals, nanotechnology, and catalysis [2]. This study is significant because it has the potential to assist with the rational design of supramolecular systems with tailored properties for specific applications. Researchers can develop novel supramolecular architectures with increased stability, specificity, and functionality by gaining a deeper understanding of the fundamental principles governing non-covalent interactions. This research could lead to better strategies for designing drug co-crystals to increase bioavailability, the development of self-assembled nanostructures for controlled drug delivery, and the creation of advanced materials with tunable properties [3]. Landmarks in the history of Supramolecular chemistry are given in Table 1.

Table 1: Landmarks in the history of supramolecular chemistry

Outcome	Ref
Dunitz described a crystal as an ideal example of a supermolecule.	[4]
R. Pepinsky proposed crystal engineering in 1955.	[5]
G. Schmidt expanded crystal engineering by working on organic solid-state photochemical processes in 1971.	[6]
Cram proposed host-guest chemistry.	[7]
Lehn proposed the term Supramolecular chemistry in 1978.	[8]
Pederson observed that crown ether showed molecular recognition in 1967.	[9]
In 1989, Desiraju defined crystal engineering as the exploration of intermolecular interactions within the context of crystal packing.	[10]
First published example of a pharmaceutical co-crystal (salicylic acid and urea).	[11]
FDA publishes guidance on the regulatory aspects of co-crystals.	[12]
Expansion of research into various therapeutic classes; first commercial Co-crystal product introduced in market.	[13]

Crystal engineering research and crystal structure prediction (CSP) research have evolved in tandem [14]. Despite improvements in methodology, computing power, and the knowledge of interactions between molecules, CSP remains a challenging task [15]. Crystal engineering can be redefined as the branch of chemistry that explores the structure, characteristics, [16] and uses of crystalline materials in the context of the numerous advancements in the subject that have taken place during the last two or three decades [17].

Various intermolecular interactions (hydrogen-binding, halogen binding, and π-π stacking) are known for their directionality and can regulate the molecular structures [18]. In supramolecular synthesis, hydrogen bonds are the most extensively researched intermolecular interactions [19]. Hydrogen-binding plays a significant role in pharmaceutical co-crystallization due to its ability to influence the physicochemical properties of drug compounds. Recent advancements in hydrogen-binding in co-crystals for pharmaceutical applications are given in Table 2.

Review methodology

For the review of the role of hydrogen bonded co-crystallization, we studied articles available in various databases, including PubMed, Scopus, and Web of Science. The review, as well as research papers published in the last five years related to the selected topic, were searched using the keyword "hydrogen bonded co-crystals."

A total of 470 articles were found, out of which 124 include hydrogen bonded co-crystals. The collected literature was screened based on the importance of hydrogen-binding in co-crystallization. The chosen articles were examined for co-crystal strategies centered on hydrogen bonded co-crystallization. The following sections discuss co-crystal design based on hydrogen-binding, along with other related aspects.

Table 2: Advancements in hydrogen-binding in co-crystals for pharmaceutical applications

Advancement	Description	Significance	Studies	Ref
Optimization of solubility	Improvisation of dissolution profile of poorly aqueous soluble drugs via hydrogen bonding	Improves bioavailability and absorption of drugs in the body	Studies on Carbamazepine co-crystals with nicotinamide and saccharin	[20]
Enhanced Stability	Co-crystals provide better stability compared to amorphous forms or individual components	Leads to longer shelf-life and consistent therapeutic effects	Co-crystals of Theophylline with acetic acid to improve thermal stability	[21]
Targeted hydrogen-binding Interactions	Design of co-crystals with specific functional groups to form desired hydrogen bonds	Allows tailoring of the drug's physicochemical properties	Use of Carboxylic Acids or Amides to form predictable hydrogen-binding networks	[22]
Improved Mechanical Properties	Co-crystals engineered to have better compressibility and tabletability	Aids in mfg & formul^{n} processes, enabling easier production of SDF	Aspirin–Paracetamol co-crystals with improved compressibility properties	[23]
Co-crystallization with GRAS co-formers	Using safe co-formers like citric acid, urea, or succinic acid to form co-crystals	Ensures safety & regulatory acceptance for pharmaceutical use	Ibuprofen–Nicotinamide co-crystals for enhanced dissolution	[24]
Polymorphic Control	Using co-crystals to control polymorphic forms of a drug, preventing undesirable forms	Improves consistency & safety by maintaining the desired crystalline form	Co-crystallization of Ritonavir to prevent the formation of less soluble polymorphs	[25]
Screening techniques for hydrogen bond donors/acceptors	Computational and experimental approaches for identifying ideal hydrogen bond donors/acceptors	Enhances efficiency in co-crystal design and discovery processes	Use of Cambridge Structural Database for hydrogen bond prediction	[26]

Hydrogen bonds

According to the book by George A. Jeffrey and Wolfram Saenger, the discovery of the hydrogen bond was significant enough to deserve a Nobel Prize [27]. This statement highlights the significance of hydrogen-binding, which is required for life on Earth because, without it, there would be no water. The history of supramolecular chemistry is presented in Table 3.

Table 3: Landmarks in the history of hydrogen-binding

Outcome	Ref
In 1935 and 1936, Bernal and Huggins first used the term "hydrogen bond".	[28]
Pimental & McClellan define a hydrogen bond as an interaction in which a hydrogen atom, covalently bonded to an electronegative atom such as oxygen, nitrogen, or fluorine, forms a bond with another electronegative atom.	[29]
Werner in 1902 and Hantzsch in 1910 focused on interactions with ammonium Ca^{++} or nebenvalenz, or minor valence.	[30-31]
Latimer and Rodebush highlighted the significance of "interaction".	[32]
Pauling invented the concept of the hydrogen bond to describe the characteristics of water and ice. The interactions between peptide nitrogen and oxygen atoms after protein denaturation were then described by Pauling using hydrogen bonds.	[33-34]
Watson and Crick suggested the double helix of DNA in 1953.	[35]
1960, Established hydrogen-binding as critical for stabilizing α-helices and β-sheets in protein folding.	[36]
1980, highlighted its importance in host-guest systems and molecular recognition.	[37]
2000, Quantum mechanical studies of hydrogen bonds.	[38]
2010’s hydrogen-binding was engineered for functional materials with applications in biomedicine and energy.	[39]
2020, hydrogen-binding elucidated in enzymatic catalysis.	[40]
2023, hydrogen-binding optimized in 3D perovskites and self-healing materials.	[41]

The dissociation energy of a hydrogen bond has four possible components: electrostatic, covalent, dispersion-repulsion, and polarization. Its range is 1.25 to 160 kJ mol^{-1} [42]. In 2011, IUPAC defined the hydrogen-binding as: 'A hydrogen bond is an attractive interaction involving a hydrogen atom bound to a molecule or molecular fragment X-H, where X is more electronegative than H' [43]. X-H...A (X = donor, A = acceptor) is a common representation of hydrogen-binding, and d, D, θ, and ϕ are the four geometric parameters that can be used to explain it.

Hydrogen atoms can be recognized with sufficient accuracy to obtain suitable d and θ values due to the relatively high quality of contemporary diffraction data. An acceptor may interact with two or more donors or a donor group may be made available to two or more independent acceptors, in a multifaceted hydrogen bond interaction. In every scenario, the interaction can be explained by the simultaneous attraction of a hydrogen atom to X and A, with the hydrogen atom serving as a kind of connection between the two atoms. The electrostatic contribution to the interaction is significant and rises with X and A's electronegativity.

Classification of hydrogen bonds

Based on interaction energy and their significant role in the synthesis of supramolecular synthons, hydrogen bonds are classified as strong, very strong, and weak [44]. Different types of hydrogen bonds and their influence on co-crystal structures are shown in Figure 1.

Very Strong hydrogen bonds

Powerful hydrogen bonds can be formed when an acid is linked with its conjugate base (X-H...X$^-$) or when a base is linked with its conjugate acid (X$^+$-H...X). The values for D and d in the situations above are both low enough to reflect covalent contributions [45].

Strong hydrogen bonds

Well-known examples of strong hydrogen bonds include base pairing in DNA, α-helix, and β-sheet structures of proteins. Because the OH and NH moieties are common in organic chemistry, these interactions are beneficial and have been widely researched in the context of crystal engineering. The interactions between OH...OH, phenol or alcohol and COOH...COOH dimer and catemeric compounds are abundant. In ionic moieties, charge-assisted N*-H...O hydrogen-binding occurs. Acid pyridine, acid amine, and phenol pyridine interactions are examples of O-HN hydrogen bonds. Supramolecular synthon can be altered and controlled using these directed strong hydrogen bonds. Moreover, they are readily identified by firm downfield shifts in H-NMR spectra and/or shifts in IR band frequencies related to the X-H moiety. A strong hydrogen bond can be determined via infrared spectroscopy, and a broad band is observed at 1600 cm-1, which is attributed to the deuterium's isotopic displacement of hydrogen [46].

Weak hydrogen bonds

Weak hydrogen bonds with an interaction energy of 416 kJ mol-1 weren't acknowledged adequately until the 1990s [47]. Sutor claimed the presence of C-HO interactions in 1962 [48], and following this, Taylor and Kennard performed neutron diffraction studies on 113 crystalline compounds to provide crystallographic proof of these interactions. They found that interactions such as C-H...N, C-H...O, and C-H...CI are hydrogen-bonded interactions [49]. In the 1990s, Desiraju contributed extensively to the literature on hydrogen bonds [50]. Various dispersive and charge transfer components related to acceptor or donor moieties have a significant impact on electrostatic interactions. C≡C-H...O and O-H...Ph is an example of the strongest electrostatic interactions. C-H...O, C-H...N, and M-HO are a few examples of the weaker electrostatic interaction. Van der Waals interactions are thought to be stronger than these interactions. Examples of lowest energy hydrogen bonds are C-H... π, S-H... π, and C-H...M. The hydrogen bonds are categorized as very strong, strong, and weak in Table 4 based on the geometrical parameters mentioned below. It has been observed that weaker interactions can alter the robust synthon synthesized by strong hydrogen bonding. For example, studies have shown that the inclination towards weaker C-H•••O hydrogen bonds in phenyl propionic acid derivatives alters the -COOH dimer synthon to the catameric synthon [51].

Mechanistic insights into co-crystal nucleation and growth

1. **Thermodynamic considerations**

Thermodynamics plays a crucial role in co-crystal formation, primarily through changes in Gibbs free energy (ΔG). The Gibbs free energy change during co-crystal formation can be expressed as:

$$\Delta G = \Delta H - T\Delta S\backslash Delta\ G\ = \backslash Delta\ H\ - T\ \backslash Delta\ S\Delta G = \Delta H - T\Delta S$$

Where: ΔH\Delta HΔH is the enthalpy change (heat absorbed or released), TTT is the temperature in Kelvin, ΔS\Delta SΔS is the entropy change associated with the system. For co-crystal formation to be spontaneous, ΔG\Delta GΔG must be negative.

Thus, a balance between enthalpic and entropic contributions is crucial

- Enthalpic Contribution: The formation of hydrogen bonds between co-formers (the API and the co-crystal former) releases energy, which contributes negatively to ΔH\Delta HΔH. The strength and number of these hydrogen bonds directly affect the stability of the co-crystal.
- Entropic Contribution: The formation of co-crystals often leads to a decrease in entropy due to the more ordered arrangement of molecules in the solid state compared to the disordered state in the solution. However, if the increase in the number of hydrogen bonds significantly outweighs this loss in entropy, the overall ΔG\Delta GΔG can still be negative.

2. Kinetic Factors

A nucleation and growth mechanism can describe the kinetics of co-crystal formation.

This process typically involves the following steps:

1. Supersaturation: The solution becomes supersaturated for the co-crystal components. This can be achieved by cooling the solution or by evaporation of the solvent.
2. Nucleation:
    - o Homogeneous Nucleation: Involves the spontaneous formation of small clusters of the co-crystal in the solution. This process is energy-intensive due to the need to overcome an energy barrier.
    - o Heterogeneous Nucleation: Occurs on the surfaces of existing crystals or impurities, requiring a lower energy barrier than homogeneous nucleation. Hydrogen-binding at the interface can facilitate this process.

3. Growth

After nucleation, the co-crystal grows as more molecules aggregate onto the existing nuclei, facilitated by the continued presence of hydrogen bonds. Growth rates can depend on the concentration of co-formers, temperature, and solvent dynamics [52].

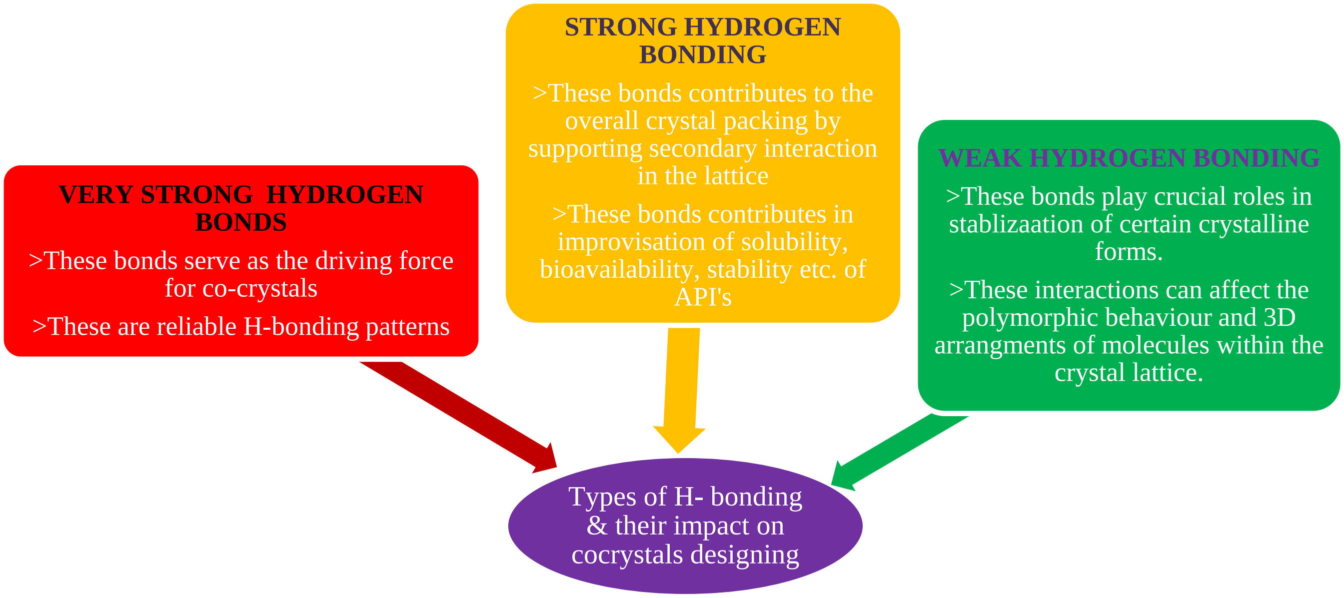

Figure 1: Types of Hydrogen-binding & their impact on co-crystal design

Table 4: Classification of hydrogen bonds based on geometrical parameters

S. No.	Parameter	Very strong hydrogen bond	Strong hydrogen bond	Weak hydrogen bond
1.	Lengthening of X-H, (A◦)	0.05 to 0.2	0.01 to 0.05	< 0.01
2.	Bond energy(Kcal/mol)	-15 to -40	-4 to -15	< -4
3.	IR, Vs relative shift	>25%	5-25	< 5%
4.	Bonds shorter than vdW	100%	100%	30-80%
5.	Effect on crystal packing	Strong	Distinctive	Variable

Hydrogen-binding and Stability

The nature and strength of hydrogen bonds significantly influence the stability of co-crystals. Various Hydrogen-binding motifs can be classified based on their geometry and interaction types.

- Linear hydrogen bonds: Typically exhibit stronger interactions and contribute significantly to the stability of co-crystals.
- Cyclic hydrogen bonds: Often lead to structural motifs that enhance the stability of the co-crystal lattice.

The stability can also be quantified using the hydrogen bond energy, which can be estimated through computational methods like Density Functional Theory (DFT) [53].

Co-Crystallization of Aspirin and Caffeine: A study demonstrated the thermodynamic feasibility of aspirin-caffeine co-crystal formation through DFT calculations, revealing the Gibbs free energy changes and hydrogen bond formations that drive co-crystal stability [54].

Mechanistic Studies on Co-Crystallization Pathways: A comprehensive mechanistic model was proposed, incorporating both kinetic and thermodynamic factors, which elucidated the pathways and energy landscapes involved in the formation of co-crystals [55].

Co-crystal design based on hydrogen bonds

In several significant contributions, Etter emphasized the potential of hydrogen-binding to synthesize various molecular assemblies and networks [56]. Etter's main achievements are summarised below.

1. Etters introduced the concept of the "graph set" in the study of crystal networks and discovered the hydrogen bond patterns, which are highly significant in the design of different molecular assemblies.
2. Etters introduced empirical rules that have proven very useful in predicting bonding between hydrogen bonds in molecular assemblies, in the absence of other strong competing forces.
3. Identification of the organic functionalities involved in strong hydrogen bond formation [57].

To study hydrogen bond networks, Etter introduced "graph sets" in the following ways: i) Identification of potential hydrogen bonds. ii) In relevant crystal formations, compare the hydrogen bond patterns observed [58].

Using graph set theory to investigate molecular aggregation for the simplification of hydrogen-bonded structures into structural motifs, which are the subsets of molecules having a specific hydrogen-binding pattern [59]. The aggregate's chemical formula was no longer required, [60] and the aggregate could now be regarded as a "topology" [61].

One of the four main structural motifs identified was hydrogen-bonded patterns: self (S, intramolecular hydrogen-bonded motifs), non-cyclic dimer (D), chain (C), and ring (R) [62]. The notation used to describe these motifs was of the form X(y), where y represents the total number of atoms contributing to the motif, where m/n denotes the count of donors and acceptors involved, and X stands for R, C, D, or S [63].

Etter proposed 16 rules, the first three of which apply to every hydrogen-linked structure.

1. Hydrogen bonds are formed by using all good acceptors and donors.
2. Six-membered rings typically exhibit greater stability in intramolecular hydrogen-binding compared to intermolecular hydrogen-binding.
3. Intermolecular hydrogen bonds are formed between the most favorable remaining proton donor and acceptor after intramolecular hydrogen bonds have been established [64].

Additional rules apply to specific functional groups and systems, including diarylureas, nitroanilines, nucleotide base co-crystals, and carboxylic acid co-crystals with 2-aminopyrimidine, among others. In brief, the groundwork for molecular crystal structure was laid by Etter's hydrogen bond rules but these rules have limitations due to numerous donor-acceptor sites, ionic interactions, steric effects, and other factors [65].

Supramolecular synthons/tectons

In 1965, Corey introduced the term synthon, defining it as structural units within molecules that can be formed and/or assembled using known or feasible synthetic processes [66]. The supramolecular targets generated by non-covalent interactions are characterized topologically rather than chemically [67]. The molecules in this scenario are essentially construction units, or tectons as Wuest refers to them [68].

Wuest and his coworkers introduced the term "tecton." According to Wuest, various associative forces regulate a molecule's interactions, resulting in an organized network with particular structural characteristics. Hydrogen-bonded networks formed from the individual ionic or molecular components are therefore referred to as tectons. For one-dimensional structures, various terms such as chain, tape, and ribbon are frequently utilized interchangeably; however, some authors have made an effort to give more precise definitions for each. An infinite one-dimensional structure having single hydrogen bonds connecting its components is called a chain, and an infinite one-dimensional structure having multiple hydrogen bonds approximately co-planar connecting its components is called a tape. Networks are three-dimensional structures, while sheets are Infinite two-dimensional structures. In the literature, one-, two-, and three-dimensional structures are referred to as a-, b-, and g-networks, respectively. These can be precisely defined as follows: a-networks have one degree of translational symmetry, b-networks have two, and g-networks have three [69].

Supramolecular Synthon Hierarchy

Desiraju coined the term supramolecular synthon in 1995, and it has proven to be critical in co-crystal synthesis [70]. Supermolecules contain structural units called supramolecular synthons, which can be created and/or put together using well-established synthetic processes involving intermolecular interactions.

Zaworotko classified the supramolecular synthons as:

- Supramolecular homosynthons
- Supramolecular heterosynthons [71].

Self-complementary molecules, such as carboxylic acid dimers and amide-amide dimers, form supramolecular homosynthons. In contrast, supramolecular heterosynthons are formed by two or more distinct functions with complementary moieties, such as pyridine-carboxylic acid relationships. Supramolecular heterosynthons, as discussed below, are particularly significant to co-crystal design. Various supramolecular synthons are represented in Figure 2. Supramolecular synthons and graph sets alone will not provide the highest level of reliability in the crystal structure. The relative intensities of all potential non-covalent interactions should be considered, as well as how competitive and non-competitive contexts impact them.

The Cambridge Crystallographic Data Centre (CCDC) oversees the Cambridge Structural Database (CSD), which contains crystal structures of organic compounds. This resource is valuable for discovering novel supramolecular synthons and accessing pertinent information about them. In terms of the CSD's utility, Allen *et. al.* stated in 1983 that the systematic study of a large number of related structures is a powerful research methodology capable of providing results that could not be achieved by any other method [73]. Supramolecular synthon hierarchy obtains information regarding the presence or absence of a specific supramolecular synthon about the existence and absence of other participating supramolecular synthons. The reliability of particular supramolecular synthon in the formation of a structure can be explored this way.

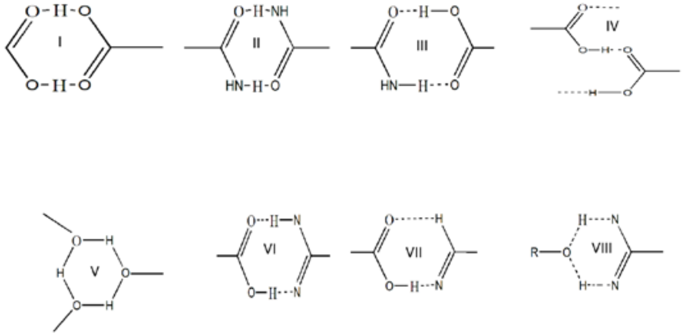

Figure: 2. Representative supramolecular synthons; I and II: homosynthons exhibited carboxylic acid and amide dimers, III: heterosynthon involving acid-amide interactions, IV: head-to-tail chains formed through carboxylic acid interactions, V: intramolecular hydrgen-bonding resulting in a six-membered ring structure, which often takes precedence over intermolecular hydrogen bonds, VI: robust synthon characterized by strong N–H⋯O and O–H⋯N hydrogen bonds, VII: less commonly favored synthon containing one weak C–H⋯O interaction alongside a strong Hydrogen bond, VIII: weaker synthon often observed in co-crystals involving diols [72].

According to Fabian, synthon formation is not controlled by the number of Hydrogen bond donors and acceptors. It depends upon the hydrogen bond strength between the molecule and the co-crystal former [74]. In co-crystal formation, heterosynthons are more favourable than homosynthons [75]. Typically, the steps involved in a thorough investigation of supramolecular synthon hierarchy would be as follows:

1. Determine which functional groups interact to form different supramolecular synthons.
2. A raw search in the CSD for the results containing a specific supramolecular synthon.

3. A refined search in the CSD for hits containing the specific supramolecular synthon in the absence of any competing groups.
4. To test the validity of the CSD report's data, model compound operations are established.

Various authors [76] have researched supramolecular synthon hierarchies. From this research, a high amount of valuable data was obtained, which can be used to develop new crystalline solids having multiple supramolecular synthons [77]. Infant *et.al.* studied the possibility of intermolecular hydrogen bond formation, which is formed between two different functional groups, in which one should be a strong hydrogen bond donor group [78]. These studies revealed that the existence of various chemical functionalities significantly influences the development of carboxylic acid supramolecular homosynthons compared to amide-amide supramolecular homosynthons. Zaworotko and colleagues have published several investigations into supramolecular synthon hierarchies. The first addressed the synthesis of hydroxyl pyridine supramolecular synthon with co-formers containing a cyano moiety [79].

They have discovered three different supramolecular synthons that might be found in a crystal structure, including C=N, O-H, and the Narom moiety. CSD analysis yielded 136 structures containing only OH and Narom moieties; supramolecular heterosynthon 1 was discovered in 135 of these structures, whereas supramolecular homosynthon III was found in only 37 structures. Based on these statistics, supramolecular homosynthon III is less favourable than supramolecular heterosynthons I. Another search was carried out for compounds containing solely C=N and O-H moieties. Supramolecular heterosynthons II were found to sustain 57 of the 77 structures, while supramolecular homosynthon III was found to sustain 17 configurations. This suggests that there is no preference for supramolecular homosynthon III over I and II.

Shattock et al. investigated co-crystals containing a hydroxyl moiety and the presence of carboxylic acid pyridine heterosynthons [80]. According to a raw CSD search, supramolecular heterosynthons were found to be preferred. Based on carboxylic acid homosynthons, a raw and refined CSD search revealed that the dimer motif is present in 92% of the structures, and the catemer motif is present in 9% of the structures. A CSD search using both raw and refined data showed that COOH...N_{arom} is the most common carboxylic acid heterosynthon (raw, 98 percent; refined, 74 percent), which features a charge-assisted COOH...Cl hydrogen bond (raw 100 percent, refined 64 percent).

The third most common heterosynthons are acid amide heterosynthons (raw 84 percent, refined 57 percent). A search for the hydroxyl group revealed that 26% of the structures consist of the OH-OH homosynthon. The complementary functionalities observed in the crystal structures, supported by various heterosynthons, were as follows: Narom (53%), chloride (73%), amides (53%), and carbonyls (43%). Therefore, structures sustained by supramolecular heterosynthons are observed in carboxylic acids and alcohols. This phenomenon is also evident in compounds containing both carboxylic acid and hydroxyl groups. A series of 15 co-crystals were synthesized to verify the model compound investigations. The co-crystals clearly show that carboxylic acid-pyridine and hydroxylpyridine supramolecular heterosynthons are as prevalent as their respective supramolecular homosynthons [81].

Kavuru *et.al.* studied carboxylate moieties with an emphasis on supramolecular synthons synthesized by carboxylate and hydroxyl groups in another work [82]. A CSD search returned 4968 matches having the carboxylate moiety, of which 23% were found to be zwitterionic. The phenolic group was found in 103 structures. In 58 of the 103 structures, the COO...O-H (phenolic) supramolecular heterosynthons were detected. Fifteen zwitterionic co-crystals were formed using amino acids, such as L-ascorbic acid, and various nutraceuticals and polyphenols, including quercetin and resveratrol. The co-crystal structures demonstrated a preference for carboxylate charge-aided hydrogen bonding [83].

Some examples of specific applications of the Cambridge Structural Database (CSD) to co-crystal design are given below. These investigations show how the CSD facilitates the rational design of co-crystals, forecasts hydrogen bond patterns, and explains molecular interactions.

- Identifying hydrogen bond donor-acceptor Pairs: The frequency and geometry of hydrogen bond interactions, such as O-H•••N and N-H•••O, were examined by the authors of this study using the CSD. To predict successful co-crystal formation, they used the data to find reliable structural motifs. The researchers were able to rationally choose co-formers to create co-crystals with various types of carboxylic acids and pyridine derivatives by identifying common donor-acceptor pairs [84].

- Evaluating hydrogen bond Propensities: The "Hydrogen bond Propensity" tool, which forecasts the probability of different functional groups forming particular hydrogen bonds, was developed using the CSD, as described in this paper. The study demonstrated how the tool can be utilized to guide the formation of co-crystals, including those used in pharmaceuticals. By assessing the ability of APIs to establish hydrogen bonds with possible co-formers, the method increased the experimental co-crystallization success rate [85].
- Synthon-Based Design: In this work, the researchers utilized the CSD to analyze the supramolecular synthons present in various crystal structures, thereby aiding in the co-crystal design of aspirin. They specifically investigated carboxylic acid-pyridine synthons (O-H⋯N hydrogen bonds) and amide-amide synthons (N-H⋯O=C). The study's analysis of synthon reliability guided the rational selection of co-formers, ultimately leading to the discovery of the elusive polymorph of aspirin [86].
- Screening for Potential Co-formers: This study utilized the CSD to screen for potential co-formers that could form salts or co-crystals with pharmaceutical compounds. By examining structural motifs and molecular interactions present in the CSD, the researchers were able to predict which co-formers would favor salt formation versus co-crystallization, thus optimizing the selection process for drug development [87].
- Statistical Analysis of hydrogen bonds: Allen and Motherwell performed a statistical analysis of the hydrogen bond geometries in the CSD to establish trends and correlations. This data has been widely used to guide the design of co-crystals, where the likelihood of specific hydrogen bonds forming between target molecules and co-formers can be statistically assessed, improving the predictability of co-crystallization outcomes.

Several case studies that utilize CSD and CSP tools to predict the structure of co-crystals, along with descriptions of typical output data, such as predicted hydrogen bond networks or structural motifs, validate the tools' utility [88].

Caffeine and Glutaric Acid co-crystal prediction

This study combined CSP methods with data from the CSD to predict the structure of a caffeine-glutaric acid co-crystal. CSP tools were used to generate possible crystal structures, and the CSD was utilized to identify common hydrogen bond motifs and structural patterns prevalent in similar co-crystals [89]. The CSP approach generated multiple low-energy crystal structures with different hydrogen-binding arrangements. The preferred structures featured O-H⋯O hydrogen bonds between the carboxyl groups of glutaric acid and the nitrogen atoms of caffeine. The predicted bond lengths for these interactions ranged from 1.8 to 2.0 Å, with bond angles of around 170–180°, indicating strong, linear hydrogen bonds. The predicted structures showed alternating layers of caffeine and glutaric acid molecules. Each layer was stabilized by intermolecular hydrogen bonds, forming a two-dimensional hydrogen-binding network. CSD analysis confirmed that this type of layered arrangement is common in carboxylic acid-based co-crystals, validating the prediction.

Carbamazepine-Saccharin co-crystal prediction

This study focused on predicting the co-crystal structure of carbamazepine and saccharin using CSP tools, with guidance from the CSD. The prediction targeted low-energy crystal structures that incorporated hydrogen bond networks typical for these molecules [90].

- Predicted hydrogen bond Networks: The CSP software predicted N-H⋯O hydrogen bonds between carbamazepine’s amide group and saccharin’s carbonyl oxygen as the primary interaction stabilizing the co-crystal. The expected bond lengths were approximately 1.9 Å, with bond angles ranging from 160 ° to 180°, indicating a strong directional interaction.
- Secondary Interactions: Weak C-H⋯O interactions were also predicted to play a role in the overall stability, with bond lengths ranging from 2.4–2.6 Å. The CSD confirmed that such interactions are often present in similar co-crystals.
- Structural Motifs: The predicted structure featured a motif in which carbamazepine and saccharin alternated along the crystal lattice, creating a zigzag arrangement supported by the primary N-H⋯O hydrogen bonds. The CSD analysis verified that these motifs were common in other carbamazepine co-crystals.

Density functional theory (DFT)

Adding computational predictions such as density functional theory (DFT) or molecular dynamics (MD) simulations to predict hydrogen bond strengths, interaction energies, or co-crystal stability can indeed bolster the credibility of studies on co-crystal design. Below are examples from the literature where computational approaches were used to predict co-crystal structures, which were subsequently validated experimentally.

DFT calculations in predicting the stability of aspirin co-crystals

As the case of aspirin co-crystals shows, Density Functional Theory (DFT) calculations have proven to be an effective tool in predicting the stability of pharmaceutical co-crystals. To determine the thermodynamic stability of possible aspirin co-crystals, such as aspirin–nicotinamide and aspirin–glutaric acid, the primary objective of this study was to employ DFT calculations to evaluate the interaction energies and hydrogen bond strengths. Binding energies were computed using a computational approach, specifically for essential hydrogen bonds like O-H•••N in the aspirin–nicotinamide system. These energies were found to be between 10 and 20 kJ/mol, indicating strong intermolecular interactions [91].

Single-crystal X-ray diffraction studies were used to experimentally validate these predictions, demonstrating that the hydrogen bond geometries and packing motifs predicted by DFT closely matched the experimental data. By allowing precise stability predictions before experimental synthesis, the results highlight the value of DFT in the rational development of pharmaceutical co-crystals and decrease the need for trial-and-error in co-crystal screening [92].

Molecular Dynamics Simulations for the co-crystal of carbamazepine and saccharin

A potent computational method for researching the stability and structural dynamics of medicinal co-crystals is the molecular dynamics (MD) simulation. In this case study, the carbamazepine-saccharin co-crystal was modelled using MD simulations to forecast its stability and comprehend important intermolecular interactions. Through the analysis of hydrogen bond lifetimes and variations in bond lengths over time, the simulations concentrated on the persistence of the N-H•••O hydrogen bond between the amide group of carbamazepine and the sulfonyl oxygen of saccharin. The findings supported the structural integrity of the co-crystal by showing a strong and stable connection. The co-crystal was created and examined using single-crystal X-ray diffraction to verify the computational predictions. The results showed that the experimental packing configurations and the MD-predicted hydrogen bonding distances closely matched. By showcasing their capacity to offer molecular-level insights into stability and support experimental methods in the rational development of co-crystals, this work emphasizes the value of MD simulations in pharmaceutical co-crystal design [93].

Combining DFT and CSP for Predicting Paracetamol co-crystals

A reliable computational approach for creating pharmacological co-crystals is the combination of Density Functional Theory (DFT) and Crystal Structure Prediction (CSP). The objective of this study was to forecast the stability and packing configurations of paracetamol co-crystals using DFT for energy calculations and structural optimization. At the same time, CSP techniques produced potential crystal packing configurations. Using lattice energy estimates, the method ranked several projected co-crystal forms, such as paracetamol with oxalic acid and paracetamol with p-aminobenzoic acid. The discovery that hydrogen bond interaction energies ranged from 15 to 25 kJ/mol indicated the presence of strong hydrogen bonding networks essential for maintaining the co-crystal structures. The computational predictions were validated experimentally by synthesizing the predicted co-crystals and using single-crystal X-ray diffraction. The results showed substantial agreement in packing patterns, hydrogen bond lengths, and crystal symmetry. The importance of integrating DFT and CSP for rational co-crystal design is demonstrated in this case study, which provides a practical method for identifying and predicting promising pharmaceutical co-crystals before experimental synthesis [94].

Synthon Interference

Molecules containing both amide and carboxylic acid functional groups can create strong synthons in the absence of other significant hydrogen-binding groups. However, interference between different potential supramolecular synthons can occur when a molecule possesses multiple functional groups. For example, in the absence of other strong hydrogen-binding groups, carboxylic acids typically form dimeric synthons. Conversely, in the presence of a pyridyl moiety, an acid-pyridine synthon can form. The molecular geometry and the balance of all intermolecular interactions play critical roles in determining the final supramolecular synthon in a crystal structure. Desiraju notes that interaction interference happens when one functional group within a molecule alters the usual interaction pattern of another functional group it contains [95]. For crystal engineering to be broadly applicable, a thorough knowledge of interference effects is necessary. The following variables affect the interference:

1. Matching of acceptor and donor strengths: Hydrogen bonds are most stable when the donor and acceptor have complementary strengths.
2. Range of hydrogen bond acceptors and donors within the molecules: Optimal hydrogen-binding occurs when there is a balanced ratio of Hydrogen bond donors and acceptors in the molecules involved.
3. Cooperative effects of a synthon: The stability of a hydrogen-bonded synthon is often enhanced by cooperative interactions between multiple donor and acceptor pairs.
4. Solvation effects: Solvation can influence the availability and accessibility of hydrogen bond donors and acceptors, affecting the strength and geometry of hydrogen bonds.

In 1990, M. C. Etter proposed the hydrogen-binding hierarchy rule, which centers on the principle of matching donor and acceptor strengths. According to this rule, hydrogen bonds form most effectively when the most substantial donor and acceptor pair together, followed by subsequent pairs in descending order of strength. This might be a possibility in a particular situation where all of the four effects mentioned above don't seem to matter. To manage interference effectively, it's essential to maintain a balanced ratio of hydrogen bond donors to acceptors. The ultimate structure is predominantly influenced by solvation effects, which play a crucial role in directing the crystallization process. Therefore, a comprehensive understanding of all the above-mentioned variables is required to predict both the structural and functional characteristics of a material [96].

Pharmaceutical co-crystals

Pharmaceutical co-crystals consist of two or more chemically distinct components, resulting in altered physical properties, particularly solubility profiles, while maintaining the pharmacological effect unchanged. Each element in these crystals adheres to a strict stoichiometric ratio. Co-crystals play a crucial role in modifying diverse drug properties. They typically consist of an Active Pharmaceutical Ingredient (API) and a co-former recognized as GRAS [97]. Table 5 lists various documented co-crystals along with their respective co-formers and methods of preparation.

Table 5: Reported pharmaceutical hydrogen bonded co-crystal

Hydrogen bonded co-crystals	Method	Outcome	Ref
Rabeprazole & $NaHCO_3$ co-crystals	Solvent evaporation	Enhanced acid stability	[98]
Diflunisal and diclofenac co-crystals with theophylline	Solvent drop grinding	Enhanced stability	[99]
Diclofenac- 2-aminopyrimidine co-crystals	Solvent assisted grinding	Altered solubility, bioavailability, thermal stability, melting point, etc.	[100]
Telmisartan-oxalic acid co-crystals	Solvent drop grinding	11.7 fold higher solubility than the pure drug	[101]
Theophylline and aspirin co-crystals	liquid assisted grinding	Different crystal habits to the starting materials.	[102]
Salicylic acid with 4,4 dipyridyl, nicotinamide, isonicotinamide, piperazine and N,N - diacetylpiperazine co-crystals	Cooling/evaporation crystallization	All the co-crystals show different solubility profile	[103]
Acetyles alicyclic acid-valine co-crystal	solvent evaporation	Increased dissolution rate	[104]
Aceclofenac-Nicotinamide co-crystals	Neat grinding and solution crystallization method	It was determined that FT-IR, DSC, and Mass spectroscopy were effective methods for screening co-crystals.	[105]
Aceclofenac-maleic acid co-crystals	solvent evaporation and dry grinding method	Solubility enhancement	[106]
Febuxostat-telmisartan co-crystals	Solvent evaporation method	Physiochemically stable	[107]

Hydrogen bonded co-crystals	Method	Outcome	Ref
Telmisartan-hydrochlorothiazide co-crystals	Solvent evaporation and solvent-assisted grinding	Improved solubility 7 times	[108]
Aclovir-tartaric acid co-crystals	Microwave-assisted synthesis	Higher solubility	[109]
Aspirin-Benzoic acid co-crystals	Solvent evaporation	Improved anti-inflammatory activity	[110]
Meloxicam-aspirin co-crystal	Solution, slurry, and drop grinding	Superior kinetic solubility	[111]
Tenoxicam-paracetamol co-crystals	Solvent evaporation	Enhanced solubility	[112]
Naproxen–caprolactam (NPX–CPL) & naproxen–oxymatrine(OMT)Co-crystals	liquid-assisted grinding	Better thermal stability	[113]
Fenofibrate tartaric acid co-crystal	Antisolvent addition method	Better dissolution	[114]
Paracetamol and mefenamic Acid Co-crystals	Solvent evaporation	Better dissolution	[115]
Ketoprofen-succinic acid and saccharin co-crystal	Slurry method	Increased solubility	[116]
Lansoprazole-nicotinamide Co-crystals	Solvent evaporation	Improvement of Acid Stability	[117]

Detailed case studies for pharmaceutical co-crystals, providing data on how hydrogen bond formation impacted the physical or chemical properties of the drugs, are given below.

Caffeine–Maleic acid co-crystal

Maleic acid and caffeine, a central nervous system stimulant, were co-crystallized in an attempt to overcome the formulation issues with caffeine, including its high hygroscopicity and poor thermal stability despite its high solubility. Strong O-H•••O hydrogen bonds are formed in the resultant co-crystal between the carboxylic acid groups of maleic acid and the carbonyl groups of caffeine. Significantly reducing moisture uptake and minimizing hygroscopic behavior, these intermolecular interactions help stabilize the crystal structure. A higher melting point, resulting from the development of a more stable lattice, indicates that the co-crystal exhibits improved thermal stability. Furthermore, the altered crystal structure enhances the powder's mechanical qualities, improving its flowability and compressibility for tablet production. The preservation of therapeutic efficacy is ensured by these physical property enhancements, which also result in more uniform dosage and streamlined production procedures [118].

Itraconazole–Succinic acid co-crystal

A widespread antifungal medication, itraconazole's oral bioavailability is limited by its poor water solubility. To improve solubility and dissolution, co-crystallization with succinic acid was investigated as a potential option for enhancing these properties. Hydrogen bonding interactions between the two components are essential to this enhancement. Itraconazole's basic nitrogen atoms and succinic acid, which has carboxylic acid groups, generate strong O-H•••N hydrogen bonds. A more open and loosely packed crystal lattice is created as a result of these intermolecular interactions, improving the absorption of water. As a result, the co-crystal exhibited a considerably faster dissolving rate and a significant increase in water solubility, approximately 20 times that of the pure drug, which promoted improved drug absorption. Furthermore, the co-crystal exhibited enhanced chemical stability, exhibiting decreased susceptibility to deterioration in humid environments. Therapeutic advantages resulted from these physicochemical improvements, which enabled the creation of oral formulations with higher bioavailability and more effective antifungal treatment at lower dosages [119].

Current drug formulations utilize hydrogen-bonding

Several current drug formulations utilize hydrogen-binding in co-crystal design to enhance properties such as solubility, stability, and bioavailability. Sacubitril/Valsartan (Entresto®) is a prominent example, where the co-crystal structure is stabilized by hydrogen bonding between the carboxyl and amide groups of sacubitril and valsartan, improving dissolution rates and bioavailability [120]. Another example is LumryzTM (Sodium

Oxybate Extended-Release Formulation), which is used to treat narcolepsy. In this formulation, sodium oxybate and co-formers form hydrogen bonds, resulting in a stable co-crystal matrix that enables regulated and prolonged drug release [121]. Similar to this, Suglat® (Ipragliflozin L-Proline Co-crystal), which was developed to treat type 2 diabetes, utilizes hydrogen bonding between ipragliflozin and L-proline to improve stability and solubility. These examples illustrate the significance of hydrogen bonding in the formation of pharmaceutical co-crystals and its potential to enhance drug formulations, leading to improved therapeutic outcomes [122].

Marketed drugs and late-stage drug candidates

The ability of pharmaceutical co-crystals to enhance the physicochemical properties of medicinal molecules without compromising their pharmacological efficacy has generated considerable interest. In particular, they are employed to improve mechanical properties, bioavailability, stability, and solubility. This list includes commercial pharmaceuticals and late-stage drug prospects that have made use of co-crystal technology:

Celecoxib-Tramadol co-crystal (CTC)

Celecoxib, a non-steroidal anti-inflammatory drug (NSAID), was co-crystallized with tramadol, an opioid pain reliever, to form the CTC formulation. This co-crystal was developed to provide enhanced pain relief through a fixed-dose combination, addressing both inflammation and pain. The co-crystal exhibited improved solubility and bioavailability compared to celecoxib alone. The hydrogen-binding interactions between the sulfonamide group of celecoxib and the amine of tramadol facilitated a more favorable dissolution profile [123].

Carbamazepine-Saccharin co-Crystal

The co-crystal of carbamazepine, an anticonvulsant medication, with saccharin was developed to improve the solubility and stability of the drug. The formation of this co-crystal resulted in a significant increase in solubility and dissolution rates compared to carbamazepine alone, primarily due to enhanced hydrogen-binding interactions [124].

Lurasidone Hydrochloride-Saccharin Co-crystal

Lurasidone, an atypical antipsychotic, was co-crystallized with saccharin to enhance its solubility. The co-crystal exhibited improved dissolution rates, potentially leading to enhanced bioavailability. The hydrogen-binding between lurasidone and saccharin contributed to the stabilization of the co-crystal [125].

Regulation of pharmaceutical co-crystals

The United States FDA published the regulatory aspects related to pharmaceutical co-crystals in 2013. According to the guidelines, pharmaceutical co-crystals are considered equivalent to a drug excipient complex; therefore, they are classified as intermediate drug products. These updates were published by the FDA in 2016. According to the guidelines issued by the FDA, co-crystals were categorized as intermediate products, specifically hydrates and solvates, and were considered equivalent to polymorphs. The USFDA and EMA address aspects related to pharmaceutical co-crystals. The EMA (European Medicines Agency) considered salt and co-crystals to be in the same category in 2014 [126]. According to the EMA, the co-crystal must demonstrate a different safety and efficacy parameter compared to the API to be considered for a new active substance status. Different regulatory parameters for co-crystals, as outlined by the USFDA and EMA, are presented in Table 6

Table 6: A comparative evaluation of pharmaceutical co-crystals as per USFDA and EMA [127]

Evaluation variables	**US Food and Drug Administration**	**European Medicine Agency**
Category	Drug polymorphs	Pure drug
Formulation	Drug & co-former	Drug & co-former (Stoichiometric ratio)
Molecular bonding	non-covalent/ non-ionic	non-covalent/ non-ionic
New active substance registration	Not applicable	If it exhibits distinctive safety parameter
Similarity with API	Similar	Similar unless shown different efficacy/safety
Categorization	Drug Polymorph	Salts formulation of API
Salt/ Co-crystal	Different intermolecular interactions & authorized guidelines	Regulatory guidelines depend upon safety parameters
Active substance master file/ DMF	Not applicable	Applicable in case of new API registration

CONCLUSION

Since crystal engineering offers a novel approach to modifying the physicochemical properties in the development of APIs, research scientists have been interested in designing and developing co-crystals over the past decade. Crystal engineering is the process for creating new crystalline solid structures with enhanced characteristics by understanding how molecules interact with one another within the crystal lattice. For both neutral and weakly ionized compounds, co-crystals offer the advantage of improving the physicochemical properties of APIs compared to salts. Pharmaceutical co-crystals have the significant advantage that, while the pharmacological properties of the API remain unchanged, the coformer's effect on improving physicochemical properties benefits the API. In the development of co-crystals, choosing a coformer is one of the most crucial and complex steps. The primary prerequisite for a coformer is that it must be categorized as generally regarded as safe (GRAS) and pharmaceutically acceptable among formulations.

Several experimental and theoretical methods have been employed in the literature to screen for coformers. Although there is no assurance that co-crystals with specific structures will form, theoretical methods are employed to select the coformers based on potential interactions between them and to modify the properties of the API. Coformer selection uses hydrogen bonding propensity to identify potential drug-coformer interactions. According to the case studies discussed in this paper, a significant understanding of crystal engineering and co-crystal design is provided, including how to develop co-crystals with desirable characteristics. Research exploring the behavior of pharmaceutical compounds characterized by multiple donor and acceptor sites in the context of various recognition motifs will enhance our comprehension and predictive capabilities regarding synthon formation in these novel and intriguing systems. Systematic investigation is very helpful in providing more knowledge and understanding of hydrogen-binding interactions, which would enable informatics to promote more efficient co-crystal structure prediction (CSP). The CSD is an excellent tool for addressing structure-related problems that other techniques cannot address. More systematic research is required to fill the information gaps that the CSD can provide. Hydrogen-binding plays a pivotal role in the rational design of pharmaceutical co-crystals, serving as a cornerstone for understanding and predicting co-crystal formation. While current theoretical frameworks provide valuable insights into intermolecular interactions and supramolecular synthon design, there remains significant potential for advancing the field through practical applications. To widely apply co-crystals in the pharmaceutical industry, the following fundamental goal must be achieved.

- Demonstrate the viability and practicality of novel hydrogen bonds.
- Understanding new intermolecular interactions is a fundamental problem that should be solved by using crystallography, spectroscopy, and computation.
- The engineering of properties remains an unexplored area. This approach centers on applying synthon theory to investigate the crystallization process of molecules.
- Pharmaceuticals often consist of multiple motifs that serve as both hydrogen bond donors and acceptors, facilitating precise interactions with small molecules. However, the diversity of hydrogen bonds that pharmaceuticals can form necessitates further advancement in predicting intermolecular interactions, particularly in crystalline systems.
- Another goal is to establish an upper limit on the number of distinct molecular components that can be integrated into a stoichiometric co-crystal.
- Additionally, efforts are underway to devise a general solution for computational crystal structure prediction applicable to molecules containing fewer than 40 heavy atoms and fewer than 10 degrees of conformational freedom.

Future research should focus on integrating computational modeling with experimental validation to streamline the identification of optimal co-crystal formers.

- Moreover, the development of machine learning algorithms trained on extensive datasets of co-crystal properties and formation conditions could accelerate the screening and design process.
- Another promising avenue lies in exploring advanced in situ characterization techniques, such as synchrotron radiation and high-resolution spectroscopy, to observe and understand co-crystal nucleation and growth in real-time.
- Additionally, translating these theoretical principles into scalable and cost-effective manufacturing methods poses a critical challenge. Addressing this requires collaboration between academia and industry to develop robust protocols

for scaling up co-crystal production while ensuring consistency in quality and performance.

- By bridging theoretical knowledge with technological innovations, the field can move toward designing co-crystals that not only improve drug performance but also overcome formulation challenges, ultimately enhancing the pipeline of safe and effective pharmaceuticals [128].

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Preeti Devi gathered all the information needed for this work. Along with discussing and validating the facts, Saloni Kakkar, Manjusha Choudhary, and Vikas Budhwar provided the essential inputs for framing the article. All authors contributed to the compilation of the final manuscript.

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