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Review Article

Pharmaceutical Co-Crystallization: Strategies for Co-Crystal Design

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Abstract: Pharmaceutical co-crystal belongs to a subtype of crystal in which one component is an active pharmaceutical ingredient (API) and the other is coformer (generally regarded as safe GRAS). In the crystal lattice, the two components are hydrogen-bonded in a fixed stoichiometric ratio. Co-crystallization is a cheap and simple alternative to the presently available techniques of solubility enhancement and has gained much interest from the formulators during the recent few years. Because co-crystals can enhance the physiochemical properties of pharmaceuticals without affecting their therapeutic effect, the area of pharmaceutical co-crystals has reached a tipping point. Besides increasing solubility, some more applications of co-crystals have also been identified to enhance physicochemical properties like permeability, bioavailability, stability, tabletability, etc. Co- crystals have been extensively studied in the literature, and there is a tremendous amount of literature on co-crystals. However, an exhaustive review of coformer selection and co-crystal regulation must be included. An effort has been made in the review to fill this void. The current study focuses on how co-crystallization can enhance the pharmaceutical characteristics of different drugs, besides giving an overview of the historical background and landmarks in discovering co-crystals. In this review paper, we have discussed the rational design of co-crystals and the selection of conformers for the synthesis of multi-component co-crystals, methods like H-bonding, PKa value, Synthonic engineering, Cambridge structural database (CSD), Hansen solubility parameter (HSP), etc. as well as the IPR related details all across the world. There is an attempt to include reported works on co-crystals, which helps understand the concept. This review paper discusses pharmaceutical regulatory bodies in the US and Europe released guidelines that are highly useful for pharmaceutical product registration in these regions. Here, we also examine various commercially available pharmaceutical drug products. It also briefly predicts the future perspective of co-crystallization.

Keywords: Cocrystallization, Design strategies, supramolecular synthone, Solubility, Stability, Bioavailability, preparation methods, characterization methods

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1. INTRODUCTION

Selecting a suitable solid form of an active pharmaceutical ingredient (API) with ideal pharmaceutical characteristics will significantly impact the entire drug development process[1]. Because of this, the pre-formulation stages of drug development emphasize identifying as many solid forms as possible and assessing their physicochemical properties. APIs can be produced as amorphous solids, solvates, hydrates, salts, polymorphs, and co-crystals in solid form[2]. Characteristics of each of these solid forms are determined by their solid-state nature, which is important in drug development. Amorphous solids often lack long-range order at the molecular level, which results in a faster dissolving rate and higher bioavailability than crystalline solids. However, because of their low physical stability and susceptibility to crystallize, amorphous solids are not the best choice for formulation development. As a result, the vast majority of marketed medicated formulations contain APIs in crystalline form. Crystalline forms are the ideal solids for formulation development due to their stability and ease of handling. Multiple crystalline forms (called polymorphs) of a crystalline form can exist, each with a unique arrangement of molecules within its crystal lattice[3, 4]. The crystal structure of polymorphic forms determines their properties like solubility, stability, bioavailability, and dissolution rate [5].The formation of hydrates or solvates is very common after incorporating solvent or water molecules in the crystal lattice. Although some of these solids have been used in marketed drugs, the volatility (hence poor stability) and toxicity of the solvent limit their usage as precursors for developing novel drug formulations. Pharmaceutical salts, derivatives of proton transfer from an acid to a base, are significantly more common in the development of pharmaceuticals than neutral solid forms [6]. It is estimated that the active ingredients in 50 percent of marketed drugs are in salt form. Salts have special features due to their ionic structure, such as increased solubility and dissolving rates, directly impacting bioavailability. Although salt formation is the most recommended technique for drug product design, it is only effective when the target API includes an ionizable functional group. There has been a tremendous increase in interest in studying co-crystals for medicinal applications over the last two decades [7]. The present study aims to summarize the ongoing research on the co-crystallization technique to give an insight into how it can be exploited simultaneously to increase one or more pharmaceutical characteristics.

2. HISTORY

In 1844, Friedrich Wohler discovered the co-crystal by combining quinone and hydroquinone, resulting in quinhydrone, which was a solid [8]. At the time, this co-crystal was still not recognized as such because X-ray examination was not possible, is composed of quinone and hydroquinone in a ratio of 1:1. In 1958, studies documenting its whole structure and intermolecular interactions were published [9]. In 1968, a triclinic polymorph was observed [10]. After this study, we learned that many co-crystals exist in nature. Scientists' intent in synthesizing new co-crystals also developed apart from identifying the co-crystals that existed in nature [9]. Many studies also came forward with a promise to exploit the co-crystallization process to get more benefits. Researchers have recently tried synthesizing co-crystals using multiple conformers associated with a single drug. The inter and intra-molecular forces of attraction require to make the co-crystals are also an interesting topic of research now a day's [11].In his book "Organische Molekulverbindungen," Paul Pfeiffer (1922) distinguished between two types of co-crystals: (a) co-crystals made of both organic and inorganic materials, (b) co-crystals entirely made of organic materials [12]. In 1937, the first co-crystal was reported [13]. In 1955, R. Pepinsky proposed "Crystal Engineering" as a novel concept for synthesizing crystals with useful properties [14]. Schmidt first uses the term "crystal engineering" in a paper published in 1971 [15]. The book Crystal Engineering by G. R. Desiraju was released in 1989. Modern organic crystal engineering began with the publication of "The Design of Organic Solids" [16].In his review for the journal Accounts of Chemical Research, M. C. Etter emphasizes that the hydrogen bond is an essential design component in crystal formation. Etters *et al*. stated three rules in 1991 for preferred H- bond patterns. After that, the term co-crystal spread frequently [17]. In 2003, Desiraju published a controversial letter explaining his choice for the term "multi-component system held together by non-covalent interactions," which started the debate on cocrystals [18]. Dunitz *et al.* state that co-crystals could be amorphous solids, encapsulated chemicals, or solid liquids [19]. Aakeroy *et al.* stated that the definition of a co-crystal must comply with three requirements [20].

1. The ingredients' neutrality,
2. The ingredients' solid state under ambient conditions,
3. The crystalline substance's homogeneity and the stoichiometry of its ingredients [21, 22].

Table - 1: Landmarks in the discovery of co-crystals.

S.No.	Outcome	Reference
1.	Friedrich Wohler Discovered quinhydrone, the first co-crystal	8
2.	Paul Pfeiffer categorized co-crystals into two groups: those that contain both organic and inorganic materials and those that contain organic materials only	12
3.	R. Pepinsky introduced "Crystal Engineering."	14
4.	Schmidt introduced "crystal engineering"	15
5.	G. R. Desiraju's book Crystal Engineering was published	16
6.	MargEtter described three Rules of hydrogen bonding in organic co-crystals that were reported	17
7.	Desiraju Gave the concept of the formation of hydrogen bonds in crystals utilizing supramolecular synthone	18
8.	Dunitz described co-crystals as amorphous solids, encapsulated chemicals, or solid liquids	19
9.	Aakeroy Stated that the definition of a co-crystal must comply with the above three requirements	20,21,22
10.	Andrew Bond described co-crystals as "multi-component molecular crystals."	23

The name "multi-component molecular crystals," which Andrew Bond proposed to characterize crystalline materials whose constituents under ambient conditions are either solid or liquid, is controversial [23]. The FDA Directive provided a

sufficient definition of the co-crystal. Still, a new disagreement has arisen over whether co-crystals should be recognized as therapeutically equivalent substances and if the required toxicity and efficacy studies should be performed. The following advantages of co-crystals over pharmaceutical salts: Although some types of molecules may have a limited or no capacity to produce salts, theoretically, any molecule can create co-crystals. Additionally, more options are available for selecting the molecules forming co-crystals. These substances are generally recognized as safe (GRAS) by the FDA. However, less acidic or basic counter ions are normally utilized in a salt API due to toxicological considerations [24, 25].

3. DIFFERENCE BETWEEN CO-CRYSTALS AND SALT

Many binary systems, like salts, hydrates, solvates, inclusion complexes, etc., have been identified, and confusion always exists between their definitions [26]. Hence, all these structures are studied under a common heading which has now been established as supramolecular chemistry. Conventional chemistry, on the one hand, deals with strong bond formation, which leads to the formation of a molecule with different physical properties. Supramolecular chemistry, on the other hand, deals with weak bond formation (π-π bond, van der Waals forces, H-bonding, or simply physical entrapment between two or more heterogeneous entities where the physicochemical properties of individual molecules remain the same because subtle forms of attraction exist between them) [27]. Transferring a proton from an acid to a base can distinguish salts and co-crystals. A complete proton transfer exists between pairs of acids and bases but not during co-crystal formation. Therefore, the pKa value can be used to predict whether co-crystals will form. The common assumption is that salts form when the pKa value is larger than 3, while co-crystals develop when the pKa value is less than 0. This parameter cannot predict exactly the formation of co-crystals between pKa values of 0 and 3, but as pKa increases, the probability of salt production increases [28,29].

4. CO-CRYSTALS' ROLE IN THE DEVELOPMENT OF DRUGS

Among newly discovered drugs, nearly 80% belong to Class II and Class IV in the biopharmaceutical classification system (BCS) [30]. The drugs in these categories are distinguished by their low solubility. To solve solubility-related problems, drug formulators use different approaches such as solid dispersion, micronization, salt formation, encapsulation, amorphous forms, etc. However, these approaches have inherent disadvantages in terms of manufacturing and potential stability issues [31]. Therefore, co-crystals are beneficial in addressing BCS Class II and Class IV drug solubility issues.

Furthermore, various solid-state problems, such as solubility, physical and chemical stability, melting point, mechanical and flow properties, etc., might be altered by selecting an appropriate co-former [32, 33]. From an intellectual property aspect, they are developing co-crystals as distinct solid forms, opening up new opportunities for prolonging the patent life of parent pharmaceuticals. Co-crystals with better physicochemical properties fulfill the three requirements for a patent: novelty, non-obviousness, and usefulness. In this sense, Trask's review is notable, as it underlines the patentability features of pharmacological co-crystals[34]. As interest in pharmaceutical co-crystals grew, several applications have been filed for co-crystals, some of which have been awarded. In addition, pharmaceutical co-crystals have given an additional way of extending the patent life of their APIs by identifying novel co-crystals, resulting in more financial gain. The US FDA (Food and Drug Administration, 2011) [35] and EMA (European Medicines Agency, 2014) [36] have provided additional impetus for developing pharmaceutical co-crystals as drug products, recognizing the importance of pharmaceutical co-crystals and issuing draft guidelines on their regulatory classification. According to the FDA, co-crystals are considered drug product intermediates, and conformers used to produce co-crystals are excipients. EMA categorizes co-crystals as solid-state variants of APIs, along with salts, polymorphs, solvates, or hydrates. Since the former is a second component of a co-crystal, the perspectives of the FDA, in particular, disagree with how the idea of pharmaceutical co-crystals is currently understood. As a result, the FDA recently classified co-crystals as a distinct category of solvates with a non-volatile second component to meet commercial concerns while easing the regulatory burden [37]. The FDA also ensured that co-crystal regulatory categorization was comparable to an API polymorph, indicating that co-crystals don't need regulatory authorization as new drugs do.

5. PROCESS DEVELOPMENT AND SCALE-UP OF CO-CRYSTALLIZATION

Many approaches for synthesizing co-crystals have been documented on the bench scale, including milling, solution-mediated transformation, melt extrusion, evaporation, solution co-crystallization, solution-mediated transformation, evaporation, and evaporation so on. Solution crystallization has advantages over other processes regarding purity control and scalability in commercial production. All the techniques mentioned above could be merged with the requirement of current good manufacturing practices in the pharmaceutical industry [7]. Spray drying has long been used to produce single-drug co-crystals and could be considered to produce multi-drug co-crystals [38]. Rehder *et al.* developed piracetam-tartaric acid co-crystals using high-shear granulation. The co-crystal formation was affected by the excipients used, the granulating liquid amount, and the impeller speed [39]. To scale up an ibuprofen-nicotinamide co-crystal, Dhumal *et al.* used hot melt extrusion up to 1 kg [40]. Twin screw extrusion (TSE) was utilized by Daurio *et al.* to produce co-crystals of caffeine-oxalic acid, nicotinamide-trans-cinnamic acid, carbamazepine-saccharin, and theophylline-citric acid in amounts ranging from 20 g to 100 g for their investigation [41]. Yu *et al.* studied the robustness of seeding-based cooling crystallization for forming caffeine-glutaric acid co-crystals in a 10-L crystallizer using first principles process modelling[42]. Ende *et al.* recently investigated the production of carbamazepine-nicotinamide co-crystals at a 22-g level utilizing resonance acoustic mixers and a variety of solvents [43]. Process developments are likely important in the production of co-crystals. This review paper gives a detailed overview of the co-crystallization technique, which includes the rational use of concepts of the crystallization technique.

6. CO-CRYSTAL DESIGN AND SCREENING

Understanding the intermolecular interactions between molecular constituents are essential for effective co-crystal design. Co-crystals are multi-component crystals of two or more solid components in a stoichiometric ratio [7]. Developing co-crystals for a particular molecule begins with

analyzing the functional groups present in the target molecule and identifying complementary functional groups that will likely interact with the target molecule's functional groups (Figure.1) [44].

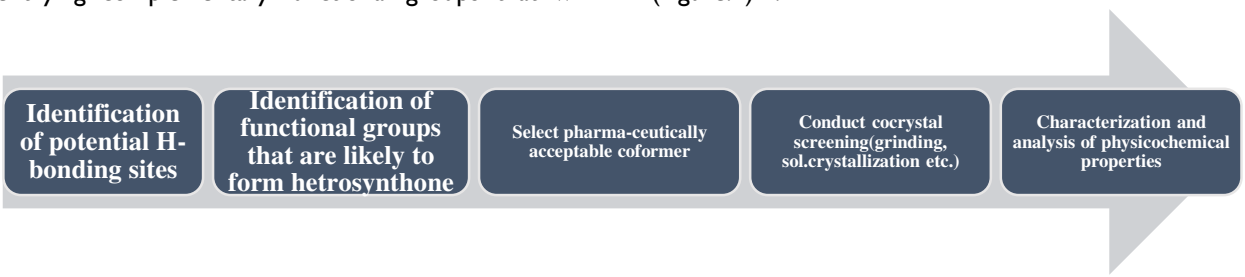

Fig 1: Design and synthesis of pharmaceutical co-crystals.

6.1. Hydrogen bonding propensity

Hydrogen bond has been proven significant in forming co-crystals by linking various molecules. Moreover, hydrogen bonds are a highly reliable design element in the screening process of co-crystals because of their inherent directionality.

Etter's Rule: Etter has done extensive work on co-crystals having H-bonding, which is highly acknowledgeable in co-crystallization. Hydrogen bonds are very useful in co-crystal designing because of their strength, frequency of occurrence (organic molecules), and directionality [45, 46]. Etter stated three rules in 1991 for preferred H- bond patterns:

- In H-bonding, all useful proton donors and acceptors are used.
- Intermolecular H-bond formation is less preferred in a six-membered ring than intramolecular H-bond formation.
- One major side of these rules is to detect 'best H-bond donors or acceptors.'

Aakeroy and co-workers calculated the relative ranking of donors/acceptors' strength by deriving a value from a calculated molecular electrostatic potential surface and associating it with each binding site [47]. Etter *et al.* also introduced graph set notation for describing hydrogen-bonded motifs/synthons [45,48]. It is shown as follows:

$$G^{a}_{d}\,(n)$$

G stands for the observed pattern, n for the total number of atoms, a denotes the acceptors, and d denotes the donors. For intermolecular hydrogen bonds, (I) S (self) is used; for infinite chains, (II) C (chain); for intermolecular rings, (III) R (ring); and for finite structures, (IV) D (discrete). The variables x and d are eliminated when a=d=1, as well as n in the case of D when there is just one hydrogen bond [49].

6.2. CSD (Cambridge Structural Database)

The Cambridge Structural Database (CSD) can be used to evaluate the potential for intermolecular hydrogen bonds between various molecules[50].Knowledge of intermolecular interactions between the two components is the basis for developing co-crystals. Crystal engineering facilitates the design of co-crystals by a selection of suitable conformers. Structural information is provided by many structural storehouses like Cambridge Structural Database (CSD) [51].CSD is used to select a suitable conformer by analysis of relevant crystal structures deposited in it. Various approaches are available to predict the co-crystal formation, which helps to understand the molecular recognition between two components. Some of these are described with representative examples in the following sections [52].

6.3. Synthonic engineering

According to Desiraju, 'Supramolecular synthone' is a structural unit within recurring intermolecular interaction. Supramolecular synthons can be classified into Supramolecular homosynthons, those consisting of self-complementary functional groups, and Supramolecular heterosynthons, consisting of distinct but complementary functional groups. The non-covalent interactions between distinct but complementary functional groups [52] formulate supramolecular hetero synthons. There are two supramolecular synthon approaches: supramolecular homosynthons and supramolecular heterosynthons. While supramolecular hetero synthons are formed by different functional groups, such as carboxylic acid-amide hetero synthons and acid-pyridine hetero synthons, they are composed of the same functional groups that are present in API and former [53]. When compared to homosynthons, supramolecular hetero-synthons are typically preferred [54]. In the development of co-crystals, synthone-based approaches have been proven very effective.The hydrogen bonding capability of functional groups present in components governs the success of crystal formation. The importance of strong intermolecular interactions in co-crystallization has also been mentioned in the literature. For example, Carbamazepine, an anticonvulsant drug, due to its capacity to form H-bonds with the functional group present in different conformers, forms more than 50 co-crystals with different conformers [55]. On the other hand, Triflusal (TFA), a platelet aggregation inhibitor practically insoluble in an aqueous medium, possesses issues in formulation development [56]. Due to its short life, it degrades rapidly and makes it incompatible with all common excipients. As a result, there is no excipient present in the marketed formulations. To resolve these problems with TFA, Co-crystallization could be a good technique. TFA has a carboxylic acid group that forms an acid-acid dimer synthon in its parent crystal structure. Identifying a complementary functional group interacting with an acid group is the first step to creating co-crystals. According to the analysis of the crystal structures deposited in the CSD, the carboxylic acid group forms hetero synthons more often, such as acid-amide and acid-pyridine hetero synthons. From the GRAS list, former from pyridine and amide functionalized compounds were screened for TFA [57].

6.3.1. Binary Co-crystals

Significant intermolecular linkers have been found as strong intermolecular interactions like hydrogen and halogen bonds

[58,59]. In crystal engineering, weaker intermolecular interactions like C-H-N, C-H...O, C-H...F, and others are also acknowledged as structure-directing elements.

6.3.1.1. Hydrogen-bonded Co-crystals

Due to their strength and directionality compared to other inter-molecular interactions, hydrogen bonds have been extensively explored in supramolecular synthesis [58]. Numerous examples of self-complementary homomeric interactions include amide, oxime dimers, and carboxylic acid. Hydrogen bonds and knowledge of strong supramolecular synthons can provide effective methods for building supramolecular designs [11].

6.3.1.2. Halogen-bonded Co-crystals

Halogen bonds (XB) have similar directionality and strength to many hydrogen bonds [46]. Consequently, during the past decade, they have been employed in constructing directed and predictable supramolecular structures [59,61]. Halogen bonds are of three types:

(a) A conventional halogen bond between an element with an electronegative charge, such as oxygen, sulfur, or nitrogen, and the electron-deficient tip of a halogen atom.
(b) Two halogen atoms interacting by van der Waals forces to form Type-I halogen-halogen connections
(c) Connections between a halogen atom's electron-rich and electron-deficient regions are known as type-II halogen-halogen interactions.

Traditional halogen-bond donors include todo/Bromo-perfluoroalkyl, iodo/Bromo-perfluoroalkyl, and iodo/bromoaromatic compounds, whereas the most commonly used halogen-bond acceptors include pyridines, nitriles, carbonyls, and thiols. Typically, the 'activation' of halogen-bond donors is achieved by fluorinating the aromatic/aliphatic donors, which in turn leads to an increased propensity for halogen-bonding of the donors, which is also reflected in shorter X. acceptor bond distances. This observation is consistent with the electron-withdrawing effect of the fluorine atoms, which increases the positive electrostatic potential on the tip of the donor halogen atoms. This 'activation' strategy has been frequently utilized in the design of halogen-bonded co-crystals [11].

6.4. pKa rule

The formulation of co-crystals is a very simple and less time-consuming method. Predicting the co-crystals or salts formation through proton transfer (within the acid and base) is possible. The synthesis of co-crystals & salt can be determined following equation:

$\Delta pKa = [pKa\ (base) - pKa\ (acid)]$.

Generally, this is believed that if the difference in the pKa values is higher than 2 or 3, proton transfer takes place from acid to base. Lessr ΔpKa value, lower than 0, resembles the synthesis of co-crystals. A greater value, higher than 2 or 3, resembles the synthesis of salts [50].

6.5. Thermal methods

If the target molecule lacks suitable hydrogen bonding sites, the synthon-based strategy does not work. For co-crystal design, identifying appropriate synthones becomes challenging due to the absence of hydrogen donors and acceptors. Close packing of molecules via van der Waals, C-H...is present in the crystal structures of these molecules. In contrast to compounds with potential hydrogen bonding sites, Co-crystal screening for such molecules has limited chances of success, unlike the molecules with hydrogen bonding capabilities. For example, Griseofulvin (GF) is a low-solubility antifungal drug. The drug contains acceptors of hydrogen bonds but no donors of hydrogen bonds. A search for GF-containing crystal structures produced a few solvated structures. The acceptor, carbonyl, and groups participate in weak C-H... O interactions in all structures indicate the difficulty of designing co-crystals for GF compared to molecules with hydrogen bond donors. The author performed a co-crystal screening using a variety of co-formers, including pyridines, amides, phenols, and carboxylic acid. Identification of 40 conformers was performed, each possessing functional groups that can interact with carbonyl groups. Screening of co-crystals was carried out utilizing solution crystallization and solid-state grinding. Except for GF and an artificial sweetener, Acesulfame (Aceh), which resulted in a co-crystal in a 2:1 stoichiometric ratio, most of these trials either produced physical mixing of GF or co-former crystallizing separately [62]. Thermal and X-ray diffraction techniques were used to characterize the co-crystals.Water molecules play a key role in co-crystal formation by forming strong O-H... hydrogen bonds with all co-crystal components. Enhancement in the solubility and dissolution rate of GF was observed after co-crystallization.Co-crystal hydrates of Spironolactone, a steroidal aldosterone agonist with former saccharine, were yielded due to an exhaustive co-crystal screening [63]. The API and the former form linear channels in which the water molecules are placed, according to the crystal structure analysis of the co-crystal hydrate. It was also determined that the co-crystal hydrate undergoes single-crystal to single-crystal dehydration, which aided in determining the crystal structure of the dehydrated co-crystal [64].It was also determined that the co-crystal hydrate undergoes single-crystal dehydration, which aided in determining the crystal structure of the dehydrated co-crystal. Because the co-crystals in each of these case studies were discovered by trial and error, co-crystal screening requires extensive experimentation, resulting in high development costs for characterization and research resources. The lack of design scope for this sort of molecule needs awareness of additional aspects such as the co-crystallization process, component solubility, and molecular size complementarily, all of which will largely affect the success and failure of co-crystal screening.

6.6. Fabian method

Many computational techniques have been developed based on structural information found in CSD. Fabian has proposed one methodology for the prediction of co-crystal formation. This methodology uses complementary molecular knowledge and depends on molecular descriptors commonly.Each molecule in this method is defined by descriptors depending on size, shape, polarity, hydrogen bond donor and acceptor counts, and so on. It was proposed that if a descriptor for the two molecules were similar enough, a co-crystal would form. The major findings of this study are:

- A component with a partner of similar polarity is more likely to form co-crystals.

- For co-crystal formation, matching whole molecular dimensions is more important than matching molecular shapes.
- To explain the complementarity of a molecule, more than counting acceptors and donors is required.
- The strength of H- bonds between co-crystal formers, rather than the number of available donors and acceptors, governs the formation of synthons [64].

The proposed statistical approach was applied to artemisinin, an anti-malarial drug with only an acceptor atom, to assess the possibility of co-crystal formation. The formation of co-crystals between artemisinin and 41 of the 75 co-formers was predicted by this method. However, despite extensive screening using solid-state grinding methods, only two co-crystals with co-formers, resorcinol, and orcinol, were produced experimentally. After the characterization of co-crystals, it was determined that hydroxyl groups form O-H... hydrogen bonds with the artemisinin's carbonyl group. However, the method represents a rational approach for simplifying co-former selection. Furthermore, experiment results indicate that the method must still be best suited to molecules with few or limited hydrogen bonding functional groups [65].

6.7. COSMO-RS

It works based on COSMO-RS fluid phase thermodynamic theory, which was used to tell of the miscibility of conformers in the liquid phase (supercooled) and a selection of suited conformers. Furthermore, the excess enthalpy, Hex, between the mixture of API & former mixture compared to pure components indicates the capacity of both compounds to co-crystallize. Therefore, it was stated that this approach provides a suitable ranking of conformers for an API [50].

6.8. Hansen solubility parameter

It is another significant parameter used to determine the miscibility of a drug and the selection of conformers used. In the solid state, the miscibility of components can predict co-crystal formation. Therefore, the synthesis of co-crystal accomplishment rate can be enhanced using components with similar miscibility. It was stated that two components are required to be miscible in case of total HSPs difference is greater than 7MPa 0.5. Otherwise, it is immiscible [50].

6.9. Cocktail co-crystal method

A new "co-crystal cocktail method" was discovered to select conformers. This approach allows four conformers to be grounded with API in the ball mill. In this way, this approach decreases the workload by 50%. It was a very convenient as well as a less time-consuming method.

6.10. Binary and ternary phase diagram

Using the phase diagram techniques, we can predict the solubility profile of a drug and conformer in any solvent. The binary phase diagram could be constructed using the DSC technique. In the case of "W" shape diagrams, chances of co-crystallization are higher, while in the case of eutectic mixtures, a "V" shaped diagram is obtained. Yamashita *et al.* Prepared a binary phase diagram for the screening purpose of co-crystals and salts. For the screening of solution based on the co-crystallization process, is solute-solute-solvent ternary phase diagram can be used[50]

6.11. Knowledge-based methods

It becomes possible to investigate how a specific functional group interacts with other hydrogen bond donors and acceptors using the wealth of knowledge contained within the crystal structures deposited in the CSD and the various software components provided by the Cambridge Crystallographic Data Centre (CCDC). In this regard, an alternative approach knowledge-based methodology to those previously described has been developed and applied for the prediction of hydrogen bond formation between acceptor and donor atoms and the selection of conformers for co-crystal formation [44]. The possibility of interaction with different functional groups is determined by examining the hydrogen bond propensity of each functional group. Once all of the interactive maps are available, the next step would be to compare the likelihood of hetero-interactions to that of homo-interactions to determine the likelihood of a co-crystal forming. The functional group of pairs with the highest probability of forming hydrogen bonds is selected for experimental trials. Wood *et al.* Selected Paracetamol as a model system and predicted co-crystal formation between Paracetamol and the co-formers by applying knowledge based on strategy [44]. According to previous studies, out of 35 conformers selected for co-crystal formation, 13 coformers forms co-crystals with paracetamol. In Paracetamol, phenol and amide groups are potential hydrogen bonding sites. An examination of the three known paracetamol polymorphs revealed that the phenol group formed an O-H... hydrogen bond with the secondary amide group. The possibility of hydrogen bond formation between the functional groups of paracetamol and the functional groups found in the 35 co-formers was evaluated using the software tools in CSD and Mercury. The probability of hetero- and homo-interactions between paracetamol and the selected co-formers was used to calculate a multi-component (MC) score.Some successful co-formers that formed co-crystals with paracetamol include 4,4-bipyridine, 1,2-bis(4-pyridyl) ethane, phenazine, citric acid, piperazine, and morpholine, while caffeine, pyrazine, malic acid, malonic acid, and benzoic acid were unsuccessful. Based on this research, Wood concluded that the synthon-based or hydrogen bond propensity methods are more successful when hydrogen bonding is dominant. In contrast, combining methods is useful when performing knowledge-based co-former screening [66].

6.12. Interaction Searching Using IsoStar

From the CSD, crystal structures having a carbonyl functional group are extracted and analyzed for their possible intermolecular interactions. Various carbonyl groups of models were tested to achieve a balance of correct description of the chemical environment and neighboring atoms of the carbonyl in Propy while ensuring that enough hits were returned to draw reliable conclusions. The IsoStar search tool [66], which was incorporated into Mercury, was used to assess the likelihood of intermolecular interactions between the pairs of functional groups chosen for the search, which includes several different descriptions of the CO_2H, OH, NH, and NH groups, which are general donors with a variety of more specific functionalities, e.g., amide, imides, and many ring systems. The search yielded the most structures with interactions involving an aromatic amine,

aliphatic hydroxyl, or carboxylic acid as the donor group. A starting point for co-former selection and an idea of the ideal functional groups that should be present in conformer molecules for co-crystal formation can be achieved.

6.13. Motif Contact Search

Interaction searching offers a more detailed and specific approach and greater flexibility in describing the chemical environment of the functional groups as it was discovered that very few examples of structures containing a carbonyl in a similar fragment as that found in Propy, several different models with different chemical environments for the carbonyl group were used in this study. As a result, the environment surrounding the carbonyl group was altered by reducing the number of constraints.Using multiple models resulted in more results and, as a result, better statistics for drawing reliable conclusions. In general, statistics indicate that NH is the preferred donor; however, the isopropyl substituent near the carbonyl in Propy may influence the interaction that an amine group can form with the carbonyl.In this regard, hydroxyl donors with lower steric hindrance may be preferred over primary amine groups. Indeed, the statistics for hydroxyl groups were similar to those for amine groups. Hydroxyl groups are preferred over carboxylic acids, with cyclic hydroxyls outperforming their acyclic counterparts. The next best group is cyclic NH donors; however, interactions with an acyclic NH are rare. As the restraints on the carbonyl fragment are released, NH donors become more favorable, resulting in a greater separation of the hydroxyl group. Carboxylic acids also become more favorable in these cases, indicating that larger, bulkier donor groups become more favorable when restraints and constraints are irrelevant than when the acceptor environment is constrained. The analysis of intermolecular interactions using the IsoStar and Motif contact searching tools revealed that aromatic amines and hydroxyls, aliphatic hydroxyls, and carboxylic acid have the highest propensity of interaction with the carbonyl of Propy, implying that molecules containing these donor groups are the best candidates for co-crystal screening with Propy [17].

7. METHOD OF PREPARATION

It has been known to take 6 months to synthesize a good-quality co-crystal. Design strategies and the formation mechanism of co-crystals still need to be understood. They can be formulated by various solid and solvent-based methods[67].

7.1. Solis state method

7.1.1. Contract Formation

Co-crystals can be prepared by mixing the drug and conformer in this method. For co-crystallization, no mechanical forces are required. In some cases, individual components can be ground before mixing [68,69].

7.1.1.1. Co-crystallization mechanism

Various factors, like the type of functional group and solubility of reactants in the solvent, influence the development of new co-crystals. Some experimental conditions also influence the synthesis of co-crystals, such as the stoichiometric ratio of API and conformer, ph, stirring, temperature, type of glassware, etc.[70]. In the co-crystal design, H-bonding, synthone formation, and graph set have proven very significant[71]. For example: For an API having a carboxylic group, a former with acidic moieties/ amides will be suitable and can increase the possibility of co-crystal formation. But there is no guarantee for the formation of co-crystals [72]. According to Jones and co-workers, co-crystallization [73] is a sequence of mechanisms that consist of molecular diffusion, eutectic formation [74], and co-crystallization through an amorphous phase [75].In the literature, various examples for each mechanism are available. If one or more reactants have high vapor pressure in the solid state, molecular diffusion is more likely to happen[76]. The eutectic formation is also a very important mechanism of co-crystal formation [77]. After incorporating grinding with eutectic mediated co-crystallization, the process can be increased by these two mechanisms: first, for eutectic formation reactant surface increased, and second, co-crystal nucleation increased in eutectic phase [78].Co-crystallization is also possible through the preparation of an amorphous phase. In the case of molecular solids having strong intermolecular interactions, this type of co-crystallization is possible [79].

7.2. Reaction co-crystallization

Rodriguez-Hornedo *et al.* first described the reaction crystallization method. This method is based on lowering the solubility of the molecule complex that makes the co-crystal, creating an environment for its nucleation and crystallization. Supersaturation is the driving force for the co-crystallization process, which is attained by the excess addition of drug and conformer in solution.Coformer's saturated solutions are used in the co-crystal formation, and an additional drug above its solubility is added. These solutions can be made by dissolving the drug and conformer in a pure solvent containing solid components or combining two solutions that already include the drug and conformer dissolved.When a drug is added to a saturated conformer solution, it dissolves to its solubility limit and precipitates as a co-crystal. The solution or slurry is stirred for the duration required for the reaction to occur, and then it is filtered. The approach which was suggested by the ternary phase diagram exhibited the prediction correlation between supersaturation and induction time as well as a robust operating range for co-crystal formation. This approach under ambient conditions was also used to create the co-crystal of carbamazepine and nicotinamide [79].

7.3. Supercritical fluid methods

Solvent, anti-solvent, and atomization enhancement are three techniques emphasizing different supercritical CO_2 aspects and have successfully produced co-crystals utilizing supercritical fluid technology, especially with supercritical carbon dioxide (CO_2).

7.3.1. Co-crystallization with supercritical solvent

By suspending the API and conformer as a liquid or supercritical CO_2 slurry. The co-crystallization with supercritical solvent (CSS) method eliminates the use of hazardous organic solvent [79].It is possible to fine-tune its solvent power and density by controlling the thermodynamic parameters of CO_2. L.Padrela *et al.* compared the co-crystallization outcome of drugs like indomethacin,

carbamazepine, theophylline, caffeine, etc., with Saccharine in liquid and supercritical CO_2. According to these authors, co-crystallization is mediated by dissolution in supercritical CO_2 despite their low solubility. They observed that an increase in the concentration of co-crystals components in the CO_2 phase [80] could increase the co-crystallization rate.

7.3.2. The rapid expansion of supercritical solvents

This technique consists of the saturation of CO_2 with the drug and conformer before the depressurization of the CO_2 phase. Finally, Mullers *et al.* used a third method to prepare microparticles of Ibuprofen-nicotinamide co-crystals. The main disadvantage of this approach is that co-crystal components should be soluble in supercritical CO_2, but most APIs need better solubility in them [81].

7.3.3. Supercritical anti-solvent co-crystallization

The concept behind using supercritical CO_2 as an anti-solvent for co-crystallization is that because supercritical CO_2 reduces the solubility of both the API and conformer, then can precipitate together in a co-crystalline structure. This method may allow for control over the API's polymorphic state or co-crystals produced [82, 83, 84].

7.3.4. Supercritical co_2- assisted spray drying

This single-step method involves spraying a solution containing the dissolved starting co-crystal components into a drying chamber at atmospheric pressure using a nozzle and supercritical co_2 [85,86].

7.4. Evaporation technique

Co-crystals can be prepared by dissolving the API and conformer in a suitable solvent, allowing the solvent to evaporate slowly.
In this method, co-crystals grow in a solution of drug and conformer. For the preparation of the solution, a suitable solvent is used. Here, evaporation removes the solvent from the solution, and supersaturation is attained. The slow rate of evaporation is required to ensure the preparation of a small number of large crystals. In discovering new co-crystal formulations, crystal structure identification is highly significant. In the literature, there are various examples of evaporative co-crystallization available. Identifying crystal structure is important for analyzing whether the obtained formulation is a co-crystal or any other polymorphic form of drug and conformer. For example, Baravoju *et al.* prepared isonorfloxacin nicotinamide co-crystals using chloroform as a solvent. In 8 ml of chloroform, after 0.1m mol of norfloxacin and 0.1m mol of isonicotinamide was dissolved, the solvent evaporated. As a result, the rod-shaped crystals of isonorfloxacin: nicotinamide 1:1 were prepared. Evaporative co-crystallization can be performed by using these three solutions. First is a 1:1 stoichiometric ratio, the second is a solution where the former is used in excess amount, and the third is a solution where the drug is used in excess amount [81].

7.5. Dry grinding

Co-crystals can be prepared by this method by using a drug, and a conformer in stoichiometric ratio's-crystals can be prepared by mortar and pestle or a ball mill. For example, Prabhakar *et al.* prepared Piroxicam co-crystals using Sodium Acetate as a conformer (dry grinding method) [87].

7.6. Wet grinding

Co-crystals can be prepared by the wet grinding method. For example, Sungyup et al. prepared co-crystals of Adefovir dipivoxil with the help of a wet grinding technique using former glutaric acid and suberic acid as co-crystal formers [88].

7.7. Isothermal Slurry conversion

Co-crystals can be prepared by using a drug and a former. Here slurry was prepared by using different solvents like organic and inorganic salts. Viz: water. In co-crystals, the solvent was added, and the obtained suspension was stirred at room temperature for some days. Now, the solid material was dried and characterized by XRD [89].This technique can be operated by adding the drug to a suspension of a former in a solvent. This method does not require the preparation of a fully dissolved, clear starting solution. Slurry conversion depends upon many variables like relative concentration of drug and conformer, solubility driving force, nucleation, and growth kinetics of the system. Zhang *et al.,* Observed the transformation time for theophylline to convert to 1:1 glutaric co-crystals. For complete conversion, 15 minutes to 5 hours were recorded. It was observed that transformation time was decreased with the enhancement of solubility in a given solvent. M. L Cheney *et al.* prepared meloxicam co-crystals and observed that for a slurry conversion of meloxicam and aspirin in tetrahydrofuran(THF), 96% co-crystal yield was achieved [81].

7.8. Anti-solvent addition

It is the method for recrystallization or precipitation of co-crystal former and API's. For eg: cocrystallization of acelofenac: chitosan. The obtained dispersion is prepared by precipitation of the drug and former solution, including sodium citrate solution [90].

7.9. Extrusion technique

In this method, hot melt extrusion and conformers are heated and mixed. No solvent is added. Kelvin *et al.* explained the synthesis of carbamazepine co-crystals by this method. The author synthesized co-crystals by using nicotinamide. The author studied co-crystal matrix using DSC, powder x-ray diffraction, IR spectroscopy, Fourier transform, etc. [91,92].

7.10. Sonocrystallization

In this technique, the solution was prepared by dissolving and sonicating the drug and the former, along with heating this solution while adding a solvent system. E.g., Prafulla *et al.* synthesize caffeine: maleic acid co-crystals with the help of ultrasonic-assisted co-crystallization. Here different phase diagrams were constructed with and without ultrasonic waves [93].

7.11. Spray drying technique

In this method, the co-crystal is formulated by preparing a solution of the drug and former with evaporating solvent [94]. The solution was evaporated with the help of hot stream air.

Ning *et al*. prepared co-crystals of CL20: DNDAP (2:1) by continuous spray drug method [95].

8. INFLUENCE OF PROCESS VARIABLES ON CRYSTAL HABIT

Rate of cooling, supersaturation, nature of the solvent, degree of solution agitation, and presence of impurity are various process variables of co-crystallization that may impact crystal habit and dosages from performance [96,97]. Ibuprofen's crystal habit has been discovered to be significantly influenced by the type of solvent. Ibuprofen co-crystallization from ethanol/acetone had a thin, platy, precisely circular shape with high surface tension, dielectric constant, and low specific gravity, whereas propylene glycol and 2 propanol produced rod-shaped co-crystals. When sodium hydroxide solution (ph-10) had its ph lowered by adding HCL, needle-shaped co-crystals formed [98]. At the same time, high temperature causes nuclei formation to be delayed and fine, symmetric crystals to develop. The low temperature of the crystallizing solvents results in crystals with uneven shapes. Ions, polymeric molecules, or other materials in the solvent or solute act as impurities for the developing crystals and change the crystal habit. It is well-known that impurity alters the developing crystals into a good shape from the perspectives of dosages from design and performance [99].

9. CHARACTERIZATION OF CO-CRYSTALS

The two crucial aspects are the prediction of the formation of co-crystals between two compounds and determining whether the co-crystals have been formed. The process of characterization of co-crystals should be precise, reproducible, accurate on the one hand and easy, less time-consuming, and cheap on the other. To date, no characterization method has promised to predict co-crystal formation. Hence, the researchers rely upon the data obtained by multiple characterization methods to confirm the same. The possibility of salt formation and the formation of other binary supramolecular additives and eutectic mixtures cannot be ruled out. Hence, a clear-cut differentiation between the spectrums of these closely related species is required. Here is a brief description of some methods employed to characterize co-crystals.

9.1. Crystallographic studies

9.1.1. Single crystal X-ray diffraction (SCXRD)

The smaller crystal samples were traditionally studied by using an anode in SCXRD. Recently, substituting a traditional anode with a liquid metal jet containing a LaB6 cathode has reduced the cooling requirements of the anode, thereby enabling it to reduce scattering and thermal motion, which has eventually improved the data obtained, both qualitatively and quantitatively. The crystals are cooled using liquid nitrogen or dry nitrogen at a specified flow rate, which can be substituted by helium to obtain a lower temperature range (15-300 K) [100-105].

9.1.2. Powder X-ray diffraction (PXRD)

The diffraction pattern of X-Rays projected on the powdered sample obtain a graph between the diffraction intensity due to 2θ value or d spacing enabling the researcher to study the structure of crystals. It can further be used to differentiate between salts and co-crystals based upon the principle of transfer of proton in hydrogen bonding [106-111].

9.2. Hirshfeld surfaces analysis

HS is fashioned by segregating space in a crystal into sections in which the electronic scattering of the addition of circular atoms for a molecule governs the analogous totaling over the crystal. With the help of Hirshfeld, we can derive the type of interactions and relative areas of surface matching to such interactions [112].

9.3. FTIR spectroscopy

Changes in the frequency and intensities of characteristic peaks obtained in FTIR spectroscopy can predict the formation of co-crystals and differentiate the formation of salts [113]. For example, in a study performed by Aakeroy *et al.,* the formation of hydrogen bonding through the participation of carboxylic functional groups was used to differentiate between salts and co-crystals [114]. Similarly, pure APIs, their physical mixture, and their co-crystals can be analyzed [113].

9.4. Terahertz spectroscopy

0.1–10 THz range is studied for solid molecules obtained from intermolecular vibrations. Due to Van der Wall interactions and intramolecular vibrations in larger macro-molecules, including combined phonon-modes in crystalline lattices and segmental motion of polymeric chains can be recorded easily. Temperature plays a crucial role in it. It differentiates between a crystalline and amorphous structure by forming sharper peaks in the former case and broader peaks in the latter [115-121].

9.5. Solid-state nuclear magnetic resonance and NMR crystallography

To evaluate the compounds like polymorphs, pharmaceutical co-crystals, and salts, this methodology is habitually utilized in its high-resolution edition to testimony carbon-13 and nitrogen- 15 spectra[122-124]. The number of signals and positions associated with intensities give data on the analyzed compound's chemical composition [125-129]. The obligation of 13C and 15N CP/MAS NMR peak is typically complete by evaluation to the equivalent solution spectrum, through spectral editing technique by testing of reliance of the CP strength and via *ab initio* calculation of the chemical shift [130-133].

9.6. Thermal analysis

9.6.1. Differential scanning calorimetry (DSC)

An increase in the temperature of a given sample in an oxygen-free environment results in changes like breakage of co-crystals, melting of the compounds, etc, that's, in turn, leads to change in ΔH, which can be recorded with respect to temperature distinction (dT/dt) in a DSC thermograph. The broadness and intensities of peaks thus obtained have been utilized as an important tool to determine the formation of co-crystals [134].

9.6.2. Thermogravimetric analysis (TGA)

Upon heating the sample in the TGA analyzer, different processes, like sorption/desorption of volatiles,

decomposition, oxidization, and reduction, may occur, which can lead to a change in the weight of the sample. The analyzer analyzes this change of weight, and the peaks thus obtained can give relevant information about sample [134].

9.6.3. Hot-stage microscopy (HSM)

Salts, solvates, and polymorphs can be analyzed and differentiated by keeping a small sample on the hot stage analyzer and analyzing the microscopic changes in its crystal structure while heating it at a given temperature[134].

10. RECENT APPLICATIONS

Co-crystallization is a process of modifying a drug at the molecular level, which changes physiochemical properties to improve the physiochemical property of a drug; no additives are required [135]. Important factors in altering the physiochemical properties are APIs & conformer properties, the type of molecular interaction between them, and synthetic procedure [136,137,138]. Variously reported co-crystals with their conformers and preparation method are given in Table- 2.

Table - 2: reported co-crystals with their conformers and method of preparation

S. No.	Drug	Conformer	Outcome/ Technique	Reference
1.	Fexofenadine	Tartaric acid	Solubility enhanced 11 and 2.47 folds in water and HCl, respectively, by using the Solvent evaporation technique	139
2.	Ketoconazole	Fumaric acid, Succinic acid, Adipic acid	Solubility enhanced 100 folds by using the Slurry conversion method	140
3.	Apixaban	Oxalic acid	Increased solubility	141
4.	Pterostilbene	Piperazine	Solubility enhanced by six times	142
5.	6-Mercapto-purine	Nicotinamide	Two times higher dissolution than a pure drug by using reaction crystallization	143
6.	Simvastatin	Nicotinamide	Three times increased solubility by using solvent evaporation	144
7.	Efavirenz	Oxalic acid dihydrate, citric acid monohydrate	Improved solubility of 1.8 and 2.7 folds as compared to the commercial sample by using a solvent drop grinding technique	145
8.	Piroxicam	Citric acid, glutaric acid etc.	Significant increase in solubility by using a dry grinding method	146
9.	2-(4-(4-chloro-2 fluorophenyl)phenyl) pyrimidine-4-carboxamide	Glutaric acid	Greater stability by using solution methods	147
10.	Indomethacin	Saccharin	Very low water sorption was observed by using slow evaporation	148
11.	Theophylline	Glutaric acid, maleic acid, oxalic acid etc.	Better stability and physical properties.	149
12.	Carbamazepine	Saccharine	Good chemical stability by using conventional cooling crystallization	150
13.	Paracetamol	4,4 bipyridine	Better stability	151
14.	Clarithromycin	Urea	Enhanced solubility and in vitro drug release profile by using solvent evaporation	152
15.	Meloxicam	Aspirin	superior kinetic solubility, greater oral bioavailability by using slurry methods, Solvent drop grinding method	153
16.	Baicalein	Nicotinamide	Peak plasma conc. is 2.49 times greater, with a 2.80 times higher area under the curve by using slow evaporation, rotary evaporation, and co-grinding	154
17.	Fenofibrate	Salicylic acid, benzoic acid, and para amino benzoic acid	Mpt. of co-crystal was significantly reduced than pure drug and individual conformers by using the solvent evaporation technique	155
18.	Carbamazepine	Nicotinamide and saccharin	Decreased mpt. by using solution method	156
19.	Paracetamol	Caffeine	The drug's compaction power and mechanical properties improved using grinding techniques, antisolvent addition, solvent evaporation, and various weight ratios.	157
20.	5-Fluorouracil	Succinic acid, malic acid cinnamic acid, benzoic acid	Increased permeability by solid-state grinding followed by slow solvent evaporation	158

Physiochemical properties like solubility, stability, bioavailability, permeability, melting point, and tabletability can be improved by pharmaceutical co-crystals, and these properties are given below:

- Solubility: As discussed before, almost 60-70% of recently discovered drugs belong to BCS Class II (Low solubility &high permeability) and IV (Low solubility & low permeability) [138]. So, there is an urgent need to enhance the solubility of these drugs to develop different formulations. Crystallization is a very helpful technique by which we can enhance the solubility of drugs.
- Stability: During the formulation of new dosages, stability studies are very important. Various studies like Thermal stability, Chemical stability, Solution stability, and Photostability are required during the formulation of pharmaceutical co-crystal.
- Bioavailability: It is referred to as the drug content that enters systemic circulation. Low oral bioavailability is a significant barrier to developing various pharmaceutical preparations. Crystallization is a common approach that has been proven very helpful in the enhancement of solubility as well as bioavailability.
- Melting point: It is used for determining the purity of solids. With a narrow range, solids melt at a sharp melting point of [156]. The melting point of an API governs its thermodynamic stability. So, a high melting point conformer has greater utility for better stability. They're also beneficial when dealing with thermolabile medicine. For the synthesis of co-crystals, the selection of a conformer is a very crucial factor [157]. Techniques that are used to determine the melting point are DSC & TGA[158].
- Tabletability: Tabletability is the capability of a substance to convert itself into tablet form. Some important parameters of pre-formulation studies are tablet ability, crystal packing, and compaction. By using a suitable former, we can change these properties.
- Permeability: A drug's permeability across biological membranes directly relates to its distribution and absorption.

11. FUTURE PERSPECTIVES

Pharmaceutical co-crystals have now established themselves as an effective solid form. From an industry standpoint, the number of patents filed by various research groups and pharmaceutical firms worldwide is rapidly increasing, owing to the regulatory and intellectual property implications. Co-crystals are an excellent way to improve drug development solubility, bioavailability, stability, and processability. Successful co-crystal development can be achieved by careful conformer screening and formulation design.During the early stages of development, conventional co-crystallization procedures such as solvent evaporation, grinding, and slurry method were used. However, as time has passed and the field has expanded, scientists in this subject have invented newer, more basic approaches to allow the co-crystallization process to overcome its earlier limits. Hot melt extrusion, spray drying, supercritical fluid technology, laser irradiation, freeze drying, microfluidic and jet dispensing, and other novel technologies for co-crystallization can be applied. Various types of pharmaceutical co-crystals can be effectively formed using these methods. The interest shown by both academics and the pharmaceutical industry indicates that pharmaceutical co-crystals will be a sustainable and important solid form of pharmaceuticals shortly for:

- Improved performance by reformulating an existing drug.
- She is managing the life cycle of recently approved pharmaceuticals.
- We are enabling novel development compounds, purification, and performance.
- Use of co-crystals as intermediates in green chemistry and synthesis [159].

12. REGULATION OF PHARMACEUTICAL CO-CRYSTALS

In 2013, the US FDA first published regulatory guidelines for pharmaceutical co-crystals. According to these guidelines, pharmaceutical co-crystals were considered equal to API-excipient molecular complexes and categorized as drug product intermediates [160].The FDA updated regulations were published in 2016. According to these guidelines, co-crystals are considered a specific case of hydrates and solvates and assigned a regulatory categorization equal to that of a polymorph [161].FDA and EMA have quite different perspectives on pharmaceutical co-crystals. EMA in 2014 placed co-crystals in the same category as salts. The co-crystals must exhibit a difference in efficacy or safety from that of API to confer the new active substances status (NAS) [162]. Various regulatory parameters for co-crystals in USFDA and EMA are mentioned in table-3.

Table-3: Various regulatory parameters for co-crystals in USFDA and EMA [163]

S. No.	Parameters	USFDA	EMA
1.	Regulatory category	Polymorph of the API	API
2.	Composition	API and a conformer	API and a conformer in stoichiometric ratio
3.	Interaction	non-covalent/ non-ionic	non-covalent/ non-ionic
4.	New active substance registration	No	If it shows a difference in efficacy/safety
5.	Similarity with API	Similar	Similar unless shown different efficacy/safety
6.	Classification	Polymorph of API	Salts of API
7.	Co-crystal and salt	Differences in interaction and regulatory pathways	Regulation dependent on efficacy/ safety
8.	Drug master file/ active substance master file	No	Required for new active substance registration

13. RECENT PATENTS OF CO-CRYSTALS

A pharmaceutical co-crystal must be innovative, non-obvious, and useful to be granted a patent, just like the claimed subject matter of any patent application. A co-crystal generally consists of unique, unpredictable physical properties distinct from other solid-state materials. Over the past ten years, pharmaceutical co-crystals have grown rapidly, and several research publications and patent applications have been made worldwide. Table-4 lists some approved patents on pharmaceutical International and multi-drug co-crystals[164-165].

Table -4: Approved patents on pharmaceutical International and multi-drug co-crystals.

S. No.	Patent	Date of issue	Compound	Assignee	References
1.	EP2334687B1	4 Jan 2012	Co-crystals of l-proline and pyroglutamic acid	Pfizer Inc.	166
2.	EP2300472B1	18 Jan 2012	Co-crystals of Phosphoric acid and acetic acid	Boehringer Ingelheim Intl. GmBH	167
3.	EP1608339B1	21 March 2012	Co-crystals of Celecoxib and nicotinamide	McNeil PPC	168
4.	WO2016156127 A1	6 October 2016	Ibrutinib and carboxylic acid co-crystals	Ratiopharm Gmbh	169
5.	WO2017115284 A1	6 July 2017	Adipic and Agomelatine co-crystals	Leiutis Pharmaceuticals Pvt. Ltd.	170
6.	US20170224724 A1	10 Aug 2017	Lithium co-crystals with1- proline and salicylic acid	University Of South Florida	171
7.	WO2017191539 A1	9 Nov 2017	dl-proline co-crystal of dapagliflozin	Aurobindo Pharma Limited	172
8.	EP3240575A1	8 Nov 2017	co-crystal of carfilzomib with maleic acid	Dr. Reddy,s laboratories ltd.	173
9.	US10287307B2	14 May, 2019	Crystalline forms of tenofovir and afafenimide	Gilead Sciences Inc	174
10.	US10328042B2	6 June 2019	Co-crystals of substituted glycine and uses thereof	Syneurx International Taiwan Corp	175
11.	US10548909B2	4 Feb 2020	Co-crystals of tramadol and coxibs	Esteve Pharmaceuticals SA	176

14. COMMERCIALLY AVAILABLE CO-CRYSTALS

The commercial approval of drugs based on co-crystals indicates that co-crystallization has been successfully introduced into the pharmaceutical sector. The pharmaceuticals on the market that incorporate co-crystal-based APIs are Suglat, Entresto, and Steglatro.Ipragliflozin, the API, and L-proline, the conformer, are both components of the diabetic medication Suglat®. Stability against hydrate formation is achieved by co-crystallization with L-proline. In 2014, Astellas Pharma and Kotobuki Pharmaceutical received approval to commercialize Suglat® in Japan [177].Novartis designed a drug-drug co-crystal called Entresto®. It is a drug that lowers the risk of getting heart failure. Valsartan and sacubitril are combined in a fixed-dose form[178].Steglatro® is used for type-2 diabetes mellitus. It includes the sodium-glucose cotransporter 2 inhibitor Ertugliflozin and the conformer L-pyroglutamic acid. Co-crystal formation with L-pyroglutamic acid at a 1:1 ratio increases Ertugliflozin's stability and physicochemical characteristics [177].An approved treatment for epilepsy is valproic acid. Both an acid and a sodium salt version of it are known. Since sodium salt is very hygroscopic, the acid form is liquid at room temperature. Valproic acid and sodium valproate are present in the co-crystal form in a 1:1 ratio of[111]. Compared to the components, this co-crystal form is less hygroscopic [179].Another drug that was subsequently discovered to be a co-crystal is Escitalopram oxalate (Lexapro®) [180]. Escitalopram cation was discovered to form a salt with the same oxalate dianion (N+-H...O, O) in the co-crystal of Escitalopram oxalate [181].Another example is Chloral Betaine (beta-chlor®), which was subsequently discovered to be a co-crystal (2016). Betaine and chloral hydrate are the co-crystals constituents. The parent compound achieves thermal stability through co-crystal formation [182].In the pharmaceutical sector, generic medications contribute to a significant market share. Co-crystals can contribute to developing generic medications that exhibit comparable quality with increased stability compared to the original drug. Ibrutinib, an anticancer medication used for chronic lymphocytic leukemia, was recently synthesized with fumaric acid to produce a co-crystal with better stability while exhibiting similar solubility to the original medication. This co-crystal is awaiting FDA approval [183].Table -5. Lists some of the commercially available co-crystals.

Table - 5: Some of the commercially available co-crystals

S. No.	Commercial name	Drug	Conformer	physicochemical property	References
1.	Sunglass	Ifragliflozin	L-proline	Stability against hydrate formation	184-186
2.	Enters to	Valsartan	Sacubitril	Improved bioavailability	178, 185
3.	Steglatro	Ertugliflozin	Z-Pyroglutamic acid	Improved bioavailability	186, 87
4.	Depakote	Valproic acid	Valproate acid	Solid phase stability less hygroscopicity	177,179
5.	Lexapro	Escitalopram	Oxalate	Improved stability	180,181
6.	Beta chlor	Chloral hydrate	Betaine	Thermal stability improved	177,182

15. CONCLUSION

Among so far discovered methods to improve the solubility of poorly water-soluble drugs, co-crystal techniques have gained interest in recent few decades due to easy and spontaneous formation, available scale-up techniques for large-scale production, availability of a variety of GRAS indexed conformers and simultaneous improvement of more than one desirable characteristics like stability, shelf-life, solubility, flow ability, etc. Yet there is a long journey to scout the benefits of co-crystallization fully. Multi-component co-crystals and nano-sized co-crystals are some unexplored areas to exploredby researchers and scientists. Moreover, only a few approved marketed co-crystal formulations emphasize a need to speed up the process.After an initial lag period since researchers discovered the co-crystallization phenomenon, it has progressed worldwide. However, with the increase in knowledge about the co-crystallization phenomenon, newer areas are opening, giving rise to newer challenges.

16. LIST OF ABBREVIATIONS

GRAS- Generally regarded as safe
API-Active pharmaceutical ingredient
BCS- Biopharmaceutical classification system
FDA- Food and drug administration
EMA- European Medicines agency
TFA- Triflusal
CSD- Cambridge structural database
CCDC- Crystallographic data center
XB- Halogen bond
GF- Griseofulvin
DSC- Differential scanning colorimetry
TGA- Thermo gravimetric analysis
MC-Multi-component score
Aceh-Acesulfame
Propyphenazone- property

17. AUTHORS CONTRIBUTION STATEMENT

Preeti Devi collected all the data regarding this work. Saloni Kakkar, Manjusha Choudhary, and Vikas Budhwar discussed the information gathered, validated it, and gave necessary inputs for framing the article. All authors contributed to the compilation of the final manuscript.

18. CONFLICT OF INTEREST

Conflict of interest declared none.

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