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REVIEW

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Pharmaceutical co-crystal: An alternative strategy for enhanced physicochemical properties and drug synergy

Jean Baptiste Ngilirabanga | **Halima Samsodien**

School of Pharmacy, Faculty of Science, University of the Western Cape, Bellville, South Africa

Correspondence
Halima Samsodien, School of Pharmacy, Faculty of Science, University of the Western Cape, Cape Town, Bellville 7535, South Africa.
Email: hsamsodien@uwc.ac.za

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Abstract

A growing number of co-crystals in the literature are proof of how significant the co-crystallization concept has become. Co-crystallization enhances physicochemical properties through the formation of intermolecular interactions between a drug and a co-former. A co-crystal is a single crystalline material consisting of at least two molecular components solid at room temperature and present in a definite stoichiometric ratio. Pharmaceutical co-crystals consist of the active pharmaceutical ingredient and the co-former selected from generally regarded as safe (GRAS) list of the United State Food and Drug Administration. Co-crystal formation requires an understanding of a drug target, a proper choice of a co-former and is only achieved experimentally after several trials. Other beneficial co-crystallization outcomes include binary eutectics, solid dispersions, amorphous forms, etc. Several key issues including design strategies, co-former selection, and co-crystallization methods; tradition and newly synthetic methods that are more efficient and suitable for large scale have been briefly described. The co-crystal preference is demonstrated with a particular emphasis on multidrug co-crystals and their contribution to the drug combination strategies used for the treatment and management of drug resistance and adverse side effects in serious medical conditions that require the administration of high doses such as HIV/AIDS, tuberculosis, and others.

KEYWORDS
co-crystal development, co-crystallization, design, pharmaceutical co-crystals, preferences, synergistic co-crystals

1 | INTRODUCTION

Less than 1% of active pharmaceutical ingredients (APIs) reach the market because of poor biopharmaceutical properties among which solubility plays a key role.[1] Poor physicochemical properties of APIs such as chemical stability, dissolution, hygroscopicity, and solubility impact therapeutic efficacy.[2] This in turn leads to treatment failure and development of different side effects, if not monitored. Poor physicochemical properties affect not only the performance of a drug substance but also impact formulation strategies and other post-formulation processes such as absorption, distribution, metabolism, and excretion, which may lead to advert effects and toxicity.[3–5]

Pharmaceutical scientists strive to find a better strategy to improve properties of the APIs owing to their therapeutic potency, without compromising their chemical identity. Various methods have been developed and used to enhance the physical properties of pharmaceutical ingredients. From a supramolecular perspective, these include the formation of the amorphous state, polymorphs, hydrates, salts, solvated forms of drugs, and the formation of pharmaceutical co-crystals/complexes.[6]

By definition, a co-crystal is a single crystalline material consisting of at least two molecular components usually solid at room temperature and present in a definite stoichiometric ratio.[7] A broad definition as per Indo-US meeting 2011, co-crystals are single-phase crystalline solid materials composed of at least two different molecular and/or ionic compounds that are neither solvates nor simple salts and exist in a stoichiometric ratio. Other co-crystal definitions as per different authors were reported.[8]

According to different literature, co-crystal formation enables the modification of fundamental physicochemical properties of pharmaceuticals such as solubility, stability towards thermal and humidity stress, dissolution rate, and compressibility.[9–23] Henceforth, the co-crystal formation of drug substances offers a great opportunity to develop drug products with better physicochemical properties without changing the pharmacological properties of the API. Due to this, there has been a very intense desire to design co-crystals for different applications which eventually make co-crystallization a preferred technique in pharmaceutical sciences.[24,25] Other physical properties such as hygroscopicity, stability, crystallinity, particle size, flow, filterability, density, and taste, which may be changed as well, preferably improved by co-crystallization leading to a better therapeutic effect.[26] Interestingly, even though the first co-crystal structure was solved by Friedrich Wohler in 1844, it is only in the present century that co-crystals have attracted much attention.

1.1 | Pharmaceutical co-crystal definition

Based on the definition given above, a co-crystal is a multicomponent molecular complex non-covalently bonded, in which one molecule is neutral and the second component is termed the co-former. A "pharmaceutical co-crystal" is made of an active pharmaceutical ingredient (API) and a co-former. This is either anionic or a neutrally safe inactive chemical selected from the Generally Regarded as Safe substance (GRAS) list mostly provided by the United States Food and Drug Association list (FDA) or it could be another API.[27,28] Both co-crystal components are solid at ambient temperature and present in known stoichiometric amounts.[29] Co-crystallization of the API with pharmaceutically acceptable co-crystal formers has gained increasing attention due to the abilities of this approach to achieve a complex without altering the chemical structure or nature of both drug components.[30]

1.2 | Co-crystal properties

Properties of a co-crystal depend mostly on the selected co-former[31,32] and the types of intermolecular interactions formed during the co-crystallization process. This is one of the advantages of co-crystal synthesis over other techniques used to improve the physicochemical properties of the drug substance[32] among which salt formation, micronization, and amorphization are found.

Pharmaceutical co-crystal formation involves APIs forming non-covalent bonds with co-formers or other APIs. The presence of either hydrogen donor or acceptor groups on molecules forming a co-crystal is fundamental because the best donor generally associates with the best acceptor in the crystal structure.[33,34]

The hydrogen donors or acceptors are functional groups such as amide, primary and secondary amine, carboxylic acid, hydroxyl groups, thioester, thiazole, and others. Different properties of a co-crystal such as melting point, physical, and chemical stability, solution stability and crystallinity, dissolution, and bioavailability, have been thoroughly discussed in the literature.[6,8,35]

2 | CO-FORMER SELECTION AND CO-CRYSTAL DESIGN

The selection of a co-crystal former compatible with an API is a crucial step in the co-crystal design but also one of the challenges faced during the co-crystal formation process. The general strategy used in co-former selection is by trial and error also known as a tactless approach during where a number of the pre-determined pharmaceutical library of acceptable compounds (drugs found in General Regarded as Safe (GRAS) FDA list of drugs) are used in the co-crystallization attempt.

A co-crystal is considered strategically on the following basis: when a co-former has a complementary functional group(s) that can join to the drug candidate through supramolecular synthons by the means of intermolecular interactions.[31] Properties (mainly physical and chemical) of the produced co-crystal depend on the co-crystal former used. This makes the selection of co-crystal former a paramount step in the co-crystal synthesis process. When the co-crystal former is selected from the US-FDA GRAS list any drug excipient, neutral, acid, or base, safe according

to this list can be considered. Further, pharmaceutically accepted salts are also used as co-formers[8] and result in multicomponent salts or co-crystal salts where there is a partial transfer of proton and formation of intermolecular interactions at the same time.

A co-crystal former may also be another active pharmaceutical ingredient (API). However, the selection of such substances should fulfill certain criteria, with the intention to improve properties and biological activity of either or both active(s) in the co-crystal system. APIs with polymorphic properties have been used as co-crystal formers. Such combinations offer better stability to the system components. This is one of the techniques used to prevent unwanted polymorphs which most of the time come with serious effects in terms of drug performances.[36] Compounds which crystallize with more than one molecule in the crystallographic asymmetric unit (Z 0 > 1) have also been suggested as good co-crystal formers.[36] Amorphous compounds are another class of drugs that have been proven relevant as co-crystal formers due to their enhanced solubility profiles.[37]

Despite their poor bioavailability, nutraceuticals which by definition refer to food or part of food that provides medical or health benefits and an ability to prevent and be used as a treatment of a disease can also be used as co-formers.[38,39] Therapeutic effects associated to these drugs is a target for solid-state chemists and when co-crystallized with APIs would enhance physicochemical properties, stability, solubility as well as bioavailability of drug product (co-crystal or hybrid) and generate priceless and cost-effective synergistic hybrids, being affordable, and easily attainable.[40] This also reflects their structures offering robust supramolecular synthons.[41] This substantial degree of freedom to select co-formers and the subsequent diversity of the co-crystals, have made the co-crystallization very attractive as a method to fine-tune properties of APIs.

A few examples of such drugs that have been previously used in co-crystal formation have been reported.[41] In addition to the synergistic effects of nutraceutical-API combinations, these drugs may also play a crucial role in interconnecting APIs in a multi-drug crystal lattice. The use of nutraceuticals has been reported; flavonoids and vitamins are examples of nutraceuticals investigated and used as co-crystal drug candidates to enhance physicochemical properties and bioavailability.[42] Systematically, the choice of co-former is usually based on a supramolecular approach.[23]

According to Duggirala et al. property optimization of drug substances was the main goal of crystal engineering scientists in the co-crystal design.[44] Authors established that the design and synthesis of co-crystals rely exclusively on the presence of supramolecular synthons. It

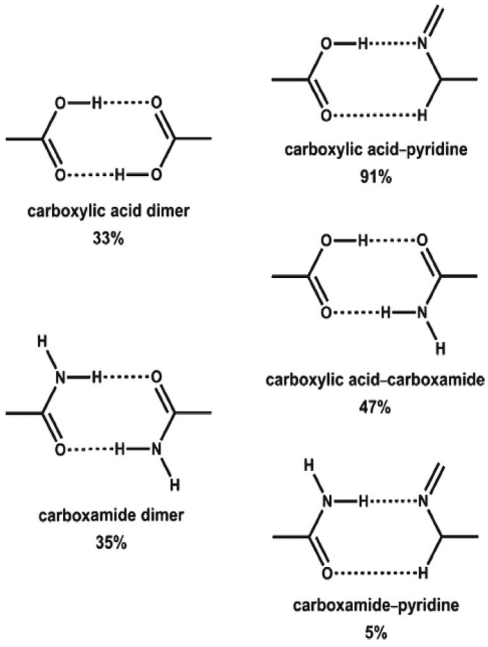

FIGURE 1 Supramolecular synthons and their occurrence percentages based on the Cambridge Structure Database (CSD). On the left are common homosynthons; acid-acid or carboxylic acid dimer and amide-amide homosynthon or carboxamide dimer. On the right are regular heterosynthons; carboxylic acid-pyridine, carboxylic acid-carboxamide, and carboxamide-pyridine heterosynthon[43]

has been demonstrated that co-crystals with strong hydrogen interactions are designed based on the supramolecular synthons approach. These supramolecular synthons are referred to as structural units within supermolecules that can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions. In a crystal system, supramolecular synthons are the smallest structural units within which is encoded all information inherent in the mutual recognition of molecules to yield that crystal (or solid-state supermolecules).[45,46]

Just like the known reactants to make specific covalent bonds, the choice of a synthon which is likely to form during a crystallization process is crucial. Examples of such synthons are depicted in Figure 1. A crystal structure is simplified as a network in which molecules are seen as nodes and molecule synthons seen as connectors of those molecules.[45,47,48] In most cases, hydrogen bonds (H-bonds) due to their strength and directionality compared to other intermolecular forces are involved in synthons. However, this doesn't withstand the contribution of various other intermolecular forces such as halogen bonds, $\pi-\pi$ interactions in aromatic structures, stacking interactions and van der Vaal interactions as these contribute to the final results of crystallization [32] as well as a significant role in the co-crystal formation.[34]

A very good understanding of synthons is also paramount for a better selection of co-crystal formers. The co-crystal design also requires a good understanding of the intermolecular interactions. Intermolecular interactions are the fundamental key of supramolecular chemistry. He also described these weak interactions as what keeps the organic world together.[49,50]

Interactions such as hydrogen bonding; strong (2.2–2.5Å), intermediate (2.5–3.2Å) and weak (3.2–4.0 Å) with angle cutoffs > 90 degree,[51] $\pi-\pi$ stacking (either in a flat configuration with face-to-face arrangement or edge configuration with edge-to-face arrangements),[52–54] electrostatic, hydrophobic, charge transfer, metal coordination, halogen bonding, and metallophilic interactions [55] interconnect molecules in the lattice via different supramolecular synthons discussed in the previous paragraphs. Molecular recognition (which is a necessary complementarity between molecules forming an aggregate) is compulsory in this formation and stabilization of supramolecular systems. In such entities, these interactions are like bridges between molecular building blocks.[56]

Among these interactions, ***H-bond*** is predominant and most explored mainly due to its directionality, its natural existence (ubiquitous), from just a drop of water, DNA to large supramolecular assemblies.[57] According to the IUPAC Recommendations 2011, H-bonds are attractive interaction between a hydrogen atom from a molecule or molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.[58] The commonly known strong hydrogen bonding in solid materials such as co-crystals is O–H···O, N–H···O or O–H···N; Figure 2 illustrates this type of interactions. The weak hydrogen bonding include C–H···O, C–H···N and N–H···π.

Attraction dispersive and (or) inductive forces between molecules promote the formation of interaction known as "***Van der Waals***". These forces are responsible for the formation of solid dispersions.

Molecules containing halogens such as Fluor tends to form halogen bonding interactions during the self-assembling process. According to Desiraju et al. ***"halogen bond"*** occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity.[60] The halogen bond is also characterized by its directionality, strength, polarity, hygroscopicity, donor-atom dimension, and its tenability.[61]

Other intermolecular interactions include **C–H—π** weak bond that plays an additional or secondary role in molecular recognition, therefore reinforcing interactions

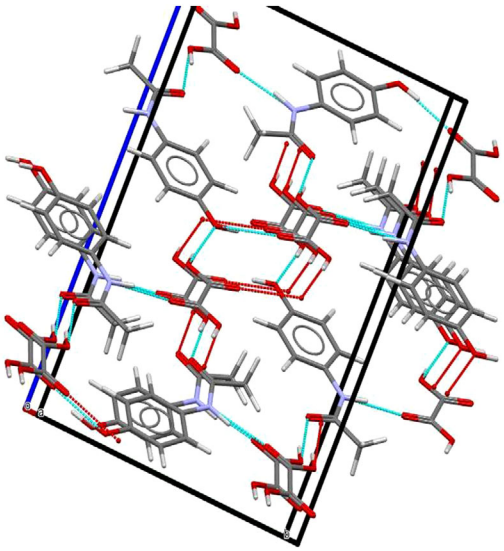

FIGURE 2 Example of O–H…O H-bonding between acetaminophen and oxalic acid space group P21/c shown alongside b-axis. (Mercury)[59]

such as hydrophobic effects. An example of how important this kind of interaction is seen in the non-polar hydrocarbon encapsulation.[62] The type of hydrogen bonding and other interactions between molecules in the co-crystal is determined by the type of supramolecular synthons available.

Furthermore, an API with abundant hydrogen bonding sites and molecular flexibility may be manipulated by a proper choice of solvent to form a specific form of crystal possessing a different arrangement and conformation to the original crystal lattice.[63] In fact, the change of molecule arrangement in the crystal lattice leads to modified solid-state properties affecting its solubility, dissolution, stability, and ultimately bioavailability. Therefore, different crystal forms can lead to changed biological activity (lower or higher than desired).[42] For co-crystals produced by solution crystallization methods, two components must have similar solubility in a chosen solvent; otherwise, it is unlikely to produce a co-crystal. This is because the difference in solubility will lead to the precipitation of the least soluble part, leaving the other component in the solution.[57]

3 | CO-CRYSTAL CLASSIFICATION

Even though co-crystals classification should primarily depend on the useful nature of component drugs, scientists and researchers approach this issue by overseeing the content of the structure rather than their utility. This is due to the diversity of co-crystals and their wide range of uses which include but not limited to medicinal or

pharmaceuticals, mineral, agrochemistry, engineering, crystallography, and energy.[64,65]

Based on factors such as the number of component molecules in the crystal structure and presence in the structure of an ion, polymorph, water, or solvent, one can divide co-crystals in two main classes:

Class 1 includes "**binary co-crystals**"; the two components single solid crystalline substances designed based on hydrogen bonding propensity, supramolecular synthons, Hansen solubility parameters, pKa values.[66] Typical examples of this type are pharmaceutical co-crystals where one structural component is an active pharmaceutical ingredient and the second being a co-former selected from the United States Food and Drug Administration (US-FDA) list of generally regarded as safe (GRAS) drugs. Binary co-crystals class is further divided in two groups depending on whether molecules in the crystal lattice are hydrogen or halogen-bonded.[57]

"**Ternary** and **quaternary co-crystals**" respectively composed of three and four neutral drugs arranged in a definite stoichiometry in their crystal structures. Using isoniazid and nicotinamide, Aitipamula *et al*. produced two tertiary co-crystals using fumaric and succinic acid.[67] In both cases, hydrogen bonding occurs via pyridine-acid synthons.[29,66] Synthesis of such multicomponent solids provides an opportunity to explore the combination of drugs usually administered separately, targeting different sites or drugs with synergistic effects. Other examples of this type were reported previously.[68]

The second class of co-crystals includes **Polymorphic co-crystals**: Investigation on different polymorphic forms of a particular compound is common in solid-state pharmaceuticals. Polymorphism is common in solid-state chemistry. Investigating polymorphism is crucial during drug development because polymorphic forms exhibit different physical and chemical properties. The future or safety post-manufacturing of a drug formulation depends on how well this step was explored. Like any other chemical entity, identifying all possible forms during the development of the co-crystals is paramount.

Even though co-crystallization has been attributed to reducing polymorphism propensity,[25,42] polymorphic co-crystals have been reported.[69] Different polymorphic co-crystals of the same drug exhibit different physico-chemical properties.[70] Polymorphism in co-crystals is promoted by different factors, among which co-crystallize drugs belonging to families with polymorphism history or use of polymorphic co-formers[71] being the primary. Compounds that exhibit polymorphism also enable the formation of heteromeric intermolecular interaction with co-former molecules (target molecules) over monomeric interactions and allow the existence of different molecules in the same crystal lattice, theoretically making them possible good co-crystallizing agents.[29] However, only practically this can be proven.

It is therefore important to investigate these aspects with vigilance as the outcomes may be catastrophic for a pharmaceutical company if unwanted polymorph is formulated. An example of co-crystal polymorphism was observed when a chloroform solution of caffeine and glutaric acid were allowed to evaporate slowly and two polymorphs having different morphologies rods (form I) and blocks (Form II) were produced.[10]

Salt co-crystals: Before the introduction of co-crystals, the salt formation was among approaches used to modify the physical properties of APIs. This is evidenced by statistics approximating that over half of the medicines on the market are administered in salt forms.[8] Salt formation suffers from the limitation that only compounds/APIs with ionizable site fit to be processed.

Formation of co-crystals involving ionic substances was introduced after the discovery of polymorphic forms (a neutral and zwitterion forms) of piroxicam/4-hydroxybenzoic acid co-crystal (1:1, v/v). Different salt-co-crystals also known as ionic co-crystals have been reported. A dozen of salt/ionic co-crystals were previously synthesized in our lab using bis(1-adamantylaminium) carbonate with neutral mono and dicarboxylic acids as co-crystal formers.[35]

Solvated/hydrated co-crystals constitute another type of co-crystals in which solvent/water molecules are part of the crystal structure. In some cases, these guest molecules are what keeps a crystal together, and collapse upon desolvation or solvent/water molecule removal. Different examples of such co-crystals have been reported.[72,73]

4 | OTHER CO-CRYSTALLIZATION OUTCOMES

Co-crystallization doesn't always produce co-crystals, solid forms such as eutectic mixtures, salts, solvated, ionic liquid, solid dispersions, solid solutions, supramolecular gelators can sometimes result from the co-crystallization process.[74] Factors such as the nature of the components, environment (solvents, temperature, pH) contribute to the occurrence of these adducts.[43]

Hydrate/solvate formation commonly occurs when water/solvent molecules are incorporated into the crystal lattice.[75] The presence of this may significantly contribute to molecular networks within a crystal and sometimes these entrapped solvent molecules are what hold the crystal molecules together (this is the case of polymorphic solvates when solvent molecules are an integral part of the crystal structure) and the crystal collapses

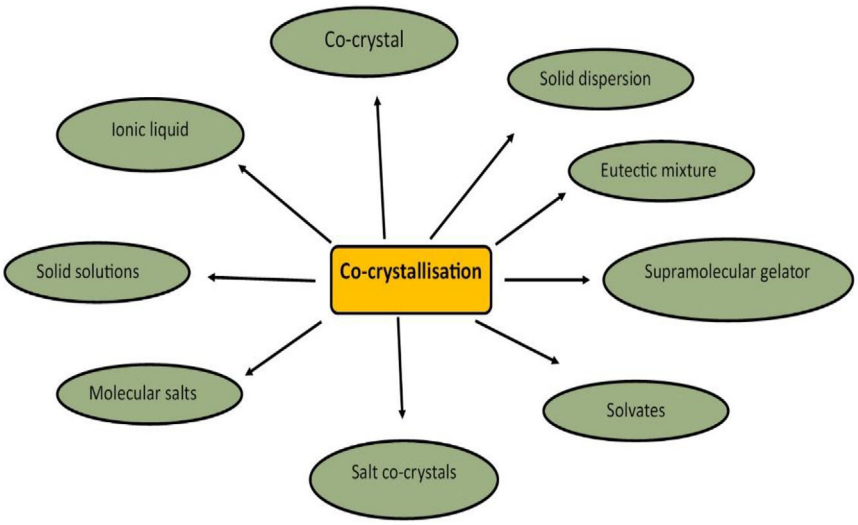

FIGURE 3 Different co-crystallization solid forms based on discussion by Cherukuvada et al[79]

upon desolvation which eventually results in a disordered system known as solid amorphous form.[76] Alternatively, the solvent molecules fill the voids in the crystal and can be easily removed by desolvation without affecting the crystal structure. This is the case of pseudopolymorphic solvates.[77] A particular example is that of caffeine where hydration maintains the order in its both polymorphic crystals. Before co-crystallization with water, molecules in both polymorphs lack orders.[43] The Cambridge Structural Database (CSD) indicates the solvation ubiquity of 43% among organic crystals reported.[59]

It happens often that instead of a co-crystal, drugs (i.e., APIs) combined via co-crystallization result in what is known as eutectic mixtures (**EM**) [78] or solid dispersions. **Eutectic Mixtures** (EM) are multicomponent solids that are recently gaining much interest of researchers in the pharmaceutical field. EMs are obtained as a result of the failed co-crystal formation. Due to an increased number of researches in pharmaceutical co-crystals, pharmaceutical eutectics are likely to increase even more.[74]

Based on the definition according to Cherukuvada and Nangia, **EMs** are conglomerates of solid solutions in which similar molecules are held together by strong cohesive interactions whereas unlike ones are bound by weak adhesive forces. However, this class of multicomponent solids lacks a distinct crystal structure despite the above interactions binding their molecules together. Instead, their crystalline nature resembles that of parent compound combinations (this can be easily justified by the similarities between diffraction patterns). Furthermore, eutectics are thermally characterized by lower melting points than that of their drug components intact and they present themselves as important in enhancing the physicochemical properties of the drug components (API(s) in case dual drug) as their co-crystals counterparts.[79] Other solid forms which may be resulted from co-crystallization but which won't be discussed here include those summarized in Figure 3.

5 | THE CO-CRYSTAL DEVELOPMENT PATHWAY

The development pathway of pharmaceutical co-crystals has been encompassed into eight stages.[44] These include:

Co-former identification : Initially, a complementary co-former to a drug molecule candidate is selected from a library (depending on the type of co-crystal to be synthesized). In the case of pharmaceutical co-crystals, the co-former is selected from a generally regarded as safe (GRAS) list provided by the FDA and Everything Added to Food in the United States (EAFUD) list approved by the FDA.[80,81]

Discovery : A stage during which co-crystal synthesis is carried out. Methods such as slow solvent evaporation, slurry mediated transformation and mechanical grinding (both neat and solvent-drop or liquid assisted) are used. Other methods used during co-crystal screening are also identified.[44]

Characterization : A stage during which physical and chemical properties are assessed is carried out using different techniques. Differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), infrared and Raman spectroscopy, powder X-ray diffraction (PXRD), single-crystal X-ray diffraction (SCXRD), and solid-state nuclear magnetic resonance (ss-NMR), are used to characterize novel co-crystals.[82,83]

Properties : This was described as a stage during which further steps would be decided. In case the produced co-crystal shows enhance desired properties such as aqueous solubility and dissolution rates, pharmacokinetics, formulation, reproduction, and scale-up will be performed. Co-crystallization also enables the improvement of properties

such as physical and chemical stability as well as manufacturability.

Evaluation of pharmacokinetics : Evaluating pharmacokinetics (Pk) of a drug is a crucial step in drug development. The drug performance and drug-action site flow are explored during this stage. It is based on this route of drug administration, and the dose for any medication is determined. Pk is often defined as a study of processes such as drug absorption, distribution, metabolism, and elimination of a patient's body. Changes in physicochemical properties which supramolecular systems such as co-crystals deliver result from changes in thermodynamics of APIs. These, in turn, affect not only drug bioavailability but also the Pk of a drug through processes outlined in the previous paragraph (timely exploring but not limited to the drug quantity (concentration) in biological fluids, tissues, and excreta.[84]

Different studies witnessed improved pharmacokinetics of APIs by co-crystallization. Of these, the study by Dooner *et al*. reported increased pharmacokinetics of both APIs in Tramadol-Celecoxib co-crystal.[85] Other examples include those highlighted by Duggirala *et al*.[44] Therefore, evaluating the Pk of a new drug substance and new delivery systems such as co-crystal is an important step in the development process of a drug.

Formulation : The formulation of a co-crystal in a dosage form is not a straight forward process. Held together by hydrogen bonds co-crystals stability in the presence of excipients that also contain hydrogen bonding groups becomes a major concern and presents a great risk. Choosing the right excipients is paramount to minimize the possible source of interactions with the co-crystal.[44]

The stability of co-crystals into formulation is of major concern. This is because co-crystals are stabilized by H-bonds and the risks associated with the use of excipients already containing H-bonds are high, especially those excipients designed to enhancing properties of a drug in the formulation.

Further, pharmaceutical co-crystals, having enhanced physicochemical properties, behave differently from their pure API. Regardless of their H-bonds-dependent stability, require an adjustment and manipulation of the excipients, amount of API required to produce the same activity, and change of the formulation method where necessary.[44,86]

Additionally, more studies are needed to address issues encountered during pharmaceutical co-crystals formulation. The use of examples to explore the implication of co-crystal in the formulation stage doesn't draw a steady conclusion. Nonetheless, different examples have been used to explore risks associated with the formulation of pharmaceutical co-crystals.[44]

Process and scale-up : Scale-up of the co-crystal produced by traditional solution methods of co-crystallization such as solvent evaporation and slurry) present challenges. Good quality co-crystals are obtained from solution crystallization, a method usually used to purify chemical substances such as APIs. Not only the problem of solvent cost and solubility of the individual component but also the tendency to crystallize which is different for these components reduce the chances of reproducing the same co-crystals with the desired yields.[87]

For many co-crystals prepared using simple and common solid-state approaches known as mechanochemical approaches, there are challenges with required high mechanical stress and the difficulty in achieving a homogeneous final product for larger-scale processes. Nonetheless, alternative methods such as extrusion (twin-screw) and resonant acoustic mixing can help prepare large volumes and only require the addition of small amounts of solvent during the process.[44,88,89]

Finally, there is regulatory approval and patenting stage during which a co-crystal undergoes different evaluations for patenting purposes. Initially, intellectual property protection must be ensured. Pharmaceutical co-crystals fulfil three primary criteria for issuing a patent. These are a novelty, non-obviousness, and utility (the drug substance has pharmacological activity and/or improved performance vs. the corresponding single component drug substance) and so can be patented.[44,90]

6 | CO-CRYSTALLIZATION METHODS

There is a wide range of different methods used successfully for co-crystal preparation. Some of these have been used for decades while others were recently introduced following the intensive growth in co-crystal applications and commercialization. Old as well as new co-crystallization methods have been extensively reviewed.[64]

Conventional methods such as solvent evaporation, slow cooling evaporation, vapor diffusion can be grouped into solution crystallization, whereas other methods include grinding (either solid-state, or liquid-assisted), slurry conversion, melt crystallization, hot-melt extrusion, and spray crystallization. With new advances in technology, different methods are now available and summarized in five classes: solid-state, solution-based, supercritical fluid, and miscellaneous co-crystal preparation.[64]

6.1 | Solid-state co-crystal preparation

Solid-state methods use different mixing exercises and manipulation of the target drug and the co-former in their powder or crystalline form to produce co-crystals. Partial wetting of the samples may be required for some of these methods.[64,91]

6.1.1 | Contact formation of the co-crystal

This is a spontaneous formation of the co-crystal upon gently mixing the API and co-former without any physical application of force. Such spontaneity requires changes in free energy evaluated from solubility and equilibrium constants.[92] Various examples have been given. Results obtained did not all agree with thermodynamics of the samples, it was then indicated that the co-crystallization rate can also be affected by other factors such as diffusivities, molecular mobility, molecular interactions and surface interactions [92] in addition to high temperature and relative humidity.[64]

6.1.2 | Solid-state grinding methods of co-crystal preparation

The most popular solid-state methods; dry (neat) grinding (DG) and liquid-assisted grinding (LAG) have been widely used in co-crystal preparation. Both DG and LAG are what constitute solid-state grinding also known as mechanochemistry; a method developed as an alternative to solution-based methods of co-crystal preparation. This method is simple, green, reproductive, clean, reliable and yield is imminent which is advantageous over solution-based methods.[93,94]

Dry grinding (DG) uses pressure generated manually (using a mortar and pestle) or by mechanical forces created by an automated ball mill to combine the target drug and the co-former. Usually, sample preparation using this technique is carried out at room temperature and where an automated ball mill is used, the temperature must be monitored and recorded to address any changes if any and reported. Despite its effectiveness, simplicity, and other advantages, DG is associated with failure or incomplete conversion to co-crystal and possible generation of unstable amorphous as a result of crystal defect.[64,95,96]

Liquid-assisted grinding **(LAG)** refers to grinding assisted by the addition of a very small amount of solvent to the mixture at the beginning and during the grinding process. The solvent places a catalytic role, therefore accelerates and promote the formation of the co-crystal. Different co-crystals have been produced using LAG.[64,96]

6.1.3 | Extrusion

Extrusion is a relatively new method that uses a twin-screw extruder to simultaneously mix and pressing the starting material or a mixture of starting materials through a die under a controlled environment. Unlike Hot melt extrusion which involves melting the samples and mixing at high temperature,[97,98] here, the process is maintained below the melting temperature of either content of the sample being processed.[99] Different co-crystals were reported to have been produced by the Twin-screw extrusion method.[64]

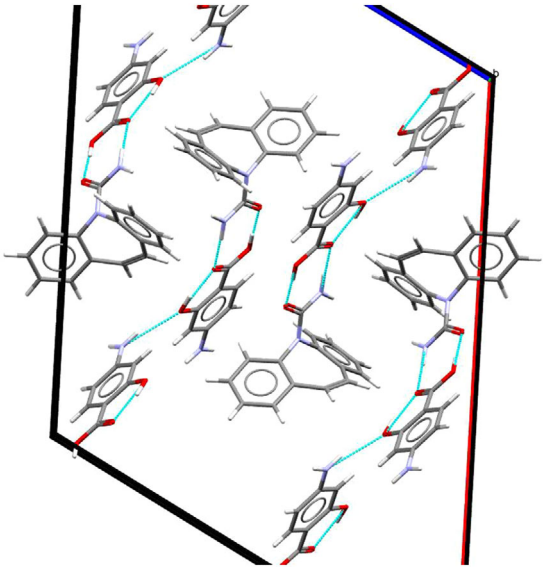

FIGURE 4 Lattice of the co-crystal between carbamazepine and para-aminosalicylic acid, view alongside b-axis, with no hanging contacts and molecules; Mercury[59]

6.2 | Solution-based co-crystal preparation

The co-crystal preparation from solution requires supersaturation of the target drug and co-former; followed by the nucleation process, then the crystal growth. Good care and conditions must be established to ensure the thermodynamic stability of the co-crystalline suspension (sample containing solution).

Apart from the conventional methods outlined at the beginning of this section, solvent-mediated and precipitation can also be used to produce co-crystals. Further, the majority of co-crystals reported in the Cambridge structural database were produced by solution co-crystallization.[64,100] A particular example is that of carbamazepine (CBZ); an anticonvulsant with para-aminosalicylic acid (PASA) an antitubercular (Figure 4).

6.2.1 | Evaporative method of co-crystallization

Evaporative co-crystallization (ECC) has been widely used to produce co-crystals. The super-saturation is achieved as solvent volume reduces upon evaporation, which in

turn increases the concentration of co-crystalline mixtures in the solution. ECC is an effective and preferred method to produce good quality single crystals fit for single X-rays diffraction. Atmospheric conditions (temperature and pressure) must remain constant throughout the experiment to ensure reproductivity, reliability of the co-crystal product and consistency between batches.[64,101]

The high evaporation rate leads to accelerated co-crystallization. However, this was associated with the formation of unstable/metastable crystals. Consequently, slow evaporation of the solvent is recommended.

6.2.2 | Cooling crystallization (CC)

Cooling crystallization is another solution method of co-crystal preparation. Supersaturation required for co-crystal growth is achieved by cooling the co-crystalline solution. A drop-in temperature decreases the solubility of both co-formers, leading to precipitation tendency and subsequent co-crystal growth. Among co-crystals produced via CC are co-crystals of carbamazepine/nicotinamide obtained from ethanol.

6.3 | Supercritical fluid methods

Supercritical fluid technology has been successfully used to produce co-crystals, using supercritical carbon dioxide CO_2.

6.3.1 | Co-crystallization with supercritical solvent

During the use of this technique, the API and the co-former are suspended as a slurry in liquid or supercritical CO_2, using the solvent power of supercritical CO_2 and not that of toxic organic solvents. First, thermodynamic of CO_2 is controlled to fine-tune its density as well as solvent power. This, in turn, allows the control over co-crystallization between components of the co-crystal.[64]

The application of this technique was shown an increased rate of co-crystallization. This is due to an intense mass transfer by convection which is promoted by stirring co-crystal components in CO_2 slurry, which in turn offer a complete co-crystallization and results in a highly pure co-crystal.[64]

6.3.2 | Rapid Expansion of Supercritical Solvents (RESS)

This method consists of saturation of the supercritical fluid (supercritical CO_2 with an API and co-former before the depressurization of the CO_2 phase through a nozzle into a drying chamber at atmospheric pressure. Unfortunately, this method requires that API and co-former be solubility in supercritical CO_2 while the majority of pharmaceutical molecules present low solubility.[64]

6.3.3 | Supercritical Antisolvent Co-crystallization (SAC)

This method uses supercritical CO_2 as an antisolvent for the co-crystallization process. On contrary to RESS, this method requires that API and the co-crystal former have reduced solubility in supercritical CO_2 to allow precipitation of two as one co-crystal structure. Once in a vessel, the CO_2 dissolves in the used solvent leading to simultaneous volume expansion, reducing the solubility of that solvent, therefore resulting in precipitation.

Using its two techniques, such as batch gas antisolvent (BGAS) during which the solution contained both API and co-crystal former, is saturated with CO_2 in a high-pressure vessel until co-crystallization takes place. The second technique is a semi-continuous supercritical antisolvent (SSAS) process during which an API-co-former solution is forced through a nozzle into a highly pressurized vessel containing supercritical.[64]

6.4 | Miscellaneous co-crystal preparation

Among the miscellaneous method of co-crystal preparation, there is the use of high-power CO_2 laser to irradiate powder blends of co-crystal formers, which then promote recrystallization to a co-crystal. This method is known as "***laser irradiation***". It is assumed that the rearrangement of co-formers molecules, as well as nucleation, occur in a vapor phase. This is because it was seen that co-crystallization can only take place if co-crystal formers sublimate enough.[64]

6.5 | Freeze-drying

Also known as lyophilization has been wildly used in preserving a variety of products including pharmaceuticals. The material solution is frozen at a controlled (reduced) surrounding pressure to allow the frozen water in the material to sublime. This method has potentially been used to prepare solid-state co-crystal forms.[102]

6.6 | Electrochemically induced Co-crystallization

Electrochemically induced Co-crystallization is another miscellaneous method that uses electrochemistry to incite co-crystallization by creating a conducive environment for the process (pH adjustment to neutral and generate necessary local forces).

6.7 | Resonant acoustic mixing

Co-crystal preparation relies on the acoustical transfer of mechanical energy to a wetted powder mixture (drug-co-former). This form of energy transfer encourages the intimate mixing of the components, therefore increasing chances for co-crystal formation.[103,104]

6.8 | Spray drying

Spray drying is a well-known method used to produce dry powder from solutions, emulsions and suspensions. The advanced technology which allows a highly-controlled environment and use of hot steam air to rapid evaporation of the used solvent, the method is very fast and produce pure co-crystals when compared to other solution co-crystallization methods. For this reason, spray drying is among the most preferred method for the preparation and scale-up.[105] The method has been widely used in the production of amorphous solid dispersions, this method can also and has used to prepared co-crystal.[64,106]

6.9 | Electrospray technology

This method leads to liquid atomization using electrical forces where the liquid flows out a capillary nozzle at high electric potential, and then the liquid is forced by the electric field into a dispersion of fine and highly charged droplets. After drying, the resulted particles are collected using a charged powder collector. All these methods have been thoroughly discussed with examples.[64]

7 | PREFERENCE OF CO-CRYSTALLIZATION

The scientific need for using the co-crystallization process as a potential tool to enhance the desired properties of drug substances has recently increased significantly due to the benefit of this approach over a variety of other techniques outlined at the beginning of this chapter. Further, the uniqueness with respect to the structure and properties, of each product of co-crystallization (novelty), a variety of solid forms (Figure 3) that can be resulted from this approach (non-obviousness), each of them exhibiting unique physicochemical properties (utility) based on which different application may be evaluated. Simplicity and the greenness of co-crystallization confer makes this a remarkable method.[43]

Additionally, co-crystallization around an API increases the protection of its intellectual property (IP), by reducing the risks and industrial crisis in case the drug loses its effectiveness over time while on market (reducing the risk of costly litigation and market erosion).[107]

Co-crystallization also stabilizes drugs known to exhibit polymorphism issues.[108] The latter being the ability of a substance to present itself in different crystalline forms (also known as polymorphs) characterized by the same chemical composition (same substance) but different physicochemical properties, structure arrangements (molecules are joined and arranged differently in lattices).[6]

It is mandatory to know that the formation of hydrogen bonds during the co-crystal screening is dependent on the molecular complementarity of the co-crystal formers and plays an important role in structure directions due to the molecular flexibility they offer. It is from this supramolecular concept where the idea of drug-drug co-crystallization comes. This concept of drug-drug co-crystallization will be discussed in subsequent sections.[109,110]

Assisted by the Cambridge structure database crystal engineering helps the understanding of intermolecular forces involved in hydrogen bonding between molecules (organic mostly). The presence of functional groups that engage in hydrogen bond formation makes the molecular nature of drugs a key factor in the co-crystallization process. This factor also makes all APIs immanently prone to co-crystal formation.[12]

8 | MULTIDRUG CO-CRYSTALLIZATION (MDCS)

Multiple drugs combination in a single dosage form for oral administration has become a popular drug development strategy mainly due to its abilities to boost the treatment effect and improvement of disease management. The advantage gained from this is also reflected in patient adherence and reduction of product development costs. Such benefits and much more can also be obtained from combined drugs in the pharmaceutical co-crystals.[111]

Despite their potential as recognized by different solid-state scientists, not much attention has been given to

them, only a little is found in the literature. However, with the present increase of complex medical conditions and increased pressure in the discovery of new APIs, these hybrids are of utmost importance.

Drug-drug or multidrug co-crystallization is the relatively unexplored technique for the design of solid APIs, and according to the literature, the use of this technique may produce co-crystals with potential applications in terms of drugs combination and improved properties for further development.[41] Hence, for Bhupinder, the idea of developing a multiple-drug co-crystal is reflected in recent publications and patent applications.[36,112–115]

According to Thipparaboina et al. multidrug co-crystals are dissociable solid crystalline supramolecular complexes comprising two or more therapeutically effective components in a stoichiometric ratio within the same crystal lattice, wherein the components may predominantly interact via non-ionic interactions and rarely through hybrid interactions (a combination of ionic and non-ionic interactions involving partial proton transfer and hydrogen bonding) with or without the presence of solvate molecules. This definition was reconstructed based on FDA guidelines according to which co-crystals are dissociable multi-component solid crystalline supramolecular complexes composed of two or more components within the same crystal lattice wherein the components are in a neutral state and interact via non-ionic interactions.[116]

The multidrug co-crystals implement the patent eligibility criteria such as non-obviousness, novelty, and utility for pharmaceutical development.[117,118] According to Ghadi et al. there was no record of multidrug co-crystals in the literature. However, this statement was later changed and now, due to an increased interest of researchers on these adducts, the number of reports is evolving in the literature.[41]

A more explicit definition of multidrug co-crystals takes into consideration the growing literature on salt/co-crystal hybrids and ionic co-crystals thus includes hybrids interactions. Benefits such as offering potential advantages of synergistic, additive effects, enhanced solubility, and dissolution of at least one of the drug components as well as bioavailability are associated with these solid-state materials. Furthermore, MDC due to intermolecular interactions can stabilize unstable components.[41,42]

8.1 | Factors influencing MDC synthesis

It is familiar that the co-crystallization process often yields complex hybrids other than co-crystals intended. The same phenomenon is likely to increase when attempting to prepare MDCs. Combining two drugs may result in either a mixture or a co-crystal in a specific ratio. In cases where a co-crystal is formed, improvements in physicochemical properties and performance of at least one drug component of the co-crystal system are observed. Alternatively, in the case where another supramolecular hybrid is produced, characterization should be conducted to determine its usefulness.[117]

Different factors are to be considered when attempting to synthesize MDC:

- Like normal drug-co-former co-crystals, the successful production of MDC depends on the method used. Mechanochemistry is likely to be the best, simple and cost-effect method to prepare MDC.
- A deep understanding of both components ensures a successful co-crystal formation. The compatibility of the MDC system components should be established. Both drugs must possess complementary functional groups necessary for intermolecular interactions.
- Many active pharmaceutical ingredients (API) with exploitable functional groups that are readily available for hydrogen bonding.
- A diversity of methods available to synthesis co-crystals some of which will be discussed in the methodology chapter of this thesis.
- Possibilities of co-crystal formation with ionic drugs. This factor favors co-crystallization over the salt formation and,
- Of course, the need for that particular co-crystal on the market motivates the search, screening and production processes.

8.2 | Synthesis of multi-drug co-crystals

Generally, MDCs are synthesized the same way as normal single drug co-crystals and conventional methods used are similar.[41] Some of the traditional methods for co-crystal formation also applied to MDCs synthesis are; simple distillation, solvent evaporation, cooling crystallization, co-grinding, and liquid assisted grinding, slurry crystallization, melting, and sonic crystallization. The successful application to MDCs of these methods has been justified by a growing number of these hybrids in the literature.[41]

8.3 | Advantages of multi-drug co-crystals

MDCs offer potential advantages of synergistic benefits in addition to enhancing solubility, dissolution as well as bioavailability offered by normal co-crystals. Multidrug co-crystallization as a subset of co-crystallization provides not only the opportunity to modify the physicochemical

properties of a drug substance but also the new strategies for the development of combination therapies. MDCs, due to the intermolecular interactions, can stabilize unstable components, [41] therefore, reducing the occurrence of drug resistance and related side effects.

Even though the production of MDC follows the same crystallographic procedures, there are other factors to consider to successfully producing MDC. Firstly, in-depth knowledge of both drug components of the co-crystal is paramount to address the purpose of the product co-crystal desired. Other factors include but not limited to co-crystallization conditions as well as methods used. Particularly, in pharmaceutical co-crystals production, the compatibility of two drugs, differential solubility and variations in dose must be considered.[41]

Examples of multi-drug co-crystals synthesized through this approach include three anti-TB drugs isoniazid (INH) and pyrazinamide (PZA) key-members of the first-line treatment and 4-aminosalicylic acid, the second-line anti-TB drug. Both drugs (INH and PZA) were co-crystallized by 4-aminosalicylic acid (PAS) and two complexes have resulted. The first complex is anhydrous formed between INH and PAS with a 1:1 stoichiometric ratio. The second complex was a monohydrate resulted from co-crystallizing PYR and PAS.[119] Other reported combinations such as molecular complexes of theophylline from its co-crystallization with 5-fluorouracil and barbital have been discussed in the literature.[108]

The co-crystallization of meloxicam a non-steroidal anti-inflammatory and aspirin resulted in a co-crystal showing a reduced time required to reach the human therapeutic concentration compared with the parent drug, meloxicam.[114] The co-crystal of Acetaminophen and theophylline in a 1:1 ratio showed a better dissolution rate than that of the physical mixture of these drugs. Other examples include Dapsone which due to its potentials therapeutic activity, was co-crystallized by different active substances.[120–123]

9 | CONCLUSION

With an intense demand for new medications due to the increasing drug resistance among available medications, the desire to discover new, co-effective, and patient-friendly compounds, force researchers to explore different alternatives, one of them being fine-tuning the physico-chemical properties of known APIs. Co-crystallization has recently evolved as a better approach/route to promising new chemical entities.

Based on a growing number of publications, co-crystals have gained potential applications in the pharmaceutical industry and other fields of chemistry and physics such as agrochemistry, catalysts, food industry, energy, etc.

Not only does co-crystallization enhance the essential properties of APIs but also plays an important role in combination therapy where APIs can be combined in a single co-crystal for multi-targets purposes. Typical examples of these include HIV, TB, cancer treatments that require high doses and therefore, involve the administration of many drugs at once to achieve the necessary doses.

Even though co-crystal formation is not always successful, the resultant multi-component adducts come with even better properties than of the co-crystal counterpart. Diversity of these solid-state materials that can under different circumstances result from co-crystallization, justify the influence of this approach in protecting the intellectual property of a drug.

Assisted by the CSD, crystal engineering helps the understanding of intermolecular forces involved in hydrogen bonding between molecules (organic mostly). The presence of functional groups that engage in hydrogen bond formation makes the molecular nature of drugs a key factor in the co-crystallization process. This factor also makes all APIs immanently prone to co-crystal formation.[12]

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CONFLICT OF INTEREST

The authors declare that the review was carried out in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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