CO-CRYSTALS: EMERGING APPROACH IN PHARMACEUTICAL DESIGN

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ABSTRACT

Crystal form can be vital to the performance of a dosage form. This is especially true for compounds that have intrinsic barriers to drug delivery, such as poor aqueous solubility, slow dissolution in gastrointestinal media, low permeability and first pass metabolism. The nature of the physical form and formulation tends to display the greatest effect on bioavailability parameters of water insoluble compounds that need to be given orally in high doses. An alternative approach available for enhancement of drug solubility, dissolution and bioavailability is through the application of crystal engineering of co crystals.

Co-crystal is crystalline structure consisting of two or more components that form a unique structure having specific properties. The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences. A pharmaceutical co-crystal is single crystalline solid that incorporates two neutral molecules one being an active pharmaceutical ingredient (API) and the other a co-crystal former. This technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number forms of an API. This review focuses on the properties of co-crystals, their method of synthesis and applications in the field of pharmacy.


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INTRODUCTION
Pharmaceutical active ingredients (APIs) can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co crystals and amorphous solids. Each form displays unique physicochemical properties that can greatly influence the bioavailability, manufacturing process, purification, stability and other performance characteristics of the drugs [1]. Chemist and engineers in the pharmaceutical industry generally seek to deliver crystalline forms of their active compounds, mainly due to the inherent stability of crystalline materials and the well-established impact of crystallization processes on purification and isolation of chemical substances [2]. Increasing attention is now being paid to the impact of material properties on drug discovery and early development as the drug substances tend to be very valuable materials [3]. Poor dissolution rate, solubility, chemical stability and moisture uptake influence therapeutic efficacy of many pharmaceuticals and significantly lower the market value of a drug. Over 40% of marketed drugs today have low solubility and in the Research and Development pipeline, 80-90% of drug candidates could fail because of solubility issues [4].

Currently, salt formation is one of the primary solid state approaches used to modify the physical properties of the APIs, and it is estimated that over half of the medicines on the market are administered as salts. However a major limitation within this approach is that the API must possess a suitable (acidic or basic) ionisable site. In comparison, co-crystals offer a different pathway, where any API regardless of acidic, basic or ionisable groups, could potentially be co-crystallised. This aspect helps complement existing methods by reintroducing molecules that had limited pharmaceutical profiles based on their non ionisable functional groups [5].

The main motivation to explore co-crystals of pharmaceuticals is to potentially modify their physical properties, primarily dissolution rate (and hence bioavailability) and hygroscopicity (physical stability). With the advent of combinatorial chemistry APIs possessing limited aqueous solubility (Biopharmaceutics Classification System Class II drugs) are becoming increasingly prevalent in the research and development portfolios of pharmaceutical companies [6]. The challenging aspects in development of such drug molecules are associated with their slow dissolution in biological fluids and thus insufficient and inconsistent systemic exposure and subsequent sub-optimal clinical efficacy. The traditional approaches (e.g. salt formation, micronization, solid dispersion formulations) which are used to address the issues of poor aqueous solubility often fail to produce a viable solid form as the achieved increase in dissolution rate is insufficient to provide adequate enhancement of bioavailability. In this context, pharmaceutical co-crystals as a distinct solid phase possessing the unique set of properties can be the advantageous alternative to the other solid-state modification techniques.

CO-CRYSTALS
Co crystals are defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions. Co-crystallisation is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single component crystals and their polymorphs) or with different molecular components (multiple component crystals or co-crystals) in the crystalline state [7].

The components in a co-crystal exist in a definite stoichiometric ratio, and assemble via non covalent interactions such as hydrogen bonds, ionic bonds, and π-π or van der Waals interactions rather than by ion pairing [8]. Generally co-crystals in their pure states are solids at room temperature and by convention, these normally excludes salts. Co-crystals can have different properties than the crystals of individual components. Further, co-crystals have different crystal structures than the pure components, contain different intermolecular spacing patterns, and as such they often exhibit widely different physical properties than the pure components. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionization sites in the API [9, 10].

The key benefits associated with co-crystallisation approach to modifying properties of pharmaceutical solids including weakly ionisable and non-ionisable, to form co-crystals, and the existence of numerous potential counter-molecules including food additives preservatives, pharmaceutical excipients as well as other APIs, for co-crystal synthesis. Additional valuable advantages that co-crystal formation may offer for the pharmaceutical industry are the opportunity of intellectual property protection and the possibility of extending the life cycles of old APIs.

PHARMACEUTICAL CO-CRYSTALS
A pharmaceutical co-crystal is simply a co-crystal in which at least one of the molecular components is an API in conjunction with another type of molecule termed a co-crystal former. More strictly, in order to be useful, the non-API component should be non toxic with no adverse side effects. Ideally the co-crystal former should be included on the USA Food and Drug Administration (FDA) “Everything added to food in the United States” (EAFUS) list which comprises over 3000 substances that are suitable as food additives, or approved as Generally Regarded as Safe (GRAS) [11].

The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences [5]. Pharmaceutical co-crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API. Scientist showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical co-crystal formation improved the performance of a drug known to have poor solubility [12]. Pharmaceutical co-crystallisation is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability, hygroscopicity and compressibility without altering their pharmacological behaviour [5, 13]. The expanding scope of crystal form selection, emergence of crystal engineering in pharmaceutical science and pharmaceutical co-crystal were reviewed [14]. Some common aspects of co-crystal formation, screening strategies and outline
methodologies for co-crystal functionality were reported [15]. The use of co-crystals in drug design and delivery and as functional materials with the potential applications as pharmaceuticals has recently attracted considerable interest [14, 16-18]. Pharmaceutical co-crystals have been described for many drugs such as acetaminophen, aspirin, ibuprofen, flurbiprofen etc [19-21]. Co-crystals of antitubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool [22].

**CO-CRYSTALS VERSUS SOLVATES**

The main difference between solvates and co-crystals is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates; if both components are solids at room temperature, the crystals are designated as co-crystals [23].

**SALT VERSUS CO-CRYSTAL FORMATION**

Co-crystal and salts may sometimes be confused. The understanding of the fundamental difference between a salt formation and a co-crystal is very important to both pre-formulation activities and chemical/pharmaceutical development aspects. Indeed, salts and co-crystals can be considered as opposite ends of multi-component structures [24-26]. Salts are often chosen instead of the free acid or base as these can improve crystallinity, solubility and stability of a pharmaceutical compound. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionisable sites in the API.

Salt formation is an acid-base reaction between the API and an acidic or basic substance. The widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs [27, 28]. Salt formation is a three component system having an acid (A), a base (B) and one or more solvents. A salt is formed by transfer of a proton (H+) from an acid (A) to base (B).

\[ \text{A-H} + \text{B} \rightarrow (\text{A}^+) \text{(B}^- \text{H}) \]

Proton transfer is thought to mainly depend on the pKa values of the components. When there is no such transfer and the components are instead present in the crystal as neutral entities, the product is generally defined as a co-crystal. In other words, a co-crystal is an A-B composite in which no proton transfer occurred [29]. Salt formation is an acid–base reaction between the API and an acidic or basic substance and large numbers of crystalline salts of APIs are available in market [26, 27]. The formation of a salt or co-crystal can be predicted from pKa value of acid (A) and a base (B). Salt formation generally requires a difference of about 2.7 pKa units between the conjugate base and the conjugate acid (A) i.e. [pKa (base) - pKa (acid) ≥ 2.7]. For example, succinic acid having pKa 4.2 form co-crystal with urea base (pKa 0.1) while succinic acid form salt with L-lysine base having pKa 9.5. Generally base pKa values are not sufficiently high to allow proton transfer when co-crystal is formed [26]. Cocystal of succinic acid-urea has two hydrogen bonds i.e. the oxygen atom in urea molecule is bonded to hydrogen atom in succinic acid molecule while oxygen atom from succinic acid molecule is bonded to hydrogen atom in urea molecule.

![Fig 1.0 Structure of co-crystal of succinic acid-urea.](image)

**DESIGN OF COCRYSTAL**

Co-crystals designed on the principal of the supramolecular synthesis; it provides a powerful approach for proactive discovery of novel pharmaceutical solid phases. Co-crystals consist of multiple components in given stoichiometric ratio, where different molecular species interact by hydrogen bonding and by non-hydrogen bonding.

The use of hydrogen bonding rules, synthons and graph sets may assist in the design and analysis of co-crystal systems. In general, prediction of whether co-crystallization will occur is not yet possible and must, at present, be answered empirically. Co-crystal formation may be rationalised by consideration of the hydrogen bond donors and acceptors of the materials that are to be co-crystallized and how they might interact. Following the extensive examination of preferential packing preferences and hydrogen bond patterns in a number of organic crystals, Etter and co-workers proposed the guidelines to facilitate the deliberate design of hydrogen-bonded solid [27]. All good proton donors and acceptors are used in hydrogen bonding, six-membered ring intermolecular hydrogen bonds form in preference to intermolecular hydrogen bonds, the best proton donor and acceptor remaining after intermolecular hydrogen-bond formation will form intermolecular hydrogen bonds to one another (but not all acceptors will...
necessarily interact with donors). These observations help to address the issue of competing hydrogen bond assemblies observed when using a particular co-crystallising agent.

A detailed understanding of the supramolecular chemistry of the functional groups present in a given molecule is the prerequisite for designing the co-crystals because it facilitates the selection of the suitable co-crystal former. Supramolecular synthons that can occur in common functional groups include hydrogen bonding and certain functional groups such as carboxylic acids, amides, and alcohols are particularly amenable to formation of supramolecular heterosynthons [28]. The strong hydrogen bonds involves (N-H---O), (O-H---O), (N-H-N) and (O-H-N). The weak hydrogen bonds involves the C-H-O and C-H-N=C-C [29].

A pharmaceutical co-crystal contains an API and a coformer molecule(s), both of which typically exist in the neutral state and interact by hydrogen bonding or by other non-covalent bonds. A few co-crystals have been synthesized in which the API is ionized, but the coformer is still non-ionized. The term co-crystal generally refers to components that in their pure states are solids at room temperature. Co-crystals may include two or more different components and in most cases to date, two and three component systems are reported with the latter being mostly cocrystalline solvates, e.g. theophylline-5-fluorouracil hydrate, carbamazepine-4-amino benzoic acid hydrate and tetroxoprim-sulfametrole methanolate.

The field of crystal engineering has focused on understanding the intermolecular interactions and connectivities that lead to the construction of supermolecules or extended architectures. Because of its strength and directionality, the hydrogen bond has been the most important interaction in co-crystal formation. By studying the hydrogen bond patterns in crystalline solids, valuable knowledge is gained to identify hydrogen-bond preferences and reliable synthons that lead to co-crystal formation. Guidelines for preferred hydrogen bond patterns in crystals include: [30, 31]

a) All acidic hydrogens available in a molecule will be used in hydrogen bonding in the crystal structure of that compound [31]
b) All good acceptors will be used in hydrogen bonding when there are available hydrogen-bond donors [30]
c) The best hydrogen-bond donor and the best hydrogen-bond acceptor will preferentially form hydrogen bonds to one another [30].

The presence of multiple competitive hydrogen-bond sites, conformational freedom, steric hindrances, or competing dipolar or ionic forces. These general principles nevertheless establish the basis for predicting likely and unlikely structures.

METHODS OF PREPARATION OF CO-CRYSTALS
Different techniques for the preparation of co-crystals are,

Solvent evaporation technique

This technique is the common way to synthesize co-crystals. In this method co-crystal components or co-crystal formers are taken in stoichiometric ratio and solubilise in a common solvent. The resultant solution is allowed to evaporate slowly. This technique works on the principle that, when different molecules of complimentary functional groups afford hydrogen bonds that are more favourable than each of the individual molecular components. In this case, the co-crystal is likely to be thermodynamically favoured [32].

Melting technique

By simply melting two co-crystal formers together and cooling, a co-crystal may be formed. If a co-crystal is not formed from a melt, a seed from a melt may be used in a crystallization solution in order to afford a co-crystal.

Solid state grinding technique

This technique is also called as mechanical milling or neat grinding technique. Co-crystal formers are taken in stoichiometric amounts and ground together manually using a mortar and pestle, using a ball mill, or using a vibratory mill. Normal milling time is 60 minutes. It has been reported that co-crystal material at first obtained exclusively by one approach may be used as seeds to subsequently obtain that co-crystal by another method, there by potentially enabling XRD structure determination via single-crystal growth. In one alternative case, co-crystal structure determination was achieved even when material could be prepared only as crystalline powder by grinding [33].

Slurrying technique

It is the Slurries-induced formation of co-crystalline phase among two or more active solid materials or between the active solid materials and the excipients. Equimolar were dissolved in small amount of methanol at ambient temperature. The solution was slowly evaporated at room temperature during 48 hours to promote co-crystallization [34].

Solvent drop technique

This technique is also called as liquid assisted grinding or kneading. This involves the grinding of stoichiometric amount of coformers with the aid of small amount of liquid. This method was developed in order to increase the rate of co-crystal formation, but has advantages over solid state grinding such as increased yield, ability to control polymorph production, better product crystallinity, and applies to a significantly larger scope of co-crystal formers. This method also enhances the co-crystallisation selectivity.

Supercritical fluid technology

Pharmaceutical co-crystals can be formed also by use of supercritical fluids. Supercritical fluids act as a new media for the generation of co-crystals. Supercritical fluid technology offers a new platform that allows a single-step generation of particles that are
difficult or even impossible to obtain by traditional techniques. The generation of pure and dried new co-crystals (crystalline molecular complexes comprising the API and one or more conformers in the crystal lattice) can be achieved due to unique properties of super critical fluids by using different supercritical fluid properties [35].

**By using intermediate phase**

Using intermediate phases to synthesize these solid-state compounds are also employed. Through the use of a hydrate or an amorphous phase as an intermediate during synthesis in a solid-state route has proven successful in forming a co-crystal. Also, the use of a metastable polymorphic form of one co-crystal former can be employed. In this method, the metastable form acts as an unstable intermediate on the nucleation pathway to a co-crystal. As always, a clear connection between pair wise components of the co-crystal is needed in addition to the thermodynamic requirements in order to form these compounds.

**NANO CRYSTAL**

A nano crystal refers to any nanomaterial with at least one dimension ≤ 100nm and it should be single crystalline. The production of drug nanocrystals by bottom up techniques (with main focus on particle diminution by high pressure homogenization) for many new chemical entities of very low solubility has been reported. The transfer of the liquid nanosuspensions to patient convenient oral dosage forms such as tablets and capsules have also been reported. Under microwave irradiation, nonlinear optical nanocrystals of aminonorbornides with benzenesulfonic acids were reported. Single-component crystalline nanorods, composed of 9-methylanthracene (9-MA) and exposed to a suspension of 1,2,4,5-tetracyanobenzene (TCNB) in water formed a 1:1 charge-transfer complex within the rods, which are transformed from crystalline 9-MA into co-crystalline 9-MA/TCNB. The co-crystal nanorods were characterized by electron microscopy, X-ray diffraction, and optical spectroscopy. These studies demonstrated the importance of organic nanostructures for supporting structure-preserving chemical transformations that were not possible in larger crystals [36].

**SYNTHESIS OF NANO CO CRYSTALS**

**Sonochemical synthesis**

Sonochemistry became means to prepare co-crystals of nanometer scale dimensions. The technique which is harsh yet transient has afforded co-crystals with components comprised of relatively simple molecules. The method affords pharmaceutical nanocrystals with a narrow size distribution. In this process the pharmaceutically active ingredients and co-former are dissolved separately in solvents and injected in an anti solvent at 0°C under ultrasonic radiation. After 15 s of sonication suspension is filtered [37].

**Wet milling technique**

The different wet-milling processes in miniature, middle and large preparation scales have been established in order to cover the various types of studies with wide scale. The powder of a poorly water-soluble model drug candidate, three general-purpose equipments with stirring, oscillating and turbulent motions was applied instead of the specific milling machine with high power to avoid much investment at such early development stage. The operational conditions were optimized to obtain finer particles using the middle-scaled oscillating beads-milling apparatus in particular. It was found that the nano co-crystals, which whole particle distribution was in the submicron range, was successfully produced within the running time around 10min [38].

**COCRYSTALS AS A MEANS OF CONTROLLING PHYSICOCHEMICAL PROPERTIES OF DRUG:**

The ability to deliver the drug to the patient in a safe, efficient and cost-effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state. This provides a significant driving force for inventing new approaches to designing pharmaceutical solid materials with specific physicochemical properties.

**Hydrate Formation**

API in cocrystals will not form solvates or hydrates during crystallization or upon storage. Since cocrystals are supra molecular assemblies and are designed based on functional groups and hydrogen bond complementarity, solvate formation that relies on this complementarity will be inhibited by the formation of cocrystals, given that the intermolecular interactions between the API and coformer are stronger than between the API and solvent molecule. Example: caffeine-oxalic acid cocrystal did not transform to caffeine hydrate under high relative humidity [39].

**Chemical Stability**

Cocrystal formation can also improve the chemical stability of an API when chemical reactivity requires that reactant molecules be in suitable positions in the solid state. Example: The single component carbamazepine (CBZ) polymorphs degrade by solid-state photochemical reaction, CBZ co-crystal formation with saccharin and nicotinamide inhibits photodegradation of CBZ by altering the molecular arrangements in the solid state such that the distance between the azepine rings is more than 4.1 Å, thereby preventing photodegradation [40].
Dissolution Rate
Co-crystals show the improved dissolution rate than the pure drug depending upon the co-former used. Indomethacin-saccharin co-crystal had a greater than 50 times increase in dissolution rate in a 200mM phosphate buffer (pH 7.4) compared to γ-indomethacin, the most stable polymorph [41].

Cocrystal Solubility
Co-crystal solubility is dependent on co-crystal component concentration, solution complexation, and ionization when one or more components are ionizable.

Bioavailability
If co-crystals are going to be a viable alternative for solid state forms of a drug, Bioavailability studies need to be performed. Carbamazepine-saccharin was reported to yield slightly higher plasma levels when compared to dosing carbamazepine monoclinic, form III, although the authors reported that the increase was not statistically significant.

CHARACTERIZATION OF COCRYSTALS [42-51]
Characterization of cocrystals is of utmost importance and there are different analytical methods ranging from simple melting point determination to complete structural determination through single crystal X-ray crystallography. Other procedures like studying the morphology of crystals by microscopic methods, observing changes in crystal forms with temperature, phase transition by thermal methods, interpreting molecular motion and chemical environment by the use of vibrational spectroscopy and solid state NMR are used depending upon the information sought.

Crystallographic methods
Crystallographic methods include both single crystal X-ray diffraction as well as powder X-ray diffraction. A successful single crystal X-ray diffraction study can provide unambiguous atomic positions and complete structural information, but obtaining a single crystal suitable for this study becomes often the bottleneck. In such cases, powder X-ray diffraction studies using microcrystalline samples become a major tool. In fact, it has become routine to take powder diffractograms to ascertain the solid state nature and purity of every batch of synthetic drugs.

Optical microscopy
Another quick and efficient method is to study the crystal morphology by optical microscopy. As unit cell repetition leads to crystal formation, this feature is reflected in the outer appearance of crystals that can be observed by simple hand lens or microscope. Further, a detailed study can be performed using polarizing optical microscopy, electron microscopy and thermal microscopy.

Thermal analysis
The third important method, which is widely used in pharmaceutical industries for characterization of polymorphism, solvation, purity, degradation and drug compatibility, is thermal analysis, which includes Thermogravimetry, Differential Thermal Analysis (DTA) and Differential Scanning Calorimetry (DSC).

Vibrational spectroscopy
The study of molecular motions by use of vibrational spectroscopy is also sometimes employed in the characterization of polymorphs. This method includes infrared absorption spectroscopy and Raman spectroscopy.

Nuclear magnetic resonance
Nowadays solid state NMR is also used for characterization. It studies the chemical environment of the nuclei which is different in polymorphs because of magnetic non-equivalence. Resonance peaks for the magnetically non-equivalent nuclei will differ in different polymorphs and can yield very useful information.

Scanning electron microscopy
Scanning electron microscopy (SEM) was conducted to characterize the surface morphology of the particles. The samples were mounted on alumina stubs using double adhesive tape, coated with gold in HUS-5GB vacuum evaporator. Then the sample was observed in Hitachi S-3000N SEM at an acceleration voltage of 10KV and a magnification of 5000X.

DRUG-DRUG COCRYSTAL [52]
Physicians prescribe combination therapy frequently to treat and manage a plethora of medical conditions. Multi-API co-crystals, relatively unexplored solid forms of APIs, have potential relevance in the context of combination drugs for pharmaceutical drug development.
Fig 1.1 Representation of drug-drug co-crystal and combination drug.

The idea of developing multi-API co-crystals is interesting. This is reflected from the number of publications and patent applications for co-crystals in recent years. Drug-drug co-crystals fulfill the criteria for patent eligibility: novelty, utility, and non-obviousness for pharmaceutical development. However, no compilation of drug-drug co-crystals information’s is available in literature. There is immense potential to explore co-crystal design of established APIs among each other to enhance solubility and bioavailability of the product. Consequently, there is a strong need to devise ways to increase the likelihood of success in generating drug–drug co-crystals. In this context, the limited available reports in literature are described here. While co-administering a combination of theophylline and phenobarbital, it was discovered that a co-crystal of 2:1 stoichiometry existed between the two compounds. The meloxicam-aspirin co-crystal decreased the time required to reach the human therapeutic concentration compared with the parent drug, meloxicam. The 1:1 acetaminophen/theophylline (AT) co-crystal had a faster dissolution rate than AT physical mixtures. Two 1:1 drug–drug co-crystals [isoniazid: theophylline; pyrazinamide: 4-aminosalicylic acid] may be exploited for the treatment of tuberculosis. Celecoxib: venlafaxine co-crystal and tramadol: celecoxib co-crystals use as medicaments, more particularly for the treatment of pain has been reported. Amoxicillin clavulanate co-crystal improved its antibiotic activity against non-beta lactamase bacterial, Sarcina lutea. Further, many pharmaceutical companies and various groups are working actively on co-crystals. Success has been achieved for various co-crystal systems such as sulfamethazine-theophylline, pyrazinamide-diflunisal, sulfamethazine-potassium salt of 4-aminobenzoic acid, theophylline: gentisic acid, ethenamide-gentisic acid.

In view of the reported generation of pharmaceutical co-crystals containing two active pharmaceutical ingredients mentioned above, drugs having similar structure and similar 3-D arrangement should be exploited for drug-drug synergism to obtain multiple API co-crystals. Co-crystal screening technology has the potential to identify and establish new IP for new drug-drug co-crystals of multiple APIs to protect the product from competition. Further, it offers immense potential in various fields such as resolution of racemic drugs to API through co-crystallization. In this way, optimization of co-crystal screening may lead to commercialization of new co-crystal product along with separated single enantiomers. In the case of commercial API-API combination, a patent of a drug-drug co-crystal with better drug properties than previously known forms could be of high commercial value. Designing drug–drug cocrystals of marketed drugs may shorten development period (including clinical trials) than those of New Chemical Entities as co-crystals do not involve structural modification of the APIs. Co-crystals are less prone to suffer polymorphic transformations and the status of polymorphism in this class of co-crystals needs investigation. Co-crystals among APIs such as aspirin, caffeine, theophylline, sulphasalazine, carbamazepine, fluoxetine hydrochloride, piroxicam, norfloxacin, indomethacin, ibuprofen, paracetamol, flurbiprofen, itraconazole are of interest for multi-API co-crystals study. A single-step, scalable, solvent-free, continuous cocrystallization and agglomeration technology developed for co-crystal agglomerates of ibuprofen: nicotinamide (1:1 ratio) using Hot Melt Extrusion, offer the flexibility for tailoring the co-crystal purity. The potential of supercritical fluids as new media for the cocrystallization of APIs has been addressed recently and screening for pharmaceutical co-crystals using the supercritical fluid enhanced atomization process might help for production of multi-API co-crystals. Experts are of the opinion that multi-API co-crystals are expected to overcome the problems associated with traditional combination drugs and it is hoped that further research in this area may have some bearing in the treatment of several diseases.

CASE STUDIES OF PHARMACEUTICAL CO-CRYSTALS

The earliest example of pharmaceutical co-crystals in the context of APIs relates to a series of studies conducted in the 1950s by Higuchi and Roy. They studied complex formation between macromolecules and certain pharmaceuticals. However, these would not be classified as pharmaceutical co-crystals according to the criteria applied herein [53, 54].

Perhaps the first application of crystal engineering to the generation of pharmaceutical co-crystals was a series of studies reported by Żerkowski et al. [55] concerning the use of substituted barbituric acid, including barbital and melamine derivatives, to generate supramolecular linear tape, crinkled tape, and rosette motifs sustained by robust supramolecular synthons with three point hydrogen bonding [54]. Despite their success in cocrystal formation, the focus of these studies was not so much the physical properties of the resulting co-crystals but rather the supramolecular functionality of barbitals and their complementarities with melamine.
Nevertheless, these studies illustrated very well the potential diversity of forms that can exist for a particular API as more than 60 co-
crystals were structurally characterized in this series of studies. Clearly, such a diversity of forms could offer an exciting opportunity
to novel and improved crystalline forms of APIs. Herein, we have chosen to focus upon several case studies that involve the formation
of pharmaceutical co-crystals with altered physical properties of clinical relevance.

Pharmaceutical co-crystals of carbamazepine (Tegretol®):

Carbamazepine (CBZ) is an important antiepileptic drug that has been in use for over three decades. Oral administration of
CBZ encounters multiple challenges, including low water solubility with high dosage required for therapeutic effect (i.e. >100
mg/day), dissolution-limited bioavailability and auto induction for metabolism. In contrast to its simple molecular structure, CBZ
exhibits complexity in its crystal forms [56, 57]. To date, four anhydrous polymorphs, a dihydrate, an acetone solvate, and two
ammonium salts of CBZ have been identified. It is noted that, in the crystal structures of all these forms, the self–complementary
nature of the amide group manifests itself in a predictable manner. Therefore, CBZ has been used as an ideal candidate to demonstrate
how APIs can be converted to pharmaceutical co-crystals, and how these co-crystals could offer optimized physicochemical properties
over existing forms of an API [56, 58]. Two strategies have been adopted for co-crystal formation of CBZ. One crystal engineering
strategy is to employ the peripheral hydrogen bonding capabilities that are not engaged in the pure form of CBZ. A second strategy for
cocrystallization of CBZ involves breakage of the CBZ amide-amide dimer and formation of a supramolecular heterosynthon
between CBZ and a co-crystal former [58]. Both strategies are successful and have afforded a number of CBZ co-crystals that exhibit
improved physicochemical properties. For example, the CBZ: saccharin co-crystal shows significantly improved physical stability (i.e.
only one co-crystal form with equivalent chemical stability to the anhydrous polymorph has been identified after sophisticated form
screening) [57]. In addition, the CBZ: saccharin co-crystal possesses favourable dissolution properties, suspension stability, and
pharmacokinetics using dog models. The pharmacokinetic study reveals that the CBZ: saccharin co-crystal exhibits a higher Cmax and
comparable Tmax when compared with the marketed form, Tegretol® [57]. In short, the CBZ: saccharin co-crystal appears to be
superior to existing crystal forms of CBZ in the following respects: stability relative to the anhydrous polymorph of CBZ; favourable
dissolution and suspension stability, favourable oral absorption profile in dogs [59].

Pharmaceutical co-crystals of fluoxetine hydrochloride (Prozac®):

The availability and marketability of a variety of APIs as chloride salts is well recognized, and, recently, an approach to
utilize such chloride salts, specifically fluoxetine hydrochloride (fluoxetine HCl), to generate co-crystals of an amine hydrochloride
salt via a chloride-mediated carboxylic acid supramolecular synthon has been reported. Fluoxetine HCl is the active pharmaceutical
ingredient found in the common antidepressant drug Prozac®. It is a solid under ambient conditions, only one crystalline phase is
known, and it is available in the salt form. It has been demonstrated that co-crystallization of this API modifies the physical properties
of fluoxetine HCl while still retaining the hydrochloride salt of the API. Fluoxetine HCl was co-crystallized with benzoic acid (1:1),
succinic acid (2:1), and fumaric acid (2:1) via traditional evaporation techniques. For all three co-crystals, the carboxylic acid was
found to form hydrogen bond to the chloride ion, which in turn interacted with the protonated amine, thus generating, in all three
cases, amine hydrochloride salt hydrogen bonding to an additional neutral molecule. Powder dissolution experiments were carried out
in water for the three novel co-crystals resulting in a spread of dissolution profiles. The fluoxetine HCl: benzoic acid co-crystal was
found to have a decrease in aqueous solubility by 50%, and the fluoxetine HCl:succinic acid co-crystal had only a slight increase in
aqueous solubility. However, the fluoxetine HCl: succinic acid co-crystal exhibited an approximately twofold increase in aqueous
solubility after only 5 min. The complex formed between succinic acid and fluoxetine HCl falls apart in solution to generate its pure
components after about 1 h. An intriguing aspect of this study is that by simply hydrogen bonding a hydrochloride salt of an API with
similar co-crystal formers, one can generate distinctively different dissolution profiles [60].

Pharmaceutical co-crystals of sildenafil (Viagra®) [61]

Sildenafil is a drug used in the treatment of pulmonary arterial hypertension, congestive heart failure, atherosclerosis,
conditions of reduced blood vessel potency and peripheral vascular disease, as well as male erectile dysfunction and female sexual
disorders. Sildenafil selectively inhibits cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 that is
responsible for degradation of cGMP in the corpus cavernosum, leading to smooth muscle relaxation in the corpus cavernosum, and
resulting in increased inflow of blood and an erection. Sildenafil citrate, with moderate water solubility, has been commercially
developed and marketed by Pfizer and is available under the trademark Viagra®.

It has been observed that sildenafil in a pharmaceutical co-crystal form could provide an improved solubility of the API
under acidic conditions. In addition, such an improvement of solubility of sildenafil could be particularly advantageous for its orally
administrable formulation. Sildenafil has been successfully co-crystallized with acetylsalicylic acid (1:1 molar ratio) by slurry or
under reflux conditions.

The crystal structure of the co-crystal of sildenafil and acetylsalicylic acid has been determined by single crystal X-ray
diffraction, and in addition, the composition of matter was confirmed by powder X-ray diffraction and infrared spectrometry.
Moreover, the differential scanning calorimetry and thermo gravimetric analyses indicate that the melting point of the co-crystal is
approximately 143°, and it remains thermodynamically stable up to 165° [62]. An intrinsic dissolution study in simulated gastric body
fluid (pH 1.2) shows that the sildenafil: acetylsalicylic acid co-crystal exhibits an intrinsic dissolution rate (IDR) of ca. 11.75
mg/min/cm vs. 6.64 mg/min/cm for sildenafil citrate under the same conditions.

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Co-crystals of theophylline:

Theophylline is useful in treatment of respiratory disease such as asthma. From the physicochemical standpoint, theophylline represents challenge to formulators in that it is known to interconvert between crystalline anhydrate and monohydrate forms as a function of relative humidity (RH). The possibility of crystalline hydrate formation complicates design of a consistent, reproducible for an API in the drug development process. Reversible hydrate formation is particularly problematic, as it indicates that neither the anhydrate nor the hydrate is fully stable across the range of common processing condition. Theophylline is structural analogue of caffeine. The co-crystals of the theophylline were prepared with oxalic acid, malonic acid, maleic acid, glutaric acid by solvent evaporation technique. The relative humidity stability comprised of the storage and subsequent PXRD analysis at four specific RH levels (0%, 43%, 75% and 98% RH) across four different time points (1 day, 3 day, 1 and 7 weeks). Over the course of 7 week study it was found that, at 75% RH and below, theophylline anhydrate converted into theophylline monohydrate. No formation of theophylline hydrate was found in any case.

The observed RH stability of theophylline co-crystal demonstrates the physical stability improvement, specifically avoidance of hydrate formation. The co-crystals formed by oxalic acid found to be more stable. This study demonstrates use of co-crystals in physical property improvement [63].

CO-CRYSTALS AND PATENTS

“New” refers to anything under the sun that is made by the man, such as new composition of matter or any useful improvements. Thus a necessary condition to claim a new composition of matter is to describe clearly with precision the composition, a great challenge in the case of co-crystals [64].

Aripiprazole co-crystals [65], the present invention relates to co-crystals comprising Aripiprazole and fumaric acid and processes for co-crystal preparation. Aripiprazole is a psychotropic drug useful for the treatment of schizophrenia and is the sixth, and most recent, of the second generation antipsychotic medications. It is available in the market under the brand name Abilify® in the form of tablets of 5, 10, 15, 20 and 30 mg strengths. Aripiprazole presents certain challenges for formulation as a rapid-onset dosage form, particularly as a rapid-onset oral dosage form. For example, Aripiprazole has a very low solubility in aqueous media (being practically insoluble) and therefore is not readily dissolved and dispersed for rapid absorption in the gastrointestinal tract when administered orally, for example in tablet form. Towards this end, it has been the endeaveur of pharmaceutical scientists to provide new forms of Aripiprazole, more specifically, a thermodynamically stable form which would have the strengths of the crystalline

Consequently, there is a need for soluble forms of Aripiprazole that can be readily formulated for use in various modes of administration, including parenteral and oral administration. Co-crystal complexes of aripiprazole would add a powerful tool in the treatment of central nervous system disorders. The present invention provided co-crystals of Aripiprazole and fumaric acid which are stable and are reproducible on an industrial scale.

T DFA is the co-crystal of tenofovir disoproxil hemi-fumaric Acid [66]. Tenofovir disoproxil fumarate (DF) is a nucleotide reverse transcriptase inhibitor approved in the United States for the treatment of HIV-1 infection alone or in combination with other antiretroviral agents. Tenofovir disoproxil DF is sold under the trade name Viread (Gilead Science, Inc.) and present in combination with other antiviral agents in the Truvada and Atripla. After analysis of several commercially available products containing tenofovir DF, it was found that these contained mixtures of solid forms of tenofovir DF in varying ratios. Indications have been found by the present inventors that the solid form of tenofovir DF in commercially available products is generally a mixture of at least two forms. It has also been found that one of these forms experiences a conversion of its crystalline form into the other form when put under stress, such as increased temperature and/or humidity. It is believed by the present inventors that the presence of water will induce or enhance the conversion of one form into the other. This suggests that the solid form currently used in the marketed product is not stable or at least has a reduced stability. The bulk molar ratio of tenofovir disoproxil to fumaric acid in the commercially available products is generally indicated as 1:1. The T DFA 2:1 co-crystal of the invention is more stable and is less hygroscopic than the presently known crystalline form of tenofovir.

Theophylline crystallized rapidly from a hot ethylene glycol solution forms theophylline co-crystals [67]. This technique was confirmed as being functional by testing for a known co-crystal of theophylline and p-nitrophenol. Salicylic acid, p-hydroxybenzoic acid, sorbic acid, 1-hydroxy-2-naphthoic acid, glycolic acid, and 2,5-dihydroxybenzoic acid were all tested as guest compounds and in each, a co-crystal formation had occurred. Raman spectra of the pure guest acid, theophylline, and the co-crystal were obtained and compared to confirm co-crystal formation. This invention provides information regarding a new method for co-crystallization i.e ethylene glycol based method.

As one aspect, novel co-crystals are provided. The novel co-crystals comprise one or more active agents, particularly of the salts of such active agents. Novel forms of salts of active pharmaceutical ingredients are provided. For example, the present invention provides novel co-crystals of fluoxetine HCl and benzoic acid; fluoxetine HCl and succinic acid; and fluoxetine HCl and fumaric acid. Novel forms or solid state phases of active pharmaceutical ingredients may be prepared for which there are no known polymorphs, solvates or hydrates, or where such polymorphs, solvates or hydrates were disfavoured [68]. Co-crystals fulfill the criteria for patent eligibility: novelty, utility, and non obviousness.
CONCLUSION
From crystal structure prediction to totally empirical screening, the quest for new crystal forms has become one of the most challenging issues in the solid state science and particularly in the pharmaceutical world. In this context, multi-component crystalline materials like co-crystals have received renewed interest as they offer the prospect of optimized physical properties.

Pharmaceutical co-crystals represent an advantageous class of crystal form in the context of pharmaceuticals. Co-crystals of drugs and drug candidates represent a new type of material for pharmaceutical development. Co-crystals are relatively new to pharmaceutical industry and pharmaceutical co-crystals have given a new direction to deal with problems of poorly soluble drugs. Co-crystals have the potential to be much more useful in pharmaceutical products than solvates or hydrates.
The relevance of co-crystals in API formulation includes the ability to fine-tune physical properties characterization of API identify and develop new proprietary forms of prescribed drugs and the opportunity to generate intellectual property.

Further research is desirable in order to scale up co-crystal systems and implement manufacturing of final dosage forms on commercial scale. Screening for solid forms is important to guarantee that the optimum form is carried forward in development and to minimize the likelihood of unexpected form conversion. Finally an important legal aspect associated with co-crystals is the opportunity for the research-based pharmaceutical companies to significantly expand their intellectual property portfolios.

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