

REVIEW ARTICLE

Pharmaceutical co-crystals - a review

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ABSTRACT

Co-crystallization alters the molecular interactions and composition of pharmaceutical materials, and is considered better alternatives to optimize drug properties. Co-crystals consists of API and a stoichiometric amount of a pharmaceutically acceptable co-crystal former. Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to address physical property issues such as solubility, stability and bioavailability in pharmaceutical development without changing the chemical composition of the API. Co-crystals can be constructed through several types of interaction, including hydrogen bonding, pi-stacking, and van der Waals forces. Co-crystals High Throughput provides information on relationship between formation and chemical structure of the API and conformer. Factors affecting co-crystal stability are reported and a co-crystal is only expected to form if it is thermodynamically more stable than the crystals of its components. Phase transformations induced during processing/storage affects the mechanisms of conversion of crystalline drugs to co-crystals. Pharmaceutical co-crystals could play a major part in the future of API formulation and can be employed for chiral resolution.

KEYWORDS: Co-crystallization. Heterosynthron. Hydrogen bonding. Pharmaceutical co-crystal. Polymorph.

INTRODUCTION

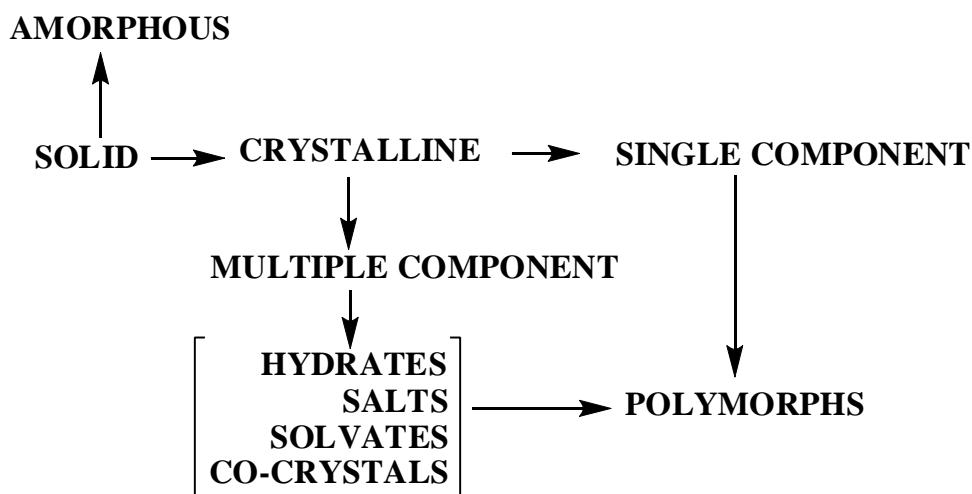
Poor dissolution rate, solubility, chemical stability and moisture uptake influence therapeutic efficacy of many pharmaceuticals, and significantly lower the market value of a drug. Multi-component crystals e.g. solvates, hydrates, co-crystals, salts play important role in the design of new solids particularly in the pharmaceutical area.

CO-CRYSTALS

Co-crystals incorporate pharmaceutically acceptable guest molecules into a crystal lattice along with the API. Co-crystals have regained attention as attractive alternate solid forms for drug development (Figure 1). Physiochemical properties of pharmaceuticals can be improved by obtaining co-crystals using co-crystallization¹⁻³. Co-crystallization with pharmaceutically

acceptable (GRAS) compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior⁴⁻⁶.

FIGURE 1. API solid form classification based on structure and composition.



New opportunities for producing a larger diversity of solid forms of drug substances exhibiting the proper balance of important properties for development into a viable and effective drug product may be met by co-crystals⁷. Furthermore, exploring the co-crystallization potential around an API increases the intellectual property protection over a particular drug product; thus, reducing the risk of costly litigation and market erosion^{1,8}.

Co-crystallization is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers⁹. 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 state⁹.

The components in a co-crystal exist in a definite stoichiometric ratio, and assemble via non-covalent interactions such as hydrogen bonds, ionic bonds, π - π or van der Waals interactions rather than by ion pairing¹⁰. 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 packing 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^{11,12}.

Co-crystals with the same active pharmaceutical ingredient will have strikingly different pharmaceutical properties (melting point, solubility, dissolution, bioavailability, moisture uptake, chemical stability, etc.), depending on the nature of the second component. Some of the co-crystals formed had higher and some lower melting points as compared to their pure components, for example, succinic acid (M. P. 135.3), urea (M. P. 188.9), co-crystal of

succinic acid-urea (M. P. 149.9)¹³. Various type of studies on co-crystals involve i) selection of co-crystal formers for a specific API, ii) co-crystal screening of pharmaceutical active ingredients with selected co-crystal formers, iii) development of reliable procedures to prepare pharmaceutical co-crystals and nanoco-crystals, iv) characterization of pharmaceutical co-crystals, v) scale up of pharmaceutical co-crystals, and vi) co-crystal polymorphism.

PHARMACEUTICAL CO-CRYSTALS

The physical and chemical property improvements through pharmaceutical co-crystals draw closer the fields of crystal engineering and pharmaceutical sciences^{14,15}. A pharmaceutical co-crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a co-crystal former¹⁶. Co-crystal former may be an excipient or another drug⁶. 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. Scientists 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 solubility¹⁷. Pharmaceutical co-crystallization is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability hygroscopicity, and compressibility without alternating their pharmacological behavior^{14,18}. The expanding scope of crystal form selection, emergence of crystal engineering in pharmaceutical science and pharmaceutical co-crystals were reviewed¹⁹. Some common aspects of co-crystal formation, screening strategies and outline methodologies for co-crystal functionality were reported¹¹. The use of co-crystals in drug design and delivery and as functional materials with potential applications as pharmaceuticals has recently attracted considerable interest^{3,16,19-21}. Pharmaceutical co-crystals have been described for many drugs such as acetoaminophen, aspirin, ibuprofen, flurbiprofen etc^{6,16,22-24}. Co-crystals of antitubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool²⁵.

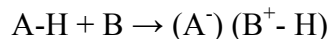
CO-CRYSTAL VERSUS SOLVATES

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.

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^{7,26,27}. Salt 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 ionizable sites in the API.

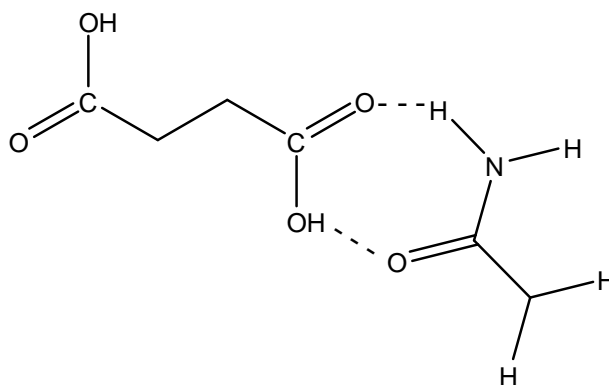
Salt formation is an acid–base reaction between the API and an acidic or basic substance. The widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs^{28,29}. Salt formation is a three component system having an acid (A), a base (B) and one or more solvents. A salt is formed by transfer of a proton (H⁺) from an acid (A) to base (B).



Proton transfer is thought to mainly depend on the pK_a values of the components. The general rules for the packing of hydrogen bonded molecules in crystals were developed by Etter³⁰⁻³². 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.

The formation of a salt or co-crystal can be predicted from pK_a value of acid (A) and a base (B). Salt formation generally requires a difference of about 2.7 pK_a units between the conjugate base and the conjugate acid (A) i.e. [pK_a (base) - pK_a (acid)] ≥ 2.7]. For example, succinic acid having pK_a 4.2 form co-crystal with urea base (pK_a 0.1) while succinic acid form salt with L-lysine base having pK_a 9.5 . Generally base pK_a values are not sufficiently high to allow proton transfer when co-crystal is formed³³. Co-crystal 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 (Figure 2).

FIGURE 2. Structure of co-crystal of succinic acid-urea.



The two-component crystals formed from pyridine or 4-dimethylaminopyridine with maleic, fumaric, phthalic, isophthalic, or terephthalic acids indicated that the two-component solid forms involving pyridine included both salts and co-crystals, while 4-dimethylaminopyridine crystallized exclusively as a salt, in agreement with the differences in the pK_a values³⁴. Relocating the acid protons in the salts to produce co-crystals and vice versa, computational modeling experiments showed that the crystal structure can be better modeled when the crystallographic designation of salt or co-crystal is used³⁴.

SCREENING OF CO-CRYSTALS

Co-crystals can be prepared from two molecules of any shape or size having complementary hydrogen bond functionalities. The ability of an API to form a co-crystal is dependent on a range of variables, including the types of co-former, the API co-former ratio, the solvents, the temperature, the pressure, the crystallization technique, etc. Experimental screening for co-crystal formers is not trivial. Synthesis/processing of co-crystals can be accomplished via a number of methods, including slow solvent evaporation crystallization from solution, solvent-reduced (e.g. slurring, solvent-drop grinding) and solvent-free [e.g. grinding, melt [(hot stage microscopy)], high throughput crystallization and co-sublimation techniques^{14, 26, 35-44}. Typically co-crystals are prepared by slow solvent evaporation that is only viable if compatible solubility in a given solvent exists between the components comprising the potential co-crystal. The potential benefits, disadvantages and methods of preparation of co-crystals were reported⁴⁵. Solvent drop grinding has been reported to be a cost-effective, green, and reliable method for discovery of new co-crystals as well as for preparation of existing co-crystals⁴⁶. A slurry crystallization technique was used in co-crystal screening of two nonionizable pharmaceutical host compounds, stanolone and mestanolone, with 11 pharmaceutically acceptable guest acids and results demonstrated the importance not only of hydrogen bonding but also of geometric fit in co-crystal formation³⁸.

Scientists reported the synthesis (via solvent-drop grinding, solution evaporation, or crystallization from solution), crystal structures, and basic physicochemical properties of six co-crystals of piracetam with l-tartaric acid, citric acid, racemic mandelic acid, l-mandelic acid, as well as a piracetam–citric acid ethanol solvate. Compared to piracetam the piracetam–l-tartaric acid co-crystal showed improved hygroscopic properties⁴⁷. Scientists reported that liquid-assisted grinding appears to be a more efficient method of screening for co-crystal hydrates⁴⁸. The combinations and variations of the above techniques may be used to cause co-crystal formation⁴⁹ [33n]. However, co-crystal screening is difficult to automate and labor intensive. The importance of understanding “supramolecular synthons” in synthesizing co-crystals containing pharmaceutical agents have been reported^{17, 44}. Recently, it has been reported that molecules which crystallize with $Z' > 1$ showed a markedly stronger tendency to form co-crystals than compounds that crystallize in the pure form with $Z' = 1$ ⁵⁰. Co-crystal formation between caffeine and adipic acid has been reported utilizing the newly developed co-crystal screening method⁵¹. The carboxylic acid–primary amide supramolecular heterosynthon has been exploited for the generation of pharmaceutical co-crystals containing two active pharmaceutical ingredients that are polymorphic in their pure forms²². The factors and conditions governing the formation and stability of co-crystals with different stoichiometry were reported with carbamazepine–4-aminobenzoic acid (CBZ–4ABA) co-crystals as the model system. A 1:1 CBZ–4ABA co-crystal was discovered by the reaction crystallization method and co-crystal characterized by carboxylic acid⋯acid and amide⋯amide homosynthons. The stability of 2:1 and 1:1 co-crystals depend on ligand solution concentration and the co-crystal richer in ligand component was more stable at higher ligand solution concentrations⁵².

A review of several aspects of co-crystallization involving sulfadimidine with a focus on

other drug molecules as co-crystallization partners has been reported⁵³. Co-crystal forming abilities of the two anti-HIV drugs (lamivudine and zidovudine) were studied to investigate the general applicability of the retrosynthetic approach in the design of new co-crystals. It was reported that both screening strategies and retrosynthetic methods were appropriate for the discovery of new active pharmaceutical ingredients co-crystals⁵⁴. Trimer co-crystals of *cis*-itraconazole-succinic acid have been prepared and characterized by single-crystal X-ray. The extended succinic acid molecule filled the pocket, bridging the triazole groups through hydrogen-bonding interactions rather than interacting with the more basic piperazine nitrogens. Further, the results suggested that co-crystals of drug molecules have the possibility of achieving the higher oral bioavailability normally observed for amorphous forms of water-insoluble drugs. In addition, the long-term chemical and physical stability provided by crystal forms was maintained¹⁷. The co-crystals (4,4'-biphenol)₃·(2-aminopyridine)₂, (4,4'-biphenol)·(caprolactam)₂, and (resorcinol)·(caprolactam)₂ were reported to self-assemble in the form of supramolecular heterocatemers and provided insight into a possibly general approach for the crystal engineering of co-crystals⁵⁵. The co-crystal of the model pharmaceutical compound caffeine with oxalic acid exhibited complete stability to humidity over a period of several weeks⁵⁶. The results on the formation of stoichiometric variations, i.e. co-crystals composed of identical molecular building blocks in different stoichiometric ratios using co-crystals composed of nicotinamide (na) and suberic acid (**sub**) as co-crystal former suggested that the co-crystal formation occurred in a stepwise manner, wherein the co-crystal (na)·(sub) appeared as an intermediate in the synthesis of the (na)₂·(sub) co-crystal⁵⁷.

Co-crystal prediction has been reported to include the following steps: (1) determining whether a given set of two or more molecular components will undergo co-crystallization; (2) identifying the primary intermolecular interactions, e.g., hydrogen-bond motifs that will exist within a particular co-crystal structure; and (3) envisioning the overall packing arrangement in the resulting co-crystal structure⁸. The comparison of the spectrum of a co-crystal to co-added spectra of co-crystal formers represents a quick and easy judgment of co-crystal formation (or otherwise). Researchers suggested that compared to infrared, Raman Spectroscopy would be the technique of choice for rapidly checking co-crystal formation⁵⁸⁻⁶⁴. Scientists demonstrated the potential of supercritical fluid techniques which include [the Co-crystallization with Supercritical Solvent technique, the Supercritical Anti-Solvent technique], and the Atomization and Anti-Solvent technique] as screening methods for co-crystals using indomethacin-saccharin co-crystalline system as model system⁶⁵.

Pure component solubilities determine the concentration regions to screen for new co-crystals, rather than the stoichiometry of the co-crystal. Based on this, new co-crystals of carbamazepine with isonicotinamide, benzamide and 3-nitrobenzamide, and of cinnamic acid with 3-nitrobenzamide have been reported⁶⁶. Scientists described the use of neat and liquid-assisted grinding for screening for hydrated forms of pharmaceutical co-crystals, and liquid-assisted grinding was found less sensitive to the form of the reactant (i.e., hydrate or anhydrate) than neat grinding⁶⁷. Results on pharmaceutical co-crystals construction involving theophylline and caffeine as pharmaceutical ingredients and L-malic or L-tartaric acid as pharmaceutical co-crystal formers showed that co-crystal formation occurred under conditions in which all co-crystal components remain saturated⁶⁸. Scientists reported a pharmaceutical

co-crystal formed between an inorganic acid and an API, which enabled the development of a stable crystalline and bioavailable solid dosage form for pharmaceutical development where otherwise only unstable amorphous free form or salts could have been used⁶⁹. Novel pharmaceutical co-crystal e.g. norfloxacin saccharinate dihydrate and its co-crystal, norfloxacin saccharinate–saccharin dihydrate, were reported⁷⁰. A role for co-crystal formers as hydrogen bond additives that favor and stabilize specific motifs for the crystallization of new polymorphs has been reported for phloroglucinol and phenazine co-crystals of 1:1.5, 1:1.75, and 1:2 stoichiometry⁷¹.

A co-crystal is only expected to form if it is thermodynamically more stable than the crystals of its components. Computational attempts have been made to predict co-crystal formation^{72,73}.

Scientists have observed that liquid-assisted grinding of two enantiomorphous co-crystals resulted in to either formation of a centrosymmetric three-component co-crystal, consisting of the left- and right-handed co-crystal former molecules and the model API or the model API along with the racemic form of the co-crystal former⁷⁴. Grinding together of theophylline and D- or L-tartaric acid produced co-crystals that contained theophylline and the co-crystal former in a 2:1 stoichiometric ratio, wherein caffeine and D- or L-tartaric acid produced co-crystals that contained the two components in a 1:1 ratio⁷⁴. Carboxylic acid co-crystals of fluoxetine hydrochloride provided the opportunity to modify physical properties while retaining the salt form in the co-crystal structure⁷⁵.

MECHANISM FOR CO-CRYSTAL SYNTHESIS

Amorphous phases generated by pharmaceutical processes lead to co-crystal formation during cogrinding and storage.⁷⁶ The mechanisms underlying moisture uptake generated co-crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid) when solid mixtures with co-crystal reactants were exposed to deliquescent conditions involve (i) moisture uptake, (ii) co-crystal aqueous solubility, (iii) solubility and dissolution of co-crystal reactants, and (iv) transition concentration^{7,77}. For carbamazepine: nicotinamide co-crystal synthesis, nucleation and growth of co-crystals were directed by the effect of the co-crystal components on reducing the solubility of the molecular complex to be crystallized⁷⁸.

A molecular-level mechanism for two cases of mechanochemical co-crystallization via halogen bonds was reported and was based on the observation and structural characterization of intermediates that appeared in early stages of the reaction. The mechanism arises from the competition of strong and weak intermolecular halogen bonds of the N...I and S...I type and involves the initial formation of finite molecular assemblies, held together via N...I bonds that subsequently polymerize into infinite chains by cross-linking through S...I bonds⁷⁹. Co-crystallizations of exemestane and megestrol acetate improved initial dissolution rates compared to the respective original crystals. The mechanism of dissolution enhancement varied. With exemestane/maleic acid co-crystal, fine particle formation resulted in enhancement, whereas with megestrol acetate /saccharin co-crystal, enhancement was due to the maintenance of the co-crystal form and rapid dissolution before transformation to the

original crystal⁸⁰.

The mechanisms of conversion of crystalline drugs to co-crystals and factors affecting co-crystal stability were reported. Coformer solution concentration controlled the formation and stability of different stoichiometry co-crystals. Studies with 1:1 and 2:1 carbamazepine-4-aminobenzoic acid co-crystals indicated that the co-crystal richer in coformer was found more stable at higher coformer concentration. Co-crystallization also occurred in solid mixtures of co-crystal reactants. Co-crystals of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with various carboxylic acid cofomers were formed due to moisture sorption and deliquescence in reactant mixtures. In the solid-state, cogrinding carbamazepine with saccharin or nicotinamide formed co-crystals^{6,77,81}.

CHARACTERIZATION OF CO-CRYSTALS

Characterization of co-crystals involves both structure (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction)⁸²⁻⁸⁴ and physical properties (e.g. melting point apparatus, differential scanning calorimetry, thermogravimetric analysis)^{84, 85}. The analytical potential of NIR spectroscopy for co-crystal screening using Raman spectroscopy as a comparative method has been reported⁸⁶. A compound-sparing, automated and 'green' differential scanning calorimetric method was developed for rapid co-crystal screening which demonstrated the formation of carbamazepine - nicotinamide co-crystals⁸⁷. Co-crystals of a phosphodiesterase-IV inhibitor with L-tartaric acid were characterized⁸⁸. Co-crystals of (-)-gossypol with a C₁₋₈ carboxylic acid or C₁₋₈ sulfonic acid which are useful as inhibitors of Bcl-2 family proteins and use of co-crystals of (-)-gossypol with a C₁₋₈ carboxylic acid or C₁₋₈ sulfonic acid for inducing apoptosis in cells and for sensitizing cells to the induction of apoptotic cell death were characterized ((e.g. (-)-Gossypol- acetic acid co-crystals)⁸⁹. Single crystals of the 1:1 co-crystal of piracetam and gentisic acid obtained via slow evaporation from acetonitrile. Co-crystal or prepared via grinding or slurring in water was characterized by IR, melting point, DSC, PXRD and single crystal X-ray diffraction²⁰.

Plots of pH versus solubility were employed to compare the solubility of molecular salts and co-crystals⁹⁰. Mathematical model was developed that describes the solubility of co-crystals by taking into consideration the equilibria between co-crystal, co-crystal components, and solution complexes and was applied to the phase diagrams of carbamazepine/nicotinamide co-crystal in organic solvents. The dependence of co-crystal solubility on solubility product and complexation constants provided a powerful approach to design co-crystal screening methods and to formulate solutions with co-crystal components where crystallization does not occurred⁹¹. A method was developed to estimate the co-crystal solubility in pure solvent and co-crystal solubility was found to be directly proportional to the solubility of constituent reactants for carbamazepine, caffeine, and theophylline co-crystals⁹². The phase transformation of API to co-crystal has been shown to depend on solution and co-crystal chemistry where non-stoichiometric concentrations of co-crystal reactants lead to thermodynamically favorable conditions for co-crystallization. A reaction crystallization method for co-crystal screening and synthesis based on the above principles has been reported as applied to various systems including the generation of co-crystals by moisture sorption

78,91

A new approach to model co-crystal phase diagrams was recently reported and its application to an active pharmaceutical ingredient and glutaric acid co-crystal demonstrated good agreement between calculated and experimental data⁹³. The indomethacin- saccharin co-crystal was formed with carboxylic acid and imide dimer synthons interconnected by weak N-H...O hydrogen bonds showed considerably faster dissolution rate than that of the stable indomethacin gamma-form⁸⁴. Researchers recently reported a stable API-glutaric acid co-crystal having 18-times-greater dissolution rate in water and three-times-higher blood plasma concentrations⁶¹. Co-crystals of the API piroxicam were characterized for many carboxylic acids⁶⁰. The scientists provided the foundation to experimentally assess the thermodynamic stability of a co-crystal with respect to its component forms using data for the carbamazepine–nicotinamide system⁹⁴. Co-crystal formation should generally be predictable by comparing the relative stability of the most stable co-crystal and its pure components found on the computed crystal energy landscapes⁷². The thermodynamically favored structure prediction of the co-crystals of p-aminobenzoic acid with 2,2'-bipyridine, based only on the atomic connectivity of the component molecules and assumed stoichiometry was reported⁹⁵.

The most stable solid form of tiotropium fumarate i.e. a new salt-co-crystal of tiotropium fumarate with fumaric acid structure consisted of matched cations and anions (a salt) together with a nonionized free acid moiety as the co-former (co-crystal), and is unique amongst the large number of tiotropium salts that have been prepared and characterized. The stoichiometry cation/anion/co-former of 2:1:1 corresponded to a simple polymorph of the 1:1 salt, and its identity as a co-crystal has been established by single-crystal X-ray diffraction with some corroborating evidence from the Raman and infrared spectra. A detailed investigation of the bonding and geometry of the three crystalline forms of the fumarate indicated that the hydrogen bonding motifs are very similar, and that conformational differences arising from the packing of the two thiophene rings into the crystal structure is probably important in determining their relative stabilities. A comparison with the structures of other tiotropium salts indicated a correlation of the dihedral angle between the two tiotropium thiophene rings with the stability of the crystal forms⁹⁶. Helical-type of chiral co-crystal of tryptamine and hydrocinnamic acid prepared by crystallization in the presence of different chiral crystals have similar crystal structures, despite spontaneous crystallization itself giving only achiral crystal⁹⁷. Curcumin, the main component of the spice turmeric, has been successfully used as a therapy to treat human multiple myeloma⁹⁸ [76a].and also has shown to possess anti-inflammatory and anti-cancer activities⁹⁹. However, curcumin has extremely poor water solubility and bioavailability. A series of pharmaceutically acceptable co-crystal formers are under investigation to screen for co-crystal formation of curcumin⁹⁹.

NANOCRYSTAL AND NANOPHARMACEUTICAL CO-CRYSTALS

A nanocrystal refers to any nanomaterial with at least one dimension $\leq 100\text{nm}$ and it should be single crystalline^{100,101}. 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 reported¹⁰². Under microwave irradiation, nonlinear optical nanocrystals of aminonitropyridines with benzenesulfonic acids were reported¹⁰³. 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 crystals¹⁰⁴. Nanostructured co-crystals exhibiting single-crystal-to-single-crystal chemical reactivity were constructed by Sonochemistry¹⁰⁵.

POLYMORPHISM OF CO-CRYSTALS

Polymorphism in multi-component crystals is gaining interest in the recent times in the context of pharmaceutical co-crystals. Polymorphs have different stabilities and may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature. In addition, they exhibit different melting points and solubilities which affect the dissolution rate of drug and thereby, its bioavailability in the body. Co-crystal polymorphs suggest additional options to modify properties, increase patent protection, and improve marketed formulations. Co-crystals of 4-hydroxybenzoic acid and 2,3,5,6-tetramethyl-pyrazine (2 : 1) exhibited the first supramolecular synthon polymorphism in a co-crystal; metastable anti-hierarchic polymorph I was converted to stable hierarchic form II¹⁰⁶. Preparation of polymorphic co-crystals I and II (temozolomide: 4,4'-bipyridine-*N,N'*-dioxide (1:0.5 and 2:1) were optimized by using solution crystallization and grinding methods. The metastable nature of co-crystal II was ascribed to unused hydrogen-bond donors/acceptors in the crystal structure¹⁰⁷.

Two polymorphs of carbamazepine-nicotinamide co-crystals and two polymorphs of carbamazepine-saccharin co-crystals were found to be polymorphic¹⁰⁸. Co-crystal polymorphs of carbamazepine and isonicotinamide having 1:1 stoichiometry were reported which were formed through a solvent-mediated transformation process upon suspending a dry mixture of the pure crystalline components in ethanol¹⁰⁹. Two polymorphs of a co-crystal between 2-ethoxybenzamide and saccharin sustained by a carboxamide-imide heterosynthon involving two N-H...O hydrogen bonds were prepared and structurally characterized by single crystal X-ray diffraction. The only metastable Form II was formed in the grinding experiments, whereas both polymorphs were reported by solution crystallization. It is worthy to note that the number of polymorphs of a co-crystal was more than the number of polymorphs of its parent API. The importance of this multiple screening techniques for co-crystal polymorphs sheds light on the ability of the solid-state grinding to produce the metastable polymorph of a co-crystal¹¹⁰. Co-crystals of piroxicam with carboxylic acids were prepared and various groups of co-crystals containing piroxicam and a guest carboxylic acid were differentiated by the piroxicam tautomer present in the co-crystal and the presence or absence of a strong hydrogen bond donor interacting with piroxicam's amide carbonyl group. Further, two 1:1 piroxicam/4-hydroxybenzoic acid co-crystals were found to be polymorphs⁶⁰.

PHARMACEUTICAL CO-CRYSTALS AS INTELLECTUAL PROPERTY

Compared to other classes of solid forms, co-crystals possessed particular scientific and regulatory advantages, and alongside these advantages were intellectual property issues which give co-crystals with unique opportunities and challenges. Researchers reported the importance regarding patents on pharmaceutical co-crystals to the pharmaceutical industry⁸. The value of co-crystals to the pharmaceutical industry should become clearer, mainly with respect to several relevant legal and regulatory issues, as products containing co-crystal technology come out from pharmaceutical development pipelines onto the market.

APPLICATIONS OF CO-CRYSTALS

Compared to other solid-state modification techniques employed by pharmaceutical industry, co-crystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution^{16, 18, 19, 111}. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization⁸.

CONCLUSIONS AND PERSPECTIVES

Pharmaceutical co-crystals represent a 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. Co-crystals – High Throughput gives vital information on relationship between formation and chemical structure of the API and co-former. Screening of API's with library of co-crystal formers requires further investigations to include all possible coformers. Studies regarding polymorphism of co-crystals should be strengthened in order to accelerate the development of new pharmaceuticals. Additional developments in screening methodology will further elevate the profile of co-crystals on the pharmaceutical and intellectual property landscapes.

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