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Pharmaceutical Co-crystal: A New Paradigm for Enhancing the Physicochemical Properties of Active Pharmaceutical Ingredient

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Abstract

Pharmaceutical co-crystal consists of a stoichiometric ration of an Active Pharmaceutical Ingredient (API) and co-crystal former. Researcher from both Pharmaceutical industry and academic has great interest in designing of pharmaceutical co-crystal due to excellent enhancement of Physicochemical Properties of drug. This article focus on Cocrystal best solubility enhancement technique in comparison to other traditional technique, Definition of cocrystal and pharmaceutical cocrystal, Advantages of cocrystal in pharmaceutical industry, Design of pharmaceutical co-crystals, Physicochemical properties of cocrystals, Polymorphism in co-crystals, Mechanical properties improvement via cocrystallisation and finally Example of co-crystal.

Key-Words: Co-Crystals, Physicochemical, Pharmaceutical

Introduction

Active pharmaceutical ingredients (APIs) are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact and generally stable format to store an API or a drug product. Understanding and controlling the solid-state chemistry of APIs, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. 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 profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drug.[1]

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1. Cocrystal best solubility enhancement technique in comparison to other traditional technique:

Biopharmaceutical classification system (BCS) divides all active pharmaceutical ingredients (API) into four classes based on drug dissolution rate and gastrointestinal permeability. BCS class II is defined by drugs of high permeability and low solubility. High permeability is a positive trait of these drugs but low solubility poses a big challenge to formulation scientists.[2] In the pharmaceutical industry, it is the poor biopharmaceutical properties rather than toxicity or lack of efficacy that are the main reasons why less than 1% of active pharmaceutical compounds eventually appear into the marketplace Among these biopharmaceutical properties, solubility remains a key issue with drugs often discarded during commercial production due to their low solubility. Improving the solubility of drugs is currently one of the main challenges for the pharmaceutical industry. Many approaches have been adopted for improving the aqueous solubility of drugs including micronisation, salt formation, emulsification, solubilisations using co-solvents, and the use of polymer drug vehicles for delivery of poorly soluble drugs. Although these techniques have been shown to be effective at enhancing oral bioavailability, success of these approaches is dependent on the specific physicochemical nature of the molecules being studied.[3] The traditional approaches to addressing the issue of poor aqueous solubility (e.g., salt formation,

micronization, solid dispersion formulations) often fail to produce a viable solid form, as the increase in dissolution rate achieved is frequently insufficient to provide adequate enhancement of bioavailability.[4] Over the last decade, there has been growing interests in the design of pharmaceutical cocrystals, which emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility.[3]

2. Definition of cocrystal and pharmaceutical cocrystal

Nate Schultheiss and Ann Newman research group includes the definition of cocrystal given by different authors in their research work as follows

Stahly, G. P. defined cocrystal as "a molecular complex that contains two or more different molecules in the same crystal lattice"

Nangia, A. defined cocrystal as "multi-component solid-state assemblies of two or more compounds held together by any type or combination of intermolecular interactions"

Childs, S. L. defined cocrystal as "crystalline material made up of two or more components, usually in a stoichiometric ratio, each component being an atom, ionic compound, or molecule"

Aakeröy, C. B. defined cocrystal as

"Compounds constructed from discrete neutral molecular species...all solids containing ions, including complex transition-metal ions, are excluded"

"Made from reactants that are solids at ambient conditions"

"Structurally homogeneous crystalline material that contains two or more neutral building blocks that are present in definite stoichiometric amounts"

Bond, A. defined cocrystal as "synonym for multi-component molecular crystal"

Jones, W. defined cocrystal as "a crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions, often including hydrogen bonding"

Zaworotko, M. J. defined cocrystal as "are formed between a molecular or ionic API and a co-crystal former that is a solid under ambient conditions"

However one broad commonality that is agreed upon is that all cocrystals are crystalline materials comprised of at least two different components (or commonly called multicomponent crystals).[5]

The issue of how one defines a cocrystal is a matter of recent debate. Whereas everyone can agree that a cocrystal is a crystalline form that contains more than one compound in the crystal. Shan and Zaworotko research group using a more restrictive operating definition:

"A cocrystal is a multiple component crystal in which all components are solid under ambient conditions when in their pure form. These components co-exist as a stoichiometric ratio of a target molecule or ion and a neutral molecular cocrystal former(s)".[6]

Pharmaceutical co-crystals can be defined as "co-crystal forms composed of a stoichiometric ration of an API and a pharmaceutically acceptable co-crystal former."[4]

Pharmaceutical cocrystals have, however, been defined as 'cocrystals that are formed between a molecular or ionic active pharmaceutical ingredient (API) and a benign cocrystal former that is a solid under ambient conditions'. It has also been suggested that any multi-component system comprising a molecular cocrystal former and an ionic API could simply be classified as a pharmaceutical cocrystal.[7]

3. Advantages of cocrystal in pharmaceutical industry

1. They are emerging as an attractive option to polymorphs, salts, solvates and crystal habit manipulation in dosage form design.
2. When using co-crystals, the bulk material and the physicochemical properties of the API can be modified while still maintaining the intrinsic activity of the drug molecule.
3. From a physical properties perspective, a key advantage of using co-crystals to transform an API into a solid form is the possibility of achieving a high dissolution rate comparable to that of the amorphous form while maintaining the long-term chemical and physical stability that crystalline forms provide. Also, the enhancement of downstream processability and functionality can be achived.
4. Co-crystal formation has several potential advantages over traditional solid-state modification techniques (e.g., salt formation).

a) All types of drug molecules in theory have the capability to form co-crystals; therefore, covalent modification of APIs is unnecessary when using co-crystals.[4]

b) According to the concept of co-crystallization, all types of molecules can form co-crystals, including weakly ionizable and non-ionizable APIs, which is considered to be a better technique in optimization of the physical properties because salt formation is either limited or has no scope at all in such APIs.

c) In case of salt formation due to toxicological reasons only 12 or so acidic or basic counter-ions are explored in a typical API salt screen,

whereas in case of co-crystal screening there are large number of potential co-crystal co-formers which are free from toxicological constraints. The US Food and Drug Administration has maintained a list of substances (e.g., FDA's GRAS list–a list of substances "generally recognized as safe") which is numbering in thousands and can be used as potential cocrystal former for pharmaceutical cocrystals.

5. Diversity shown by pharmaceutical cocrystals alone will afford a number of forms with a variety of cocrystal former which is anticipated to improve physical properties such as solubility, stability, hygroscopicity and dissolution rate etc
6. Isolation and purification of APIs can also be achieved through co-crystallization by discarding the cocrystal former before formulation.[8]

The co-crystal approach can offer valuable advantages for pharmaceutical companies in terms of opportunities for intellectual property protection and the possibility of extending the life cycles of established APIs.[4]

4. Design of pharmaceutical co-crystals:

The design of pharmaceutical co-crystals is a multi-stage process, as schematically illustrated in (Figure1) The key step in this process is the formation of supramolecular synthons non-covalent bonds between self-complementary functional groups.[4]

In order to get a desirable cocrystal product of an API with limited aqueous solubility, the first step is to study the structure of the target API molecule and find out the functional groups which can form intermolecular interaction with suitable coformers. As explained before, these intermolecular interactions include van der Waals contacts, π-π stacking interactions, and the most common interaction in cocrystal structure of the hydrogen bonding. The next step is to choose a cocrystal former. The primary request for a coformer is to be pharmaceutically acceptable, for example, pharmaceutical excipients and compounds classified as generally as safe (GRAS) for use as food additives. Coformer selection is the crucial step for designing a cocrystal. During the design process, there are lots of worthwhile reference resources, including both empirical and theoretical resources, such as Cambridge Structural Database (CSD), hydrogen bond theories, and many empirical conclusions. CSD is valuable tool to study intermolecular interactions in crystals. It can be utilised to identify stable hydrogen bonding motifs, through referring to structural property relationships present in classes of known crystal structures contained in the CSD. A supramolecular library of cocrystal formers has been developed based on the information of CSD, within this library a hierarchy of guest functional groups is classified according to a specific contribution to a crystal packing arrangement, which is dependent on the functionalities contained on the host molecule . As a general guideline, the hierarchy of the supramolecular synthons within a range of common functional groups can be utilised. According to these studies, certain functional groups, such as carboxylic acid, amides, and alcohols are particularly amenable to the formation of supramolecular heterosynthons.[9]

Hydrogen bonds are the basis of molecular recognition phenomena in biological and pharmaceutical systems. They are also key elements in the design of molecular assemblies and supermolecules in the liquid and solid states. In the crystalline state, hydrogen bonds 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 cocrystals).[10]

Because of its strength and directionality, the hydrogen bond has been the most important interaction in cocrystal 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 cocrystal formation.[11]

Etter research group proposed hydrogen bonding are as follows

1. All good proton donors and acceptors are used in hydrogen bonding.
2. Six-membered ring intramolecular hydrogen bonds form in preference to intermolecular hydrogen bonds.
3. The best proton donor and acceptor remaining after intramolecular hydrogen bond formation form intermolecular hydrogen bonds to one another.[12]

pKa can also be used to predict the posiibility of cocrystal formation.[13] Based on Δ p*K*a, it is generally considered that, if the API and its excipient(s) have a ΔpKa (pKa (base) - pKa (acid)) < 0, there will be negligible proton transfer and the molecular complex will be a co-crystal. If the ΔpKa > 3, there will be complete proton transfer resulting in complete ionization and formation of a salt as opposed to a co-crystal.[14] There are many exceptions to the use of ΔpKa method.[13]

Cocrystal screening is an experimental process to determine that a particular coformer candidate is able to cocrystallise with a targeted API. In Cocrystal screening proper coformers could be selected to do scale up experiments. Various screening methods have

been developed for cocrystal screening. Solution method is usefully utilised for cocrystal screening. In solution method small amounts of stoichiometric cocrystal components are dissolved in solvent and then the products are obtained by slow evaporation for testing. Zhang et al. extended the established physical stability treatment for hydrates/solvates to cocrystals with solid coformers to improve the screening efficiency. Based on the proposed treatment, a suspension/slurry cocrystal screening technique was developed and tested in sixteen pharmaceutical cocrystal systems.[15]

Cocrystal characterisation is used to investigate the physical, chemical, and crystallographic properties of Cocrystals. Cocrystal characterisation includes the chemical structural conformation and crystallographic analysis, thermal features, stability and solubility of the newly formed supramolecular synthon. The performance of newly formed compounds is tested in the final step of cocrystal design which includes both in vitro and in vivo tests. In vitro tests include intrinsic dissolution and dissolution tests, while in vivo tests include animal bioavailability measurements, the measurement of the rate and extent of an API that reaches systemic circulation.[16]

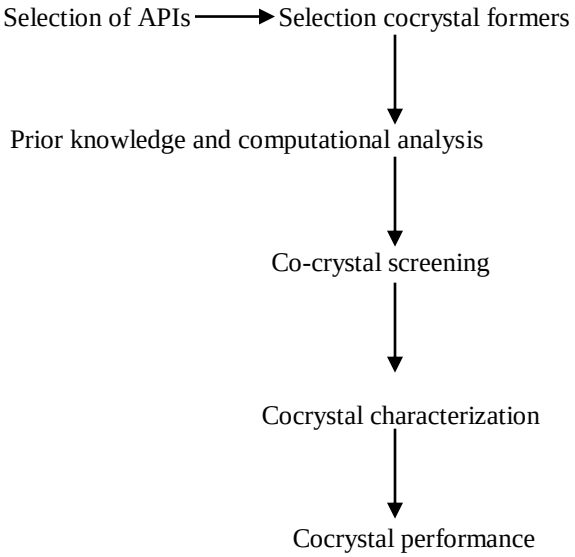


Fig. 1: Schematic of steps for co-crystal design
Abbreviation: API: Active pharmaceutical ingredient

5. Physicochemical properties of cocrystals

The application of molecular complexes and co-crystals in pharmaceutics is driven by the need to improve the physicochemical properties of an active pharmaceutical ingredient (API) during drug development. The overall motivation of examining API co-crystals as an alternative during the drug development is one of physiochemical property adjustment to improve the overall stability and efficacy of a dosage form.[17]

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.[18]

The physical and chemical properties of a cocrystal need to be investigated in the same manner as any other solid form in order to determine developability into a marketed dosage form. Physicochemical properties, such as crystallinity, melting point, solubility, dissolution, and stability, are important when moving a new compound, such as a cocrystal, through early development.

Melting Point

The melting point is a fundamental physical property, which is determined by the temperature at which the solid phase is at equilibrium with the liquid phase. Since melting point is a thermodynamic process where the free energy of transition is equal to zero, the value is determined by the ratio of change in the enthalpy of fusion over the change in the entropy of fusion. If available, differential scanning calorimetry (DSC) is the preferred technique for obtaining comprehensive melting point data, over a standard melting point apparatus or Kofler method, because additional thermal data such as the enthalpy of fusion can be determined. For example, the melting point and heat of fusion, both determined from DSC, are necessary when attempting to characterize a polymorphic pair of compounds as monotropic or enantiotropic. One literature example compares the melting points of 10 cocrystals to the API AMG517 and their respective coformers. Each of the cocrystals displayed a melting point that fell between the melting point of AMG517 and their coformer. the melting point can typically be tuned according to which coformer is chosen; for example, if a higher melting cocrystal is desired, then a higher melting coformer should be selected and vice versa. if any correlation can be drawn, with regard to where the melting point of the cocrystal falls: higher, lower, or in between that of the API and coformer. Melting point is an important consideration during development. High melting points are usually desirable, but may contribute to poor solubility and are as troublesome as low melting points, which can hinder processing, drying, and stability. Correlation of melting points with other development parameters is an ongoing area of study, and the multicomponent nature of the cocrystals will add another level of complexity to these analyses.[5]

Stability

Stability is a very important parameter for evaluating the properties of a pharmaceutical cocrystal. The stability of a newly developed cocrystal is tested by relative humidity stress, thermal stress, chemical stability, and solution stability.

Relative humidity stress

It is used to identify the best storage conditions for the product because the amount of water present in the cocrystal can lead to quality deterioration.[19]Automated moisture sorption/desorption studies are commonly performed to determine problem areas and to provide direction for more detailed studies when the need arises. Limited water sorption/desorption data were found in the literature for cocrystals.[5]

For Example Indomethacin- saccharin cocrystal cocrystals sorbed negligible water (<0.05%); less than the stable form of Indomethacin at 95%RH.[20]

Cocrystal of glutaric acid with 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide is considered non hygroscopic as it sorbs less than 0.08% water even at high humidities (95% RH) through repeated sorption and desorption cycles.[21]

Thermal Stress

High temperature stress is another common condition used to determine chemical and physical stability based on accelerated stability conditions. Very few reports discuss thermal stress experiments on cocrystals. For the cocrystal of a monophosphate salt with phosphoric acid an 8-week exposure at 60 °C resulted in no detectable degradation or form change. These limited reports show that heating studies can provide valuable information about physical and chemical stability.

Chemical Stability

Chemical stability is commonly investigated early in the development of a new compound and during formulation studies in order to minimize any chemical degradation that may occur. Accelerated stability conditions, such as 40 °C/75% RH and 60 °C/75% RH, are commonly used for early studies on solid materials. Very few reports of chemical stability of cocrystals were found when reviewing the literature. In one example, a pharmaceutical cocrystal of a monophosphate salt with phosphoric acid was reported to have no detectable degradation after 8 weeks of storage at 40 °C/75% RH and 60 °C.

Solution Stability

Solution stability for this discussion is defined as the ability of the cocrystal components to stay in solution and not readily crystallize. Solution stability can be an important parameter to assess during development, not only for solutions or suspensions, but also for solid dosage forms that will dissolve in the GI tract.[5]

Solubility

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. In the other words the solubility can also define as the ability of one substance to form a solution with another substance.[22]

Shiraki et al. (2008) tried to improve the solubilities of two APIs, exemestane (EX) and megestrolacetate (MA), in which two novel cocrystals, exemestane/maleic acid (EX/MAL) and megestrol acetate/saccharin (MA/SA), were prepared from organic solutions with different particle sizes. Cocrystallisations of the EX and MA improved initial dissolution rates compared to the respective original crystals. Cocrystal EX/MAL showed a high dissolution rate even with large particles. Cocrystal MA/SA showed supersatura-tion with fine particles .The supersaturated concentration of MA from MA/SA cocrystal at 15 min was about six times greater than the saturated concentration of fine MA and was two times greater within 4 h. The transformation from cocrystal EX/MAL to EX was observed within 1 min in suspension. Cocrystal MA/SA was transformed to MA within 2–4 h, indicting the mechanisms of dissolution enhancement for the two drugs were different. With cocrystal EX/MAL, a fine particle formation resulted in enhancement, whereas with cocrystal MA/SA, enhancement was due to the maintenance of the cocrystal form and rapid dissolution before transformation to the original crystal.[3]

Intrinsic dissolution

Dissolution is the process in which a solid substance gets dissolve in a given solvent i.e mass transfer from the solid surface to the liquid phase.[23] Intrinsic dissolution measures the rate of dissolution without the effect of particle size. This is accomplished by pressing a disk or pellet, commonly using a Woods apparatus in a dissolution vessel. Solution concentration is measured over time to determine the dissolution rate (in $mg/cm^2 \cdot min$). The disk needs to remain intact during the experiment, so compression pressures may be critical for poorly compressible powders. It is also important that there is no form change upon pressing the pellet or during the dissolution study. XRPD data can be obtained on the initial disk and the remaining

disk after completion of the experiment to determine any major form changes that may affect the dissolution data. Intrinsic dissolution is an important parameter to investigate, but it may become more complicated with cocrystals. Various factors need to be considered and extra experiments may be needed to correctly obtain and interpret intrinsic dissolution data on cocrystals.[5]

Example: cocrystal of glutaric acid and 2-[4-(4-chloro-2-fluorphenoxy) phenyl]-pyrimidine-4 carboxamide. Drug 2-[4-(4- chloro-2-fluorophenoxy) phenyl] pyrimidine-4-carboxamide possesses extremely low solubility characteristics (<0.1 mg/ml) in aqueous systems. Use of the cocrystal increased the aqueous dissolution rate by 18 times as compared to the homomeric crystalline form of the drug.[21]

Bioavailability

Bioavailability is a measurement of the rate and extent of the active drug that reaches systemic circulation. Animal bioavailability is an important parameter to consider when preparing new forms of a compound, and studies can be set up in a number of different ways to obtain specific information for development. A limited number of animal bioavailability studies have been reported using cocrystals.[5] Example: cocrystal of glutaric acid and 2-[4-(4-chloro- 2-fluorphenoxy) phenyl]-pyrimidine-4 carboxamide used for bioavailability study. Single dose dog exposure studies confirmed that the cocrystal increased plasma AUC values by three times at two different dose levels.[21]

6. Polymorphism in Co-crystals

Polymorphism is defined by McCrone as "a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state."[24] Polymorphism means that a compound is found in more than one crystalline manifestation which, in turn, indicates that such compounds display a degree of structural flexibility.[25] Polymorphs have different crystal structure and hence show different physical and chemical properties like solubility, stability, hygroscopicity etc.[8] 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.[26]

It was believed that only few co-crystals exist in polymorphic forms, but some recent advances in the field revealed that a good number of co-crystals can show polymorphism. The increasing interest in the pharmaceutical co-crystal development has resulted in an increase in the number of co-crystal polymorphs in recent years.[8] 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 II . 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 structure. Two polymorphs of carbamazepine-nicotinamide co-crystals and two polymorphs of carbamazepine-saccharin co-crystals were found to be polymorphic. 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 ethanol.[26]

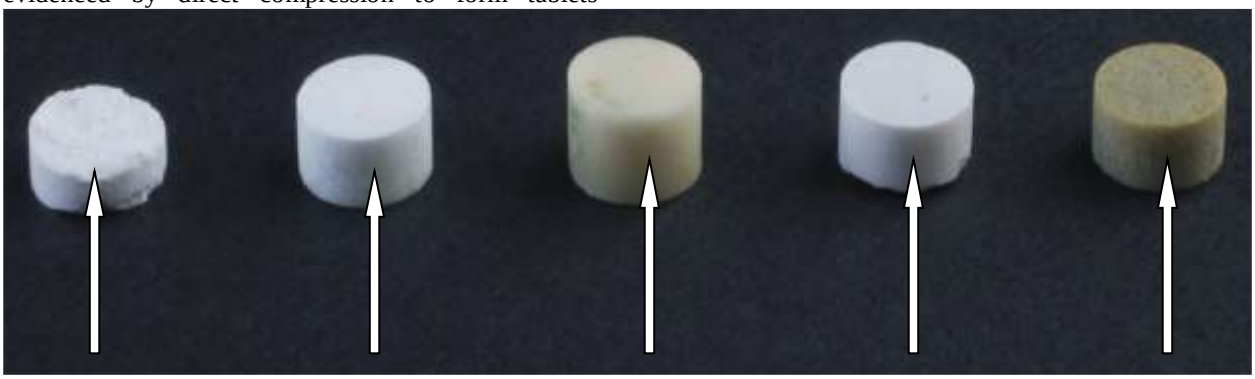
The number of polymorphs associated with a pharmaceutical co-crystal is five for Furosemide: Nicotinamide 1:1 cocrystal and three each for Barbituric acid–Urea 1:1 co-crystal, Pimelic acid–4,4′-Bipyridine co-crystal, and Ethenzamide–Gentisic acid 1:1 co-crystal. Thus, screening of polymorphs and co-crystal characterization is finding importance due to the rise in the number of polymorphs found in the pharmaceutical co-crystals, which may lead to increase in the number of solid forms to look for better physicochemical properties and to keep a check on the undesired form.[8]

7. Mechanical properties improvement via cocrystallisation

The ability to modify the solid-state arrangement of molecules provides a way to control the intrinsic mechanical properties of solids. Such control is paramount in pharmaceutical materials science where it is used to adjust the compression of compounds into tablets. This control was first demonstrated by Sun *et al*. for cocrystals of caffeine and methyl gallate. The cocrystal was demonstrated to have much higher tensile strength and improved tabletting properties compared to either of its constituents in pure form. The improvement in mechanical properties was rationalised by reference to the layered structure of the cocrystal.

The ability to modify the tabletting properties of an API by cocrystallisation has also been demonstrated by Karki *et al*. using the example of paracetamol. Karki and co-workers have successfully constructed three-layered structures of paracetamol as a result of

extensive screening for cocrystals using LAG methodology. Only planar molecules were utilised as potential cocrystal formers, in that way increasing the likelihood of forming a layered material. Paracetamol formed cocrystal with three cocrystal formers oxalic acid, theophylline naphthalene. As verified by measurements and calculations, all three cocrystals based on a layered structure exhibited compression properties superior to those of form 1 of paracetamol, evidenced by direct compression to form tablets (Figure 2). One more cocrystal, of paracetamol with the non-pharmaceutical compound phenazine, was also constructed and demonstrated excellent tabletting properties. Crystal structure analysis demonstrated that (phenazine)2·(paracetamol) consists of molecular assemblies that interact through p-stacking and weaker van der Waals interactions, suggesting an alternative approach for constructing compressible solids.[27]



Paracetamol form1 (a) (b) (c) (d)

Fig. 2: Results of tabletting experiments involving paracetamol form I. (a) Cocrystal with theophylline; (b) cocrystal with naphthalene; (c) cocrystal with oxalic acid; (d) cocrystal with acridine.

8. Example of co-crystal:[4]

Table1. Selected examples of pharmaceutical co-crystal systems reported in the literature

Active pharmaceutical Ingredient	Co-crystal former	Preparation method	Enhanced property
Caffeine	Oxalic acid Glutaric acid	Solvent-assisted grinding	Physical stability
Carbamazepine	Nicotinamide Saccharin	Cooling crystallization	Physical stability Dissolution rate Oralbioavailability
Fluoxetine hydrochloride	Benzoic acid Succinic acid Fumaric acid	Solvent evaporation	Intrinsic dissolution rate
Ibuprofen	4,4-Dipyridyl Nicotinamide	Solvent evaporation	Solubility
Indomethacin	Saccharin	Solvent evaporation or solvent-assisted grinding	Physical stability Dissolution rate
Itraconazole	Malic acid Tartaric acid Succinic acid	Solvent evaporation	Dissolution rate
Norfloxacin	Isonicotinamide Succinic acid Malonic acid Maleic acid	Solvent evaporation	Solubility

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