REVIEW ARTICLE JPAR 2018

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Co-crystals – A Rising horizon for formulating poorly soluble drugs

Parag Das*, Animesh Maity, Uday Kumar Yeluri

Oman Pharmaceutical Products Co. LLC, Muscat, Sultanate of Oman.

Received: 27.06.2018 Revised: 30.07.2018 Accepted: 8.08.2018 Published: 31.08.2018

ABSTRACT: Co-crystallization is nowadays considered as a better alternative to optimize drug properties wherein the molecular interactions and composition of pharmaceutical materials are altered. Co-crystals consist of an Active Pharmaceutical Ingredient (API) and a stoichiometric amount of a pharmaceutically acceptable co-crystal former that together can be termed as a nonionic supramolecular complex. This complex helps in addressing physical property issues such as solubility, stability and bio-availability in pharmaceutical development without changing the chemical composition of the API. Co-crystals can be created through several types of interaction, including hydrogen bonding, pi-stacking and van der Waals forces. Factors affecting co-crystal stability have been well studied, documented and reported. A co-crystal is expected to form if and only if it is thermodynamically more stable than the individual crystals involved during the formation. Physical phenomenon's like that of phase transformations that get induced during processing/storage largely affects the mechanism of conversion of crystalline drugs to co-crystals. Co-crystals could play a major part in the future of API formulation and could be greatly used for chiral resolution and developing novel formulations.

Corresponding author*
Dr. Parag Das
Vice President – Technical
Oman Pharmaceutical Products Co. LLC
Muscat, Sultanate of Oman, Oman.
Mail ID. paragdas@omanpharma.com
Tel No. +96-897044187

Keywords: Co-crystallization, Hydrogen bonding, Pharmaceutical co-crystal, Polymorph, API.

INTRODUCTIONS:

Definition of the term "Pharmaceutical co-crystal" has still not being defined clearly but can be broadly defined as a multi-component compound which has been formed between a molecular or ionic API (Active Pharmaceutical Ingredients). Co-crystals exhibit solid appearance under ambient conditions. Paul Pfeiffer bifurcated co-crystals into two categories based on the nature of the components involved during the crystallization process; firstly, those made of inorganic: organic components, and secondly, those made only of organic components [1].

The inorganic: organic co-crystals would by enlarge include organic molecules co-crystallized with alkali and alkaline earth salts, mineral acids and halogens. A majority of the organic: organic co-crystals contain aromatic compounds with a significant fraction containing di- or trinitro aromatic compounds. Pharmacodynamically, co-crystal former is a supporting molecule (the same applies to salts) to which the GRAS (Generally Recognized as Safe) rules would apply. Nevertheless, even a co-crystal former can be an active molecule. The stoichiometric ratio of API and co-crystal former in a pharmaceutical co-crystal is mostly simple (1:1, 1:2, 1:3 or vice versa). Co-crystals are not necessarily binary compounds; ternary and quaternary co-crystals are known and documented. Co-crystals can be divided into: co-crystal anhydrates, co-crystal hydrates (solvates) and co-crystals of salts (unsolvated, unhydrated or solvated, hydrated). The borderline between salts and co-crystals is very thin and can be differentiated by the location of the proton between an acid and a base. In salts, carboxyl proton is moved to the hydrogen of the base while in co-crystals the proton remains on the carboxyl group of the acid. In cases when 'pK_a = pK_a (base), then pK_a (acid) = 0to 3, the transfer of proton is not clearly defined and we talk about the salt-co-crystal continuum [2-5].

CLASSIFICATION OF SOLID STATE FORMS:

A general subdivision of solid state materials (treating solvates separately from other co-crystals) is summarized in the Fig 1.

In the current scenario, the numerous marketed crystalline salts of active substances which have been often selected over the free acid or base individual components due to the improved stability, solubility profiles and/or bulk physical properties. Co-crystallization would be an economical alternative to salt formation which would have a wide application (i.e. also where salts cannot be formed) as well as a versatile tool that could be used for achieving more appropriate solid state properties [6].

DEFINITION OF CO-CRYSTALS:

Broadly, a pharmaceutical co-crystal can be dined as a single crystalline solid that has been synthesized by the incorporation of two neutral molecules, one being an API and the other being a co-crystal former. A co-crystal former can be an excipient or another drug (GRAS) which would not affect the pharmacological activity of the API but would improve upon the physical properties such as solubility, hygroscopicity, compaction behavior etc [7,8].

Co-crystallization is the outcome of competing molecular associations between similar molecules (homomers) or different molecules (heteromers). Hydrogen bonding is the basis of molecular recognition phenomena in pharmaceutical systems and is responsible for the generation of the 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 [9].

The components in a co-crystal exist in a definite stoichiometric ratio and arrange themselves through non-covalent interactions such as hydrogen bonding, ionic bonding, π-π or van der Waals interactions rather than just by ion pairing. By enlarge, co-crystals are solids at room temperature in their pure state and by convention, these normally excludes salts [9].

Co-crystals may or may not 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 individual pure components. Co-crystals are the most viable or economical alternative to salts when these do not exhibit the appropriate solid state properties or cannot be formed due to the absence of ionization sites in the API.

Co-crystals with the same active pharmaceutical ingredient will have markedly 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 in the past had higher and some lower melting points as compared to their pure entities; for example, succinic acid (m.p. - 135.3 °C) and urea (m.p. - 188.9 °C) whereas the co-crystal of succinic acid-urea (m.p. - 149.9 °C) [10-12].

Various types of studies on co-crystals involve;

- Selection of co-crystal formers for a specific API.
- Co-crystal screening of pharmaceutical active ingredients with selected co-crystal formers.
- Development of reliable procedures to prepare pharmaceutical co-crystals and nano co-crystals.

- Characterization of pharmaceutical co-crystals.
- Scale up of pharmaceutical co-crystals.
- Co-crystal polymorphism.

Pharmaceutical co-crystals have been described for many drugs such as acetoaminophen, aspirin, ibuprofen, flurbiprofen etc. Co-crystals of antitubercular drugs with dicarboxylic acids were reported using carboxylic acid-pyridine synthon as a reliable tool [13].

ADVANTAGES OF CO-CRYSTALS [14-17]:

- 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-crystals.
- Exploring the co-crystallization potential around an API increases the intellectual property protection over a particular drug product; thereby reducing the risk of costly litigation and market erosion.
- With the constantly increasing number of insoluble drug molecules in development pipelines, pharmaceutical companies need for new strategies and approaches that enable the reliable solubility enhancement of APIs for a specific drug delivery system are significantly increasing which can be addressed by co-crystals.
- In addition to efficacy, one desirable attribute of any pharmaceutical product is its cost effectiveness, which co-crystals do provide as a novel tool in formulation development of insoluble molecules.
- Particle size reduction, particularly nano crystallization, is another proven approach to enhance the biopharmaceutical performance of APIs, with at least three oral nanocrystalline products being currently marketed — Rapamune (sirolimus;Wyeth/Pfizer), Tricor (fenofibrate; Abbott Laboratories) and Emend (aprepitant; Merck Co.). The key challenge that hinders widespread commercial implementation of this technology is the potential regrowth of small crystals into larger ones during storage. If inadequately controlled, this phenomenon, also known as Ostwald ripening, may eventually compromise the success of the entire technology.
- The most critical advantage of co-crystallization for dissolution rate enhancement is avoiding a probable conversion - either during manufacturing, storage, or clinical use - from a meta-stable form to a more stable one in an unpredictable manner when compared to traditional API's. For eg.: Itraconazole, an extremely water-insoluble antifungal agent, provides an excellent example in this respect.

Due to failure of finding a suitable crystalline form, amorphous Itraconazole seemed to be the only option and was released to the market as Sporanox (Janssen Pharmaceutica).

More recently, however, it has been discovered that co-crystals of cis-Itraconazole with various carboxylic acids exhibit a higher solubility and a faster dissolution rate compared with those for the free base. Moreover, the dissolution profile of the Itraconazole: L-malic acid co-crystals has matched that of Sporanox.

DIFFERENCE BETWEEN CO-CRYSTAL AND 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 [18].

SALT VERSUS CO-CRYSTAL:

The terms "Co-crystal" and "salts" may be sometimes considered as one due to the thin demarcation between the two. Stressing more upon the borderline difference existing amidst salts and co-crystals, they can be considered as the opposite ends of multi-component structures. Salts are often chosen when it has been well understood and concluded that the free acid or base would not be able to improve upon the crystallinity, solubility and stability of a pharmaceutical compound. Co-crystals are an alternative answer 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 [19].

Salt formation is an acid–base reaction between the API and an acidic or basic substance. 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).

$A\text{-}H + B \rightarrow (A^-)\ (B^+\text{-}H)$ …….(1)

The transfer of proton mainly depends on the pK_a values of the individual components. The general rules for the packing of hydrogen bonded molecules in

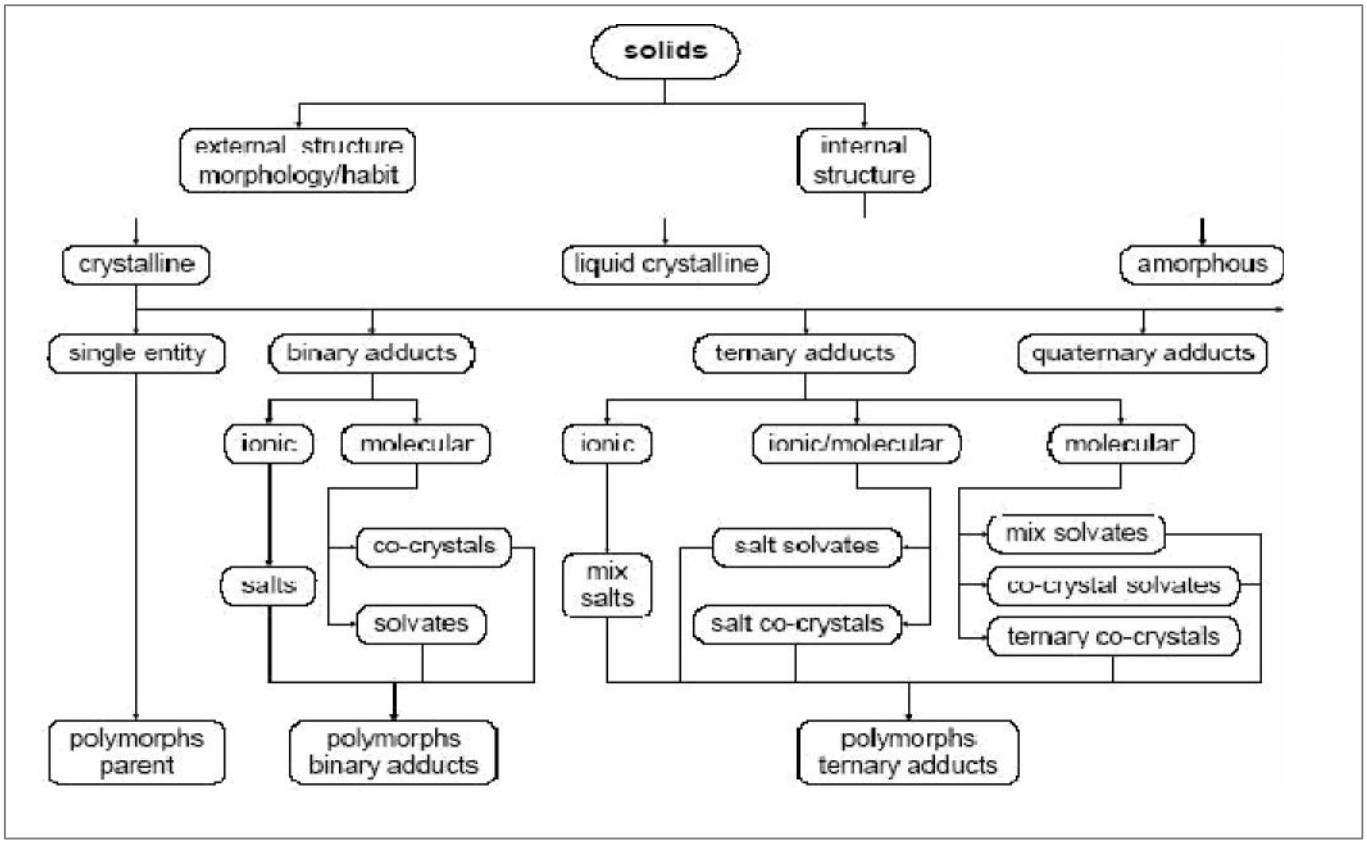

Fig 1. Subdivision of solid state materials.

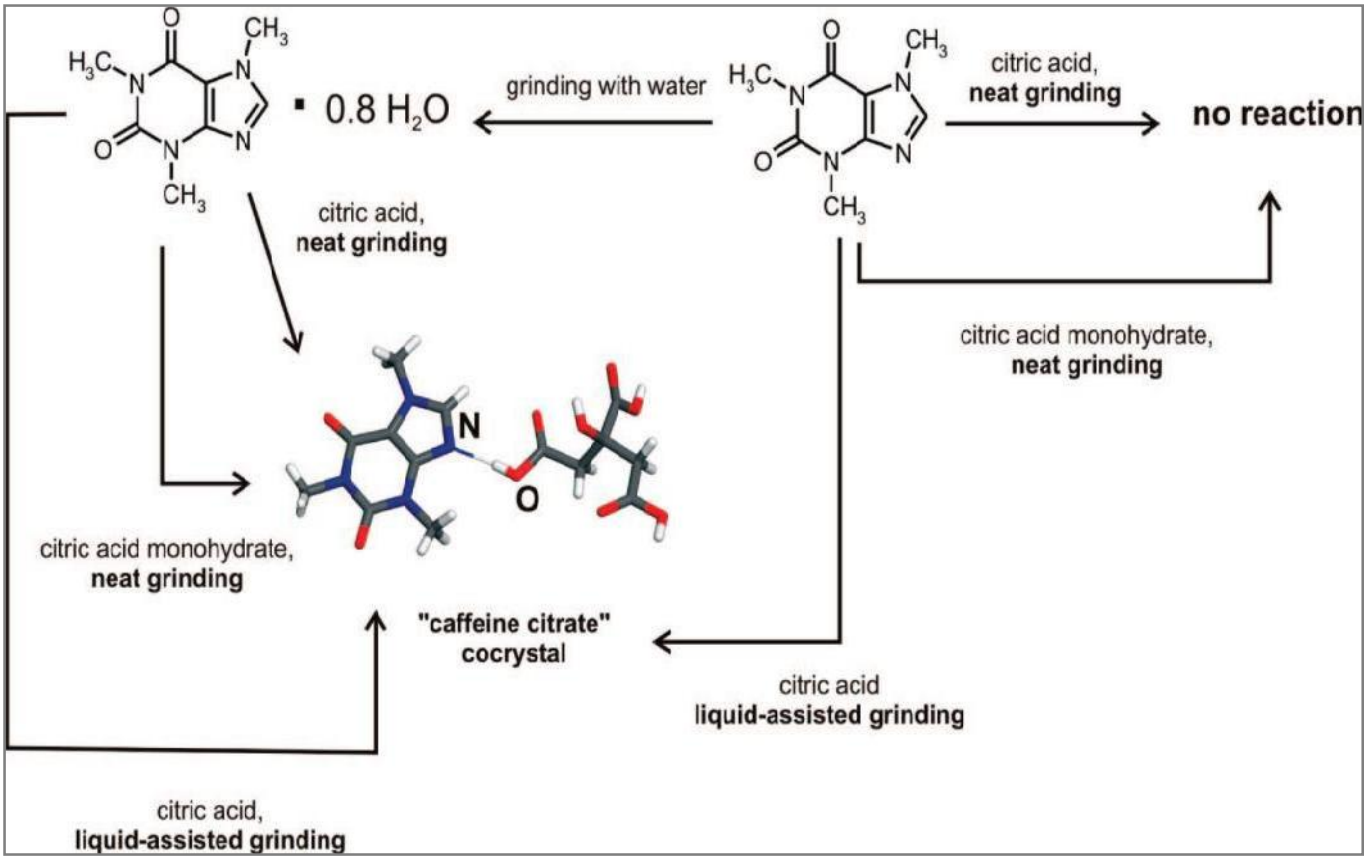

Fig 2. An overview of solid-state reactions of hydrated and non-hydrated forms of caffeine and citric acid.

crystals were developed by Etter. When there is no such transfer of protons and the components present in the crystal are instead neutral entities, the product is generally defined as a co-crystal. Coining in simple ways, a co-crystal is an A-B composite in which no proton transfer has taken place or is not possible.

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 formed. 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.

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 values. 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 used [20-23].

DRAWBACKS OF SALTS:

Salt formation relies on the presence of one or more ionizable functional groups in the molecule, while many APIs and development compounds lack this chemical feature. A prior prediction regarding the existence of a crystalline salt (or salts) of a given compound is impossible [24].

SCREENING OF CO-CRYSTALS:

Co-crystals can be prepared from two molecules of any shape or size having complementary hydrogen bond functionalities. There are many variables which decide the ability of an API to form a co-crystal that are the API co-former ratio, the solvents, the temperature, the pressure and the crystallization technique. Screening of co-crystals formers experimentally is not an easy task and is a significant step and involves a lot of work. Co-crystals can be synthesized by a number of methods, including slow solvent evaporation crystallization from solution, solvent-reduced (e.g. slurrying, solvent-drop grinding) and solvent-free (e.g. grinding, hot melt stage microscopy), high throughput crystallization and co-sublimation techniques [25-28].

Co-crystals can be screened / manufactured by the following methods;

Slow solvent evaporation:

This technique is considered viable only if the potential co-crystal individual components have the solubility in a particular given solvent

Solvent drop grinding:

This technique 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-crystals.

Slurry crystallization: This technique is used in co-crystal screening of two non-ionizable pharmaceutical host compounds. The results of this technique have demonstrated the importance not only of hydrogen bonding but also of geometric fit in co-crystal formation. 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 properties. Scientists reported that liquid-assisted grinding appears to be a more efficient method of screening for co-crystal hydrates. The combinations and variations of the above techniques may be used to cause co-crystal formation. 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. 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 $Z' = 1$. Co-crystal formation between caffeine and adipic acid has been reported utilizing the newly developed co-crystal screening method. 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 forms.

Co-crystal prediction has been reported to include the following steps: (a) determining whether a given set of two or more molecular components will undergo co-crystallization; (b) identifying the primary intermolecular interactions, e.g., hydrogen-bond motifs that will exist within a particular co-crystal structure; and (c) envisioning the overall packing arrangement in the resulting co-crystal structure. 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 formation. 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 system. Pure component solubility's determine the concentration regions to screen for new co-crystals, rather than the stoichiometry of the co-crystal.

METHODOLOGIES FOR THE CHARACTERIZATION OF CO-CRYSTALS:

Characterization of co-crystals involves both structure (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction) and physical properties (e.g. Melting point apparatus, Differential Scanning Calorimetry, Thermogravimetric Analysis). The analytical potential of NIR spectroscopy for co-crystal screening using Raman spectroscopy as a comparative method has been reported. Co-crystal or prepared via grinding or slurring in water was characterized by IR, melting point, DSC, PXRD and single crystal X-ray diffraction.

Plots of pH versus solubility were employed to compare the solubility of molecular salts and co-crystals. 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 occur. 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-crystals. 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

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 data. 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-form. Researchers recently reported a stable API-glutaric acid co-crystal having 18-times-greater dissolution rate in water and three-times-higher blood plasma concentrations.

Curcumin, the main component of the spice turmeric, has been successfully used as a therapy to treat human multiple myeloma and also has shown to possess anti-inflammatory and anti-cancer activities. 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 curcumin [29-32].

SYNTHESIS OF CO-CRYSTALS:

The preparation of co-crystals involves a number of techniques, in gas, liquid or solid phase. The most important is the joint co-crystal growth from solution or joint solid state grinding, often with the addition of a small amount of a "molecular lubricant" (methanol, cyclohexane, chloroform etc.), so-called liquid assisted

grinding. Furthermore, co-crystals can be synthesized by evaporation, sublimation, melting, sonication etc. It often holds that identical starting components may not yield the same product under different co-crystallization techniques.

A multitude of other methods exist in order to produce co-crystals. Crystallizing with a molar excess of one co-crystal former may produce a co-crystal by a decrease in solubility of that one component. Another method to synthesize co-crystals is to conduct the crystallization in slurry. As with any crystallization, solvent considerations are important. Changing the solvent will change the intermolecular interactions and possibly lead to co-crystal formation. Also, by changing the solvent, phase considerations may be utilized. The role of a solvent in nucleation of co-crystals remains poorly understood but critical in order to obtain a co-crystal from solution. The intermolecular interactions and resulting crystal structures can generate physical and chemical properties that differ from the properties of the individual components. Such properties include melting point, solubility, chemical stability, and mechanical properties. Some co-crystals have been observed to exist as polymorphs, which may display different physical properties depending on the form of the crystal [32-35].

As an example of co-crystallization, production of "Caffeine citrate" co-crystal is shown on Fig 2.

The co-crystallization potential of some active molecules is studied in detail, e.g. carbamazepine, itraconazole, piroxicam, norfloxacin, fluoxetin, caffein and others. The reason is to achieve a wide variation in solid-state properties of APIs. These efforts stem from principles of supramolecular chemistry and crystal engineering to affect the properties of API through the "bottom up" approach. This is illustrated in the following examples. By the co-crystallization of antifungal drug itraconazole with 1,4-dicarboxylic acids (succinic acid, L-tartaric acid or L-malic acid) a modification of the dissolution profile is achieved compared to the amorphous form of itraconazole (Sporanox, Janssen-Cilag).

A 1:1 carbamazepine/saccharin co-crystal compared to polymorph III of carbamazepine (Anticonvulsant Tegretol, Novartis) shows no polymorphous behaviour and is not prone to hydration. The co-crystallization of pregabalin with S- mandelic acid separates from the mixture of R and S isomers only the (1:1) co-crystal (S)-pregabalin/(S)-mandelic acid. This technology is used by Pfizer in manufacturing dosage form Lyrica.

The co-crystals of paracetamol show improved tablet formation ability than free paracetamol, polymorph I (Panadol, GlaxoSmithKline). Caffeine tends to form hydrates at high RH (relative humidity) while its co-crystals with oxalic acid or malonic acid do not have this unwanted property (never form hydrates) . However, general trends of variation of properties during the transition from APIs to their co-crystals are not so far evident because fundamental causes of co-crystallization are not known so far [36,37].

NANOCRYSTAL, NANOPHARMACEUTICAL CO-CRYSTALS:

A nanocrystal 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 nanoco-crystals of aminonitropyridines 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. Nanostructured co-crystals exhibiting single crystal to single crystal chemical reactivity were constructed by Sonochemistry [37,38].

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 solubility's 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 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. 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-crystal [27-39].

APPLICATIONS AND EXAMPLES OF CO-CRYSTALS [38-41]:

Among many recent patents relating to potential commercial co-crystal products, the possibility of combining two active ingredients in a single co-crystal is an interesting one and has been claimed in the co-crystallization of quercetin (a plant-derived flavonoid, used as a nutritional supplement and reputed to offer some anti-cancer properties) with antidiabetic agents such as metformin or tolazamide. The combination drug has been suggested to have physical properties and biological activity that are distinct from the individual properties of the two components. Interesting research pointing the way to applications of co-crystals in the modification of drug pharmacological action has been reported for insulin, a peptide hormone used for the treatment of diabetic patients. Insulin has poor oral bioavailability and is commonly injected. Human insulin has been co-crystallized with lipophilically modified, closely related insulin analogue octanoyl-N-LysB29-human insulin. The lipophilic formulation was designed to provide a slow release profile compatible with an improved physiological insulin profile [38,39]. 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. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through co-crystallization.

Light stability:

Light stability is an issue for the drug substance as well as for the drug product as light needs to be controlled or excluded during drug substance synthesis, storage and drug product formulation and storage. Higher light stability could lead to easier formulation and packaging while keeping or improving shelf life time of the product.

Rosuvastatin is a lipid lowering drug substance. It inhibits the HMG-CoA reductase and is formulated as amorphous hemicalcium salt. The amorphous salt is light sensitive. Several crystalline forms of Rosuvastatin hemicalcium are reported. The vanillin co-crystal of Rosuvastatin hemicalcium overcomes the light sensitivity. A remarkable improvement regarding degradation can be detected by HPLC. The new solid state form also shows a good thermal stability and is easy to prepare. Further tests regarding formulation showed that it is directly compressible and an uncoated tablet from a standard dry formulation can be developed.

Hygroscopicity:

Hygroscopicity describes the water uptake when applying different relative humidity. The more hygrosopic the compound the higher the difference in the water content at different relative humidity. APIs that change water content during formulation processes and in the final formulation need to be handled with more care with regard to climate control during production and packaging. Nilotinib is a tyrosine kinase inhibitor. It is used in the treatment of chronic myelogenous leukemia. The drug product is a formulation of the Nilotinib hydrochloride monohydrate. Nilotinib hydrochloride exists in several different solid forms. The selected monohydrate of the API salt is slightly hygroscopic. Hygrospcopicity can be reduced by producing a co-crystal with fumaric acid. The crystal structure proves that in the 1:1 co-crystal of Nilotinib hydrochloride and fumaric acid, Nilotinib is protonated and fumaric acid is neutral. On the basis of hygroscopicity classification of pharmacopoeia, the

hydrochloride salt is slightly hygroscopic whereas the co-crystal of the salt is not hygroscopic. Reduced hygroscopicity simplifies drug substance handling during manufacturing and storage of the drug product; shelf life time may be increased and packaging costs reduced.

Various polymorphic forms:

If different solid forms of the API exist, the producer has to make sure to always obtain and retain the desired form. During formulation and storage the solid form should not change. A special control of the solid form has to confirm the registered form throughout the whole process. Nilotinib hydrochloride exists in several crystalline forms: dihydrate, monohydrates, anhydrates and solvates. A new solid form that does not show polymorphism would be a great advantage. The fumaric acid co-crystal of Nilotinib hydrochloride in all experiments only resulted in one crystalline form. This form is therefore much more stable under various conditions regarding the crystalline form compared to the selected hydrochloride salt.

Solubility related properties: kinetic solubility, dissolution rate and bioavailability:

As mentioned above, low solubility leads to low dissolution rates and bioavailability. APIs with low solubility are bundled in biopharmaceutics classification system (BCS) classes II and IV. Many projects of formulation scientists deal with increasing solubility of these APIs.

Besides its hygroscopic behaviour, the marketed solid form of Nilotinib also shows disadvantageous solubility. Although the Nilotinib hydrochloride salt was selected as API form for the drug product, it has a very low bioavailability. The co-crystal has a much higher dissolution than the hydrochloride salt. The co-crystal also reaches a much higher kinetic solubility which is stable for 2 h, the time of the experiment. This higher solubility is a kinetic effect as the solubility of the pure Nilotinib hydrochloride is lower and crystal seeds of the hydrochloride would lead to crystallization of this crystalline form. However, retaining a metastable solubility for 2 h is sufficient to enhance the absorption of the API due to higher concentration gradient.

REGULATORY CONCERNS AND GUIDELINES:

A key question concerning the practical application of a co-crystal of a commercial API is whether the co-crystal is in some sense a physical mixture and hence might fall within current compendial guidelines, or whether the co-crystal should be regarded as a new chemical entity with all the concomitant safety and toxicological testing such substances require. The USA Food and Drug Administration (FDA) have released draft guidance on the regulatory classification of pharmaceutical co-crystals for applicants for New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs). The FDA defines co-crystals as “solids that are crystalline materials composed of two or more molecules in the same crystal lattice” - the implication is that it is two or more types of molecules that are referred to here [42].

The FDA also regards co-crystals as dissociable “API-excipient” complexes, blurring the boundary between co-crystals and physical mixtures. This guidance has generated a strong response from some researchers in the co-crystal field who propose alternative, yet also potentially controversial definitions that distinguish multi component APIs and their co-crystals from solvates and hydrates [43].

The understanding of co-crystals and other solid state forms of active substances from a regulatory point of view may be of importance for:

- Co-crystals and abridged applications.
- Co-crystals and New Active Substance (NAS) status for applications with such claims.
- Acceptance of different forms in the same marketing authorization.
- Acceptance of an ASMF.
- Applicability of Good Manufacturing Practice (GMP) for active substances or finished products.
- Suitability of co-formers.
- Acceptance of co-crystals containing more than one therapeutic moiety.

Co-crystals and abridged applications:

An abridged application makes reference to the safety and efficacy documentation of an approved reference product containing the same active substance. Directives 2001/83/EC Article 10(2)(b) and 2001/82/EC 13(2)(b) define what can be considered as the same active substance in the context of accepting an abridged application.

Co-crystals, hydrates and solvates are held together by weak interactions that are in most cases broken upon dissolution. This is the same situation as with salts. Hence, with respect to oral administration, dissolution

of such different forms of a drug substance in the stomach or the intestinal canal will lead to the release of the same substance, independent on the form that was taken in. The validity of this assumption is verified by the demonstration of bioequivalence. Co-crystals, hydrates and solvates will therefore be considered eligible for generic applications in the same way as salts are (Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC) unless they differ w.ith respect to safety and/or efficacy. This may also apply to other routes of administration provided that it is possible to show that there is no difference with respect to safety and/or efficacy. Polymorphic forms of a single entity active substance, or of salts, co-crystals, hydrates or solvates, will also be considered eligible for generic applications in the same way [43,44].

Co-crystals and New Active Substance (NAS) status:

To avoid misuse of the benefits of data protection given to new active substances when first receiving a marketing authorization, an assessment is done by the competent authorities to ensure that when an active substance is claimed to be new, it is indeed new. Since co-crystals, hydrates and solvates are held together by weak interactions that are in most cases broken upon dissolution, when such a form, already authorized as a medicinal product in the EU, is administered orally it will expose a patient to the same therapeutic moiety. Just as for salts, they will therefore not be considered as NASs in themselves unless they are demonstrated to be different with respect to efficacy and/or safety. For other routes of administration (e.g. topical, inhalation) the NAS status will be dependent on what is actually the therapeutic moiety at the site of action in comparison to the authorized product [44,45].

Polymorphic forms of a single entity active substance, or of salts, co-crystals, hydrates or solvates, will also not be considered as NASs in themselves. An active substance exposing patients to a new therapeutic moiety compared to already authorize medicinal products in the EU may be considered as NAS independent of whether it is presented as a molecule, a salt or a co-crystal etc [45].

Acceptance of different solid state forms in the same marketing authorization:

The directives (Directives 2001/83/EC Article 10(2)(b) and 2001/82/EC Article 13(2)(b)) list the different forms that are regarded as the same active substance in the context of accepting different forms in the applied product in an abridged application and the reference product. This may also apply to co-crystals, hydrates, solvates as well as polymorphic crystal forms. Not all of these different forms will, however be accepted as alternatives in the same medicinal product. For example, within a single marketing authorization the same salt should always be used. The same applies also to co-crystals, including also solvates.

Under the condition that any difference in, e.g., solubility lacks any clinical significance, it is possible to include forms with different degree of hydration (hydrates, including anhydrous forms) as alternatives in the marketing authorization for a single medicinal product. Any such proposal must be justified and the lack of clinical significance demonstrated, e.g., by comparison of the intrinsic solubility, etc. The relevant sections of the dossier such as manufacturing description and formula, specifications, etc., must take into account the actual forms used. The SmPC may use wording under section 2 that expresses the content without defining the hydrated state. Different crystal forms of the same composition (polymorphic forms) may be accepted as alternatives in the marketing authorization for a single medicinal product provided that any chemical or pharmaceutical differences in properties have no clinical significance. If alternative forms are applied for in one marketing authorization, the relevant specifications for each form must be established [45,46].

Co-crystals and GMP requirements:

According to part II of the European Union (EU) good manufacturing practice (GMP) guide, an active pharmaceutical ingredient (API) is defined as any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. In this context, the term ‘mixture’ refers to cases where the active substance is not a single chemically defined substance (e.g., herbal extracts) and not a mixture of a chemically defined active substance with other active substances or excipients. The blending of active substances or the blending of an active substance with an excipient is not within the scope of this Reflection Paper [47,48].

The formation of co-crystals just like salts is normally subject to compliance with part II of the EU GMP

Guide (active substances) and ICH Q7. If however, in more rare cases where a co-crystal is formed in a step during the drug product manufacturing process such as a wet granulation or hot melt extrusion the formation falls under part I of the EU GMP Guide (finished product), while the part II applies to active component(s) forming the co-crystal [48].

Acceptance of ASMF for co-crystals:

In accordance with Directives 2001/83/EC and 2001/82/EC, the quality documentation of an active substance may under certain conditions be submitted directly from a manufacturer of the active substance to the competent authority in the form of an Active Substance Master File (ASMF). This is further elaborated in the Guideline on Active Master File Procedure (CHMP/QWP/227/02 Rev 3/Corr; EMEA/CVMP/134/02 Rev 3/Corr). In regarding GMP, it can be concluded that it is possible to present a single active substance master file for a co-crystal [48].

Suitability of co-formers:

Many active substances are converted to salts for various reasons and even if many counter ions may be used, in practice the number is limited to only relatively few common species. With co-crystals it is generally considered that for a given active substance there are a larger number of possible co-formers available to tailor the solid state properties wanted[6], although simple, well-known molecules such as succinic acid, saccharin and caffeine are often used in the literature[13]. Just as for any other component of a medicinal product, e.g. excipients or counter ions, co-formers must be pharmaceutically acceptable, i.e. their safety and quality must be ensured. If not used previously in medicinal products within the EU/EEA, they should be justified. This may be documented in the same way as for a novel excipient which may, if applicable, include e.g. cross-references to Community provisions based on toxicological data concerning additives in food stuffs.

Acceptance of co-crystals containing more than one therapeutic moiety:

It may be possible to form co-crystals containing more than one active substance. A medicinal product containing such a solid state form should be applied for as a fixed dose combination. The co-crystals should be characterized from a chemical and pharmaceutical point of view, being the physical material used in the manufacture of the product. The individual active substances must be documented in line with current guidance on fixed dose combinations. The stoichiometry of the co-crystal does not have to be limited to equimolar amounts. A careful justification of the dose ratio of the individual active substances is required since it is determined and restricted by the relative stoichiometry within the co-crystal. Influence of the co-crystallization on the bioavailability of the individual active substances should be discussed. Normally, the strength of the medicinal product must be given as for other fixed dose combinations, i.e. stating the amount of each active substance rather than the amount of the co-crystals [49,50].

The individual active substances of co-crystals with more than one therapeutic moiety may qualify for NAS status if it does not expose the patient for the same therapeutic moiety compared to already authorize medicinal products in the EU [50].

Documentation of co-crystals:

As outlined above, co-crystals and salts share many conceptual similarities and therefore also similar principles for documentation should be applied. All quality-related information should normally be provided in part 3.2.S of the dossier (for veterinary applications in part 2.C). This includes general information, as well as information regarding the manufacture, characterization, and control of the drug substance, reference standards or materials, container-closure system and stability. If desired, and if the prerequisites mentioned are met, the applicant may employ the ASMF procedure. The pharmaceutical acceptability of co-formers must be addressed. In line with ICH Q11, commonly available chemicals employed as co-formers in the co-crystal manufacture would be considered as reagents. However, for more complex or novel co-formers, details of the manufacture, characterization and controls, with cross references to supporting safety data should be provided for them, according to the drug substance format. In these cases, the applicant is encouraged to seek scientific advice on the classification of the co-former from the European Medicines Agency or national competent authorities prior to submission. If a co-crystal is claimed, and to rule out the possibility of the formation of a purely physical mixture of two or more crystalline compounds, the formation of a co-crystal should be unambiguously demonstrated by means of

adequate analytical techniques. Results from more than one technique and an orthogonal approach may be necessary. The (solid state) form of the active substance should be discussed in Module 3.2.P (or veterinary equivalent) in relation to its fate during manufacture of the drug product. Where relevant for product performance, the preservation of integrity of the co-crystal should be evaluated and if appropriate experimentally confirmed [50,51].

CONCLUSION:

Co-crystallization is a viable alternative to salt formation as well as a versatile tool that can be used to achieve more appropriate solid state properties. From a scientific point of view, solvates including hydrates can be considered as a subgroup of co-crystals; nevertheless the regulatory context may sometimes differ. Co-crystals and salts share many conceptual similarities and therefore also similar principles for documentation should be applied. In case of a complex co-former additional documentation may be required; a scientific advice procedure is recommended.

ACKNOWLEDGEMENT:

Authors wish to thanks all the Organizations who had helped in Literature survey study for successful completion of this review article.

REFERENCES:

1. Stahly GP. A Survey of Co-crystals Reported Prior to 2000. Crystal Growth & Design, 2009; 9(10): 4212-4229.
2. Ranjit T, Amit D, William J, Maya PL, Lilly Roy. Pharmaceutical co-crystals and poorly soluble drugs. Int J Pharm, 2013; 453(1): 101-125
3. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. J Pharm Sci, 2006; 95(3): 499-516.
4. Friscic T, Jones W. Recent Advances in Understanding the Mechanism of Co-crystal Formation via Grinding. Crystal Growth & Design, 2009; 9(3): 1621-1637.
5. Morissete SL, Almarsson O, Peterson ML, Remenar J, Read M, Lemmo A, *et al*. High-throughput Crystallization: Polymorphs, Salts, Co-crystals and Solvates of Pharmaceutical Solids. Adv Drug Deliv Rev, 2004; 56: 275-300.
6. Hickey MB, Peterson ML, Scoppettuolo LA, Morisette SL, Vetter A, Guzman H, *et al*. Performance comparison of a co-crystal of carbamazepine with marketed product. Eur J Pharm Biopharm, 2007; 67: 112-119.
7. Harry GB. Co-crystal Systems of Pharmaceutical Interest 2011. Cryst Growth Des, 2012; 12: 5823-5832.
8. Jonathan WS. The role of co-crystals in pharmaceutical design. Trends in Pharmacol Sci, 2013; 34(3): 185-190.
9. Shan N, Zaworotko MJ. The role of co-crystals in pharmaceutical science. Drug Discovery Today, 2008; 13: 440-446.
10. Trask AV, Motherwell WDS, Jones W. Physical stability enhancement of theophylline via co-crystallization. Int J Pharm, 2006; 320:114-123.
11. Jones W, Motherwell WDS, Trask AV. Pharmaceutical co-crystals: An Emerging approach to physical property enhancement. MRS Bull, 2006; 31: 875-879.
12. Zaworotko M. Crystal engineering of co-crystals and their relevance to pharmaceuticals and solid-state chemistry. Acta Cryst, 2008; A64: C11-C12.
13. Sun CC, Hou H. Improving mechanical properties of caffeine and methyl gallate crystals by Co-crystallization. Cryst Grow Des, 2008; 8:1575-1570.
14. Rodríguez-Hornedo N, Nehm SJ, Jayasankar A. Cocrystals: design, properties and formation mechanisms. In: Encyclopedia of Pharmaceutical Technology. 3rd ed. London: Taylor & Francis; 2007. pp. 615-635.
15. Aakeroy CB, Fasulo ME, Desper J. Cocrystal or salt: Does it really matter? Mol Pharma, 2007; 4: 317–322.
16. Trask AV. An overview of pharmaceutical co-crystals as intellectual property. Mol Pharma, 2007; 4: 301–309.
17. Jayasankar A, Somwangthanaroj A, Shao ZJ, Rodrıguez-Hornedo N. Co-crystal formation during co-grinding and storage is mediated by amorphous phase. Pharm Res, 2006; 23: 2381-2392.
18. Aakeroy CB, Salmon DJ. Building co-crystals with molecular sense and supramolecular sensibility. Cryst Eng Comm, 2005; 7: 439-448.
19. Miroshnyk I, Mirza S, Sandler N. Pharmaceutical co-crystals–an opportunity for drug product enhancement. Expert Opin Drug Del, 2009; 6: 333-341.

20. Schultheiss N, Newman A. Pharmaceutical co-crystals and their physicochemical properties. Cryst Growth Des, 2009; 9: 2950-2967.
21. Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ. Pharmaceutical co-crystals. J Pharm Sci, 2006; 95: 499-516.
22. Remenar JF, Morissette SL, Peterson ML, Moulton B, MacPhee JM, *et al*. Crystal engineering of novel co-crystals of a triazole drug with 1,4-dicarboxylic acids. J Am Chem Soc, 2003; 125: 8456-8457.
23. Peterson ML, Hickey MB, Zaworotko MJ, Almarsson O. Expanding the scope of crystal form evaluation in pharmaceutical science. J Pharmacy Pharm Sci, 2006; 9(3): 317-326.
24. Mc Namara DP, Childs SL, Giordano J, Iarriccio A, Cassidy J, *et al*. Use of a glutaric acid co-crystal to improve oral bioavailability of a low solubility API. Pharma Res, 2006; 23: 1888-1897.
25. Sarma B, Reddy LS, Nangia A. The role of π-stacking in the composition of phloroglucinol and phenazine cocrystals. Cryst Growth Des, 2008; 8: 4546-4552.
26. Stahl PH, Wermuth CG, editors. Handbook of pharmaceutical salts: properties, selection, and use. New York: Wiley-VCH; 2002. pp. 374-380.
27. Serajuddin ATM. Salt formation to improve drug solubility. Adv Drug Del Rev, 2007; 59: 603-616.
28. Etter MC. Resolution of chiral olefinic hydrocarbons and sulfoxides by high-performance liquid chromatography via diastereomeric platinum complexes. J Am Chem Soc, 1982; 104: 1095-1096.
29. Whitesides GM, Wong AP. The intersection of biology and materials science. MRS Bull, 2006; 31: 19-27.
30. Trask AV, Jones W. Crystal engineering of organic co-crystals by the solid-state grinding approach. Top Curr Chem, 2005; 254: 41-70.
31. Shekunov BY, York P. Crystallization processes in pharmaceutical technology and drug delivery design. J Cryst Growth, 2000; 211: 122-136.
32. Morissette SL, Almarsson O, Peterson ML, Remenar JF, Read MJ, Lemmo AV, *et al*. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Adv Drug Del Rev, 2004; 56: 275-300.
33. Blagden N, De Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Del Rev, 2007; 59: 617-630.
34. Caira MR. Sulfa drugs as model co-crystal formers. Mol Pharm, 2007; 4: 310-316.
35. Karki S, Friscic T, Jones W, Motherwell WDS. Screening for pharmaceutical co-crystal hydrates via neat and liquid-assisted grinding. Mol Pharm, 2007; 4: 347-354.
36. Velaga SP, Basavoju S, Boström D. Norfloxacin saccharinate–saccharin dihydrate co-crystal – A new pharmaceutical co-crystal with an organic counter ion . J Mol Struct, 2008; 889: 150-153.
37. Karamertzanis PG, Kazantsev AV, Issa N, Welch GWA, *et al*. Can the formation of pharmaceutical co-crystals be computationally predicted? Crystal structure prediction. J Chem Theory Comput, 2009; 5: 1432-1448.
38. Jayasankar A, Good DJ, Rodríguez-Hornedo N. Mechanisms by which moisture generates co-crystals. Mol Pharm, 2007; 4: 360-372.
39. Cincic D, Friscic T, Jones W. A stepwise mechanism for the mechanochemical synthesis of halogen-bonded co-crystal architectures. J Am Chem Soc, 2008; 130: 7524-7525.
40. Basavoju S, Bostrom D, Velaga SP. Indomethacin-saccharin co-crystal: Design, synthesis and preliminary pharmaceutical characterization. Pharm Res, 2008; 25: 530-541.
41. Alleso M, Velaga S, Alhalaweh A, Cornett C, Rasmussen MA, *et al*. Near-Infrared Spectroscopy for cocrystal screening. A comparative study with Raman Spectroscopy. Anal Chem 2008; 80:7755–7764.
42. Lu E, Rodríguez-Hornedo N, Suryanarayanan R. A rapid thermal method for cocrystal screening. Cryst Eng Comm, 2008; 10: 665-668.
43. Ainouz A, Authelin JR, Billot P, Lieberman H. Modeling and prediction of co-crystal phase diagrams. Int J Pharm, 2009; 374: 82-89.
44. Schartman RR. On the thermodynamics of co-crystal formation. Int J Pharm, 2009; 365: 77-80.
45. Pop M, Sieger P, Cains PW. Tiotropium fumarate: an interesting pharmaceutical co-crystal. J Pharm Sci, 2009; 98: 1820-1834.
46. Handler N, Jaeger W, Puschacher H, Leisser K, Erker T. Synthesis of novel curcumin analogues and their evaluation as selective cyclooxygenase-1

(COX-1)inhibitors. Chem Pharm Bull, 2007; 55: 64—71.
47. Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharma Biopharm, 2006; 62: 3-16.
48. Butar DK, MacGillivray LR. Preparation and reactivity of nanocrystalline co-crystals formed via sonocrystallization. J Am Chem Soc, 2007; 129: 32–33.
49. Sreekanth BR, Vishweshwar P, Vyas K. Supramolecular synthon polymorphism in 2 : 1 co-crystal of 4-hydroxybenzoic acid and 2,3,5,6 – tetramethylpyrazine. Chem commun, 2007; 3375-3377.
50. Badu N J, Reddy SL, Aitipamula S, Nangia A. Polymorphs and polymorphic co-crystals of temozolomide. Chem Asian J, 2008; 3:1122–1133.
51. Aitipamula S, Chow PS, Tan RBH. Dimorphs of a 1:1 co-crystal of ethenzamide and saccharin: solid-state grinding methods result in metastable polymorph. Cryst Eng Comm, 2009; 11: 889-895.

Conflict of Interest: None
Source of Funding: Nil

Paper Citation: Das P, Maity A, Yeluri UK. Co-crystals – A Rising horizon for formulating poorly soluble drugs. J Pharm Adv Res, 2018; 1(6): 292-305.