



## PHARMACEUTICAL CO-CRYSTAL: AN EMERGING APPROACH TO IMPROVE PHYSICAL PROPERTY

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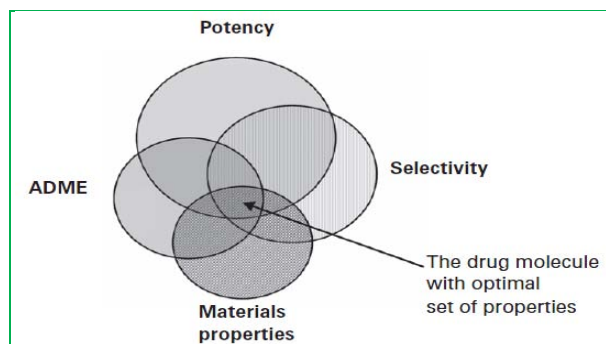
### ABSTRACT

Pharmaceutical co-crystals are nonionic supramolecular complexes and can be used to altered physical property issues such as solubility, stability and bioavailability in pharmaceutical development without affecting chemical composition of API. co-crystal comprising of API and desired stoichiometric acceptable co-crystal that can be made by various types of interaction like hydrogen bonding, pi-stacking and Vander wall forces. Pharmaceutical co-crystal is more thermodynamically stable than crystal form of drugs. The recent advancement in the co-crystal development arises the possibility to produce material by designing with an improved physical property.co-crystal not only provide a technique for improvement of physiochemical property but also provide opportunity to the researchers of pharmaceutical companies regarding intellectual property.co-crystal approach especially used to enhance the specific properties of pharmaceutical solids such as dissolution rate of poorly water soluble API and the physical stability of moisture liable APIs. Cocrystallization property creates opportunity for polymorphs, hydrate and also for salt selection. The various factors which will affect co-crystal stability will be taken in consideration and can be managed with the help of crystal engineering and thermodynamically stable product only accepted. Phase transformation during processing affect the mechanism of conversion of crystalline drugs to co-crystal.

**Keywords:** Co-crystallization, Heterosynthion, Hydrogen bonding, Supramolecular synthesis, Polymorphism.

### 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<sup>1</sup>. The ability to deliver the drug to the patient in a safe, efficient and cost-effective manner depends largely on the physico chemical properties of the active pharmaceutical ingredient(API) in the solid state (**Figure 1**). This provides a significant driving force for inventing new approaches to designing pharmaceutical solid materials with specific physicochemical properties<sup>2-3</sup>. In the last years, crystal engineering of APIs through co-crystallization has gained an increased interest as means of optimizing the physical properties and/or stability of solid dosage forms.

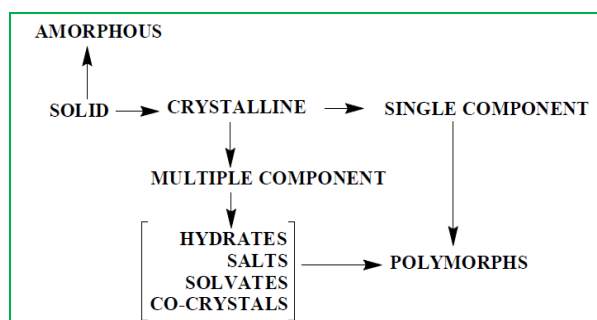


**Figure 1:** A simplified schematic overview of the properties vital for a successful drug candidate (adapted from Gardner et al 2004).

Co-crystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions (primarily hydrogen bonding)<sup>4-5</sup>. The formation of pharmaceutical co-crystals involves incorporation of a given API with another pharmaceutically acceptable molecule in the crystal lattice. The resulting multi-component crystalline phase will maintain the intrinsic activity of the parent API. The key benefits associated with co crystallization approach to modifying properties of pharmaceutical solids including weakly ionizable and non-ionizable, to form co crystals, and the existence of numerous potential counter-molecules, including food additives, preservatives, pharmaceutical excipients as well as other APIs, for co-crystal synthesis. Additional valuable advantages that co-crystal formation may offer for the pharmaceutical industry are the opportunity of intellectual property (IP) protection and the possibility of extending the life cycles of old APIs<sup>6</sup>.

Pharmaceutical co-crystals possess the unique feature that beneficially distinguishes them from any other solid state form — polymorphs, salts, solvates or amorphous solids (**figure 2**)<sup>7-8</sup>. Explicitly, these multicomponent assemblies can be designed by employing crystal engineering strategies, which opens enormous possibilities for pharmaceutical developers in terms of tailoring the physical and material properties for the target drug<sup>9-10</sup>. The most comprehensive list of the key attributes of pharmaceutical co-crystals as a solid state form of APIs.





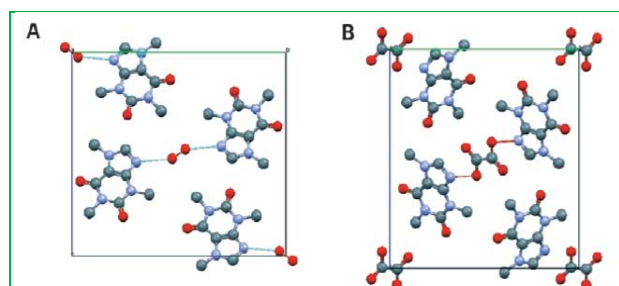
**Figure 2:** API solid form classification based on structure and composition.

Co-crystals incorporate pharmaceutically acceptable molecules into a crystal lattice along with the API. Co-crystals have regained attention as attractive alternate solid forms for drug development. Physicochemical properties of solid drug can be improved by obtaining co-crystals using co-crystallization<sup>11-12</sup>.

Co-crystallization with pharmaceutically acceptable compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior<sup>13</sup>.

#### DIFFERENCE BETWEEN CO-CRYSTAL AND SOLVATES

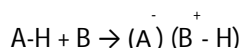
The main difference between co-crystal and solvates is the physical state of compound if one component is a liquid at room temperature, the crystals are designated as solvates; if both components are solids at room temperature, and the crystals are designated as co-crystals (**figure 3**)<sup>14-15</sup>. According to a recent analysis by SCCI, the solid-state chemistry polymorph screens of 245 compounds revealed that about 90% of them exhibit multiple solid forms. Overall, half the compounds were polymorphic, often having one to three forms. About one-third of the compounds formed hydrates, and about one-third formed solvates. Data from co-crystal screens of 64 compounds showed that 60% formed co-crystals other than hydrates or solvates.



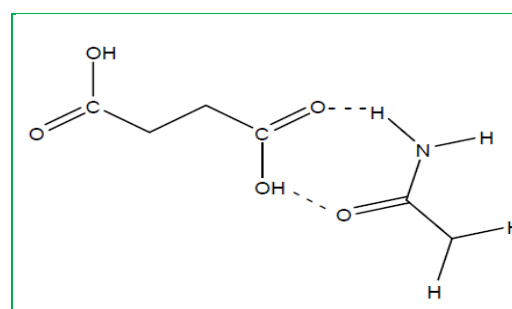
**Figure 3:** Example of two-component caffeine crystals, the monohydrate (A) and the co-crystal with oxalic acid (B). The unit cells of the crystals viewed along the a-axis is shown. The hydrate incorporates the solvent (water) molecule in the crystal lattice, while the co-crystal consists of two solid compounds. Note that in both structures, the same hydrogen bridges (shown by dotted lines) are involved to connect the host (caffeine) with guest (water or oxalic acid) molecules.

#### DIFFERENCE BETWEEN CO-CRYSTAL AND SALT

The fundamental difference between a salt formation and a co-crystal is very important for pre-formulation activities and chemical/pharmaceutical development drugs. salts and co-crystals can be considered as opposite ends of multi-component structures.<sup>16-17</sup> Salt are often chosen in case of the free acid or base as these can improve crystalline, solubility and stability of a pharmaceutical compound. Co-crystals are an alternative to salts when these do not have the proper solid state properties or cannot be formed due to the absence of ionizable sites in the API. 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<sup>+</sup>) from an acid (A) to base (B).



Salt formation is an acid–base reaction between the API and an acidic or basic substance and large number of crystalline salts of APIs are available in market<sup>18-19</sup>. The formation of a salt or co-crystal can be predicted from pKa value of acid (A) and a base (B). Salt formation generally requires a difference of about 2.7 pKa units between the conjugate base and the conjugate acid (A) i.e. [pKa (base) - pKa (acid) ] ≥ 2.7]. For example, succinic acid having pKa 4.2 form co-crystal with urea base (pKa 0.1) while succinic acid form salt with L-lysine base having pKa9.5. Generally base pKa values are not sufficiently high to allow proton transfer when co-crystal is formed<sup>20</sup>. 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 4**).



**Figure 4:** Structure of co-crystal of succinic acid-urea.

#### POLYMORPHISM OF CO-CRYSTAL

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. Two polymorphs of

carbamazepine-nicotinamide co-crystals and two polymorphs of carbamazepine-saccharin co-crystals were found to be polymorphic<sup>21</sup>. 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<sup>22</sup>. 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 polymorphs: Two polymorphs of a co-crystal between 2-ethoxybenzamide<sup>23</sup> and saccharin sustained by a carboxamide-imide Hetero synthon involving two N-HO 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-crystal.

### COCRYSTALLIZATION

Generally it involves the slow evaporation of solutions with equimolar or stoichiometric concentrations of the components. In this process, there's always the risk of crystallizing only the single components.

In analogy to precipitating salts by changing the pH, conditions developed under which co-crystals become less soluble and form from solutions or other wet phases.<sup>24-25</sup> It has shown mathematically how solubility depends on the equilibrium between the co-crystal and its components. Based on this solubility behavior, her group has been able to rapidly generate carbamazepine-nicotinamide and other co-crystals by reaction crystallization. The process entails either mixing solutions of the reactants to achieve nonstoichiometric amounts or dissolving a nonstoichiometric excess of one in a solution of the other.

At a certain point, the mixture is supersaturated with respect to the co-crystal complex, which precipitates out because it is less soluble than the reactants. Nonstoichiometric concentrations and supersaturation can also be achieved in small quantities of solvent by using solid reactants with different dissolution rates. The ability to change the thermodynamic relationship between the co-crystal phase and pure API crystal is valuable to control co-crystal formation and stability. In solvents where the co-crystal is more soluble than the pure API, the reaction can be reversed to form the co-

crystal by increasing the concentration of the co-crystal former above a critical value.<sup>26</sup> These methods work in both organic and aqueous solvents, although both components must be at least somewhat soluble. Test of methanol, ethanol, and water.

The methods are also easily scaled up, applicable to high-throughput crystallization screens, and offer prospects for greener synthetic routes. To test stability it was found that moisture, simply from the air, facilitates co-crystal formation in physical mixtures that contain a deliquescent component, which dissolves as it absorbs moisture in the air. Co-crystal ingredients dissolve in this deliquesced solution and then co crystallizes. It increase molecular mobility via amorphous phases made during grinding. For example the physical stability of caffeine and the asthma drug theophylline could be increased in co-crystals with oxalic acid.<sup>27</sup>

The factors which affect drug formulation frequently involve mechanical stress from grinding, milling, or blending. And products may be exposed to different levels of humidity during storage. These changes could either induce co-crystal formation or lead to degradation. The driver behind making co-crystals is, of course, to improve upon the properties of an API, for example, co-crystals with an ionizable guest can impart pH solubility dependence to nonionizable APIs. "It offers the possibility of tailoring the pH dependence of the dissolution. For many years, crystal engineering focused on optical and mechanical properties of materials. Ongoing study in our laboratory demonstrates that co-crystal formation of theophylline with capric or stearic acid can be a promising approach to enhance physical stability of this moisture-labile API.

### NANOPHARMACEUTICAL CO- CRYSTAL

A nanocrystal refers to any nanomaterial with at least one dimension  $\leq 100\text{nm}$  and it should be single crystalline<sup>28</sup>. 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<sup>29</sup>. Under microwave irradiation, nonlinear optical nanocrystals 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.<sup>35</sup> Nanostructured co-





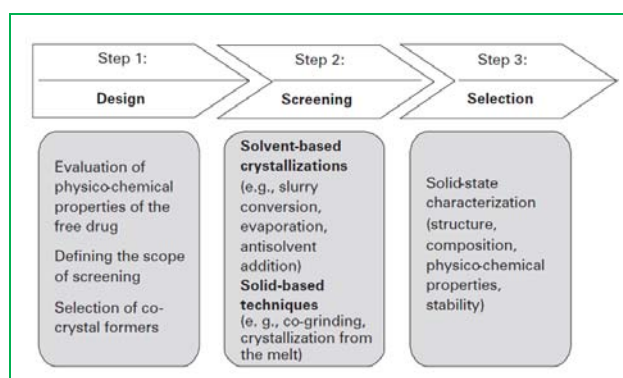
crystals exhibiting single-crystal to-single-crystal chemical reactivity was constructed by Sonochemistry.

### SCREENING OF CO-CRYSTAL

The ultimate goal of co-crystal screens is to discover a solid form of an API with improved physical properties. From this perspective, an efficient co-crystal screening protocol can be split into three phase:

- (1) Co-crystal design.
- (2) Co-crystal screening.
- (3) Co-crystal selection.

A general guideline for co-crystal screening is schematically presented in (Figure5).



**Figure 5:** A general guideline for co-crystal design and screening.

A distinguishing feature of co-crystals, as compared to other crystalline forms of APIs, is that these multicomponent systems are susceptible to design by crystal engineering consequently, an important initial step in co crystal screening is the selection of co-crystal formers from supramolecular libraries of co-crystallizing agents<sup>30</sup>. Like in polymorph screens, the major experimental techniques to generate co-crystals are solution based crystallization methods especially solvent evaporation and slurry conversion.

It should be emphasized; however that solid-based approaches (e.g., neat grinding and liquid-assisted grinding) have been proved to be a viable synthetic method for pharmaceutical co-crystals<sup>31</sup>. Moreover, in a number of instances co-crystal synthesis by employing solid-based techniques offers enhanced selectivity as compared with that of solution crystallization.

For example, in a model system of co-crystals with caffeine and several monocarboxylic acids, neat grinding generated polymorphs, which were initially inaccessible from solution. Liquid-assisted grinding involves co-grinding of two or more materials with the addition of a minor quantity of solvent, which plays a catalytic role and thus further enhances selectivity of the solid-state synthesis<sup>32</sup>. In the final stage of the screen, the co-crystals are characterized and their properties are compared with other possible solid state forms (free API, salt, hydrate) to ensure that the best form will be selected for further

development. 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.
- (3) 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.

Researchers suggested that compared to infrared, Raman Spectroscopy would be the technique of choice for rapidly checking co-crystal formation<sup>33</sup>. 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<sup>34</sup>.

### CONCLUSION

Co-crystals are new aspect for pharmaceutical industries and provides new ideas to deal with poorly soluble drugs. Co-crystals have the potential to be much more useful in pharmaceutical product than solvates or hydrates. Future research also focused on the scale-up of co-crystal system and implement manufacturing of final dosage form on commercial scale. Studies regarding polymorphism of co-crystals provide stringent in order to accelerate the development of new pharmaceuticals. A future challenging aspect is related to the development of efficient co-crystals screening technologies. This can be achieved by implementation of solid based techniques need grinding and liquid assisted grinding. A key advantage of co-crystal as a solid form of API is possibility of achieving the high dissolution rate comparable to that of amorphous form.

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