

# Applications of Co-Crystals in Pharmaceutical Drugs

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## ABSTRACT

Co-crystal synthesis has become a field of high interest in the last decade. This category of solid forms has a variety of applications in industries such as textile, paper and electronics. For many purposes co-crystals will have superior properties in comparison to traditional salt crystals. This review article will focus on the application of co-crystals in pharmaceutical drugs. Co-crystals have opened doors to rein-troduce previously poor performing bioactive ingredients in new and improved solid structures. They have also allowed for the introduction of a new range of compounds for pharmaceutical therapy. Most importantly, co-crystals can create new medicines with increased solubility and hence improve the efficiency and safety of the treatment.

**Key words:** Co-crystal, Solid state characterization, Solubility, Stability, Xrd, Moisture.

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## INTRODUCTION

The exact definition of a co-crystal is debated, but it can be defined as a crystalline compound in which two or more neutral molecular components are present in a definite stoichiometric ratio.<sup>1</sup> By this consideration, a co-crystal differs from a salt crystal because the latter contains cationic and anionic components in arrangement. Co-crystals and salt crystals can be viewed as end points of a continuum with no definite borderline between the two.

Most co-crystal design strategies are based on strong hydrogen bonds.<sup>2</sup> It is therefore a possibility that the proton involved in the hydrogen-bonding will be transferred from the acid to the base. To determine whether or not a co-crystal or salt crystal is formed, the pKa-value is often considered. As a rule of thumb, a difference in pKa between the acid and the acid of the conjugate base greater than 3 units will form a salt, otherwise it will form a co-crystal.<sup>3</sup> Figure 1 displays a co-crystal formed by hydrogen bonding.

*Pharmaceutical co-crystals* contain at least one API (active pharmaceutical ingredient) and one or several secondary components called crystal co-formers. The API can be a wide range of compounds, like caffeine acting as a psychoactive drug or piracetam to treat epilepsy. The co-former is an organic compound, often a carboxylic acid, amino acid, alcohol or sugar.<sup>5</sup> Although binary co-crystals are the most abundant, numerous ternary co-crystals have been synthesized.<sup>6</sup> The API maintains its physiochemical properties in the co-crystal as the neutral arrangement preserves the API's chemical structure.

Co-crystals have become a field of interest because any API can be formed in a co-crystal. Many APIs lack an acid or base group and will therefore not be able to form a salt crystal. In 2014, it was estimated that more than half of the medicines available on the market were salts,<sup>7</sup> but this fraction might decrease in the future. The co-crystals offer a different pathway for stabilizing APIs. They enable non-ionizable compounds of medical importance to be solidified in a crystal structure of neutral components.<sup>8</sup>

The main goal of a pharmaceutical co-crystal is to increase an API's solubility and it can also alter its melting point, hygroscopicity and physical and chemical stability. The molecular arrangement within a crystalline form dictates its characteristics and a rearrangement of the molecules will usually impact the compound's properties.<sup>9</sup> Therefore, a wide range

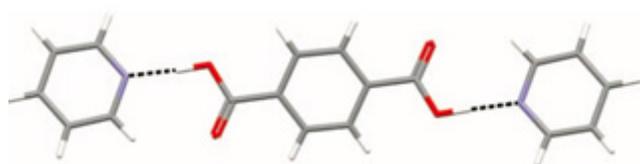
of co-formers must be considered to create the optimal co-crystal.

Approximately 70-80 % of the drugs currently under development are either Class 2 or Class 4 compounds as characterized by the biopharmaceutical classification system. Class 4 drugs have low permeability and low solubility while Class 2 drugs have low solubility and high permeability.<sup>10</sup> Class 2 drugs are therefore obvious candidates for co-crystal formation to improve solubility and deliver a high performance drug with both high solubility and permeability.

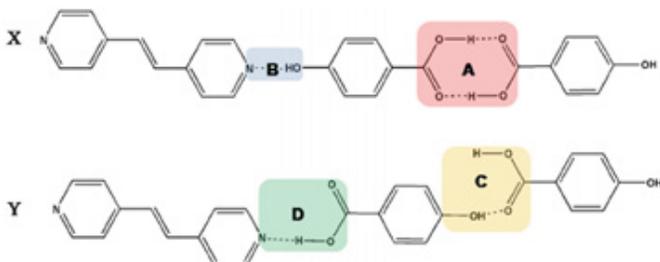
Co-crystals are patentable subject matter and are therefore of commercial interest to pharmaceutical companies. To obtain a patent the invention must be novel which a co-crystal almost always satisfies because it is a new composition of matter. It must also contain a non-obvious step, meaning something a skilled person in the art would not think to be obvious.<sup>11</sup> Here lies the important distinction between a co-crystal and a salt. If an acidic API is to be stabilized in a salt crystal, it is obvious that a base is needed as a co-former. In contrast, the co-former is rarely routine to find for a co-crystal. Careful consideration must be made as the co-crystal likely possesses very different properties from the API and co-former. Therefore, the synthon theory approach is often used in crystal engineering design. The approach has a high degree of strategy and design, further proving the non-obviousness in choosing the optimal co-former.

## DESIGN STRATEGIES

The supramolecular synthon approach is a chemical-based approach to crystal design strategy. It accounts for the specific, anisotropic interactions between molecules. In addition, the approach considers the geometrical requirements of crystal packing. *Supramolecular synthons* are defined as "spatial arrangements of intermolecular interactions" which occur frequently within crystal structures.<sup>12</sup> In other words, a synthon is a prominent bond between two functional groups acting as a building block in the crystal. In strategic co-crystallization, two compounds of different functional groups are brought together to form the desired synthons. The Cambridge Structural Database provides a register of reported stable molecular crystal structures including their synthons. The database contains the module Materials Mercury where searchers can identify supramolecular synthons that occur by combining particular



**Figure 1:** Dotted lines indicate the hydrogen bonds in the co-crystal terephthalic acid: pyridine (1:2).<sup>4</sup>



**Figure 2:** Synthons labeled A-D are a few of many possible bonds.<sup>14</sup>

functional groups.<sup>13</sup> Examples of synthons are displayed in Figure 2 below.

Organic materials with highly specific properties can be designed if the crystal structure product is correctly predicted. Therefore, the prediction methods are always improved in hopes of obtaining a highly reliable and consistent model. The uncertainty is due to the fact that the solid final product may have several crystal structures, called polymorphism. *Polymorphism* arises from a combination of thermodynamic and kinetic considerations and different polymorphs will in some cases alter the compound's properties greatly.<sup>15</sup> As there are often small differences in stability energies, calculations have to be as accurate as possible to predict the correct crystalline structure. The trade-off for improved accuracy is usually more calculations which are time-consuming and costlier. There are two important aspects to predicting the most abundant structure. One is to rank the stability of crystal packing alternatives for the target compound and the other is to generate a list of all stable and metastable polymorphs.

The most stable crystal form of a compound at a given temperature and pressure is the form with the lowest free energy.<sup>16</sup> The free energy can be calculated using the principles derived by Gibbs and is called lattice energy calculations. The volume change of a co-crystal versus a single-compound crystal is small, so the enthalpy changes,  $H$ , are assumed to be equal to the internal energy changes,  $E$ . Further, the co-crystal vibrational modes and single-crystal vibrations are likely very similar so the entropy change is close to zero. For a crystal  $A_a B_b$  formed by compounds A and B, the change in free energy for crystal formation is<sup>1</sup>

$$\Delta G^{cocrystal} \approx E(A_a B_b) - aE(A) - bE(B) \quad (1)$$

A negative Gibbs free energy indicates a spontaneous crystal formation. Clearly, the energies for the co-crystals and single-crystals must be known, so independent structure predictions for all three crystals must be performed. A higher number of independent molecules in the crystal unit cell increases the complexity of these calculations.

*Molecular dynamics* and *Monte Carlo methods* are two important approaches to structure prediction by geometry optimization.<sup>17</sup> Molecular dynamics predict the dynamic behavior of a system by integrating Newton equations of motion forward in time. Monte Carlo methods use reversible iterations, changes in the structure's properties to investigate

whether the new system is more stable or not. These iterations include a change in volume, pressure, rotation around a bond or a swap of two molecules in the crystal. The energy of the new system is calculated, and the new state is accepted if the energy is lowered. The new state may be accepted even if the energy is higher, depending on the Boltzmann

$$P = \exp\left(\frac{E_{old} - E_{new}}{k_B T}\right) \quad (2)$$

$E$  is energy,  $k_B$  is the Boltzmann constant and  $T$  is temperature. Both methods are valid for thermodynamic equilibrium, but the Monte Carlo method is not used for dynamic systems as it has no intrinsic concept of time. Both methods are important because of their algorithms for calculating thermodynamic properties. They are also convenient computational tools for exploring the conformational energy landscape of a crystal.<sup>17</sup>

The search for potential structures is achieved through identifications of minima on the potential energy landscape. A grid scan is performed as one degree of freedom in the molecule is varied to explore energy variations. These degrees of freedom include translational and vibrational modes of the molecules as well as the size and shape of the unit cell.<sup>17</sup>

By combining lattice energy and potential energy landscape calculations, the relative thermodynamic stability of co-formers is ranked for a final crystal structure prediction. While the prediction of smaller organic molecules often proves correct, more flexible and larger molecules are harder to predict because other factors such as crystallization kinetics and solvent effects play a bigger part.<sup>18</sup>

## CO-CRYSTAL SYNTHESIS

There are several ways of producing co-crystals with methods such as neat grinding, liquid-assisted grinding and co-crystallization from solution. This chapter will focus on liquid-assisted grinding and crystallization from solution. They are the preferred methods in lab scale and industrial scale respectively.

The *mechanochemical grinding method* has proven to be an efficient way of producing single- and multi-component crystals. This is because the supramolecular interactions that account for co-crystallization such as hydrogen bonding, halogen bonds,  $\pi$ - $\pi$  stacking interactions and other weaker bonds are easily broken and reformed under mild mechanical agitation.<sup>19</sup>

The grinding method has been further improved with liquid-assisted grinding, or LAG for short. In LAG a small amount of liquid phase is added to the grinding process. The liquid acts as a catalyst, creating hydrogen and halogen bonds between the reactants faster. The presence of liquid also allows a wider range of compounds to co-crystallize. Mechanochemical synthesis with LAG has proved to be beneficial because of its simplicity, product crystallinity and control of co-crystal stoichiometry. It also enables creating co-crystals independent of each component's relative solubility (as opposed to co-crystallization from solution).<sup>20</sup> The method is very efficient and could reduce energy- and solvent-requirement compared to the solution based approach.

For industrial production, co-crystallization is performed in solution for economic reasons.<sup>20</sup> The solution is supersaturated with the crystal components and the difference in chemical potential between the supersaturated species and saturated species is the driving force for nucleation and growth. The growth kinetics depend on internal factors (bonds, structure and defects) as well as external factors (temperature, medium, supersaturation and hydrodynamics). To speed up the process a seeding strategy can be used. A small crystal is added to the supersaturated solution, providing an interface for further crystal growth.<sup>20</sup>

## Co-crystal Characterization and X-Ray Diffraction

From early stage development to final product, solid state characterization techniques are used to analyze the compound. X-Ray diffraction is

<sup>1</sup> See ref. (17) p. 47- 48 for a more detailed derivation.

a very important tool in gaining structural information. Single crystal diffraction is preferred if co-crystals of appropriate size and quality are produced.<sup>21</sup> The method provides detailed information about molecular and crystal structures. The three dimensional diffraction intensity is captured with an area or CCD detector. The information is converted to a model of electron density where the unit cell parameters are determined from indexing the reflections. Then, the atoms are located in the unit cell by analyzing the diffraction intensities.<sup>22</sup> The detailed structural information allows modeling properties such as stability, hygroscopicity and morphology of the compound using theoretical chemistry.<sup>23</sup>

## PHARMACEUTICAL CONSIDERATIONS

Co-crystals can improve drugs in several properties. For all drug candidates, these properties should be tested to ensure that the improvements (significantly) outweigh potential shortcomings of the new drug form.

Firstly, the stability of a drug is an important parameter. Several types of stability such as moisture, chemical structure, air sensitivity and the influence of acids and bases has to be considered. These will impact the shelf life of the drug but also its effect in the body. The drug could face very different environments, for instance the pH in the mouth should always be higher than 5.5<sup>24</sup> while gastric acid in the stomach has a pH between 1.5 - 3.5.<sup>25</sup> Often, the co-crystal dissolves and there is a risk of precipitation of a less soluble compound. A possible solution is to add surfactants to the drug to prevent unwanted re-crystallization. Sensitivity to moisture is also an important factor in processing, packaging and storage. Moisture could possibly lead to unwanted phase transformations of the API.<sup>26</sup>

Solubility kinetics also play a big role in a drug's efficiency. Long dissolution rates may result in less absorption of the drug. This in turn requires a larger compound dose which could be a toxic dose. It may also lead to super-saturation in solution of one or more components of the co-crystal. The solution is then unstable and precipitation will occur, possibly inhibiting the effect of the API.<sup>27</sup>

## CONCLUSION

Co-crystals allow numerous APIs to become relevant in pharmaceutical therapy. The increased solubility and chemical and physical stability it provides are some of the most attractive properties of co-crystallized APIs. They are also attractive from an economical and legal point of view because of their patentability. Several challenges arise in the attempt of developing co-crystals. Predicting the crystal structure of larger molecules is costly and complicated. In some cases, the predicted structure will not match the experimental result. Even though methods such as liquid-assisted grinding are very efficient in lab scale, they are still unfavorable in large-scale synthesis on economic grounds. Overall, co-crystals are expected to have an important role in future drug development because of improved drug delivery performance, stability and an important intellectual property status.

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## CONFLICT OF INTEREST

None.

## ABBREVIATION USED

**LAG:** Liquid-assisted grinding; **CCD:** Charge-coupled device; **API:** Active pharmaceutical ingredient.

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