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REVIEW ARTICLE

Impact On Bioavailability Of Apis In Drug-Drug Co-Crystallization: A Review

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ABSTRACT

The pharmaceutical industries are observing a developing crisis in the procedure of drug development due to the failure of some successful drug candidates exhibiting poor aqueous solubility. The oral absorption of drugs with high permeability but low solubility (class II of the Biopharmaceutics classification system, BCS) is limited due to their poor solubility. Pharmaceutical scientists constantly seek to optimization of physical properties of active pharmaceutical ingredients (APIs) such as bioavailability, solubility, hygroscopicity, melting point, stability. Though numerous approaches like formation of salts, solvates, polymorph etc., are being used to improve performance characteristics of API, but these existing strategies are found to have limited success. In addition to these available strategies, bioavailability of drugs can be improved by formation of co-crystal. It is as an alternative approach based on crystal engineering to enhance physicochemical properties of drug. Co-crystals are crystalline structure composed of at least two components, where the components may be atoms, molecules or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. The components interact via non-covalent interaction such as hydrogen bonding, van der Waals interaction. The present paper would highlight effect of drug-drug co-crystallization on the bioavailability of drug molecule.

Keywords: Cocrystallization, solubility, pharmaceutical, coformer, synthon

INTRODUCTION

During establishment of new drug and formulation development, it is important to optimise and control the quantity of an active drug which is delivered to the body system. Alterations to the solid-state chemistry of drug molecules are common within the pharmaceutical industry as they enable modification of the physical properties of a drug, without changing the pharmacology and molecular structure of the active pharmaceutical ingredient (API) [1,2]. Every year many drug products reach the pharmaceutical market, out of which around 70% of new chemical entities (NCE) are being identified by combinatory screening programme have the issues of poor solubility and low systemic bioavailability [3,4,5]. The bioavailability of the drug is determined by Biopharmaceutics Classification System (BCS), mainly depends upon the two parameters: Solubility and Permeability. This classification system further divided into four classes, Class-I high solubility and high permeability, Class-II low solubility and high permeability, Class-III high solubility and low permeability, Class-IV low solubility and low permeability [6].

Many of the researchers/ scientists developed various approaches to enhance the solubility by salt formation [7], alteration of pH of the drug [8], co-micronization [9], nanotechnology (particle size reduction) [10], high-pressure homogenization [11], so on.

In addition to the above strategies, bioavailability of drugs can be improved by formation of co-crystal (Figure 1). Various research articles describes that the co-crystallization process improves the

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solubility, solution rate and oral bioavailability of the drug i.e., acetazolamide [12], ketoconazole [13], carbamazepine [14], so on. One of the researcher scientist group defines the co-crystals as 'Co-crystals are solids that are homogeneous single phase material composed of two or more different molecular/ or ionic compound, these components co-exist as a stoichiometric ratio (1:1) which are neither salts nor solvates. It brings two different components into one crystal lattice via intermolecular force; hydrogen bonding, π- π stacking, van der Waals forces, etc. [2,15]. One molecule should be active pharmaceutical ingredient (APIs) and another is coformers. The coformers are API or non-API, which are non-toxic in nature. Main challenge in formation of pharmaceutical co-crystals is 'screening of coformers' and 'selection of coformers'. Ideally, conformer should be listed in USFDA 'Everything added to food in the United States' (EAFUS) list, approved as Generally Regarded as Safe (GRAS). Selections of coformers are mainly done by experiment methods and knowledge methods. Experiment method include 'Hit and Trial' (used with all type of coformers for an API); to confirm the structure of co-crystal by various suitable techniques [16]. Screening methods includes Supramolecular synthon[17], Virtual coformer screening[18], Cambridge Structural Database[19], Thermal analysis[20], Hansen solubility parameter[21], Conductor- like screening model for real solvents[22] and many more.

Pharmaceutical Co-crystals

The first reported co-crystal in 1844 was quinhydrone, studied by Friedrich Wöhler.[23] FDA issued draft guidance on pharmaceutical co-crystals and defined co-crystals as, 'Crystalline materials composed of two or more different molecules, one of which is the API , in a defined stoichiometric ratio (1:1) within the same crystal lattice that are associated by non-ionic and non-covalent bonds'[24].

The term co-crystal and rules for hydrogen bonding were first purposed by Etter's (1990) [25,26]:

1. The acidic hydrogen available in a molecule is used in hydrogen bonding.
2. The good proton acceptors are used in hydrogen bonding when hydrogen-bond donors are available.
3. The best hydrogen-bond donor and the best hydrogen acceptor will preferentially form hydrogen bonds to one another.
4. The intramolecular hydrogen-bond formation form intermolecular hydrogen-bonds due to the best hydrogen-bond donor and best hydrogen acceptor.

The crystals are categorized on the basis of physicochemical properties i.e., covalent crystals, metallic crystals, ionic crystals, molecular crystals.

Crystal Engineering

Desiraju G. R. defined the crystal engineering as, 'the concept of intermolecular interactions and design/ framework of the crystal packing with preferred physical and chemical properties without altering the modifying the structure of drug' [27].

Synthon is defined, 'Structural units within the molecules which can be formed by known or feasible synthetic operation'[28]. In research field, growth of crystal engineering builds the interest in the nature of intermolecular interaction (hydrogen bonds and coordination bonds) and their use in the formation of solid- state modification structure [29]. APIs which are rich in functional groups that are capable of forming strong hydrogen bonds are more prone to co-crystal formation [30].

Preparation Techniques

Co-crystallization process broadly divided into three categories i.e., solid-state methods, solution based methods and other methods (Figure 2). For the synthesis of co-crystals, conventional methods of solvent evaporation are used [31]. However, strong demand for environmentally sustainable and safer synthetic processes has increased, leading to increased concentration on conducting solvent-free green methods of chemical reactions that are more energetic, more effective and are easily scalable. Such demands have fuelled recent interest in developing appropriate co-crystallization methods through mechanochemical reactions. The fact that by applying mild mechanical conditions, supramolecular interactions involving co-crystal formation can be altered has motivated the implementation of this mechanism [32, 33].

Dry powder process

It includes mainly mechanochemical processes. For supramolecular bond-based structures, these methods are used successfully. Mechanochemistry in earlier studies usually dealt with the breaking and formation of covalent bonds. However, in more recent studies under the thrust of supramolecular chemistry, besides covalent interactions, the use of mechanochemistry has now been expanded to break and shape non-covalent interactions. These non-covalent interactions are responsible for the crystal's structure and its stability within the molecular solid [34].

Mechanochemical co-crystal preparation methods can involve

1) Solid state grinding or smooth grinding at room temperature or often at high temperature: crystallization may be accomplished by grinding API and coformer, using pestle and mortar, in a stoichiometric ratio e.g. 1:1 or 1:2 or some other, for a given period. This procedure has a serious downside from incomplete co-crystallization, and there is a number of studies to support this disadvantage [35].

2) Solvent-drop grinding or liquid-assisted grinding: It is the same as solid-state grinding except in this case API is ground with coformer in a certain stoichiometric ratio, with limited addition of solvent, drop by drop, of suitable polarity. The addition of liquid here will significantly increase mechanochemical efficiency [34, 35]
3) High shear granulation: API and coformer are combined in this process and the liquid granulation is then applied. The mixture is first wet-massed, which is then accompanied by drying. Transformations can occur during this process which can be described by various analytical techniques [36].
4) Assisted grinding of polymers: Polymers are used here to help shape stable and highly energetic solid forms. The physical and chemical properties of these polymers are of paramount importance and need to be carefully considered. This co-crystallization process is the result of continuous efforts to improve the mechanochemical method's competence. In addition to grinding this method uses polymers to facilitate the co-crystallization process. This process can deliver comparable advantages with the process of Liquid Assisted Grinding [37].
5) Hot melt extrusion: In mechanochemical method development, an easily scalable, continuous and solvent-free method was developed and used, i.e. hot melt extrusion technique, for the synthesis of co-crystals using meltable binders. Extrudable hot melt excipients that are chemically inert and are capable of producing a co-crystal suspension enclosed in a matrix. Such inert meltable excipient will promote the formation of the solid extrude and the catalysation of the co-crystallization cycle during melt extrusion [38]. The use of sugar alcohols such as mannitol as a matrix excipient has been well known and is capable of significantly enhancing the intrinsic rate of dissolution of drug substances with low aqueous solubility. However, it is preferred to use xylitol that melts at a much lower temperature than mannitol (160 °C melting point). Regardless of the benefits offered by the sugar alcohols, usage of thermoplastic polymers was further investigated, as because of the inflexibility of the crystalline structure it is very difficult to shape them extrusion process, as these sugar alcohol possess rapid solidification property in addition to low melt viscosity [39].

Solvent-based or solution-based approaches include
1) Evaporation crystallization
2) Cool crystallization
3) Antisolvent process
4) Reactive co-crystallization

Conventional crystallization techniques such as anti-solvent addition, cooling or solvent evaporation are also very commonly used. Because the use of these solution-based co-crystal preparation techniques has many benefits, the yield is primarily higher, well-formed single crystals. Any alteration in the co-crystallization solvent and conditions will dramatically alter the resulting co-crystal properties which include flow properties, particle form, agglomeration, compaction, etc., which in turn influence their thermodynamic properties [40]. But the use of such methods may be restricted by the solubility problems of the materials i.e. in order to produce co-crystal of a material it must have ample solubility in a suitable solvent.

Other Methods:
In addition, several brand new methods have evolved in recent years to conventional co-crystallization methods and are being successfully used. A few are listed below.
1) *Spray drying technique*: This process is used mainly for amorphous and metastable materials and co-crystallization is encouraged as the solvent evaporates instantaneously due to hot air. This process was used for the formation of urea-succinic acid co-crystals in the stoichiometric ratio of 1:1 and 2:1 [41]. But these amorphous or metastable products are not thermodynamically stable and can affect both pureness and co-crystal yield.
2) *Sublimation*: Comparatively, it is a newer co-crystallization technique and, as compared to solvent-based processes, it is a solvent-free cleaner process and can prevent issues caused by material solubility issues [42].
Characterization of co-crystals
Multicomponent solid forms can be characterised using several well established analytical techniques like infrared spectroscopy (IR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), scanning electron microscopy (SEM) (Figure 3).
PXRD is the primary characterization technique that detects changes in the crystal lattice and therefore confirms the formation of a unique phase. The electron surrounding the atoms diffracts X-rays in a manner described by the Bragg equation at an angle which is used to calculate the spacing between the planes. The plot of intensity versus the diffraction angle a fingerprint of a crystal structure and is useful for determining the crystallographic similarity of samples by pattern comparison [43].
DSC is the most widely used technique to study thermal nature of various crystalline forms. DSC technique is used for obtaining melting point data and other thermal parameters, such as the heat capacity and heat of fusion. The DSC thermal

profile different from the starting material indicates the formation of a new co-crystal [44].
Scanning electron microscopy is another technique used to obtain a visual differentiation between the co-crystal and cocystal formers at microscopic level. FTIR has found wider applications in the study of pharmaceutical solids in recent years due to the availability of cost effective [45]. FTIR has been used traditionally as an aid in structure determination; vibrational changes also serve as a probe of intermolecular interactions in solid materials. It also provides a fingerprint of a molecular solid. These methods are especially important for characterization patterns often differ among forms and the functional group affected will display shifts to varying degrees. IR requires a change in dipole moment whereas Raman requires a change in polarizability for observation. Near infrared (NIR) spectroscopy is being increasingly used in combination with, or as replacement for classical techniques for the monitoring of production processes of co-crystals.
Finally, the co-crystals are evaluated for solubility and bioavailability enhancing properties. These studies give the basis for selection of best co-crystal that is to be forwarded for formulation.
The stability studies are used to monitor drug stability studies to determine which product actually from under room temperature and accelerated stability conditions.
In the present review, various co-crystals which contain another drug molecule as coformer have been discussed on the basis of the use of API and the benefit of using another drug molecule as the coformer.

CASE STUDIES

Erlotinib -Furosemide Co-Crystal:

Erlotinib (Tarceva) is an effective anti-cancer drug used for treating non-small cell lung cancer (NSCLC), pancreatic, breast cancer. According to USFDA approval it is a second line chemotherapy drug. It acts by inhibiting intracellular phosphorylation of tyrosine kinase. It is a BCS class II drug having low solubility and high permeability. It is administered orally to the patients. As per the reported studies, its solubility depends upon pH and solubility decreases with increase in pH. Furosemide (Lasix) is a diuretic drug used for treating hypertension, heart failure and edema. The presence of furan ring in furosemide confirmed its polymorphism. Erlotinib and furosemide were taken in 1:1 stoichiometric ratio to form a co-crystal, done by grinding and slow evaporation method. By single crystal x- ray crystallography studies ETB+FSM co-crystal was found to be effective. By measuring the enthalpy change on differential scanning calorimetry its thermal action was explored. The co-crystal form dissolution rate is found to be ca. 1.3 times higher compared to the pure API [46].

Flufenamic acid- Ethenzamide Co-Crystal:

Flufenamic acid is used for the treatment of analgesic, anti-inflammatory and anti- pyretic properties. According to biopharmaceutical classification system, flufenamuc acid belongs to class II drug with low aqueous solubility approximately 9.09mg/ml and high permeability. Out of its 9 polymeric forms, form I and form III are used and are available. Ethenzamide ETZ is a non-steroidal anti-inflammatory drug largely used in combination with drugs such as aspirin, dipyrone, allyl iso-propyl acetyl urea, caffeine, and ibuprofen for the treatment of mild to moderate. The co-crystallization was prepared by solvent evaporation method and solvent drop assisted grinding method. FFA and ETZ form a co-crystal by formation of a robust supramolecular acid- acid homosynthon which lead to increase in solubility of FFA by 2 folds .Three spectral studies were done by single crystal x-ray diffraction, powder x-ray diffraction and H^1 NMR spectroscopy .The FFA having low solubility earlier was resolved and increased by using ETZ as a coformer with it [47].

Piroxicam and Sodium Acetate Co-crystal:

Piroxicam is a non- steroidal anti-inflammatory drug (NSAID) used for curing inflammation and pain caused by osteoarthritis and rheumatoid arthritis. It can be treated as a pain killer. Its mechanism of action is to inhibit prostaglandins. Due to its low solubility it reaches systemic circulation very slow that is within 3-5 hours after administering it orally so as to increase its solubility it was co-crystallized with sodium acetate by dry grinding method. Sodium acetate acts as an electrolyte replenisher. It is a highly hygroscopic drug which can easily solubilize in water and correct the sodium level in a patient suffering from hyponatremia. The co-crystal formed was studied by analyzing its various characteristics such as infrared spectroscopy (IR), X-ray diffraction (XRD), differential scanning calorimetry (DSC). The co-crystal was formed in a 1:1 stoichiometric ratio which lead to increase in solubility as well as increase in dissolution rate by 30%. Hence it was found to be an effective and safe co-crystal [48].

Carvedilol (CAR) And Hydrochlorothiazide (HCT) Co-Crystal:

As the treatment of many diseases involve use of combined therapies, the formation of co-crystals using combination drugs is an effective way to improve the physicochemical properties of one of the API. The co-crystal of carvedilol with

hydrchlorthiazide as coformer is on such example. Carvedilol belongs to a class of drug known as non-selective alpha-1/ beta blocker used in high blood pressure, heart attack, edema, CHF and other problems associated with kidney whereas hydrochlorthazide is helps to relieve the edema caused due to increase blood pressure. A significant increase in dissolution rate (2.7 folds) and solubility (7.3 folds) of carvedilol was observed when co-crystals in stoichiometric ratio of CAR: HCT as 2:0.5 were prepared by using slurry conversion method and solvent evaporation method. The further evaluation of these cocrytals may produce synergistic or additive effects resulting in improved patient compliance [49].

Ibuprofen - Nicotinamide Co-Crystal:

Ibuprofen and nicotinamide co-crystal was made using solvent evaporation technique. This co-crystallization was done to enhance solubility of ibuprofen. It belongs to NSAIDs (non-steroidal anti-inflammatory drug) class of drug however, it shows compromised solubility. The drug acts as an analgesic to relieve pain, inflammation also acts as anti-pyretic drug. Due to its delay in absorption through GIT which served as the rate limiting step for ibuprofen it was co-crystallized with nicotinamide. Nicotinamide has water soluble property. It is a GRAS drug (general regarded as safe). It is a form of vitamin B3 also called as niacin. It is used to cure skin related problems and niacin deficiencies. By performing various tests such as writhing test, Duncan's multiple range tests it was concluded that co- crystallization of ibuprofen with nicotinamide as a coformer improved its solubility and their co-crystal characteristics were studied by PXRD (powder X-ray diffraction), Scanning electron microscopy (SEM), and Differential thermal analysis (DTA). In vivo study, analgesic activity was done by male Swiss-Webster mice; which shows the result, enhanced the solubility of co-crystal formation as compared with the physical mixture and pure drug [50].

Carbamazepine (CBZ) – Para-aminosalicylic acid Co-Crystal:

Carbamazepine is an anti-convulsant medication used in patients to control seizures and apart from this it is also used to treat patients with bipolar disorder. It belongs to BCS class II drug with low water solubility and high permeability that mainly restricts its absorption whereas para-amino salicylic acid i.e. (PASA) is an anti-tubercular medication. As per the reports of Swart and Harris earlier, the interaction of CBZ with first line anti-tuberculosis drug isoniazid and rifampicin were experimented and they showed that their concurrent administration results in significant side effects. Then they selected a second-line anti-tuberculosis compound, PASA for co-crystallization with CBZ. By varying the molar ratios of carbamazepine to para-amino salicylic acid i.e. (1:1 and 2:1) their co-crystals were prepared and studied by using the liquid-assisted grinding (LAG), slurry and solution crystallization techniques. As per the previous studies, three new CBZ and PASA co-crystal forms were synthesized with multiple stoichiometric ratios: [CBZ+PASA] (1:1), [CBZ+ PASA+H_2O] (2:1:1) and [CBZ+ PASA+ MeOH (methanol)] (2:1:1). The co-crystal of carbamazepine and para-amino salicylic acid exhibited a 1.5 fold increase in solubility. The characteristics of CBZ and PASA was conducted and shown by single X-ray diffraction and differential scanning calorimetry [51].

Diclofenac – Theophylline Co-Crystal:

In the present study, the authors have used diclofenac and difunisal for the preparation of co-crystals with theophylline. The co-crystals showed the presence of two molecules of API and one molecule of theophylline in each crystal lattice as suggested by crystal structure studies performed using single crystal X-ray analysis. The lattice energies of drugs and co-crystals are found to be comparable. Also the values of enthalpies of formation of crystal lattice in both co-crystals are low. On the basis of these observations, the authors have suggested that the hydrogen bond energies in both the co-crystals are comparable and the packing energy gain is obtained mainly from weak vander Waals forces. Theophylline is able to improve the solubility of both the drug molecules resulting in a novel solid dosage form. However, the solubility improvement in diflunisal-theophylline co-crystal follows the 'spring and parachute' effect. During the long term dissolution study, a 2.3 times improvement was observed diflunisal-theophylline co-crystal while no improvement was observed in intrinsic dissolution study. The diclofenac-theophylline co-crystal also showed an increase of 1.3 folds as compared to pure drug in intrinsic dissolution studies and no spring effect can be seen. Both the co-crystals were found to be physically stable at different relative humidities [52].

Glibenclamide – Ascorbic Acid Co-Crystal:

Glibenclamide is an oral anti-diabetic medication belonging to class of second-generation sulfonyl ureas which is used in patients that are suffering from Type- II diabetes mellitus and it works by increasing the insulin that pancreas produces itself. Glibenclamide belongs to BCS class II with high permeability and low solubility (insoluble in water). As per the previous studies done by researchers the co-crystals of glibenclamide – ascorbic acid were

prepared in equimolar ratios of 1:2. The co-crystal was characterized by differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR) and powder X-ray diffraction (PXRD). As per the studies the prepared co-crystal of glibenclamide- ascorbic acid showed an increase in dissolution rates by 26 folds in comparison with the pure drug [53].

Diflunisal – Theophylline Co-crystal:

Diflunisal is again a nonsteroidal anti-inflammatory drug which works by inhibiting the production of prostaglandins through the arachidonic acid pathway. Diflunisal is employed in patients that are suffering from rheumatoid arthritis as well as osteoarthritis. Diflunisal belongs to BCS class II category with poor solubility and higher permeability so to improve its solubility theophylline was used as a coformer. Theophylline is an adenosine receptor blocker as well as phosphodiesterase inhibitor having cardiac stimulant activity as well as a diuretic. As theophylline is soluble in water so after co-crystallising it with diflunisal it can improve the solubility of drug. By varying the molar ratios of diflunisal to theophylline i.e., 1:1 and methanol as solvent their co-crystals were prepared and studied by using the solvent-drop grinding techniques and three spectral studies were done by differential scanning calorimetry (DSC), X-ray diffraction as well as solution calorimetry. The formed co-crystal of diflunisal – theophylline exhibited an improvement in the solubility by 2.3 times in comparison with the pure diflunisal drug [52].

Theophylline and aspirin co-crystal:

Theophylline (THP) is used for the treatment of the respiratory disease such as asthma therapy, whereas aspirin (ASP) is considered as GRAS (generally regarded as safe) API that has been employed as a coformer in pharmaceutical co-crystals. A narrow stability window was found for the THP-ASP co-crystal when the phase diagram was constructed at 20 °C and 40 °C. The co-crystals were prepared in this stability region by isothermal slurry method. The co-crystal prepared were characterized by Single Crystal X-ray Diffraction, Powder X-ray diffraction, Differential Scanning Calorimetry, Thermogravimetric analysis and Fourier Transform Infrared analysis. The authors also supported the results with visual images performed by scanning electron microscopy [54].

CONCLUSION

Drug – drug cocrystals improve the physicochemical and biopharmaceutical properties of an API by addition of suitable coformer without chemical modification. These cocrystals are expected to be used more frequently in pharmaceutical research as their advantages are confirmed and common manufacturing methods are validated. The two main factors driving this expanding trend are the requirement to target many receptors for the efficient treatment of complicated illnesses, single dose leading to patient compliance as well as the growing demand to facilitate the decrease of medication manufacturing costs. These benefits allow for the creation of new patent and copyright areas, thanks to drug-drug cocrystals.

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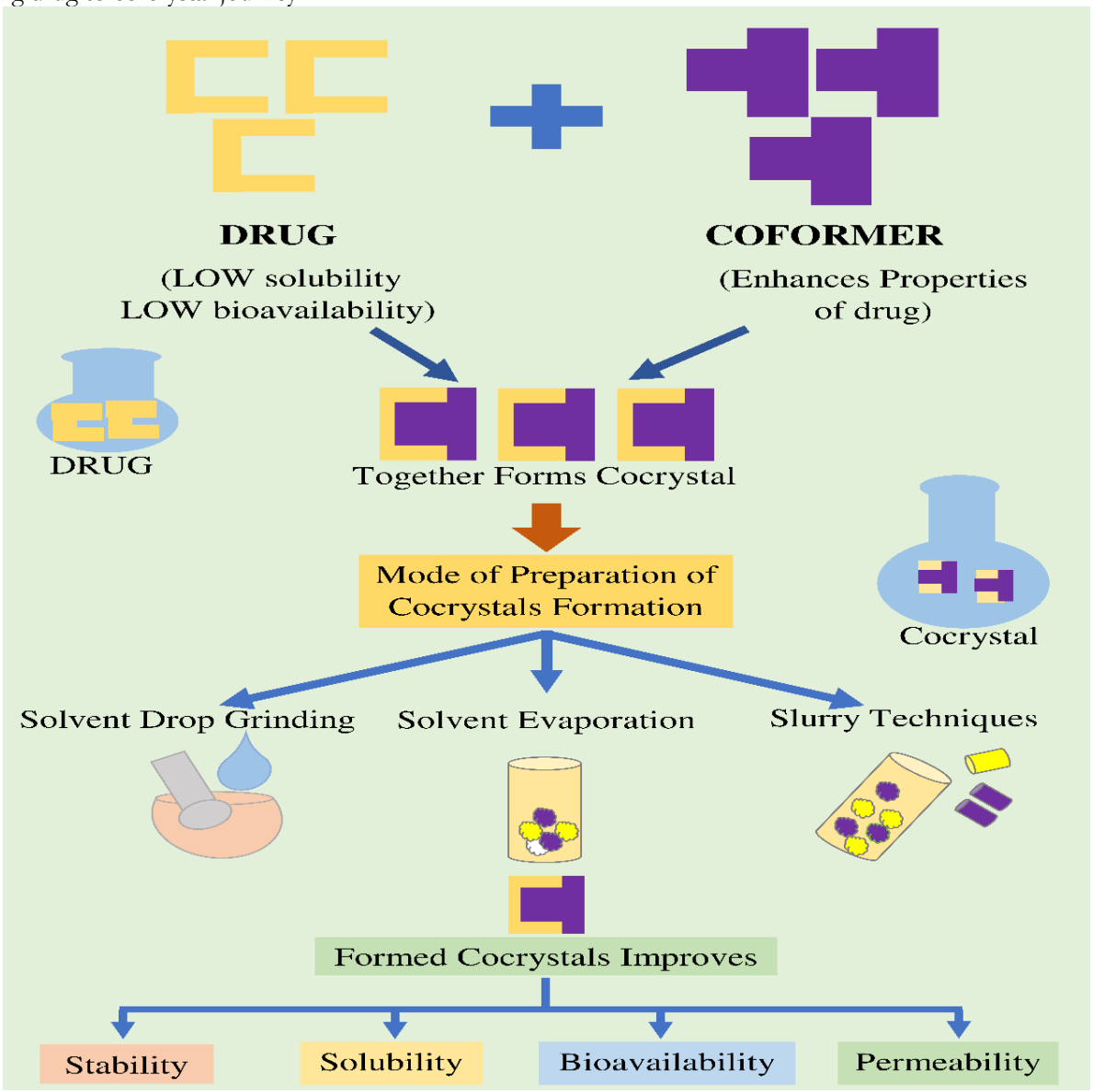
Figures legends

Fig. 1: Schematic view of improvements observed during drug to co-crystal journey

Fig. 2: Methods of preparation of co-crystals

Fig. 3: Characterization methods of cocrystals



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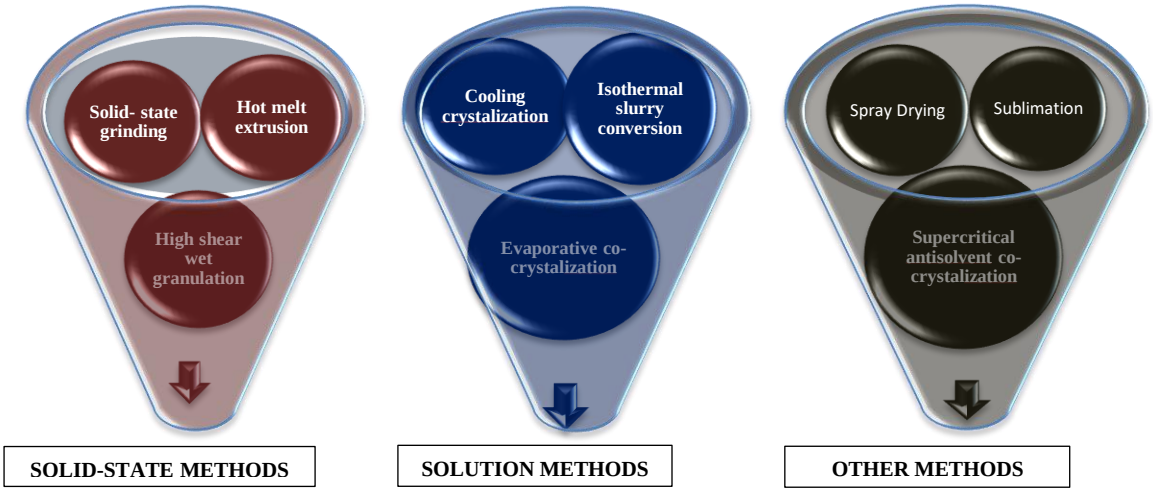

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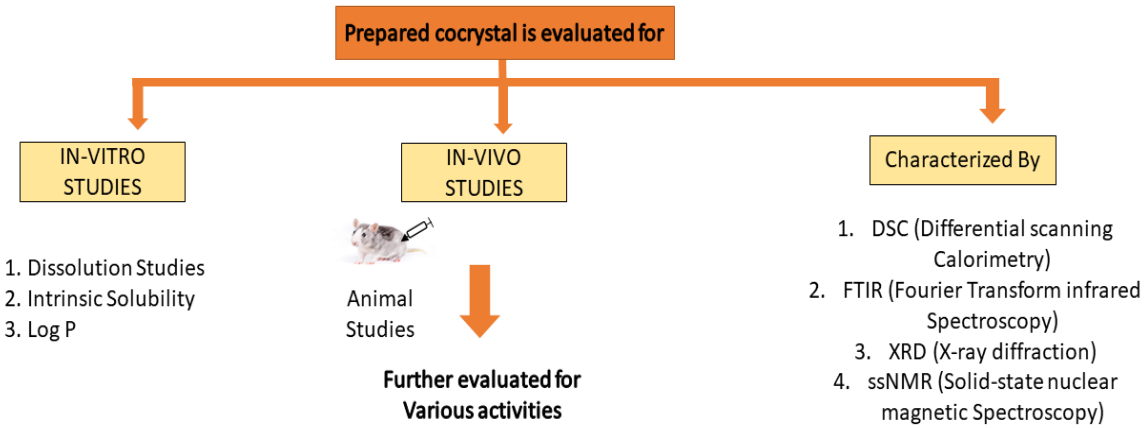

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