REVIEW ARTICLE

Co-Crystals: A Review of Recent Trends in Co Crystallization of BCS Class II Drugs

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ABSTRACT:

Poor aqueous solubility and low oral bioavailability of an active pharmaceutical ingredient are the major constraints during the development of new product. Various approaches have been used for enhancement of solubility of poorly aqueous soluble drugs, but success of these approaches depends on physical and chemical nature of molecules being developed. Co-crystallization of drug substances offers a great opportunity for the development of new drug products with superior physicochemical properties such as melting point, flow ability, solubility, stability, bioavailability and permeability, while preserving the pharmacological properties of the active pharmaceutical ingredient. Co-crystals are multi-component systems in which two components, an active pharmaceutical ingredient and a co-former were present in different stichiomentric ratios and bonded together with non-covalent interactions in the crystal lattice. This review article presents a systematic overview of pharmaceutical co-crystals. Differences between co-crystals with salts, solvates and hydrates are summarized along with the advantages of co-crystals with examples. The theoretical parameters underlying the selection of co-formers and screening of co-crystals have been summarized and different methods of co-crystal formation and evaluation have been explained.

KEYWORDS: Pharmaceutical co-crystals; Co-crystallization; Solubility; Supramolecular synthons.

1. INTRODUCTION:

Pharmaceutical co-crystals area unit crystalline elements created from an API and one or additional co-former or another API. A pictorial sketch of multi-component system i.e., co-crystals is displayed within the following (Figure1 in Scheme I and Scheme II) Co-crystals area unit at the moment the foremost dynamically developing cluster of solid pharmaceutical substances. Pharmaco-dynamically, co-crystal former could be a stability molecule (the same applies to salts), and therefore the GRAS rules apply.

The advance of crystal engineering has remodeled the pace of analysis in molecular solids. Attaining the specified properties in molecular solids by controlled manipulation of unit interactions holds the key to success during this space of analysis. For that matter, strength and radial asymmetry of weak unit interactions area unit necessary options to be taken under consideration. Crystal engineering, through supramolecular synthons, permits US to style co-crystals with desired chemistry properties. Co-crystallization and polymorphism area unit necessary applications of crystal engineering. A co-crystal entails or additional neutral molecules to be control along by weak unit interactions in an exceedingly definite quantitative relation. Since unit interactions guide properties of molecular solids, co-crystal formation is of nice interest to crystal engineers.

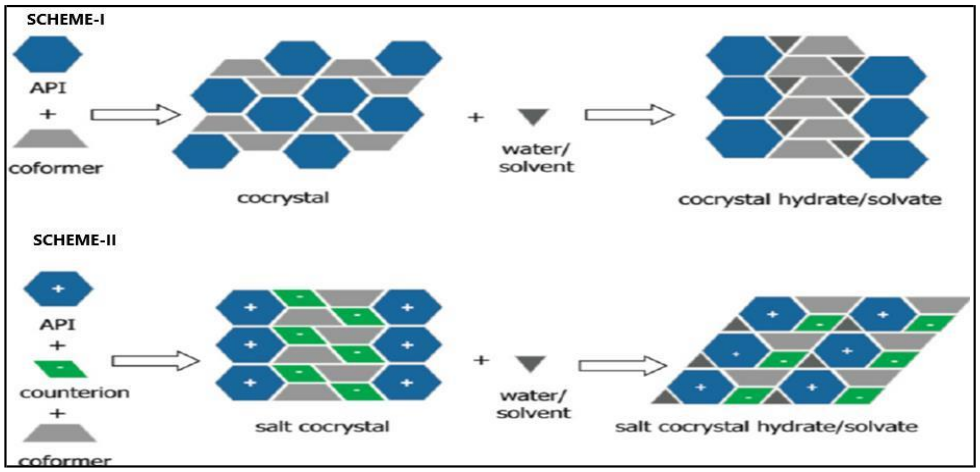

Fig 1. Solid state strategies of API

Initially, co-crystals are exploited in pharmaceutical analysis to change the chemistry properties of a drug like solubility, stability, temperature and shelf life.

Crystal engineering is generally considered to be the design and growth of crystalline molecular solids with the aim of impacting material properties. A principal tool is that the bond, that is answerable for the bulk of directed unit interactions in molecular solids. Co-crystals area unit multi-component crystals supported chemical element bonding interactions while not the transfer of chemical element ions to make salts; this is often a crucial feature, since bronsted acid-base chemistry isn't a demand for the formation of a co-crystal. Co-crystallization could be a display of directed self-assembly of various elements. Co-crystals have been described of various organic substances over the years [1, 2] and given numerous names, like addition compounds [3, 4] molecular complexes [5, 6] and hetero molecular co-crystals[7]. Despite naming convention, the essential which means is that of a multi-component crystal wherever no valency chemical modification of the constituents happens as a result of the crystal formation.

Pharmaceutical active ingredients (APIs) will exist in an exceedingly kind of distinct solid forms, as well as polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Every kind displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drugs

2. Co-crystals, Salts, Solvates and Hydrates:

USFDA defined the co-crystal, salt and polymorphs in the draft guidance. The polymorphs are defined as the compounds which are present in different crystalline forms such as solvates or hydrates (also known as pseudo polymorphs) and amorphous forms. Polymorphs have different lattice arrangement and also, they have different physicochemical properties due to their crystal lattice structures. Salts are the compounds which are formed by complete transfer of proton from one compound to another [8].

Salts and co-crystals can be differentiated based by a proton transfer from an acid to base. A complete transfer of proton takes place between acid-base pairs, whereas, no proton transfer occurs during co-crystal formation. Two components are bound to each other by non-covalent interactions such as hydrogen bonding, π-π stacking, and Vander Waal forces. A prediction can be made by Δp*K*a value whether co-crystals are formed or not. It is generally accepted that a salt will be formed if the Δp*K*a value is greater than 3 and ΔP^{Ka} value less than 0 will lead to the formation of co-crystals. This parameter is not accurate to predict the formation of co-crystals in solids between the Δp*K*a values 0 and 3 but the possibility of salt formation will increase when the Δp*K*a increases [9, 10].

Co-crystals and solvates can be differentiated based on their physical state of the components. The compounds which are liquid at room temperature are called as solvates whereas those compounds which are solid at room temperature are called as co-crystals. If the solvates contain water as a solvent in their crystal lattice then they are known as hydrates [11] Solvates/hydrates are commonly formed during the co-crystallization via solution or liquid assisted grinding and they can alter physicochemical properties of API's. Stability of solvates will be different from un-solvated forms because of presence of solvent in crystal lattice.

Solvates/hydrates are quite unstable, because they lose solvent/water at high temperature and low humidity during storage and the physiochemical properties will be different for hydrated/dehydrated forms [12, 13]. Dissolution rate of the drug was enhanced by the solvated forms of spironolactone [14]. Different

polymorphic co-crystals and solvates of caffeine and anthranilic acid were prepared by using different solvents via liquid assisted grinding. [15]

2.1 Advantages of Co Crystals:

- Stable crystalline form as compared to amorphous kind.
- Give exaggerated solubility; so exaggerated bioavailability.
- Technique is used for purification.
- Co-crystals having benefits like stable crystalline kind (as compared to amorphous solids).
- No need to make or break covalent bonds, theoretical capability of all types of API molecules (weakly ionizable/non-ionizable) to form co-crystals.
- The existence of diverse potential counter-molecules (food additives, preservatives, pharmaceutical excipients, and alternative APIs).
- The only solid form that is designable via crystal engineering patentable expanding IP portfolios and can be produced using solid-state synthesis green technologies high yield, no solvent or by-products.

2.2 Design of Co-Crystals:

The crystal engineering experiment usually involves the Cambridge Structural information (CSD) survey followed by the experimental work. Co-crystals designed on the principal of the supramolecular synthesis; it provides a strong approach for proactive discovery of novel pharmaceutical solid phases. Co-crystals incorporates multiple elements in given ratio quantitative relation, wherever completely different molecular species move by chemical element bonding and by non-hydrogen bonding.

The use of chemical element bonding rules, synthons and graph sets could assist within the style and analysis of co-crystal systems. Normally tho', prediction of whether or not co-crystallization can occur isn't however attainable and should, at present, be answered through empirical observation. Co-crystal formation could also be rationalized by thought of the bond donors and acceptors of the materials that area unit to be co-crystallized and the way they may move. Following the intensive examination of discriminatory packing preferences and bond patterns in an exceedingly variety of organic crystals, Etter and associates projected the rules to facilitate the deliberate style of hydrogen-bonded solids.[16] All smart nucleon donors and acceptors area unit employed in chemical element bonding, membered ring unit chemical element bonds kind in preference to unit chemical element bonds, the most effective nucleon donor and acceptor remaining when unit chemical element-bond can form unit hydrogen bonds to 1 another (but not all acceptors can essentially move with donors). These observations facilitate to handle the difficulty of competitive bond assemblies ascertained once employing a specific co crystallizing agent.

A detailed understanding of the supramolecular chemistry of the functional groups present in a given molecule is the prerequisite for designing the co-crystals because it facilitates the selection of the suitable co-crystal former. Supramolecular synthons that can occur in common functional group in order to design new co-crystals and certain functional groups such as carboxylic acids, amides and alcohols are particularly amenable to formation of supramolecular heterosynthon.[17] The strong hydrogen bond includes (N-H---O), (O-H---O), (-N-H---N,) and (O-H---N). The weak hydrogen bonds involves the −C-H---O and C-H---O=C [18]

2.3 Different Strategies of Co-crystals Formation:

Till date, completely different strategies are reported for the preparation of co-crystals by the researchers. Few ancient strategies supported the answer and grinding was reported for the synthesis of co crystals [19]. An appropriate form of solvent is employed in answer methodology for the preparation of co crystals. Differing kinds of strategies like solvent evaporation [20], crystallization technique [21], anti-solvent addition [22], suspension conversion methodology [23] and reaction crystallization methodology [24] area unit mentioned with appropriate examples in table 1. Grinding strategies area unit of 2 types: neat grinding and solvent drop grinding [25,26]. Some new rising strategies used for the formation of co crystals area unit ultrasound aided methodology [27,28], critical fluid atomization technique [29,30] spray drying technique [31,32] hot soften extrusion technique [33,34].

2.3.1 Solution-Based Strategies:

2.3.1.1. Solvent Evaporation method:

In solvent evaporation method, for both API and coformer are dissolved in a suitable solvent and the solution is allowed to evaporate the solvent slowly.

During dissolution, the functional groups in the drug and conformer interact with each other and form hydrogen bonds [30]. This is most commonly used method for the preparation of co-crystals by researchers [23,35].

In solution crystallization technique, drug and co-formers are dissolved in boiling solvent with stirring and the boiling of the solution would be continued until the volume of the solution become small Co crystallization takes place rapidly when the boiling solution is allowed to cool about 15 min. Co crystals are separated by filtration and kept in oven or air for drying [21,36].

Table 1 Different Strategies of Co-crystals Formation with Examples

S. No	Drug name	Conformer/ Polymer	Method of preparation	Results	Reference
1	Piroxicam	Piroxicam Sodium acetate	Dry grinding method	Improve the solubility and dissolution.	68
2	Clarithromycin	Erythromycin, common solvents	Solvent evaporation technique	Improved solubility of CLN and in turn higher dissolution rate than the pure drug	69
3	Carbamazepine	Nicotinamide (NIC) and saccharin (SAC	Solution methods	Characterization results show that in ethanol-water solvent mixture, pure CBZ-NIC co-crystal can be prepared	70
4	Paracetamol	5-Nitro isophhthalic acid (5NIP)	Solvent evaporation technique	Improves its tablet ability	71
5	Acyclovir	Common solvents	Solvent evaporation technique	improved solubility which may result in improvement of bioavailability	72
6	Ibuprofen-nicotinamide	Nicotinamide	Slow evaporation method.	Improves the in vivo analgesic effect, as compared with intact ibuprofen and its physical mixture.	73
7	Naproxane-nicotinamide	Sodium naproxen anhydrate	solid-state nuclear magnetic resonance (NMR)	Improved initial naproxen dissolution and less water vapor adsorption, indicating better pharmaceutical properties of naproxen	74
8	Indomethacin-Saccharin	Saccharin	Cooling batch crystallization without seeding	Improved aqueous solubility of the co-crystals leads to improved bioavailability of IND.	75

2.3.1.2. Slurry Crystallization:

Slurry crystallization is that the method during which suspension is ready by addition of various solvents within the mixture of API and appropriate co-formers. The solvent is decanted and therefore the solid material is dried and characterized by completely different strategies for analysis. This methodology is chosen for the preparation of co crystals once the drug and coformer ought to be stable within the solvent [23, 37, 38, and 39].

2.3.1.3. Anti-Solvent method:

This is one in all the strategies for precipitation or recrystallization of the co-crystal former and active pharmaceutical ingredient. Solvents embrace buffers (pH) and organic solvents. As an example preparation of co-crystals of aceclofenac victimization chitosan, during which chitosan answer was ready by soaking chitosan in glacial ethanolic acid. A weighed quantity of the drug was spread in chitosan answer by victimization high dispersion homogenizer. This dispersion was extra to H2O or atomic number 11 change states to precipitate chitosan on drug [40].

2.3.1.4. Crystallization by reaction:

Reaction crystallization methodology is employed for speedy preparation of co-crystals at microscopic and macroscopic scale at close temperature during which nucleation and co-crystallization relies upon the co-crystal elements and their solubility. The saturated of the lesser soluble part (drug) is formed in methyl alcohol and filtered, and so the additional soluble part (coformer) is extra in a quantity just below its solubility limit. The goal isn't to own any excess drug or coformer within the beginning solutions that would be confused as a co-crystal. What is more [40, 41], by not exceptional the solubility limits of the elements, the co-crystals that precipitate out of answer area unit pure. Answer concentrations area unit monitored by HPLC throughout the crystallization method to judge whether or not the solid ascertained gave the impression to be a fancy of the reactants (co-crystals). The solid precipitates are collected and analyzed by HPLC to work out the ratio of the complicated. If the solid gave the impression to be a co-crystal supported the HPLC results, it's additional characterized by DSC, TGA, and PXRD [24,42,43].

2.3.1.5. Grinding Method:

Grinding strategies are wide used for the for the co-crystal formation over the past few years and located to be superior than alternative strategies (solution or melt) [25, 26]. Grinding techniques area unit of 2 types: dry grinding and wet grinding. In dry grinding, drug and coformer area unit mixed along in an exceedingly ratio quantitative relation and ground them by victimization either mortar or pestle or ball mill [44]. Wet Grinding was performed in an exceedingly similar manner that of neat grinding by addition of some drops of solvent within the mixture [45,46].

2.3.1.6. Ultrasound Aided Co-crystallization:

Sonochemical methodology has been developed for the preparation of co-crystals of terribly little size i.e. for preparation of nanocrystals [47]. During this methodology, API and co crystal former area unit dissolved along in an exceedingly solvent and therefore the answer is unbroken in an exceedingly sonoreactor to make the answer opaque. Cold water is provided throughout the sonication to take care of the constant temperature of sonicator and forestall fragmentation. The answer is unbroken nightlong for drying. Pure co-crystals were obtained by this methodology and therefore the purity of co-crystals is assessed by victimization X-ray diffraction study [48].

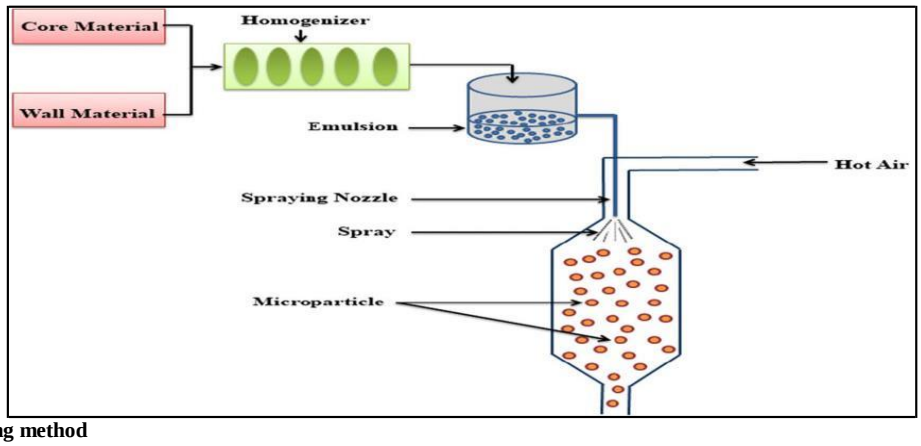

Fig 2. Spray drying method

2.3.1.7. Supercritical Fluid Atomization Technique:
In critical atomization technique, the drug and co-formers area unit mixed with one another by victimization high pressurized critical fluid i.e. CO2. Co-crystals area unit ready by atomizing this answer with the assistance of sprayer. In critical anti-solvent (SAS) methodology, the co-crystals area unit ready from answer by the anti-solvent result of critical fluid [47-49].

2.3.1.8. Spray drying technique:
In spray drying method, Co-crystals area unit ready by spraying the answer or suspension of drug and coformer with hot air stream to evaporate the solvent. This is often the foremost most well-liked technology as a result of this is often a quick, continuous, and ballroom dancing method. Thus, spray drying method can supply a novel atmosphere for the preparation and scale-up of co-crystals. [30,31] (Figure 2)

2.3.1.9. Hot Soften Extrusion Technique:
In hot soften extrusion technique, the co-crystals area unit ready by heating the drug and co-formers with intense intermixture that improved the surface contacts while not use of solvent. The restrictions of this methodology embrace each coformer and API ought to be compatible in liquefied kind and not used for unstable medicine [32,33].

3. EVALUATION OF COCRYSTALS:

3.1. Fourier transforms infrared radiation (FTIR):
FTIR spectrographic analysis is employed to predict the unit interactions and compatibility study between drug and co-formers. This system is wide accustomed predict the chemical conformation of compounds. Aakeroy et al. used FTIR to tell apart the co-crystals from salts by evaluating the acid involvement within the bond formation [50,51]. Pure drug, coformer, physical mixture and co-crystals area unit analyzed by FTIR within they vary of 400-4000 cm-1. FTIR study is additionally used alongside alternative techniques like DSC or XRD for the screening of the co-crystals [52,53,54].

3.2. Differential scanning colorimetry (DSC):
DSC has been used for screening of co-crystal formation. Screening of co-crystals formation is determined by the presence of heat-releasing peak followed by endoergic peak in DSC spectra. The presence of those peaks within the physical mixture of elements indicates the chance of formation of co-crystals. Pure drug, coformer, physical mixture and co-crystals were weighed out (1.5-2.5 mg) in atomic number 13 pans and analyzed with heating rates of five-30° victimization similar empty pan as a reference. The gas with rate of flow fifty ml/min maintained the inert atmosphere. Temperature, glass transition temperature, polymorphic nature, heat of fusion, endoergic or heat-releasing behavior is determined by victimization DSC [42,55].

3.3. Thermo gravimetric analysis (TGA):
Physical and chemical properties of solids area unit determined by victimization thermal analysis as a operate of skyrocketing temperature (with constant heating rate) or as a operate of your time (with constant temperature and/or constant mass loss). TGA could be a appropriate methodology for determination of hydrates/solvates sorts of co-crystals or presence of volatile elements still as decomposition or sublimation temperature. Thermal stability, compatibility and purity of co-crystals is foretold by TGA analysis. The burden losses of sample mass throughout the TGA analysis is that the indication of loss of volatile part or decomposition of co-crystal [56,57,59].

3.4. Terahertz time domain-spectroscopy (THz-TDS):
Terahertz time-domain-spectroscopy (THz-TDS) is another tool to PXRD for the characterization of co-crystals. Chiral and racemic molecular and supramolecular structures is distinguished by rate

spectrographic analysis [52] rate spectrographic analysis was accustomed distinguish the identical molecular structure co-crystals of bronchodilator with completely different co-formers (such as malic acid and salt acid) that were gift in chiral and racemic forms [60].

3.5. Solid-state NMR:

Solid-state NMR (SSNMR) is employed to characterize solid phases that can't be studied by SXRD [52]. SSNMR was accustomed investigate the character of complicated by crucial degree of nucleon transfer. Thus, SSNMR is a crucial tool for the identification of co-crystal or salt. SSNMR may be accustomed appraise the co-crystal structure by estimating chemical element bonding and native conformation changes by couplings [61,62].

3.6. Powder x-ray diffractometer:

PXRD is often used for screening and determination of co-crystal structure [29]. The PXRD patterns obtained from diffractometer were compared to every alternative for analyzing the structure of co-crystals. The various PXRD pattern of co-crystals from their elements is that the indication of co-crystal formation [47,63]. Crystal structure of solids at atomic level co-crystals is set by victimization single crystal X-ray diffraction (SXRD). The most important downside associated with this system is that usually single co-crystal cannot be made that is appropriate for SXRD analysis [52]. Scanning microscope is that the instruments accustomed verify the particle size and morphological analysis of co-crystals. A high energy lepton beams scan the atoms that give the knowledge regarding the sample surface's topography. [31,52].

3.7. Invitro Dissolution:

Dissolution study is employed to work out the quantity of drug enhances with time in dissolution medium and predict the in vivo performance of the formulation. Dissolution studies for the co-crystals are performed with the assistance of the dissolution equipment. The dissolution study for the co-crystals is done at intervals the acceptable dissolution medium delineated in drug protocol of referred assemblage. The drug samples is collected within the appropriate amount at preset measure and might be examined with the assistance of appropriate suggests that like HPLC or UV. [64,65]

3.8. Solubility study:

Solubility study is assessed by Higuchi and tennis player methodology for solubility determination. The solubility of pure drug, physical mixture and co-crystals is determined in water or appropriate medium given within the referred assemblage. Drug sample and medium ought to be extra in an exceedingly cone-shaped flask, and will be agitated for twenty-four h at temperature on rotary flask shaker. The complete samples ought to be protected against light-weight by wrapping the flask by aluminum foil if the drug is sensitive to light-weight. When twenty four h samples area unit filtered through Whatman paper and aliquots area unit befittingly diluted and assayed by HPLC or actinic radiation at appropriate wavelength [66,67].

3.9. Stability study:

Stability study provides the knowledge regarding time period of drug product below completely different storage conditions. Medicine product ought to be unbroken in glass vials below variable environmental factors (such as wetness, temperature, light) for various intervals of time. After that, the samples area unit analyzed for thermal study, drug dissolution study, XRD study and FTIR study and compared with the results obtained before stability study [68].

4. APPLICATIONS OF CO-CRYSTALS:

- Co crystallization has a bonus to optimize the chemistry properties of medicine while not sterilization the molecular structure of medicine.
- The chew over whether co-crystals or salts will have the desired properties depends upon the API and specific project.
- Co-crystals with negative ΔpKa value will give non-ionized drug when dissolved whereas salt will give ionized API, which is more soluble in water.
- Whenever dissolution rate of drug should be important rather than equilibrium solubility, co-crystals can be better than salt form of drug.
- Co crystallization is an alternative way to enhance the solubility and bioavailability of poorly water soluble drugs, especially for those compounds which are neutral or weakly ionized in nature [68-70]. Further, co-crystallization also offers possibility of altering improving the melting point, tablet ability, solubility, stability, bioavailability and permeability.

5. CONCLUSION:

Co-crystals are very interesting and useful product. The co-crystals are solid substances, which consist of few components mixed together; the co-crystals can be applied in medicine and pharmaceutical industry for improving different properties such as dissolution rate, melting point, solubility, chemical stability and decreasing dose size. Co-crystal produced supersaturating with respect to the parent drug and improving the drug penetration and diffusion due to an enhanced amount of free drug in the medium. Moreover, the co-crystal intrinsic solubility, dissolution and coformer ionization reduced the media pH, enhancing the proportion of the unionized species and thus drug transport through passive diffusion absorption mechanism. Co-crystallization is a very useful method

for a crystal engineer to change the physical properties of solid materials. In current the results of applications of co-crystallization in pharmaceuticals are useful only at microscopic level. Strategies to produce co-crystals in larger scales are yet to be focused into, in order to get maximum useful results of whatever has been achieved at microscopic level.

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7. DECLARATION OF INTEREST:

Nil.

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