AN OVERVIEW OF THE PROMISING APPROACH TO ENHANCE THE PHYSICAL PROPERTY OF API BY PHARMACEUTICAL CO-CRYSTALLISATION TECHNIQUE

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Abstract

Co-crystals are defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions. This article summarized about the co-crystal definition, its importance along with characterizations and screening and production methods. From the literature survey, it can be concluded that improvement of performance characteristics of APIs using co-crystallization is a shows potential approach. One of the key aspects of this technique is that it can be useful to all APIs affliction from poor aqueous solubility. Co-crystallization moves toward is flourishing now adays due to its immaculate effect of solubility on poorly dissolvable drugs, especially those having weakly ionisable group and neutral compounds. Meanwhile co-crystallization will also put an effort into upgrading of other physicochemical properties of drugs such as chemical stability, flowability etc.

Keywords: Co-crystals, characteristics, screening, productions, solubility.

Introduction

Co-crystallisation is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers. Hydrogen bonds are the basis of molecular recognition phenomena in pharmaceutical systems and are responsible for the generation of families of molecular networks with the same molecular components (single component crystals and their polymorphs) or with different molecular components (multiple component crystals or co-crystals) in the crystalline state [1].

Generally co-crystals in their pure states are solids at room temperature and by convention, these normally excludes salts. Co-crystals can have different properties than the crystals of individual components. Further, co-crystals have different crystal structures than the pure components, contain different intermolecular spacing patterns, and as such they often exhibit widely different physical properties than the pure components. Co-crystals are an alternative to salts when these do not have the appropriate solid state properties or cannot be formed due to the absence of ionization sites in the API [2,3].

PHARMACEUTICAL COCRYSRTALS

Pharmaceutical cocrystals offer an alternative method to alter the dissolution rate and solubility of BCS Class II drugs. Cocrystals consist of an API and a generally regarded as safe (GRAS) molecule, with specific stoichiometric compositions (Figure 1). However, there is no single definition as to what a pharmaceutical cocrystal is. Multiple definitions appear in the literature, but a common definition is “a stoichiometric multi-component system connected by non-covalent interactions where all the components present are solid under ambient conditions” [4-6]. As both the API and coformer in a cocrystal must be solid on their own under ambient conditions, solvates and hydrates are not classed as cocrystals. However, other restrictive definitions define a cocrystal as “a crystalline complex of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, often including hydrogen bonding” [5]. This definition specifies that the API and coformer must be in the neutral form. However, there are many reports of “ionic cocrystals” in the literature, where the molecules in the crystal lattice interact via ionic bonds as well as hydrogen bonding [7-9].

![Figure 1: Multi Component Co-crystals](image-url)
Co-crystal chemistry has recently attracted supramolecular scientists. Co-crystals comprise of hydrogen bonding assembly between different molecules. Many issues related to performance characteristics of an active pharmaceutical ingredient (API) can be resolved using co-crystallization approach. Proper understanding of crystal structure of an API is required for successful formation of co-crystals with the selected co-former. This review article focused on explanation about co-crystals, intellectual property rights, their advantages and limitations. Co-crystallization can be achieved using different methods like co-grinding slurry based, solvent evaporation method, etc. Methods of co-crystallization are simple and increase the purity of the final product. Co-crystallization can be applied to the drugs prescribed in combination therapy. Stoichiometric composition of different drugs used in combination therapy can be co-crystallizing to form one solid state form. Physicochemical properties of APIs such as solubility and stability can be improved using co-crystallization approach. With due regards co-crystallization should be used with caution because of some issues during manufacturing of final product [10].

Approximately 40% of newly synthesized drugs are not able to enter market due to biopharmaceutical issues like poor solubility and poor permeability. Most number of drugs marketed is administered orally hence solubility enhancement plays a major role. There are different techniques to upgrade the dissolvability of inefficiently soluble drugs including pro-drug approach, salt formation, particle size reduction, complexation and solid dispersion. Out of all other techniques, salt formation is one of majorly used technique to improve physicochemical characteristics of drugs which includes formation of ionic bond. But nowadays development of co-crystals has evolved as a suitable technique towards improving the solubility and bioavailability of ineffectively soluble drugs that includes non-ionic bond formation. In this paper a brief and accurate précis of pharmaceutical co-crystals is stated with specific spotlight on co-crystal preparation methodologies, mechanism of co-crystal formation, characterization methods and some of the examples of pharmaceutical co-crystals are additionally outlined. The difference between salts and co-crystals, regulatory facet and also the future prospective of co-crystallization is being discussed [11].

**CO-CRYSTALLIZATION TECHNIQUES**

Crystal engineering techniques can modify solubility, permeability, bioavailability, tabletability, physicochemical properties (physical and chemical stability etc.) of a chemical entity [10].

Co-crystallization is a process in which two different molecules attached by hydrogen bonding without breaking covalent bonds. A survey from crystallographic data revealed that heteromeric molecules prefer to form hydrogen bond as compared with homomeric molecules [Figure 2]. The reason may be the two different molecules stacked firmly as compared to the same molecules [1, 10].

Co-crystallization of APIs can be achieved using different methods like solvent evaporation (solution co-crystallization), grinding method, antisolvent addition, ultrasound assisted Co-crystallization. Co-crystal formation using solvent evaporation method involves the formation of undesirable solvates or hydrates. It also suffered from the risk of formation of homomeric molecules [10, 12]. Solvent drop grinding method is a classical method, which involve the addition of only few drops of solvent and hence it is environmentally friendly [10, 13].

**CRITERIA FOR CO-CRYSTAL FORMER SELECTION**

Possible intermolecular hydrogen bonding between different molecules can be assessed using Cambridge Structural Database [10, 14]. Hansen solubility parameters (HSPs) may be used for the predicting of miscibility of two different molecules. HSPs are a simple mathematical approach, which requires knowledge of chemical structure of the molecules [10, 15]. Crystal lattice energy calculation using computational methods can predict possibility of formation of co-crystals, if the predicted lattice energy is large enough. With systematic structural studies one can easily design supramolecular synthesis for successful formation of co-crystals between two different molecules [10, 14].
CLASSIFICATION OF COCRYSTALS [16]

- Cocrystal containing drug products will not be considered to contain new APIs.
- New drug applications, NDAs, and abbreviated NDAs, ANDAs, claiming to contain a cocrystal form will have to prove the extent of proton transfer.
- The cocrystal must be shown to dissociate in vivo prior to reaching its active site. The nature and location of the putative active site varies greatly between different drug classes, such that there is significant ambiguity about how to address the dissociation requirement, especially in the case of topically active drugs (applied on skin or orally active within the GI tract, for instance).
- The API cocrystal which by definition is a crystalline multicomponent chemical compound would be considered analogous to the “API-excipient” blend that overwhelmingly represents a physical mixture of an API and excipients.

CO-CRYSTAL SCREENING

The ultimate goal of co-crystal screens is to discover a solid form of an API [17] with improved physical properties. From this perspective, an efficient co-crystal screening protocol can be split into three phase: (1) co-crystal design; (2) cocrystal screening and (3) co-crystal selection. A general guideline for co-crystal screening is schematically presented in Figure 3.

METHOD OF PRODUCTION OF COCRYSTALS [18-21]

Solid State Methods
- Contact formation
- Solid state grinding
- Twin screw extrusion
- Hot melt extrusion
- High shear wet granulation

Solution based Methods
- Evaporative co-crystallization
- Cooling crystallization
- Reaction co-crystallization
- Isothermal slurry conversion

Supercritical Fluid Methods
- Co-crystallization with supercritical solvent
- Rapid expansion of supercritical solvent
- Supercritical antisolvent co-crystallization
- Supercritical CO2 assisted spray drying

Miscellaneous Cocrystal Preparation
- Laser irradiation
- Electrochemically induced co-crystallization
- Resonant acoustic mixing
- Spray drying
- Freeze drying
- Electrospray technology
- Microwave assisted co-crystallization

DRUG PARAMETER ALTERED BY CO-CRYSTALLIZATION [22-24]

- Melting point
- Stability
- Relative humidity stress
- Thermal stress
- Chemical stability
- Solution stability
- Solubility
- Intrinsic Dissolution
- Bioavailability

CHARACTERIZATION OF CO-CRYSTALS

- Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase [25]. Melting point of pure API, co-formers and cocrystals are obtained by capillary method using liquid paraffin [26] or DSC is the preferred for obtaining melting point data and thermal data such as enthalpy of melting. DSC has recently been used as a tool for rapid cocrystal screening [27].
- SEM is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons. The electrons interact with the atoms that make
up the sample producing signals which provide information about the sample’s surface topography. It is used to determine the cocrystal micrograph and particle size [28-30].

- Single X-ray diffraction (SXRD) is a technique for determination of the solid-state structure of cocrystals at an atomic level. The problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, powder X-ray diffraction (PXRD) are utilised more frequently to verify the formation of cocrystals [28-30].

- Raman spectroscopy is used to study vibrational, rotational, and other low frequency modes in a system. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products [28-30].

ADDITIONAL ADVANTAGES OF COCRYSAL APPROACH

- Co-crystals having several advantages such as no necessitate to make or break covalent bonds, as compared to amorphous solids it is stable crystalline form, theoretical ability of all types of drug molecules such as weakly ionizable/non-ionizable to form co-crystals, the existence of numerous potential counter molecules such as food preservatives, pharmaceutical excipients, additives, and other 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 [31].

- Compared to other solid-state modification techniques employed by pharmaceutical industry, cocrystal formation appears to be an advantageous alternative for drug discovery (e.g. new molecule synthesis, nutraceutical co-crystals), drug delivery (solubility, bioavailability) and chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through cocrystallization [32].

3. SOME EARLIER REPORTED WORK

Some earlier reported work are mentioned below after searching thoroughly on various review and research article-

Maciej Przybyłek et al has reported co-crystals of salicylamide and ethenazamide using aromatic carboxylic acid co-formers such as acetylsalicylic acid, 4-acetamidobenzoic acid (acedoben) as well as mono- and dihydroxybenzoic acids via droplet evaporation crystallization resulted in increased solubility of salicylamide and ethenazamide by forming heterosynthons [33]. Co-crystals of hydrochlorthiazide using sucralose as co-former via wet co-grinding method is reported by Mona F. Arafa et al has shown significant increase in solubility and dissolution rate [34]. Rui-Zhen Lin et al has reported solvent assisted grinding method to prepare co-crystals of adefovir using gallic acid as co-former shown greater physical and chemical stability [35]. Inese Sarcevica et al used mechanochemical co-crystallization/neat grinding method to prepare co-crystals of isoniazid using benzoic acid as co-former in a stoichiometric ratio of 1:1 which have shown a good physical stability [36]. Sanaa A. El-Gizawy et al has prepared the co-crystals of hydrochlorothiazide via liquid assisted grinding with help of aerosil 200 as co-former which enhanced the solubility and dissolution rate of co-crystals [37]. Renu Chadha et al has reported solvent drop grinding method to successfully prepare co-crystals of efavirenz with the two different co-formers such as oxalic acid dihydrate and citric acid monohydrate has exhibited 1.8 and 2.7 fold enhancement solubility of co-crystals respectively [38]. Yogesh K. Nalte et al has prepared the co-crystals of nevirapine via neat grinding method using maleic acid as a co-former which shown increased solubility of drug [39].

Cherian AB et al., (2019) developed FSM Alginate beads of Vildagliptin in streptozotocin induced diabetic rats. In the present work, 6 formulations of Vildagliptin nano-particles beads (F1 to F6) were prepared by ionotropic gelation method. Fenugreek seed mucilage and sodium alginate was used as polymers and calcium chloride as cross-linking agent. Among all the formulations, F3 containing FSM and sodium alginate in the concentration of 0.6 gm and % DEE of 97.89 resulting in the highest drug release rate of 97.86% at the end of 10 h. Hence, it was considered as the optimized formulation [40]. Bhalkekar M et al., (2019) screened pharmaceutical cocrystal of fenofibrate and coformers. Preparation and evaluation of fenofibrate-coformer cocrystal and In-Vitro drug release and Ex-Vivo Permeation study was done. Cocrystal of Fenofibrate with tartaric acid was successfully prepared. The cocrystals displayed enhanced dissolution rate by 2.36-fold, similarly the ex-vivo drug uptake through everted chicken intestine model was improved by 4.38-fold. The formation of cocrystals of fenofibrate with tartaric acid was evaluated by DSC, IR and XRPD. The fenofibrate-tartaric acid cocrystal exhibited increased % drug release and permeation compared to fenofibrate [41]. Nugrahani I et al., (2018) Non-steroidal anti-inflammatory drugs (NSAID) belong to class BCS II which exhibit low aqueous solubility. The crystal engineering technique such as cocrystallization is an effective strategy to improve the solubility of drugs. The drugs are: mefenamic acid, ketoprofen, and diclofenac acid meanwhile L-proline was used as a co-former. Cocrystal screening was conducted by liquid assisted grinding (LAG) with ethanol using the equimolar ratio of drug and L-proline. The formation of the crystalline phase by LAG occurred faster than NG method. The dynamic of the cocrystal arrangement also was shown influenced by the method, in which LAG was faster than NG method [42]. Abbas G et al., (2017) developed pectin raft forming tablets for controlled release delivery of pantoprazole...
sodium sesquihydrate (PSS). The raft strength, thickness, resilience, and reflux resistance through a 10mm orifice of optimized formulation PR9 were 7.43 ± 0.019 g, 5.8 ± 0.245 cm, greater than 480 min, and 2490 ± 0.004 g, respectively. The buffering and neutralizing capacity was 11.2 ± 1.01 meq and 6.5 ± 0.56 meq, respectively. Dissolution studies were performed by using simulated gastric fluid at pH 1.2, and the cumulative percentage release of PR9 was found to be 97%. First order release kinetics was followed, and non Fickian diffusion was observed as the value of n was greater than 0.45 in the Korsmeyer–Peppas model [43]. Tekade BW et al., (2017) formulated the floating drug delivery system containing Pantoprazole tablets were prepared by direct compression technique. Formulations contained Limonia acidissima, Xanthan gum, and gas generating agent such as sodium bicarbonate and citric acid. Percentage drug content in all floating tablet formulations was found to be 90% to 110%. The in vitro drug release profiles obtained for tablets (F3) made with combinations of Limonia gum and xanthan gum showed lesser floating lag time (46 s) and a prolonged floating duration (18 hrs) which was a sustained release characteristic (94.30%) for 18h. Among all the formulation, F4 showed drug release upto 94.30% at the end of 18 hours [44]. Ganesh M et al., (2015) prepared chitosan co-crystals of aceclofenac and its entrapment into alginate matrix a super saturated drug delivery system (SDDS). The result revealed that the primary co-crystals enhanced the solubility of the drug and the thick gelled polymer matrix that formed from swelling of calcium alginate beads makes it to release the drug in continuous and sustained manner by supersaturated drug diffusion. The Cmax, Tmax and relative bioavailability for aceclofenac co crysal and aceclofenac SDDS were 2.06 ± 0.42 µg/ml, 1 h, 159.72 ± 10.84 and 2.01 µg/ml, 1 h, 352.76 ± 12.91, respectively. Anti-inflammatory activity of aceclofenac was significantly improved with the SDDS [45]. Mounika P et al., (2015) formulated co crysal based solid dosage form consisting of a stoichiometric amount of parent drug Fexofenadine with a pharmaceutically acceptable co-former Tartaric acid. Firstly, co-crystals are prepared through Solvent evaporation method by taking Fexofenadine and Tartaric acid in 1:1 ratio. When compared to the formulation of Fexofenadine the formed co crysal has shown max drug release of 86.9% with 0.01 N HCL as a dissolution medium. From the pharmaceutical characterization, prepared molecular complex has shown increased solubility and increased drug release profile [46]. Ullah M et al., (2015) explored the influence of three commonly used polymers, that is, cellulose and noncelluloses, for example, Methocel K4M, Kollidon VA 64, and Soluplus, on the phase disproportionation and drug release profile of carbamazepine succinic acid (CBZ-SUC) co crysal at varying drug to polymer ratios (1:1 to 1:0.25) in matrix tablets. The percent drug release from HPMC formulations (CSH) showed inverse relation with the concentration of polymer. On contrary, direct relation was observed between percent drug release and polymer concentrations of Kollidon VA 64/Soluplus (CSK, CSS). At similar polymer concentration, drug release from pure carbamazepine was slightly lower with HPMC formulations than that of co crysal; however, opposite trend in release rate was observed with Kollidon VA/64 and Soluplus [47]. Joseph J et al., (2014) developed and evaluated floating microspheres of Pantoprazole Sodium. Floating microspheres of Pantoprazole Sodium were prepared by solvent evaporation method using HPMC K15M and ethyl cellulose as polymer. Seven different formulations were developed. Results show that as the concentration of polymer ethyl Cellulose increases it affects the particle size, percentage yield, in vitro buoyancy and drug release of microsphere. Results of present study suggest that floating microsphere of Pantoprazole sodium can be successfully designed for controlled drug delivery [48]. Gobinath T et al., (2014) prepared tablets of pantoprazole sodium were prepared by direct compression method using different concentration of, microcrystalline cellulose as filler, mannitol and dicalcium phosphate as diluents, croscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. The prepared tablets were coated using enteric coating polymer such as cellulose acetate phthalate, Eudragit L100 and by dip coating method. Prepared all batch’s C2F9 was found best, with hardness 5.60 ± 0.24 (Kg/cm2), drug content 99.08 ± 0.35(%), disintegration time 7.02± 0.21(min), and percentage cumulative drug released which started after 120 min and reached 99.72 after 180 min [49]. Allam AN et al., (2013) illustrated the influence of chitosan on the dissolution rate and bioavailability of acyclovir through the preparation of co-crystals by simple solvent change method. Chitosan was precipitated on acyclovir crystals using sodium citrate as the salting out agent. The results obtained showed that the practical yield of the prepared co-crystals was found to be inversely proportional to chitosan concentration. The drug content of the co-crystals was uniform among the different batches. The prepared co-crystals showed a slower drug release when compared to that of pure drug. The considerable change in the dissolution rate of acyclovir from optimized crystal formulation was attributed to the wetting effect of chitosan, the reduction in drug crystallinity and the altered surface morphology [50]. Childs SL et al., (2013) prepared cocrystals in order to establish improved solubility of danazol, a 1:1 danazol:vanillin cocrystal was formed. The neat aqueous suspension of the danazol:vanillin cocrystal had a modest in vivo improvement of 1.7 times higher area under the curve compared to the poorly soluble crystal form of...
 danazol dose under identical conditions, but the formulated aqueous suspension containing 1% vitamin E-
TPGS (TPGS) and 2% Klucel LF Pharm hydroxypropylcellulose improved the bioavailablility of
the co-cystal by over 10 times compared to the poorly soluble
danazol polymorph [51]. Shibkar A et al., (2011)
formulated and characterized co-crystals of
Carbamazepine (CBZ) and Nicotinamide (NCT) and
inclusion complexes of these co-crystals with γ-
cyclodextrin (CD). Gas anti-solvent method of supercritical
fluid process (SCF) was used as the method of preparation.
The dissolution studies show a 2.5-fold increase in
dissolution rate in the case of co-crystals and a 40-fold
increase when co-crystals were complexed with CD. A
lower melting point (160 °C) was observed in the case of
co-crystals and the exothermic peaks were missing for
pure CBZ and co-crystals when they were complexed with
CD [52]. Gupta NV et al., (2009) developed Superporous
Hydrogel (SPH) and SPH composites (SPHC) as pH-sensitive
drug delivery system for Pantoprazole sodium.
Superporous hydrogels containing poly(methacrylic acid-
copolymer) with interconnected pores of several
hundreds of micrometer were prepared using radical
polymerization of methacrylic acid and acrylamide in the
presence of N,N-methylene-bis-acrylamide as crosslinking
agent. A gas blowing method using bicarbonate as a
foaming agent was applied to introduce the porous
structure. Results indicated that SPH polymers have more
pores and higher swelling ratio but less mechanical
stability compared to SPH composite polymers, which have
less pores and lower swelling ratio but a higher mechanical
stability [53]. Liu SP et al., (2006) investigated the
preparation and stability of pantoprazole sodium enteric
tablets. The formulation of (l)-pantoprazole sodium enteric
tablets was optimized by an orthogonal design involved in
3 factors and 3 levels [quantity of sodium carbonate (0.5%
,10%), types of binders (MC, HPMC, PVP) and
concentration of binders (2% ,5%, 8%)]. The PVP and
sodium carbonate were considered the optimal binder and
stabilizer, respectively. No changes in the content and the
related substances of the tablets were observed after the
tablets were placed under an accelerated storage
condition for 6 months [54].

CONCLUSION

This article summarized about the co-crystal definition, its
importance along with characterizations and screening
methods. From the literature survey, it can be concluded that
improvement of performance characteristics of APIs
using co-crystallization is a promising approach. Although
there are some limitations but applying practical
knowledge can resolve the issues related to co-crystal
formation of an API. One of the important aspects of this
 technique is that it can be applied to all APIs suffering from

poor aqueous solubility. Co-crystallization approach is
blooming nowadays due to its impeccable effect of
solubility on poorly dissolvable drugs, especially those
having weakly ionisable group and neutral compounds.
Meanwhile co-crystallization will also put an effort into
improvement of other physicochemical properties of drugs
such as chemical stability, flowability etc. The involvement
of nutraceuticals as co-formers is found to be highly
successful in terms of treating multiple diseases or to
exhibit synergistic effect. The expansion of industrially
significant methodologies for the production of co-crystals
and using nutraceuticals as co-formers for the additional
benefits can be expected in near future.

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