REVIEW ARTICLE

Co-crystallization: An approach to improve the performance characteristics of active pharmaceutical ingredients

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Co-crystal chemistry has recently attracted supramolecular scientists. Co-crystals are comprising of hydrogen boding 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 focus 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-crystallize 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.

Key words: *Chiral switch, crystal engineering, hydrogen bonding, intellectual property rights, polymorphism*

INTRODUCTION

Pharmaceutical Industry involved in formulation development are facing huge problem while dealing with undesirable performance characteristics of active pharmaceutical ingredients (APIs). Unfortunately many API with very good pharmacological activity display unfavorable bioavailability due to undesirable physical properties.[1] Numerous approaches exist like formation of salts, solvates, polymorph etc., to improve performance characteristics of API as shown in Figure 1. All these strategies often depend on the physicochemical nature of the considered molecules, which limit widespread application. To deal with poor solubility of API of concerned, various strategies applied like salt formation, physical stabilization, encapsulation etc.

The formation of salts of APIs is widely used approach to improve the physical properties of APIs. Salt formation is an acid–base reaction between the API and an acidic or basic compound. The widespread use of salt formation is evidenced by the large number of marketed crystalline salts of APIs. Salt formation requires a difference of about 2.7 pKa units between the conjugate base and the conjugate acid that is, (pKa [base]-pKa [acid] $\geq$2.7). Salt formation requires ionizable center on the API of interest. Limitation of this strategy includes only fewer number of nontoxic, pharmaceutically acceptable acids and bases are available for salt formation. Literature review revealed that only 10 salt forming acidic counter ions with a market usage rate of over 1% and the number of comparable basic counter ions is even less.[2] Many strategies exist to improve the bioavailability of an API concerned but they had limited success. Along with these available strategies to improve the bioavailability of drugs, formation of co-crystal of an API opened a new avenue as an alternative approach [Figure 2].

Co-crystals are different from the traditional pharmaceutical solid-state forms. They are assembly

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Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.160309

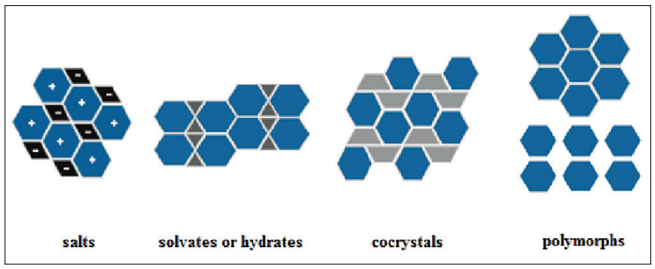

Figure 1: Molecular structural difference between co-crystals, salts, solvates or hydrates and polymorphs

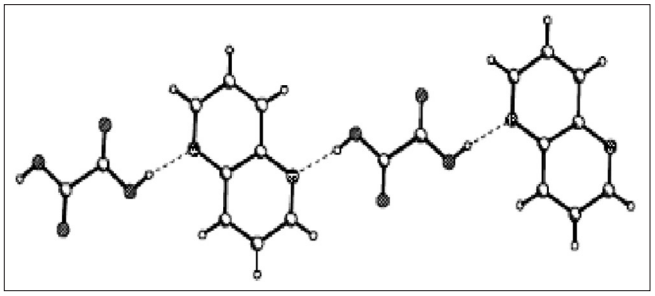

Figure 2: Hydrogen bonding framework between two different molecules

of two or more different molecules whose physical properties are often superior with respect to individual component.[3] Neutral molecules involved in co-crystal formation are solids at ambient temperature and in definite stoichiometric amounts. Co-crystals are classified as 0-D, 1-D, 2-D or 3-D assembly depending upon the type of intermolecular interactions that are present within and between collections of certain molecules. As per the early publications, nomenclature of the co-crystals provided based on the chains, dimers, rings and intermolecular hydrogen bonding. Pattern recognition in co-crystals is denoted using widely used descriptors such as $R^2_4(8)$ (an eight membered ring with four hydrogen bond donors and two hydrogen bond acceptors) and $R^2_2(8)$ (e.g., the carboxylic head to head dimer).[4] The reason for selecting co-crystal formation is its modularities to have tailored properties for enhancing bioavailability as well as processability of the solid material inputs in final product manufacturing.[5] Many issues can also be addressed by co-crystallization along with bioavailability.

ISSUES RELATED TO PERFORMANCE CHARACTERISTICS OF ACTIVE PHARMACEUTICAL INGREDIENTS

Processability of an active pharmaceutical ingredient during formulation and development (formulation processability)

Solid oral dosage forms are most preferred due to patient compliances. And there are many issues during formulation of drugs like flow property, stickiness, electrostatic charge development in solid particles. It is very difficult to develop formulation of hygroscopic compounds. Bioavailability of Biopharmaceutical Classification System Class II and IV drugs depend on the aqueous solubility. Hence in order to increase bioavailability of such drugs, improvement of aqueous solubility plays an important role. In order to improve aqueous solubility of drugs it is requisite to consider particle size (should be D50 and D90) of solid particles. Masking taste of an API for pediatric formulation is a big challenge in formulation development.

Stability (chemical stability)

"A racemic or chiral switch may be defined as the development of a single enantiomer from a previously marketed racemate."[6] Number of drugs remarketed as single enantiomeric products as a result of chiral switching. To get entry into market it is very critical if the sponsor of the single enantiomer is not responsible for the original one. Regulatory authorities give permission only if single enantiomer show comparable pharmacokinetic profile with the previously marketed racemate. With this, scientific justification also required based on quality, safety and efficacy, together with the risk-benefit ratio. There are many examples of drugs which undergone chiral switch like levofloxacin ((S)-ofloxacin), dexibuprofen ((S)-ibuprofen), levalbuterol ((R)-salbutamol) and so on.[7]

Generation of co-crystals during pharmaceutical manufacturing processes and storage

During storage of solid dosage forms, co-crystal formation may be possible if hydrogen bonding is more favored in heteromolecules as compared to homomolecules. Furthermore, amorphous form of API is more prone to form co-crystals under condition, which favored molecular mobility. Co-grinding during manufacturing may also result in the co-crystal formation and is more prominent in hydrated molecules. Hence, it is important to include co-crystal transformation during specified storage condition and manufacturing of an API in the document list along with polymorphs and solvates.[8]

Polymorphism

Physical stability of final product during the formulation and shelf life is equally important with chemical stability. If the product is affected by polymorphism can lead to serious pharmaceutical consequences. Also reproducibility of the process to make the desired form again and again is very critical in dealing with polymorphism. Due to the difference in physical as well as chemical properties of polymorphs it is very critical from regulatory as well as intellectual property point of view.[9]

DIFFERENT APPROACHES TO IMPROVE SOLUBILITY

Solubility of API may be improved using either physical modifications or by chemical modifications. Physical modification includes particle size reduction, amorphous

form, solid dispersion, co-crystallization etc., while chemical modification includes change of pH, derivatization, complexation and salt formation.[3]

Hot melt extrusion technology

Drug is embedded in thermoplastic carrier by heating with help of intense mixing. Hot melt extrusion is a viable option for the formulation development of poorly soluble drugs. Use of right polymer/solubilizers, plasticizers is required for glass solution formulation. Usually amorphous form of drug is obtained. Simple technique but not suitable for thermolabile drugs. One more limitation includes both carrier and API should be miscible in molten form.[10]

Nano emulsions

A clear, isotopic, thermodynamically stable dispersion of one liquid into another with size <200 nm. Discovery of nanoformulation leads to improvement of performance characteristics as well as better drug delivery. Nano emulsion shows enhanced permeability and bioavailability, which can be enhanced 1000–5000-fold. Although having many advantages, nano formulations are not cost effective and involve complex formulation methods.

Supercritical fluid method

It involves particle size reduction of solid via supercritical fluid processes. Drug particle size can be reduced greatly to submicron levels to enhance solubility. Critical temperature and pressure control are required to get supercritical fluids, which behave as a liquid and gas.[11,12]

Cryogenic techniques

The technique involves an increase in the surface area of drug particles by the formation of amorphous aggregates. Solubility of drug particles may be improved with an increase in surface area. The main limitation includes complex technical requirements.[13-15]

Inclusion complex

The dissolution rate of the drug may be improved more precisely using inclusion complex techniques. It involves insertion of the nonpolar molecule in to the cavity of other molecule usually cyclodextrins. By kneading technique, inclusion complex can be prepared very easily at laboratory scale. It is simple and cost effective method to improve the physical properties of drug molecules. The drawbacks of this technique are very poor flowing property of solid particles and involves long process time.[16]

Micellar solubilization

Surfactants are used to improve the dissolution profile of poorly water soluble APIs. Surfactant reduces surface tension and increase the solubility of hydrophobic drugs in aqueous solution. It suffers from several limitations like poor drug solubilizing ability, poor stability in water after drug loading and poor stability in case of higher content.[17]

Hydrotrophy

It is a technique which involves salt out effect. The addition of a large amount of solute increase water solubility of API of concern. Hydrotrophs improve solubility by the formation of self-assembly in solution. The main disadvantage includes the method is not applicable to all APIs suffering from poor solubility.[18]

CO-CRYSTALLIZATION TECHNIQUES

Crystal engineering techniques can modify solubility, permeability, bioavailability, tabletability, physicochemical properties (physical and chemical stability etc.) of a chemical entity. 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 3]. The reason may be the two different molecules stacked firmly as compared to the same molecules.[4]

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.[8] Solvent drop grinding method is a classical method, which involve the addition of only few drops of solvent and hence it is environmentally friendly.[19]

Criteria for co-crystal former selection

Possible intermolecular hydrogen bonding between different molecules can be assessed using Cambridge Structural Database.[20] Hansen solubility parameters (HSPs) may be used for the predicting of miscibility of two different molecules. HSPs is a simple mathematical approach, which requires knowledge of chemical structure of the molecules.[21] 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

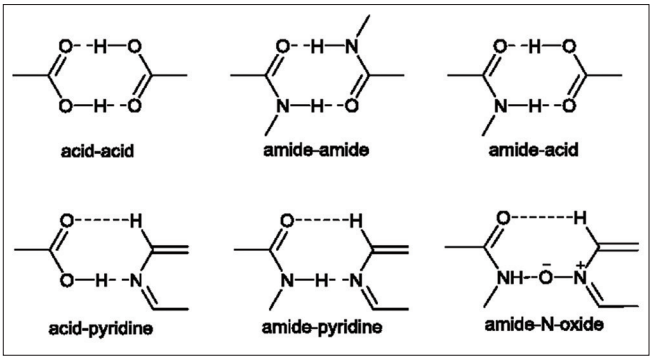

Figure 3: Examples of some common strong hydrogen bonded homosynthons and heterosynthons

successful formation of co-crystals between two different molecules.[20]

ADVANTAGES

In place of salt formation, pharmaceutical co-crystallization may be employed to all APIs. There are large number of counter molecules available like food additives, preservatives, pharmaceutical excipients, vitamins, minerals, amino acids and other biomolecules, as well as other APIs for co-crystallization.[20]

Co-crystal formation from polymorphic compounds is easier as compared to compounds that never display polymorphism. Molecules which show polymorphism can potentially form hydrogen bond in several well-defined and robust intermolecular interactions.[4]

Co-crystallization and recrystallization find only difference in dealing with heteromeric molecules and homomeric molecules respectively. So, it may be used as a tool to purify API in the form of co-crystals.

As per the industrial applicability synthesis of co-crystal using solvent drop grinding method required less quantity of solvent. Solvent drop grinding method or kneading does not involve evaporation of large quantities of solvent. Hence, it is economic as well as demonstrate green chemistry approach.[19]

In addition grinding method also does not require any purification or filtering procedure.[5]

Intellectual property rights

Co-crystallization of an API results in new chemical form with improved physicochemical properties and hence it satisfy the novelty requirement as well as utility. Recently it was also reported that co-crystal formation of an API, may reduce its susceptibility to show polymorphism. Patent protection of approved solid form can be extended by making co-crystals of core chemical structure, which will lead to increase in revenue and improved market position. There is also a chance of early market entry of a solid form with enhanced performance characteristics using co-crystal formation. The invention is not novel if it was disclosed in prior publication with respect to inherent anticipation. For example the case involving paroxetine HCl, patent was filed by SmithKline Beecham Corporation first for anhydrate form than as hemihydrate form.[22] Hemihydrate form claimed to be superior quality as compared to anhydrate form.[22] So when earlier patent covering anhydrate form was expired Apotex Corporation, filed an abbreviated new drug application with generic anhydrate paroxetine HCl. Patent litigation was done whether the generic product would infringe the hemihydrate claim of SmithKline. In one argument SmithKline proved that during crystallization along with anhydrate form, some hemidydrate form also crystallized out.[23] Based on the argument court decided that generic product would infringe the patent. With this also the validity of patent of the SmithKline hemihydrate form was in trouble. Since in the patent of anhydrate form method described would have generated some hemihydrate form also. As a result generic company got regulatory approval for paroxetine HCl as the hemihydrate crystal form expired. This kind of inherent anticipation is less possible with co-crystals. During crystallization methods co-crystallizing molecules, generally not introduced because it (co-crystal formation) was not intended. Hence with significant research on an API in the past, discovering co-crystals may be less prone to inherent anticipation.[20]

Co-crystallization approach for combining multiple drugs

Drugs prescribed in combination for a particular disease may be co-crystallize to obtained single solid dosage form. Recently, this strategies attracted supramolecular scientists. It reduces administrative and production costs. Combining two or more drugs by co-crystallization improves physical properties of APIs along with patient compliances. Žegarac *et al*. screened multidrug co-crystals of sildenafil with Aspirin and also discuss about their potential to improve the therapeutic effects.[24]

LIMITATIONS

Although preparation of co-crystals is simple but exact relationship between co-crystal structure and physical properties still unexplored.[23]

The optimum temperature range should be known for solid-state grinding method because excessive heating may cause accidental phase transition, conglomerate crystallization or polymorphism.[25]

Solid state grinding method results in too small particle size and hence it is difficult to identify structure using X-ray crystallography.[25]

Phase separation of co-crystals into individual component up on storage at certain relative humidity condition also a concern for its applicability.[20]

Another limitation includes phase change during formulation development of API. Co-crystals may also be susceptible to counter ion displacement with excipients during manufacturing.[20]

CONCLUSION

This article summarized about the co-crystal definition, its importance along with limitations. 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 aspect of this technique is that it can be applied to all APIs suffering from poor aqueous solubility. As per the intellectual property right perspective if a molecule satisfy all the criteria then the patent may be granted for co-crystal drug product intermediate. Finally, we conclude that systematic structural exploration of molecules and their possible hydrogen boning pattern can lead to the formation of very good co-crystals.

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How to cite this article: Savjani JK. Co-crystallization: An approach to improve the performance characteristics of active pharmaceutical ingredients. Asian J Pharm 2015;9:147-51.

Source of Support: Nil. **Conflict of Interest:** No.