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Review Article

Pharmaceutical Cocrystals: Modern solubility enhancement approach based on crystal engineering.

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ABSTRACT
Over 40% of active pharmaceutical ingredients in development are poorly water soluble drugs which limit formulation approaches, application and marketability because of their low dissolution and bioavailability. Pharmaceutical Co-Crystal is a promising tool to modify solubility, dissolution rate and physical and chemical stability of drug substances while keeping the pharmacological effect of drug unchanged. Co crystals are defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non covalent interactions.Cocrystallization is a flourishing research field with direct application to the pharmaceutical industry.Co-Crystal are stoichiometric multi-component system connected by non-covalent interactions in which two distinct components are solid under ambient conditions. A pharmaceutical Co-Crystal constitutes active pharmaceutical ingredient and benign substance called a coformer. Co-Crystallization is a result of competing molecular associations between similar molecules, or homomers, and different molecules or heteromers .Co-Crystal is used in medicine and pharmaceutical industry for improving different properties such as dissolution rate, melting point, solubility, chemical stability etc. Pharmaceutical co crystals, is most promising method for enhancing the bioavailability of drugs with low aqueous solubility. This review focus on various aspects of Pharmaceutical Cocrystal.

KEYWORDS
Co- crystallization, Pharmaceutical Co-Crystal, Slurring technique, polymorphs, co solvents.

1. INTRODUCTION

Over the last decade, there has been growing interests in the design of pharmaceutical co crystals, which emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility[1]. Crystallization is defined as alteration of physical properties of by modifying drug at molecular level. For Cocrystallization drug and coformer for formation of cocrystal is needed[2].

Co-Crystal incorporated pharmaceutically acceptable guest molecules into crystalline lattice along with the API. Co-Crystal have regained attention as attractive alternate solid forms for drug development[3,4]. Physiochemical properties of pharmaceuticals can be improved by obtaining Co-Crystal using Co-Crystal lization. Co-Crystal lization with pharmaceutically acceptable compounds does not affect pharmacological activity of API but can improve physical properties, such as solubility, hygroscopicity, compaction behavior[5, 6].

A pharmaceutical Co-Crystal is a single crystalline solid that incorporates two neutral molecules, one being an API and the other a Co-Crystal former. It may be an excipient or another drug. Pharmaceutical Co-Crystal technology is used to identify and develop new proprietary forms of widely prescribed drugs and offer a chance to increase the number of forms of an API. Scientists showed that modifying the physical properties of a pharmaceutical compound through pharmaceutical Co-Crystal formation improved the performance of a drug known to have poor solubility[7]. Pharmaceutical Co-Crystal lization is a reliable method to modify physical and technical properties of drugs such as solubility, dissolution rate, stability hygroscopisity, and compressibility without alternating their pharmacological behavior.[8]

1.1 Role of Cocrytal technology in solubility Improvement

BCS class II is defined by drugs of high permeability and low solubility. High permeability is a positive trait of these drugs but low solubility poses a big challenge to formulation scientists. In the pharmaceutical industry, it is the poor biopharmaceutical properties rather than toxicity or lack of efficacy that are the main reasons why less than 1% of active pharmaceutical compounds eventually appear into the marketplace Among these biopharmaceutical properties, solubility remains a key issue with drugs often discarded during commercial production due to their low solubility. Improving the solubility of drugs is currently one of the main challenges for the pharmaceutical industry. Many approaches have been adopted for improving the aqueous solubility of drugs including micronization, salt formation, emulsification, solubilization using cosolvents, and the use of polymer drug vehicles for delivery of poorly soluble drugs. Although these techniques have been shown to be effective at enhancing oral bioavailability, success of these approaches is dependent on the specific physicochemical nature of the molecules being studied[8, 9].

1.2 Advantages of Co-Crystal

1. When using Co-Crystals, the bulk material and the physicochemical properties of the API can be modified while still maintaining the intrinsic activity of the drug molecule.
2. From a physical properties perspective, a key advantage of using Co-Crystal to transform an API into a solid form is the possibility of achieving a high dissolution rate.

3. Diversity shown by pharmaceutical cocrystals alone will afford a number of forms with a variety of cocrystal former which is anticipated to improve physical properties such as solubility, stability, hygroscopicity and dissolution rate etc.
4. Isolation and purification of APIs can also be achieved through Co-Crystallization by discarding the cocrystal former before formulation.
5. They are emerging as an attractive option to polymorphs, salts, solvates and crystal habit manipulation in dosage form design.[10]

1.3 Techniques of Preparation of Co-Crystals

Different techniques for the preparation of Co-Crystal are:

Solvent evaporation technique

This technique is the common way to synthesize Co-Crystal s. In this method Co-Crystal components or Co-Crystal formers are taken in stoichiometric ratio and solubilize in a common solvent. The resultant solution is allowed to evaporate slowly. This technique works on the principle that, when different molecules of complimentary functional groups afford hydrogen bonds that is more favorable than each of the individual molecular components. In this case, the Co-Crystal is likely to be thermodynamically favored.

Melting technique

By simply melting two Co-Crystal formers together and cooling, a Co-Crystal may be formed. If a Co-Crystal is not formed from a melt, a seed from a melt may be used in a crystallization solution in order to afford a Co-Crystal.

Solid state grinding technique

This technique is also called as mechanical milling or neat grinding technique. Co-Crystal formers are taken in stoichiometric amounts and ground together manually using a mortar and pestle, using a ball mill, or using a vibratory mill. Normal milling time is 60 minutes.

Slurring technique

It is the Slurries-induced formation of Co-Crystal line phase among two or more active solid materials or between the active solid materials and the excipients. Equimolar were dissolved in small amount of methanol at ambient temperature. The solution was slowly evaporated at room temperature during 48 hours to promote Co-Crystal lization.

Solvent drop technique

This technique is also called as liquid assisted grinding or kneading. This involves the grinding of stoichiometric amounts of coformers with the aid of small amount of liquid. This method was developed in order to increase the rate of Co-Crystal formation, but has advantages over solid state grinding such as increased yield, ability to control polymorph production, better product crystallinity, and applies to a significantly larger scope of Co-Crystal formers. This method also enhances the Co-Crystallization selectivity.

Supercritical fluid technology

Pharmaceutical Co-Crystal can be formed also by use of supercritical fluids. Supercritical fluids act as a new media for the generation of Co-Crystal s. Supercritical fluid technology offers a new platform that allows a single-step generation of particles that aredifficult or even impossible to obtain by traditional techniques. The generation of pure and dried new Co-Crystal can be

achieved due to unique properties of super critical fluids by using different supercritical fluid properties.

By using intermediate phase

Using intermediate phases to synthesize these solid-state compounds are also employed. Through the use of a hydrate or an amorphous phase as an intermediate during synthesis in a solid-state route has proven successful in forming a Co-Crystal. Also, the use of a metastable polymorphic form of one Co-Crystal former can be employed. In this method, the metastable form acts as an unstable intermediate on the nucleation pathway to a crystal. As always, a clear connection between pair wise components of the Co-Crystal is needed in addition to the thermodynamic requirements in order to form this compounds.[9]

1.4 Mechanism for Co-Crystal synthesis

Amorphous phases generated by pharmaceutical processes lead to Co-Crystal formation during cogrinding and storage[10]. The mechanisms underlying moisture uptake generated Co-Crystal of carbamazepine-nicotinamide, carbamazepine-saccharin, and caffeine or theophylline with dicarboxylic acid ligands (oxalic acid, maleic acid, glutaric acid, and malonic acid) when solid mixtures with Co-Crystal reactants were exposed to deliquescent conditions involve (i) moisture uptake, (ii) Co-Crystal aqueous solubility, (iii) solubility and dissolution of Co-Crystal reactants, and (iv) transition concentration[11] For carbamazepine: nicotinamide Co-Crystal synthesis, nucleation and growth of Co-Crystal were directed by the effect of the Co-Crystal components on reducing the solubility of the molecular complex to be crystallized[12].

A molecular-level mechanism for two cases of mechanochemical Co-Crystal lization via halogen bonds was reported and was based on the observation and structural characterization of intermediates that appeared in early stages of the reaction. The mechanism arises from the competition of strong and weak intermolecular halogen bonds of the N...I and S...I type and involves the initial formation of finite molecular assemblies, held together via N...I bonds that subsequently polymerize into infinite chains by cross-linking through S...I bonds[13] Co-Crystal lizations of exemestane and megestrol acetate improved initial dissolution rates compared to the respective original crystals. The mechanism of dissolution enhancement varied. With exemestane/maleic acid Co-Crystal, fine particle formation resulted in enhancement, whereas with megestrol acetate /saccharin Co-Crystal, enhancement was due to the maintenance of the Co-Crystal form and rapid dissolution before transformation to the original crystal[14].

1.5 Characterization of Co-Crystal

Characterization of Co-Crystal involves both structure (infrared spectroscopy, single crystal x-ray crystallography and powder x-ray diffraction) [15-17] and physical properties (e.g. melting point apparatus, differential scanning calorimetry, thermogravimetric analysis)[17,18]. The analytical potential of NIR spectroscopy for Co-Crystal screening using Raman spectroscopy as a comparative method has been reported[19]. A compound-sparing, automated and green differential scanning calorimetric method was developed for rapid Co-Crystal screening which demonstrated the formation of carbamazepine – nicotinamide Co-Crystals[19]. Co-Crystal of a phosphodiesterase-IV inhibitor with L-tartaric acid was characterized [20]. Co-Crystal of (−)-gossypol with a C_{1-8} carboxylic acid or C_{1-8} sulfonic acid which are useful as inhibitors of Bcl-

2 family proteins and use of Co-Crystal of (−)-gossypol with a C_{1-8} carboxylic acid or C_{1-8} sulfonic acid for inducing apoptosis in cells and for sensitizing cells to the induction of apoptotic cell death were characterized ((e.g. (-)-Gossypol- acetic acid Co-Crystal)[21]. Single crystals of the 1:1 Co-Crystal of piracetam and gentisic acid obtained via slow evaporation from acetonitrile. Co-Crystal or prepared via grinding or slurrying in water was characterized by IR, melting point, DSC, PXRD and single crystal X-ray diffraction[22].

1.6 Polymorphism of Co-Crystal

Polymorphism in multi-component crystals is gaining interest in the recent times in the context of pharmaceutical Co-Crystals. Polymorphs have different stabilities and may spontaneously convert from a metastable form (unstable form) to the stable form at a particular temperature. In addition, they exhibit different melting points and solubilities which affect the dissolution rate of drug and thereby, its bioavailability in the body. Co-Crystal polymorphs suggest additional options to modify properties, increase patent protection, and improve marketed formulations. Co-Crystal of 4-hydroxybenzoic acid and 2,3,5,6-tetramethyl-pyrazine (2 : 1) exhibited the first supramolecular synthon polymorphism in a Co-Crystal ; metastable anti-hierarchic polymorph I was converted to stable hierarchic form II[23] Preparation of polymorphic Co-Crystal I and II (temozolomide: 4,4-bipyridine-N,N-dioxide (1:0.5 and 2:1) were optimized by using solution crystallization and grinding methods. The metastable nature of Co-Crystal II was ascribed to unused hydrogen-bond donors/acceptors in the crystal structure[24]

Nanocrystal and Nanopharmaceutical Co-Crystal

A nanocrystal refers to any nanomaterial with at least one dimension ≤ 100nm and it should be single crystalline[25,26]. The production of drug nanocrystals by bottom up techniques (with main focus on particle diminution by high pressure homogenization) for many new chemical entities of very low solubility has been reported. The transfer of the liquid nanosuspensions to patient convenient oral dosage forms such as tablets and capsules have also been reported[27].

1.7 Applications of Co-Crystal in Pharmaceutical sector

Compared to other solid-state modification techniques employed by pharmaceutical industry, Co-Crystal formation appears to be an advantageous alternative for drug discovery, drug delivery and chiral resolution. Experts are of the opinion that pharmaceutical intellectual property landscape may benefit through Co-Crystallization[29,30]

1.8 Few examples of drugs having Cocrystal are reported by various Researcher

Theophylline, Nalidixic acid, Piroxicam, Fluoxetine, Caffeine, Griseofulvin, Danazol, Clarithromycin, Ketoprofen, Simvastatin, Flurbiprofen, Itraconazole, Carbamazepine, Adefovir, Dipivoxil, Furosemide, Paracetamol, Norfloxacin, Celecoxib,Temozolamide, Isoniazid, Ethenzamide, Lamivudine, Myricetin[31,32].

2. CONCLUSION

Co-Crystal of drugs and drug candidates represent a new type of material for pharmaceutical development. Co-Crystal is relatively new to pharmaceutical industry and pharmaceutical Co-Crystal has given a new direction to deal with problems of poorly soluble drugs. Pharmaceutical Co-Crystals possess a high potential for API physical and biopharmaceutical

Property enhancement, and therefore constitute a field of study that is currently experiencing rapid development.Co-Crystal have the potential to be much more useful in pharmaceutical products than solvates or hydrates. Application of pharmaceutical cocrystals is very important alternative way to improve the bioavailability of poorly water-soluble drugs. Researcher working on pharmaceutical Co crystals should focus on exploring Co crystals application is drug pharmacological action modification.

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