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A Concise Review On Pharmaceutical Cocrystals: An Approach Of Solubility Enhancement Of Drug

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Abstract

The poor aqueous solubility of drugs presents significant challenges in pharmaceutical development and clinical efficacy. Understanding the underlying factors contributing to poor solubility is essential for the design of effective drug delivery systems and formulations to improve therapeutic outcomes. The solubility of a drug in water is a critical factor influencing its absorption, distribution, metabolism, and excretion (ADME) within the body. However, many drugs exhibit poor aqueous solubility, posing significant challenges in their formulation and therapeutic efficacy. Cocrystals represent a promising approach in pharmaceutical science to address the challenge of poor drug solubility. These crystalline structures consist of two or more molecular entities, typically a drug molecule and a coformer, held together by non-covalent interactions. By altering the solid-state properties of the drug, cocrystallization offers a pathway to enhance solubility, stability, and bioavailability, thereby improving therapeutic outcomes. Thus, present concise review highlights use of cocrystals in solubility enhancement of drug.

Keywords: Poor solubility, Cocrystallization, Cocrystals

Introduction

The poor aqueous solubility and dissolution rate of active pharmaceutical ingredient is one of the main challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase. The lead molecules discovered utilizing these screens is increasingly larger and more lipophilic. The improvement of solubility and dissolution profiles of these lipophilic drug molecules without altering the molecular structure is a particular challenge for the successful development of pharmaceutical products. According to the Biopharmaceutics Classification System (BCS), a drug compound is poorly soluble if the highest dose strength is not soluble in 250 ml aqueous media over the pH ranges of 1.2 – 6.8 at 37^0C. These compounds mostly belong to Class II, which are poorly soluble and highly permeable according to the pH of the gastrointestinal fluid and tend to present dissolution-limited absorption. Despite of their high permeability, these drugs often have low oral bioavailability because of their slow and limited release of drug in gastrointestinal fluid. Therefore, one of the major challenges of the pharmaceutical industry is to

apply strategies that improve the dissolution and/or apparent solubility of poorly soluble drugs to develop such problematic compounds into orally bioavailable and therapeutic effective drugs.

In the pharmaceutical industry, many life-saving drug compounds have to be discarded during the commercial production due to their low solubility. Solubility improvement of poorly water soluble drug compounds is one of the main challenges for the successful development of new drugs. Many approaches have been adopted for improving the aqueous solubility of drugs such as micronisation, salt formation, emulsification, solubilisations using co-solvents 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. Over the last decade, there has been growing interest in the design of pharmaceutical co-crystals, which emerges as a potential approach to enhance the solubility of drug compounds. Co-crystallization as a method of obtaining new forms of Active Pharmaceutical Ingredients (APIs) with improved physicochemical properties (e.g. solubility, stability and melting point) has gained much attention in recent years and is a promising alternative to so far employed preparation of salts, hydrates, solvates and other forms. Co-crystal design for a specific API is based on evaluating possible heteromolecular synthons, which are reliable hydrogen bonding motifs sustaining crystal structures.

The particle engineering consists of number of approaches ranging from the conventional size reduction approaches to the newer particle technologies, to modify the drugs solubility characteristics and to develop drugs which have better solubility in water and hence in biological fluids and therefore can be readily formulated into various dosage forms (Khadka *et al.*, 2014). A type of particle engineering approach is crystal engineering (Khadka *et al.*, 2014), which is emerging as an interesting alternate and fruitful method for modification of drugs having compromised biopharmaceutical properties (Blagden *et al.*, 2007). Crystal engineering was introduced by Pepinsiky and established by Schmidt in 1955 through the topological reaction of cinnamic acid. This field gained importance from the 1900's with the advent of metal organics, organometallics and organic solids and since then the field of crystal engineering has advanced resulting in greater understanding of how to design viable crystalline forms.

Crystal Engineering field, defined crystal engineering as "the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties (Shan and Zaworotko, 2008). Intermolecular forces, more importantly non-covalent interactions which includes hydrogen bonding, hydrophobic forces, Van der Waals forces, electrostatic forces and π-πinteractions, which help in crystal packing and self-assembly plays an important role in crystal engineering. An important term used in the field of crystal engineering is "supramolecular synthons". Desiraju defined supramolecular synthons as "the structural units within the supramolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interactions" in the context of a set of compounds known as "Co-crystals" (Qiao *et al.*, 2011). Supramolecular synthons are further categorised into two classes:

1. Supramolecular homosynthons: consists of identical self-complementary functionalities
2. Supramolecular heterosynthons: consists of different but complementary functionalities

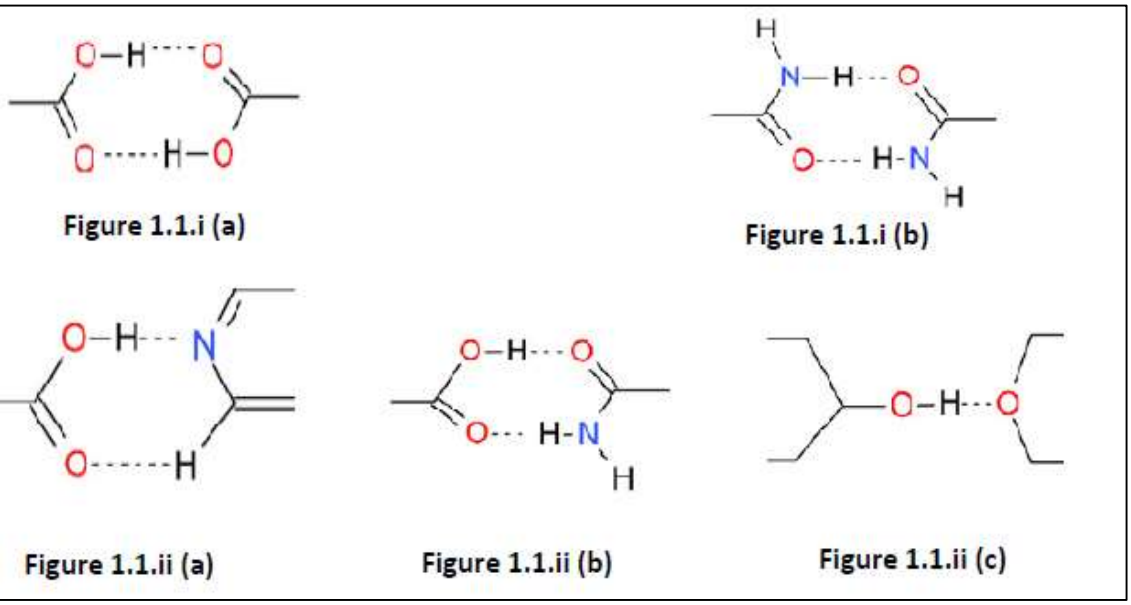

Figure No.1 Illustration of homosynthon and heterosynthon supramolecular (Qiao *et al.,* 2011).

Recent advances in crystal engineering have led to the design of co-crystals in which two or more molecular compounds are incorporated within the same crystalline lattices in specific stoichiometric amounts. Synthesis of co-crystals does not involve making/breaking of covalent bonds and it may therefore be possible to fine-tune physical properties by exercising precise control over the supramolecular assembly, since the crystal structure determines the resulting physical properties of the compound (Aakeröy *et al.,* 2009).

Co-crystals

A restrictive definition given by Aakeroy and Salmon is that co-crystals are structurally homogeneous crystalline materials that contain definite stoichiometric amounts of two or more discrete neutral molecular reactants which are solids at room temperature. This definition excludes solvatomorphs being termed as co-crystals as the solvent of crystallization, water or organic solvent would be liquid under ambient conditions and not solid (Qiao *et al.*, 2011).

Recently co-crystals have gained much importance owing to their amenability to design and their ability to tailor physicochemical properties. The development of co-crystals was resulted by designing crystals with a purpose, as the properties of a compound depend on the arrangement of the atoms in the crystal structure which helps in modifying its properties. Co-crystals are "long known but little studied" group of compounds and was popularized by Etter. The first co-crystals to be synthesized were Quinhydrone, a 1:1 co-crystal between benzoquinone and hydroquinone and was synthesized by Wohler in 1844. In 1963 Hoogsten synthesized a complex between 1-methyl thiamine and 1- methyl adenine as seen in DNA base pairing and used the term "co-crystal" for the first time (Shan and Zaworotko, 2008).

1.2. Pharmaceutical co-crystals

Generally, chemists and engineers in pharmaceutical industry seek to deliver crystalline forms of their active compounds due to inherent stability of crystalline materials. Active pharmaceutical ingredients (API's) can exist in different solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids, which are schematically depicted in figure 2. Each solid form displays unique physicochemical properties that can influence bioavailability, purification, stability, manufacturability and other performance characteristics of the drugs (Shan and Zaworotko, 2008).

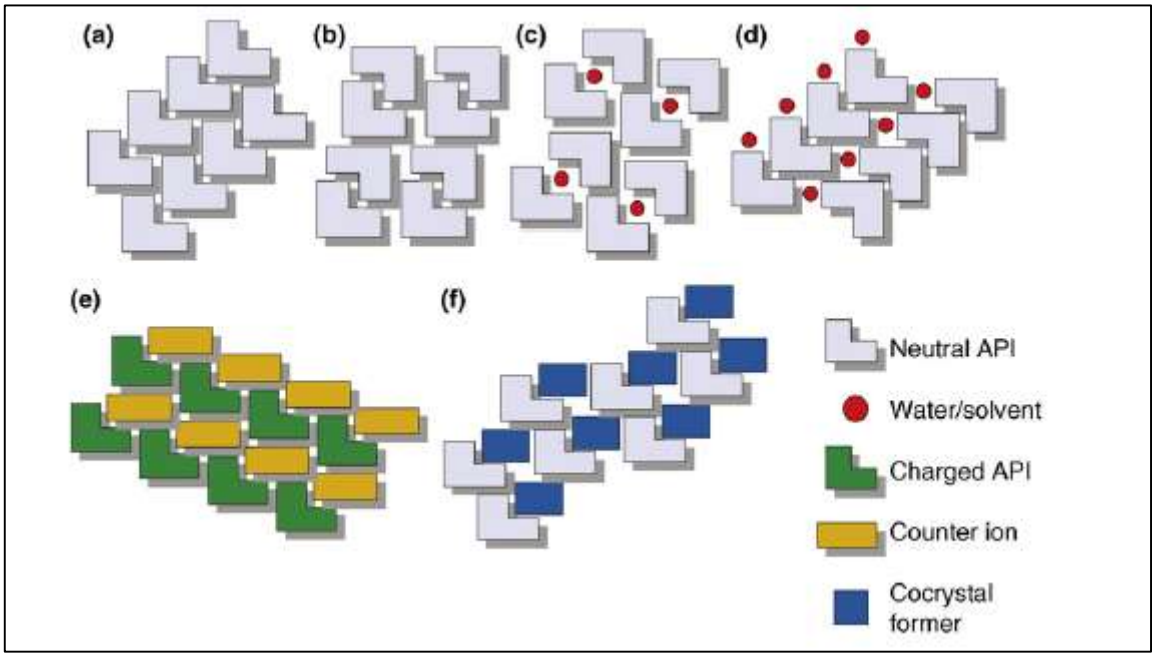

Figure No. 2. Different single crystalline forms of drug

A pharmaceutical co-crystal is a co-crystal with one of the co-crystals components as an API and the other components as co-formers connected by non-covalent interactions where all the components are solid under ambient condition. Appropriate co-formers would be those substances appearing on the Generally Recognized As Safe (GRAS) list (Blagden *et al.*, 2007) for example, saccharin, vanillin, nicotinamide, maleic acid, succinic

acid, benzoic acid and itaconic acid etc. to mention few. The newly emerging class of pharmaceutical co-crystals have been studied in the context of improving the physicochemical properties including modifying the solubility of parent API.

Crystalline forms of API are used in pharmaceutical industry due to their stability and purity characteristics, but these also have their own sets of complications arising from low aqueous solubility. With the advent in crystal engineering a new platform has been created to improve these problems.

In pharmaceutical industry a new API with limited solubility is converted into salt form of the drug based on the ionisable functional group present in it. Though salt formation is an effective tool for improving the properties of drug without affecting its biological properties, the presence of ionisable group makes it a limited approach for neutral molecules (Blagden *et al.,* 2007). The distinction between a salt form and a co-crystal is that a proton is completely transferred in a salt which does not occur in a co-crystal. In case of acidic and basic co-formers, the degree of transference can be estimated by considering the difference in the pKa values, where ΔpKa greater than 3 would be characteristic of a salt, and ΔpKa less than 2 would be characteristic of a co-crystal (Qiao *et al.,* 2011). Pharmaceutical co-crystals on the other hand opens door for multiple functional groups, including weakly or non-ionisable, and molecules that possess a broader range of hydrogen bonding properties (Childs *et al.*, 2004). Moreover, since pharmaceutical co-crystals have new physical properties, it is considered as a new compound and hence can be patented (Shan and Zaworotko, 2008). Thus the overall inclination for investigating pharmaceutical co-crystals as an alternative approach in drug development is because it helps in adjusting the physicochemical properties to enhance the overall stability and efficacy of dosage form (Blagden *et al.,* 2007). Physicochemical properties extensively studied include melting point, solubility, dissolution and stability (Qiao *et al.,* 2011).

1.2.1. Pharmaceutical Co-crystal Formation Method:

1. Solution methods (Childs *et al.,* 2008)

Solution co-crystallization method is based on two strategies:

i. By using solvents or solvent mixtures where the co-crystal congruently saturates and thus the components have similar solubility.

ii. By using non-equivalent reactant concentrations in order to reach the co-crystals stability region in non-congruently saturating solvents.

a) Evaporation co-crystallization

This technique is based on strategy one and is an important tool for co-crystals screening. It is important to consider reactant solubility while designing co-crystals with this technique as reactants are required to have similar solubility's to be formed by this technique.

b) Reaction co-crystallization

This technique is used when the co-crystal components have nonequivalent solubility's and solution co-crystallization of such components in equimolar concentration may result in the formation of single component crystals because supersaturation is generated with respect to less soluble reactant or both less soluble reactant and co-crystal and hence there is a risk of crystallizing a single reactant or mixture of individual reactant and co-crystal. Reaction co-crystallization experiments are done by adding reactant B to saturate or close to saturated solution of reactant A and then the solution become supersaturated with respect to co-crystal AB.

c) Cooling co-crystallization

Cooling co-crystallization involves varying the temperature of the crystallization system and is used in large scale production of co-crystals. In this technique firstly, large amounts of reactants and solvents are mixed in a reactor and then the system is heated to a higher temperature to ensure that all solutes are totally dissolved in the solvent and then is followed by a cooling down step.

Precipitation of co-crystals will occur when solution is supersaturated with respect to co-crystal as temperature drops down.

d) Antisolvent crystallization

Antisolvent crystallization is widely used method of co-crystals preparation. In which antisolvent of drug is added in solution of drug and co-former. The addition of antisolvent results in precipitation of drug and co-former in new crystalline form. The method has been utilized for preparation of indomethacin co-crystals. The

saccharin was used as co-former. A solution of indomethacin saccharin was mixed in methanol and water was then added to the solution as an antisolvent. On addition of water, the co-crystals are precipitated in the medium.

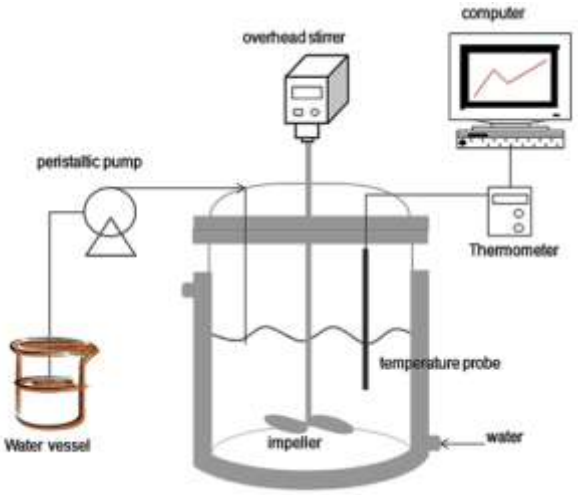

Figure No. 3. Schematic representation of anti-solvent crystallization technique

2. Grinding co-crystallization (Qiao *et al.*, 2011)

a) Neat grinding (Dry grinding)

This method consists of mixing stoichiometric concentrations of co-crystals components and grinding them either manually, by using motor and pestle or mechanically, using ball mill or vibratory mill. To form co-crystals using this method, one or both the reactants used must exhibit significant vapour pressure in the solid state.

b) Liquid assisted grinding (Kneading, solvent-drop or wet co-grinding)

Unlike dry grinding co-crystallization method, co-crystallization in this technique is achieved by using minor amounts of appropriate solvent. This technique markedly improves the kinetics of co-crystal formation when compared to neat grinding as various degrees of conformation and orientation freedom open to molecules at various interfaces as well as the enhancement of opportunities for molecular collisions. The choice of solvent is an important criterion in this technique and selected solvent should be such that it should be able to dissolve at least part of the original components.

Characterization of pharmaceutical co-crystals (Qiao *et al.*, 2011); (Childs *et al.*, 2008); (Aakeröy, 2006); (Mohammad *et al.*, 2011); (Mcnamara *et al.*, 2006); (Modi *et al.*, 2014)

Characterization of developed co-crystals is an important part within co-crystal research as it helps in development of co-crystal formulations. Co-crystals are usually characterized by Infrared spectroscopy (IR), Differential Scanning Calorimeter (DSC), Single crystal X-Ray Diffraction (SXRD), Powder X-Ray Diffraction (PXRD), Ultraviolet spectroscopy (UV), Raman Spectroscopy (RS), Contact angle measurement.

Infrared spectroscopy (IR) is a widely used analytical technique in determining chemical conformation of compounds. This technique aids in differentiating whether a salt or co-crystal has been formed especially when carboxylic acid group is involved in hydrogen bond formation. A neutral carboxylic group (–COOH) has a strong carbonyl (C-O) stretch around 1700 cm−1 and a weak C–O stretch around 1200 cm−1; however, if deprotonation happens, a carboxylate anion (–COO−) having only a single C–O stretch in the fingerprint region of 1000–1400 cm−1 is observed. Moreover presence of additional bands at wavenumbers other than those of drug and co-former indicate formation of co-crystalline compound with changed vibrational properties. The decline in the intensities of bands characteristic for drug indicate the changes in the concentration of drug that take place when a drug participates in co-crystal formation with a co-former.

Differential Scanning Calorimeter (DSC) is used to study the thermal properties of co-crystals. It aids in determining the melting point data along with enthalpy of melting point data. DSC is used as a screening tool for rapid co-crystal screening in recent times. DSC helps in identifying presence of low or high melting peaks other than the endothermic peaks characteristic for drug and co-former thus indicating the formation of new co-crystalline substance.

Single crystal X-Ray Diffraction (SXRD) is a characterization technique which helps in determining solid state structure of co-crystals at an atomic level. However, a single pharmaceutical co-crystal for analysis by SXRD is difficult to produce.

X-Ray diffraction (PXRD) is often used for analysis of co-crystals.
Raman Spectroscopy (RS) is used to study vibrational, rotational and other low frequency modes in a system. It aids to determine characteristic peaks of co-crystals compound. It is an advanced analytical tool based on Raman scattering principle which helps in understanding detailed vibrational characteristics of drug and co-former present in the co-crystal.
Contact angle measurement is used as a tool for understanding the impact of co-crystallization on hydrophobic drug used and helps in understanding the wetting tendency of co-crystal of drug developed. A reduction in contact angle indicates increase in hydrophobicity of the drug by conjugation with co-former.
Scanning Electron Microscopy (SEM) is a type of electron microscope that analyses sample by scanning it with a high energy electron beam in a raster scan pattern. The electrons from the beam interact with the atoms in the sample that gives information about the surface topography of the sample. It helps in determining the micrograph and particle size of co-crystals.
Solid State Nuclear Magnetic Resonance (SSNMR) is used as a tool for studying pharmaceutical co-crystals and is a complementary technique to that of XRD and used to analyze systems that cannot be studied by SXRD.
As stated earlier, pharmaceutical co-crystals have physicochemical properties different from the parent API and thus helps in tailoring its physical and chemical characteristics. Physicochemical properties exclusively studied by the researchers include melting point, solubility, dissolution and stability (Qiao *et al.,* 2011). Few examples indicating impact on physicochemical properties of drugs via co-crystal formulation, reported in literature are as follows:
An important physical property considered during solid drug development is melting point. Melting point of pharmaceutical substance and its solubility, process ability and stability have complex correlations (Qiao *et al.,* 2011). According to a review published by Schultheiss and Newman in 2009, it was stated that out of 50 co-crystalline compounds analyzed, 51% had melting point between those of API and co-former, while 39% had melting point lower than either API or co-former, only 6% had higher and 4% had same melting point as either the API or co-former. The changes in melting point of co-crystals were attributed to the impact of crystal packing. The review also reported a work by Stanton and Bak on AMG517, which stated that there exist some correlations between a compound's melting point and its solubility. It was found that co-crystals having high melting points may contribute to poor solubility (Schultheiss and Newman, 2009).
Mulye et al reported remarkable improvement in the physicochemical properties of poorly aqueous soluble drug ezetimibe via crystal engineering process using benzoic acid and salicylic acid as co-formers owing to modification of crystal habit. The results indicated a remarkable improvement in flow properties, saturation solubility and dissolution profile of ezetimibe co-crystals (Mulye *et al.,* 2012).
Childs et al applied crystal engineering approach to form co-crystals of fluoxetine hydrochloride with benzoic, succinic and fumaric acids. The salt form of the drug when co-crystallized with these carboxylic acids showed that the co-crystal with succinic acid dissociated quickly in the solution and finally recrystallized as the API while the co-crystal with fumaric acid showed solubility higher than the parent API indicating higher bioavailability and with benzoic acid, a decrease in solubility was observed.(Childs *et al.,* 2004) This shows that co-crystals can modify the intrinsic solubility of a molecule by either increasing or decreasing the solubility (Childs *et al.,* 2004).
Carbamazepine is an anti-epileptic drug with limited solubility and therefore has limited bioavailability. Hickey et al observed carbamazepine when designed as a co-crystal with saccharin, the so formed co-crystal of carbamazepine is 2-10 times more soluble than the API. The bioavailability of carbamazepine when tested in vivo in dog plasma showed that the co-crystal had improved bioavailability than the pure API. This exemplifies usefulness of co-crystallization technique in improving the bioavailability of drug otherwise having limited bioavailability (Hickey *et al.,* 2007).
Another example displaying importance of co-crystallization as a valuable technique for improvement of physical and chemical properties is co-crystals of indomethacin with saccharin. Jung et al reported that the formed indomethacin saccharin co-crystals had improved physical properties and significantly higher dissolution rate than plain indomethacin. Significantly higher dissolution rate implies improvement in aqueous solubility and this resulted in an increased bioavailability when studied in beagle dogs (Jung *et al.,* 2010).
Remenar et al in their experiment developed co-crystals of itraconazole, a very poorly aqueous soluble drug marketed in its amorphous form in order to achieve appropriate bioavailability. Various co-formers were screened for this purpose and itraconazole co-crystals were developed using succinic acid, L-malic acid, and L-tartaric acid as co-formers. The dissolution rates of itraconazole co-crystals were then compared with amorphous and crystalline forms of itraconazole. The results indicated in 4-20 fold improvement in dissolution for all the three co-crystals when compared to crystalline itraconazole. Co-crystal of Itraconazole with L-malic

acid demonstrated optimal dissolution rate similar to that of amorphous Itraconazole. Moreover, Remenar et al observed that co-crystal of itraconazole with succinic acid had improved handling properties, particularly easy to filter and free flowing powder (Remenar *et al.*, 2003).

Cheney et al reported a crystal engineering study on meloxicam, a BCS class II non-steroidal anti-inflammatory drug. To be used as an anti-inflammatory agent, therapeutic concentration should be achieved within 30 min after dosing but for meloxicam owing to its low solubility in acidic conditions, it takes more than 2hr to reach therapeutic levels. This prevents it from its application for the relief of mild to medium acute pain. Cheney et al based on supramolecular synthon approach, used aspirin as a co-former with meloxicam. The meloxicam-aspirin co-crystal resulted in 44 fold enhancement in solubility (0.22 mg/ml) compared to pure meloxicam (0.005 mg/ml). Further it was reported that co-crystal resulted in 12 fold reduction in the time required to reach concentration of 0.51 µg/ml compared to pure meloxicam (Taylor *et al.*, 2010).

Goud et al reported eight co-crystals of furosemide, a BCS class IV drug with low solubility (6 mg/L) and low permeability. Co-crystals of furosemide were developed with caffeine, urea, p-aminobenzoic acid, acetamide, nicotinamide, isonicotinamide, adenine and cytosine. Goud et al reported that co-crystals of furosemide with caffeine, adenine and cytosine demonstrated 6-, 7-, and 11- fold higher solubility respectively when compared to pure furosemide (Goud *et al.*, 2012).

McNamara et al reported a glutaric acid co-crystal of 2-[4-(4-Chloro-2- flurophenoxy) phenyl] pyrimidine-4-carboxamide, an API belonging to a class of sodium channel blocker and used in the treatment and prevention of surgical, chronic and neuropathic pain. The developed cocrystals exhibited 18 times enhancement in dissolution rate compared to pure API (Mcnamara *et al.*, 2006).

Shikari et al screened 15 co-formers with different solvents for crystallization of megesterol acetate, a BCS class II drug used in the treatment of advanced carcinoma of breast and endometrium. Out of 15 co-formers screened, Shikari et al found that saccharin was found to form co-crystal with megesterol acetate. This co-crystal resulted in 3-4 times higher dissolution rate when compared to pure megesterol acetate (Shiraki *et al.*, 2008).

Another usefulness of crystallization process is in improving the stability of APIs. Trask et al reported in their studies that caffeine-oxalic acid co-crystals exhibited higher stability to moisture than pure caffeine itself (Trask *et al.*, 2005). They also reported an enhanced physical stability of theophylline-oxalic acid co-crystals than theophylline anhydrate, crystal form used in the treatment of respiratory ailments (Trask *et al.*, 2006).

Crystallization approach has now been applied to nutraceuticals also. Nutraceuticals are molecules of food that provide medical and health benefits such as prevention or cure of diseases (Thakuria *et al.*, 2013).

Sanphui et al. reported co-crystals of curcumin, an active nutraceutical compound found in the Indian spice Turmeric having anti-inflammatory, antifungal, anti-bacterial and anti-oxidant properties. However, curcumin have poor aqueous solubility. Co-crystals of curcumin with resosrcinol and pyrogallol were developed by Sanphui et al. which exhibited 5 and 12 times faster dissolution respectively than curcumin in intrinsic solubility experiments (Sanphui *et al.*, 2011).

Smith et al. reported a crystal engineering approach for extensively studied flavonoid quercetin. Co-crystals of quercetin were formed with caffeine, isonicotinamide and theobromide. The quercetin-caffeine co-crystals demonstrated 14 fold increase in solubility than pure quercetin (Smith *et al.*, 2011).

Conclusion

Cocrystals represent a versatile platform for enhancing drug solubility and optimizing pharmaceutical properties. With ongoing research and development efforts, cocrystallization holds promise for addressing unmet medical needs, improving drug delivery, and advancing the field of pharmaceutical sciences.

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