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Cocrystal development and evaluation: A Crystal engineering approach

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Abstract: Solid crystalline materials having more than two ionic or molecular compounds preferably in a stoichiometric ratio that are in single phase and not either simple salts or solvates are called as cocrystals. Cocrystalization is useful method as it can improve bioavailability of drug also improve physicochemical properties without affecting pharmacological activity of the drug. Formation of cocrystal was found to be pH dependent and coformer selection is one of very important aspect to be considered while forming Cocrystals of API. In the present Review properties of API that are modified by cocrystals has been discussed. Thereafter Coformer selection and methods used for preparation of cocrystas are described. The formation of cocrystals has been confirmed by various screening methods such as virtual cocrystal screening, thermal methods (DSC, TGA), Saturation stability testing etc. Cocrystls are evaluated for the stability, dissolution etc. by different methods. Cocrystal formation is an alternative approach in the betterment of bioavailability and solubility of poorly soluble API when it is neutral or weakly ionized. This approach offers improved melting point, tabletablity, solubility, stability, permeability and hence bioavailability and all Therese aspects are described in the present review. The Cocrystal approach is still not widely explored but in future it is expected to increase the industrial interest in pharmaceutical cocrystals Though there is inadequacy in marketed products and issues about safety and toxicity of coformers, we found heightened interest and activity in this specific area aiming for better understanding of cocrystal formation and methods of preparation.

Key words - Cocrystals, API, Coformer, Screening, DSC, Stability

I. INTRODUCTION

Concept of crystal engineering firstly introduced in 1955 by Pepinsky and Schmidt implemented to the organic solid-state photochemical reactions [(1)]. Around 1980's, it is observed that the development in the crystal engineering field takes place in large amount. The understanding of intermolecular interactions relating to packing and its utilization in the design of new solids with desired physical and chemical properties is defined as Crystal engineering [(2)]. This was the base for the advances in crystal engineering. After that Crystal Engineering has subsequently become prototype in the synthesis of Organic Solids and also Metal Organic Frameworks with desired structures and properties that has been engineered at the molecular level [(3)]. Numerous drugs that have been developed recently are with low aqueous solubility, 60-70% of which belong to BCS Class II (High permeability/Low solubility) and BCS Class IV (low permeability/low solubility) [(4, 5)]. Low aqueous solubility causes the bioavailability problem in the formulation development. By using advancements in crystal engineering technology modification in solubility, dissolution, stability of the API in crystalline state can be achieved, this is done by using various approaches like solvation, Polymorphism, habit modification, surface modifications and cocrystalization[(6)]. Each technique is unique in correspondence of the advantages and disadvantage [(7)] cocrystals approach is one of the useful methods as it can improve bioavailability of drug also improve physicochemical properties without affecting pharmacological properties of the drug.

II. Cocrystals

Cocrystal term and the hydrogen bonding pattern in them were first reported by Elter [(8)]. Solid crystalline materials having more than two ionic or molecular compounds preferably in stoichiometric ratio that are in single phase and not either simple salts or solvates are defined as cocrystals [(12)]. As per USFDA draft guidance published in 2013, Cocrystals are defined as solids that are crystalline materials composed of two or more molecules in the same crystal lattice [(13)]. After 2004 Cocrystals has been referred as a separate class of novel crystalline materials that modifies physicochemical properties of drug substance and new era in crystal engineering has begun [(9)]. Two types of cocrystal depending on coformer types were described by Duggirala and coworkers that are molecular cocrystal in which non-ionized or neutral cocrystal forming agents are present in defined ratio and ionic cocrystal having ionic cocrystal forming agents in a defined ratio which are formed by hydrogen bond or coordination bonds [(10, 11)]. The basic difference between cocrystals, salts, solvates and hydrate is; polymorphs represent compounds present in different lattice arrangement, complete proton transfer between two compounds lead to the salt formation [(13)], there is no proton transfer during cocrystal formation. Formation of cocrystal was found to be depending on ΔpKa value; it

has been found that ΔpKa value greater than 3 lead to formation of salt and less than 3 ΔpKa values leads to cocrystal formation. Though this was not an accurate prediction, possibility of salt formation increases at higher ΔpKa [14]. Formation of solvates or hydrates takes place during solution or liquid assisted grinding which affects physicochemical properties and stability [9]. Various Pharmaceutical cocrystal formulations are existing such as Entresto, Viagara and many more under formulation development [15].

III. Properties of cocrystals

1. Melting Point

Purity and thermodynamic stability of solid is determined by melting point. This is basically depends on coformer selection, if the coformer of high melting point is selected, then the API thermal stability can be increased. In case of thermo labile APIs crystals with low melting point has to be designed [15, 16]. Melting point and thermal analysis carried out by using different techniques such as DSC, TGA etc. [16]. Melting point is an important characteristic which is to be considered at the time of formulation of cocrystal. Study of this specific consideration has been required since high melting point crystals leading to aqueous solubility problem, whereas low melting point has caused processing and drying problems creating stability issues [15].

2. Tabletability

Formation of a cocrystal is the result of specific crystal packing that can affect compaction parameters. Tabletablity is ability of the excipient or API to compact into the tablet. While doing preformulation study compaction behavior of cocrystals was found to be better than pure API as in case of paracetamol, Trimethylglycine and oxalic acid [17]. Variation in crystal packing in cocrystals alters the mechanical properties of the tablet formulation [15].

3. Solubility

Solubility of the API has been found to be increased when its cocrystals are formed. When cocrystals of an antifungal drug Ketoconazole synthesized solubility increased 100 times than the pure form, whereas 53 times increase in solubility in salt form. Hence, as compared to salt form cocrystal has a higher solubility [18]. Since higher solubility leads to higher dissolution rate cocrystalization is effective to enhance dissolution as in case of 6-mercaptopurinrand nicotinamide showing dissolution rate twice than pure API [19]. As per one of the findings cocrystal solubility equation describing solubility of cocrystals in terms of solubility of product, coformers, ionization constants, pH of the solution has been used for Amphoteric, acidic, basic and zwitterionic component containing cocrystals [20, 21]. Cocrystals solubility is determined by a theoretical method using the ratio of concentrations of cocrystal component solution at eutectic point i.e. Keu [22].

4. Stability

Pharmaceutical cocrystal development is associated with various stability studies such as Chemical stability, Thermal stability, Solution stability, Photostability and various humidity stress conditions [15]. The chemical stability study gives idea about any change or chemical degradation at accelerated stability conditions. Glutaric acid cocrystals along with API at different conditions (400/75% RH and 600/75% RH) for two months has found to show no degradation and good chemical stability [23] and cocrystals of carbamazepine and saccharin showed good chemical stability [24]. Cocrystals have been observed for better thermal stability as in case of Paracetemol crystals with 4, 4-bipyridine [25]. Another important parameter in cocrystal development and stability study is solution stability which provides information about crystal behavior in the release medium [15]. Study of carbamazepine cocrystals showed that cocrystals with highly soluble coformers lead to conversion into dehydrates wheras cocrystals of less soluble coformers remain in solution [26]. Photo stability study is to be done to determine impact of light on light sensitive API since many of them are sensitive to light. Cocrystals of nitrofurantoin with different coformers were studied and they show higher photo stability than physical mixture or pure API. Cocrystals show less than 3% photo degradation hence light sensitive drugs are protected by cocrystlization [27]. Relative humidity stress conditions applied to cocrystals by automated water sorption/desorption techniques and the effect of water on them is studied. Behavior of cocrystals of indomethacin-saccharin crystals under relative humidity stress condition showed low water sorption and no dissociation or transformation [15, 28]. Hence it is concluded that physical and chemical stability has been improved by forming cocrystals. [29]

5. Permeability

Permeability is a key parameter in drug absorption and distribution across the biological membrane and is depended upon n-octanol/water partition coefficient for an unchanged form of API with the help of log P [15]. BCS class-III drug, %-fluorouracil, was studied by forming cocrystals with different coformers and found to show increased in permeability than pure drug [15, 30].

6. Bioavailability

The rate and extent to which pure drug reaches into the systemic circulation is called as bioavailability of drug [15]. During drug development and designing new formulation, low systemic bioavailability is a major problem. It is found that pharmaceutical cocrystals have more bioavailability than pure API. Cocrystals formation of baicalein with nicotinamide showed better bioavailability [32].

IV. Selection of coformers and cocrystals screening [31]

Coformer selection is an important aspect in cocrystal formulation and screening. The Cocrystal forming agent may be a drug, excipient or any substance that should be with zero toxicity, non-reactive and safe [33]. In this process of coformer selection Coformers listed in GRAS by USFDA and EAFUS database are referred but they don't assure its use as a cocrystal forming agent [34]. Coformer selection is done by knowledge based and experimental based approaches. The use of trial and error method for all types of coformers for an API for selection of coformers also confirmed the structure of crystals, but this is expensive as well as time consuming. Use of knowledge based method for coformer selection, such as Synthonic engineering, hydrogen bonding propensity, pKa based methods, superamolecular compatibility by CSD, Fabian method, hasen solubility parameter, lattice energy calculation, and COSMO-RS has been commonly used by researchers [5, 8]. In synthonic engineering the formation of cocrystals is depend on the functional groups of API and coformer. Synthons are known as basic structural units of supermolecules and are associated with noncovalent bond and these are of two types viz. Homosynthons having same functional groups in coformer and API and heterosynthons having different functional groups in coformer and API [15]. Superamolecular heterosynthons are preferred always e.g. Acid-pyridine /Acid-amide heterosynthons are preferred over carboxylic acid-amide homosynthons [35]. CSD is one of the tools to study intermolecular packing and it gives the idea about functional group for molecular association of drug and coformers. These approaches reduce the time and cost of research with high accuracy [15]. It has been found that ΔpKa value greater than 3 lead to formation of salt and less than 3 ΔpKa values leads to cocrystal formation. Possibility of salt formation increases at higher ΔpKa [14]. Hansen solubility parameter detects miscibility of drug with coformer for the coformer selection [37]. COSMO-Therm software based on COSMO_RS fluid phase thermodynamic approach is used for screening of coformers [15].

Cocrystal screening

Virtual cocrystal screening approach showed that if the ΔE energy difference of cocrystals and pure API is greater than 11kJ/mole then the probability of cocrystal formation was found to be 50% more [56]. Cocktail cocrystal method has been developed for cocrystal screening and done by grinding all the coformers with API in ball mill and hence formation of synthons between drug and coformer is detected [56, 57]. A thermal method of analysis has been used in the cocrystal screening such as DSC, TGA, and DTA [58]. Thermal screening is rapid and small amount of sample is required, but the problem associated with this is some physical transformations during scanning [58, 56]. Hot stage microscopy is used to identify cocrystals and to make screening more effective [59] by identifying no of phases in the system by direct visualization [60]. Another approach of cocrystal screening is the determination of Saturation solubility of coformer and API at specific temperature. Saturation temperature with respect to reference temperature is determined by heating the solution at the rate of 0.3^0C/min. More than 10^0 rises in saturation temperature with respect to reference temperature is the indication of formation of cocrystals [61].

V. Cocrystal Formation Techniques

1. Solution based methods

1.1. Solvent evaporation method

This is the most common method used in which coformer and API dissolved together in solvent, then the solvent slowly evaporated from this solution. Dissolution makes synthon of API and coformer interacts and formation of hydrogen bonding takes place [38, 39].

1.2. Solution crystallization technique

In this method cocrystallization takes place while the rapidly cooling boiling solution. API and coformers are solubilized in solvent and boiled with stirring, this is continued until volume reduced. Formed cocrystals are then separated by filtration followed by drying [40, 15].

1.3. Slurry crystallization

This method is preferred when the API and coformer have to be kept stable in solvent. In the mixture of API and suitable coformers different solvents are added to make slurry. Cocrystals obtained by drying solid material after decanting the solvents [41].

1.4. Antisolvent addition method

With the help of the dispersion Homogenizer API is dispersed in the coformer solution, whereas coformers are previously dissolved in different organic solvents. Thereafter, these solutions are mixed with distilled water or other solution. This leads to precipitation of coformer onto the drug [42].

1.5. Reaction crystallization method

The method offers quick formation of macroscopic and microscopic cocrystals at a favorable temperature where the nucleation and cocrystallization depends on coformer type and solubility. Prepare the saturated solution of less soluble component or API in methanol and add more soluble coformer in amount under solubility limit. The formation of cocrystals is evaluated by monitoring solution concentrations by HPLC throughout the crystallization process thereafter cocrystal screening by PXRD, TGA and DSC [22, 42, 43].

2. Grinding methods

These are superior to other techniques [45]. In dry grinding coformers are mixed together in fixed ratio and then grind by using a suitable technique [46] and in wet grinding few drops of solvent is added to API and coformer mixture while grinding [47,48].

3. Ultrasound assisted solution cocrystallization

Cocrystals of very small size such as nanocrystals has been prepared by this method [49]. During the technique API and coformers are dissolved in a solvent and place the solution in sonicator. Sonication makes this solution turbid. While sonication the constant temperature is maintained by supplying cold water so the fragmentation is prevented. Cocrystals are obtained by overnight drying and the purity checked by XRD [50].

4. Supercritical fluid atomization method

In this method drug and coformers are mixed with the help of high pressurized supercritical fluid such as CO2 and this solution is atomized by atomizer to get cocrystals. The Antisolvent effect of supercritical fluid leading to the formation of cocrystals in supercritical antisolvent (SAS) method [50, 38, 52].

5. Spray drying method

Spray drying technique is most preferred due to Fast, continuous and one step operation. The suspension or solution of API and coformer is sprayed along with a stream of hot air so that solvent from the solution is evaporated to form cocrystals [40, 55].

6. Hot melt extrusion

In Hot melt extrusion method, drug and coformers are heated by intense mixing leading to the formation of crystals. The method is used for thermostable substances only [53, 54].

VI. Evaluation of Cocrystals

1. Spectroscopic Analysis

FTIR differentiates the salt and cocrystals by involvement of carboxylic acids in hydrogen bond formation [61]. Analysis of the API, coformers, and cocrystals has been performed by FTIR in the wavelength range of 400-4000cm-1 [15, 62,63]. Terahertz time-domain-spectroscopy (THz-TDS) has been used for the characterization of cocrystals [66]. Solid-state NMR is one of the important tools that identifies salts and cocrystals and evaluates the structure by detecting local conformation changes and hydrogen bonds by coupling [67,68]. PXRD study gives diffraction patterns from diffractometer which indicate formation of cocrystal and by comparing them with each other structure of cocrystals are analyzed [69]. SEM is used for determination of particle size and morphological analysis [28, 15].

2. Thermal Analysis

Cocrystal formation is also determined by endothermic and exothermic peak patterns in the DSC spectrum [58, 63, 42]. TGA is another method which determines hydrated or solvated forms of crystals detect the volatile component, analyze decomposition or sublimation from cocrystals. Prediction of crystal purity, thermal stability and compatibility can be possible with TGA analysis [34, 65].

3. Dissolution study

The amount of drug release in dissolution medium with respect to time and in vivo performance of the formulation is determined by the dissolution study. This study is performed on the dissolution apparatus in the suitable dissolution medium as per official compendia. The samples collected At specified time interval are analyzed by HPLC or UV spectrophotometer [15, 44].

4. Solubility study

Higuchi and Connors method is used to determine solubility of cocrystals. Solubility of cocrystals, pure API and physical mixture of API and coformer are determined in water and different medium as mentioned in official compendia [35, 31, 15].

5. Stability study

Stability studies are performed at different temperature and humidity conditions for predetermined time intervals which gives an idea about cocrystal product shelf life at various storage conditions [42, 15].

VII. Applications

Cocrystalizationas a crystal engineering approach gives improved physicochemical properties without modifying the basic structure of API molecule. Pharmaceutical cocrystals improve solubility, dissolution of poorly soluble drug and improve bioavailablity. The properties such as tablatablity, permeability and stability are improved by forming cocrystals.

VIII. Challenges and future aspects

Cocrystals has been found to be an excellent approach to optimize various properties of the API. But though the selection of coformer is one of very important aspect it is very challenging to select perfect conforming agent. In the process of coformer selection Coformers listed in GRAS by USFDA and EAFUS database are referred but they don't assure its use as a cocrystal forming agent. Also the detailed study of the supramolecular chemistry of functional group of API and coformers is a major concern in cocrystal design since it affects the selection of the suitable cocrystal former. After the successful cocrystal formation, stability issue arises in the presence of excipients. This may lead to further study regarding the formulation with cocrystals. Research into the cocrystal is continuously growing so as in the drug products in the market it is expected to gain a step in drug development also. The Cocrystal approach is still not widely explored, but in future it is expected to increase the industrial interest in pharmaceutical cocrystals. Though there is inadequacy in market products and issues about safety and toxicity of coformers, we found heightened interest and activity in this specific area aiming for a better understanding of cocrystal formation and methods of preparation.

IX. Conclusion:

Cocrystal formation is one of the useful crystal engineering approach which offers advantage of higher solubility or dissolution of less soluble API to improve bioavailability. The selection of coformer is quite difficult due to stability aspects but if proper selection of the cocrystal forming agent can overcome all the issues. Preparation methods of cocrystals are easy and can produce good results. The screening and evaluation of synthesized cocrystals has been performed by using analytical techniques such as FTIR, DSC, TGA, Terahertz time-domain-spectroscopy, dissolution testing, stability testing etc. various formulations having cocrystals are present in market and numerous in clinical trial still we need to focus on this specific area. We found growing interest and activity aiming for a better understanding of cocrystals.

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