THINK INDIA JOURNAL

ISSN:0971-1260
Vol-22-Issue-37-December -2019

Synthesizing Cocrystals: A Brief Overview on Cocrystals and its Rapid Screening.

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Abstract

In recent years the interest in design, synthesis and characterization of cocrystals has grown significantly because of its ability to modify the physical properties of solid materials relevant to pharmaceutical and fine chemical industries.This brief overview is an attempt to give readers a flavour of cocrystals: what it is, whatits current possible applications are, what distinguishes it from other multicomponent crystals such as solvents and salts, and how to predict whether or not the target molecule will form cocrystal using some commonly available techniques.

Keywords: *Cocrystal, Salt, Supramolecular synthon, Vibrational spectroscopy, Hot Stage Microscopy, Differential Scanning Calorimetry.*

Introduction

A wide range of properties exhibited by a molecule in gas or liquid phase depends upon its structure and chemical composition. However, many of the bulk properties exhibited by solids such as density, solubility, thermal stability, mechanical strength etc., depends upon the three-dimensional orientation and organization of the molecules in crystalline lattice [1]. From industrial point of view this aspect is of considerable importance given the effectiveness, safety and shelf-life of the product requires its manufacture in desired crystal form.Conversely from a more fundamental point of view, the occurrence of molecule in different crystalline forms provides the unique opportunity to investigate how the intermolecular interactions determine crystal packing which in turn influences the properties of the solid. The understanding of these interactions is the foundation of crystal engineering where the gained expertise can be used to model solids with desirable physical and chemical properties.This unique opportunity to adjust the physicochemical properties of significant synthetic substances, for example, drugs, agrochemicals, explosives, without changing the chemical

ISSN:0971-1260
Vol-22-Issue-37-December -2019

properties of the molecules involved has gain tremendous attention recentlyand has resulted in several literature reporting multicomponent crystals as a tool to achieve the same [2].Multicomponent crystals are crystalline assemble which contain multiple neutral and/or ionic species in crystal lattice, the examples of which are salt, solvates and cocrystals[3].It is the structure of molecule which determine the type of multicomponent system a molecule can form. For example, molecules which lack functional group generally do not form salt and thus formation of solvate or cocrystal are only the feasible option. Likewise, there are limited number of counterions and solvents that can be safely incorporated into crystal lattice more specifically of pharmaceutical importance.Also, most of the hydrates have been shown to undergo undesired phase transformation during manufacturing processes and storage.Cocrystallization on the other hand is a novel approach to modify physiochemical property and has two fundamental advantage over salt and solvate formation. Firstly, cocrystal formation may be used for all APIs, including acidic, basic and non-ionizable molecules, and secondly, there are many possiblecoformers or counter molecules, many of which are categorised as GRAS (Generally Regarded As Safe) and many more in EAFUS (Everything Added to Foods in the United States) list of U.S which enlists thousands of food additives [3].By the use of cocrystallization several pharmaceutically important active pharmaceutical ingredients (APIs) have displayed enhanced properties in comparison to the original drug. The physiochemical properties that can be modified by co-crystallization techniques are melting point, tabletability, solubility, stability and bioavailability. For example, the cocrystals of Ibuprofen-nicotinamide and flurbiprofen-nicotinamide have been shown to possess higher intrinsic dissolution rate, higher tabletability and lesserhygroscopicitycompared to the individual precursors [4]. Similarly,the fixed dose combination of isoniazide, rifampicin, pyrazinamide, ethambutol dihydrochloride, used for the treatment of tuberculosis, was found to be unstable due to interaction between isoniazide and rifampicin. This formulation was however stabilized by the inclusion of pharmaceutical cocrystal of isoniazide with caffeic acid or vanillic acid in place of isoniazide [5]. Not only cocrystallization is useful in pharmaceutical industry but it is also being used to improve the performance of explosives, pigments and agrochemicals. For example, the energetic co-crystal of CL-20 with TNT was found to have better detonation performance and approximately double impact stability as compared to pure CL-20 [6]. Fluorescein, a colourant is found to exist in three tautomeric forms each with different colour. Authors have shown that cocrystallization can be used as a tool to alter the optical properties of this pigment by preparing colour tuned solids displaying variety of colours in comparison to the original colours exhibited by fluorescein [7].Similarly, the volatile nature of two agrochemicals, cyprodinile and pyrimethanilwere overcome by co-crystallization technique which produced solids with reduced volatility [1]. Over the last decade, synthesis of

ISSN:0971-1260
Vol-22-Issue-37-December -2019

cocrystals with promising results has seen enormous growth which has led to several filing of patents with a number of them been even granted for example cocrystal of metformin-oleoylethanolamide (antidiabetic-anti-obeseity), cyprodinil-dithianon (fungicides), Ciprofloxacin and norfloxacin with various co-crystal formers (antibacterial) etc. [8]. Given thewide scope of cocrystals in pharmaceutical and fine chemical industry the better method for screening and production of cocrystal is highly desirable. This brief review aims to provide an insight into cocrystals, what makes it different than other multicomponent crystalline forms and what methods are currently being utilized for rapid screening of cocrystals.

Difference between Cocrystals, Solvates, Salts and their classification

Like co-crystals, solvates and salts are also multicomponent crystals. These three classes of multicomponent crystals differ on the basis of components which can be either a solvent, an ion or a coformer. A solvent is a neutral component which is liquid under standard conditions. An ion is a component (solid or liquid) with a formal charge that is non-zero and a coformer is a neutral component that under standard conditions is not a liquid.A crystalline salt is made up of at least two ions, while a crystalline solvate is made up of a solvent molecule plus either a coformer or two ions.On the other hand, a cocrystal consists of a coformer plus either another coformer or two ions atleast. Solvates, Salts and cocrystals can be further divided into seven categories based on the combinations of various components [3]:

a) True solvates: It consist of one or more solvents, only one conformer and no ions.
b) True salts: It consist of only ions
c) True cocrystal: It consist of only coformers
d) Salt solvate: It consist of two or more ions, one or more solvents and no coformer
e) Cocrystal solvate: It consist of two or more coformers, one or more solvents and no ions
f) Cocrystal salt: It consist of one or more coformers, two or more ions and no solvents
g) Cocrystal salt solvate: It consist of one or more coformers, two or more ions and one or more solvents.

Definition of Co-crystals

Despite the widespread popularity, cocrystals do not have any universally accepted definition. Most authors have however agreed that cocrystals are crystalline materials consisting of at least two different neutral components which are solid under environmental conditions and present in

ISSN:0971-1260
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a certain stoichiometric quantity[9]. Recently Aitipamula and coworkers have put forward a broader definition of cocrystals which includes the salts. According to this definition, "*Cocrystals are solids that are crystalline single-phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts*" [10].

Salt vs Cocrystal

Cocrystal are having special significance in pharmaceutical industry where the solid-state formulation is an integral part of drug development. Pharmaceutical cocrystal are generally formed by an acidic component and a basic component. If the complete transfer of proton takes place between two components i.e., proton resides on base, then salt is formed whereas if no transfer of proton takes place between two components, then cocrystal is formed. In fact, the hydrogen bonding interaction found in cocrystal can be regarded as incipient proton transfer reaction [11]. If an acidic component and a basic component with similar solubilities (If not, the least soluble component will first precipitate) are dissolved in a solvent then the resultant precipitate will be a salt or cocrystal can be predicted by 'pK_a Rule'. It is shown that generally if the pK_a difference between acidic and basic component is greater than 3([ΔpK_a = pK_a of protonated base – pK_a of acid]> 3), salt formation can be expected whereas if ΔpK_a< 0, cocrystal formation can occur. [12] However,if the Δp$K_a$lies between 0 and 3 (0 <ΔpK_a< 3), it is difficult to predict whether salt will be formed or a cocrystal and so no specific ΔpK_a value can be estimated which can divide salt portion from cocrystal portion. It must be remembered that pK_a is related to equilibrium behaviour in aqueous solution and that its value depends upon solvent, temperature, measurement techniques and other factors. However, it still acts as a reliable indicator for salt (ΔpK_a> 3) and cocrystal (ΔpK_a< 0) formation and a judicious selection of components can lead to formation of cocrystals.

Intermolecular Interactions in Cocrystals

Cambridge Structural Database (CSD) is a tool of choice for crystal engineering and has contributed greatly to our understanding of interaction between components within the crystal system. Analysis within the CSD reveals that hydrogen bonds are the predominant form of

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interaction between the functional groups found on target molecule and coformer. It also reveal different pattern of hydrogen bonding between functional groups which forms structural units and are referred to as supramolecular synthon [13].The idea of 'Supramolecular synthon' with respect to crystal engineering was proposed by G.R Desiraju in 1995 which according to him plays a similar role to Corey's organic chemistry synthon. Corey's word ' synthon ' in the sense of organic chemistryis defined as *"structural units withinsupermolecules which can be formed and/or assembled by known or conceivable intermolecular interaction"*[14]. Supermoleculeis to molecules and intermolecular bond what a molecule is to atoms and to covalent bond.Desiraju defined 'supramolecular synthon' as *"a structural units within supermolecules which can be formed and/or assembled by known or conceivable synthetic operations involving intermolecular interactions"*[15].Crystal engineering is therefore conceptually a supramolecular equivalent of organic synthesis. The pattern of interaction can be called as a supramolecular synthon when crystal patterns replicate regularly. There are two types of supramolecular synthon approach , i) Supramolecular homosynthon which is composed of same functional group present on both target molecule and conformer such as acid-acid, amide-amide homosynthon and ii) supramolecular heterosynthon which is composed of different functional group on both target molecule and conformer such as acid-pyridne, acid-amide heterosynthon. Generally heterosynthon are more strongly preferred than homosynthon[16].Which synthon is more robust than the other is determined by its frequency of formation among all structures containing the necessary functional group components [17]. The identification of robust synthon is crucial and effective in designing cocrystals.

Etter [18, 19] proposed a graph set notation system that is used to label motifs bonded with hydrogen (a set of molecules bonded by one type of hydrogen bond to each other). The preferred hydrogen bond pattern can be visualized by assigning this notation to series of crystal structures that contain one type of functional group.Based on the CSD statistical analysisEtter also published a set of empirical rulesas a guideline to predict solid state hydrogen bonding of molecules having multiple proton donor and acceptor.

- All best proton donors and acceptors in the molecule are used in the crystal structure of the compound for the formation of hydrogen bonds.
- Intramolecular hydrogen bond will be preferred over intermolecular hydrogen bond in six membered ring.
- The remaining best proton donor and acceptor will form intermolecular hydrogen bond with each other after the formation of the intramolecular hydrogen bond.

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Vol-22-Issue-37-December -2019

One can design cocrystals by understanding hydrogen bonding pattern using these guidelines.

Rapid Screening of Cocrystals:

Cocrystalsare generally prepared using either solid state method or solution based method. Solid state method involves grinding the two component (target molecule and coformer) which can be can be either assisted by addition of small amount of solvent (solvent assisted grinding) or without solvent (neat grinding). In solution based method cocrystals are prepared by either solvent evaporation, cooling crystallization or slurry conversion among which solvent evaporation method is considered to be the method of choice from industrial point of view and scale-up. The cocrystal obtained from these methods are then characterized using powder X-ray diffraction or single crystal X-ray diffraction (if single crystal suitable for structure determination is obtained).). The solid obtained from the solid state grinding may not be sufficiently pure due to incomplete conversion and there are possibility of formation of disordered crystals. On the other hand due to difference in solubility of two components, the solution based method may lead to crystallization of cocrystal components along with cocrystal which will result in phase impurity. This issue can be resolved by constructing ternary phase diagram of target molecule and conformer in the suitable solvent to optimize the experimental condition. However this requires multiple laboratory experiments and is time consuming. Due to increased interest in cocrystal, the demand for the rapid, simpler and reliable method for screening new cocrystal has grown which can be performed with small amount of sample and commonly available laboratory equipment. This section highlights few of such techniques.

1. Vibrational Spectroscopy:

As discussed earlier the 'pK_a rule' can be used to predict whether solid formed will be a salt or a cocrystal. However when the value of ΔpK_alies between 0 and 3, it is difficult to make any prediction due to existence of salt-cocrystal continuum.At this stage, the degree of proton transfer can be calculated either by finding the proton or by measuring the bond length of the atoms involved using single crystal X-ray diffraction (SC-XRD) [12]. In many cases however it is difficult to obtain single crystal suitable enough for SC-XRD. In such cases spectroscopic techniques such as Infrared spectroscopy can be used. The proton involved in hydrogen bonding forming supramolecular synthon is more likely to be shared than transferred during cocrystal formation.The vibrational modes associated with functional groups are influenced by any degree of proton transfer. Thus, the interactions involved in the

ISSN:0971-1260
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formation of supramolecular synthon can be studied by evaluating the patterns of molecular vibration [20].

2. Thermal Methods:

*a) Hot Stage Microscopy (HSM):*Berry et al.[21] used HSM for the screening of cocrystals. They used the Kofler mixed fusion method to analyze the binary phase behavior of a given cocrystal system successfully.In this method, one component is melted and then solidified before bringing second molten component in its contact which will solubilize a portion of first component. A mixing zone will be created after recrystallization.This mixing zone is similar to the two-component binary phase diagram with one side of the mixing zone representing 100% of one component, another side representing 100% of the second component and gradient of concentration across the zone.When this sample is heated again until melting and viewed under crossed polarized light, it is possible to observe the zone of cocrystal formation, flanked by two eutectic mixture zone in the mixing zone. The cocrystal forming zone retains birefringence and can be clearly differentiated from the eutectic zone and two components in general. The cocrystal formed from this method can be used as a seed to grow cocrystal from the solution suitable enough to study through SC-XRD.

*b) Differential Scanning Calorimetry (DSC):*Cocrystalscreening using DSC is based on the assumption that cocrystal's melting point will be different from its pure components. The cocrystal melting point is lower than both the target molecule and the conformer in more than 50 percent of cases.Generally, when the physical mixture of component A and component B (1:1 molar ratio) capable of forming cocrystal is heated in DSC, all component A and part of component B, melts at a metastable eutectic temperature ($T_{m\text{-}E}$) forming cocrystal, which in turn melts at a fusion temperature (T_C) considered to be similar to the congruent melting point.The component B then recrystallize at incongruent point or peritectic point T_P. Component B then slowly melts at a temperature above T_p.In DSC thermogram, this phenomenon can be seen as a strong endothermic peak associated with the melting of metastable eutectic mixture accompanied by exothermic peak associated with cocrystal formation at $T_{m\text{-}E}$. Another endothermic peak associated with the cocrystal melting at (T_C) is then observed.Anexothermic peak at T_p which is associated with recrystallization of component B is observed next which is followed by broad endothermic deflection above T_p.When two components (1:1 molar ratio) that are unable to form cocrystal are heated in

ISSN:0971-1260
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DSC, an endothermic peak at T_E is observed followed by a broad endothermic deflection above T_E. It can be pointed out that exothermic peaks are detected only for those physical mixtures which are capable of forming cocrystals [22, 23].

Vibrational spectroscopy complemented with XRPD and thermal techniques such as DSC, HSM are enough to characterize the cocrystal and are widely being used.

Concluding Remark:

It is clear that in near future cocrystals will become integral part of solid state development. The selection of suitable conformer will however remain the challenge in the synthesis of cocrystals. Design, synthesis and characterization of novel cocrystals requires time and money, however due to some knowledge based approach the screening of cocrystals have become reliable and easier. As the research into cocrystalgrows, a need for more reliable, fast and cheaper method for screening of suitable coformer will develop. Combination of knowledge based approach and experimental method will lead the way into new era of cocrystal screening and development.

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