Review Article

Pharmaceutical Cocrystallization : A Review

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ABSTRACT

Pharmaceutical cocrystals are emerging as a new class of solid drugs with improved physicochemical properties, which has attracted increased interests from both industrial and academic researchers. They are attractive to pharmaceutical scientists because they can significantly diversify the number of crystal forms that exist for a particular active pharmaceutical ingredient (API), and they can lead to improvements in physical properties of clinical relevance. Cocrystals not only provide a technique for improvement of physiochemical property but also provide opportunity to the researchers of pharmaceutical companies regarding intellectual property. Cocrystal approach especially used to enhance the specific properties of pharmaceutical solids such as dissolution rate of poorly water soluble API and the physical stability of moisture liable APIs. In this paper we focus on Design strategies of corystal, formulation method, characterization of cocrystals with the help of suitable example.

Keywords: Cocrystallisation, Supramolecular synthon, Solution cocrystallisation.

INTRODUCTION

Poorly water soluble drugs pose significant hurdles for drug bioavailability that in turn affect in vivo efficacy and safety in all stages of formulation[1]. Among the 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 micronisation, salt formation, emul-sification, 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.

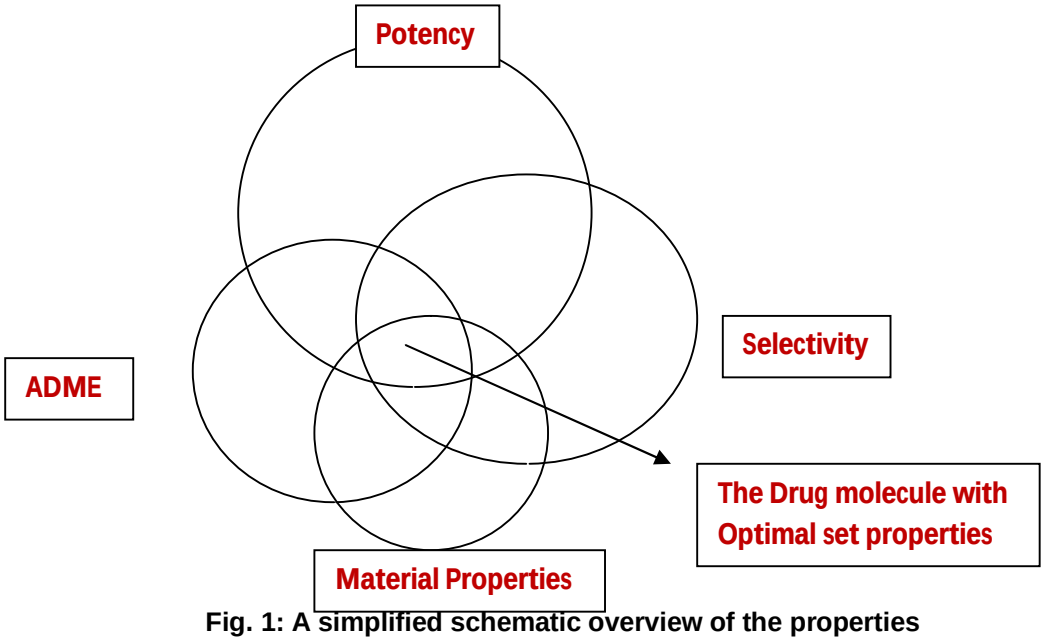

Fig. 1: A simplified schematic overview of the properties vital for a successful drug candidate

Over the last decade, there has been growing interests in the design of pharmaceutical cocrystals, which emerges as a potential method for enhancing the bioavailability of drugs with low aqueous solubility[2]. The ability to deliver the drug to the patient in a safe, efficient and cost effective manner depends largely on the physicochemical properties of the active pharmaceutical ingredient (API) in the solid state (Fig 1). This provides a significant driving force for inventing new approaches to designing pharmaceutical solid materials with specific physicochemical properties[3, 4].

Cocrystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through noncovalent interactions (primarily hydrogen bonding) (Fig 2). The formation of pharmaceutical co-crystals involves incorporation of a given API with another pharmaceutically acceptable molecule in the crystal lattice. The resulting multi-component crystalline phase will maintain the intrinsic

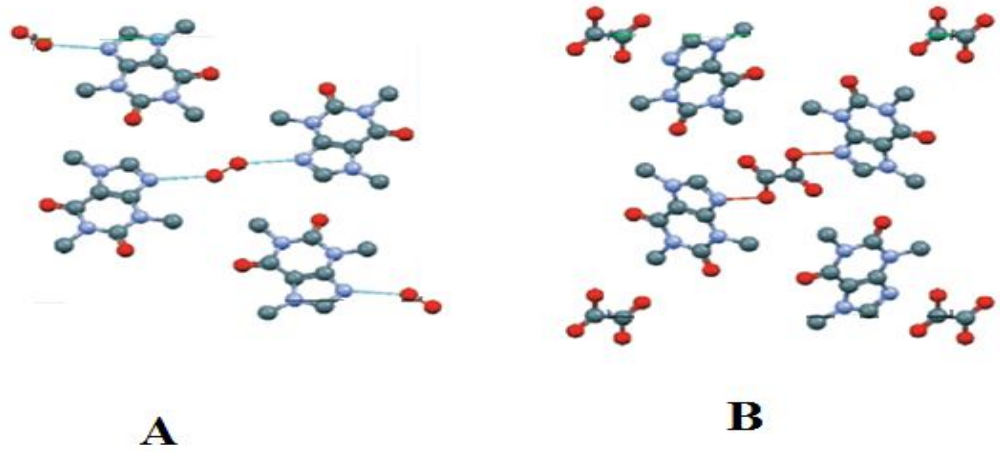

Fig. 2: Example of two-component caffeine crystals,the monohydrate (A) and the cocrystal with oxalic acid (B).

activity of the parent API while possessing a distinct physicochemical profile. The key benefits associated with cocrystallization approach to modifying properties of pharmaceutical solids are the theoretical capability of all types of drug molecules, including weakly ionisable and nonionizable, to form cocrystals, and the existence of numerous potential counter-molecules, including food additives, preservatives, pharmaceutical excipients as well as other APIs, for cocrystal synthesis. Additional valuable advantages that co-crystal formation may offer for the pharmaceutical industry are the opportunity of intellectual property (IP) protection and the possibility of extending the life cycles of old APIs[5].

CRYSTAL ENGINEERING AND SUPRAMOLECULAR CHEMISTRY IN COCRYSTAL FORMATION

A pharmaceutical cocrystal can be designed by crystal engineering with the intention to improve the solid-state properties of an API without affecting its intrinsic structure. Crystal engineering affords a paradigm for rapid development of pharmaceutical cocrystals. It can be defined as an application of the concepts of supramolecular chemistry to the solid state with particular emphasis upon the idea that crystalline solids are actual manifestations of self-assembly[4, 6]. Cocrystals are constructed from intermolecular interactions such as van der waals contact forces, π-π stacking interactions, and hydrogen bonding. Crystal engineering involves modification of the crystal packing of a solid material by changing the intermolecular interactions that regulate the breaking and formation of noncovalent bonds, such as hydrogen bonding, van der waals force, π-stacking, electrostatic interactions, and halogen bonding[7]. The term supramolecular synthon is frequently used in the research field of cocrystals. It is defined as structural units within supramolecules which can be formed and/or assembled by known conceivable

synthetic operations involving intermolecular interactions[8]. Supramolecular synthons are spatial arrangements of intermolecular interactions and the overall goal of crystal engineering is therefore to recognise and design synthons that are robust enough to be interchanged between network structures. This ensures generality ultimately leading to the predictability of one, two and three dimensional patterns formed by intermolecular interactions. Representative examples of pharmaceutically acceptable cocrystal formers that are able to cocrystallise with APIs include carboxylic acids, amides, carbohydrates, alcohols, and amino acids. The most common supramolecular synthons utilised in pharmaceutical cocrystals are shown in Fig. 3

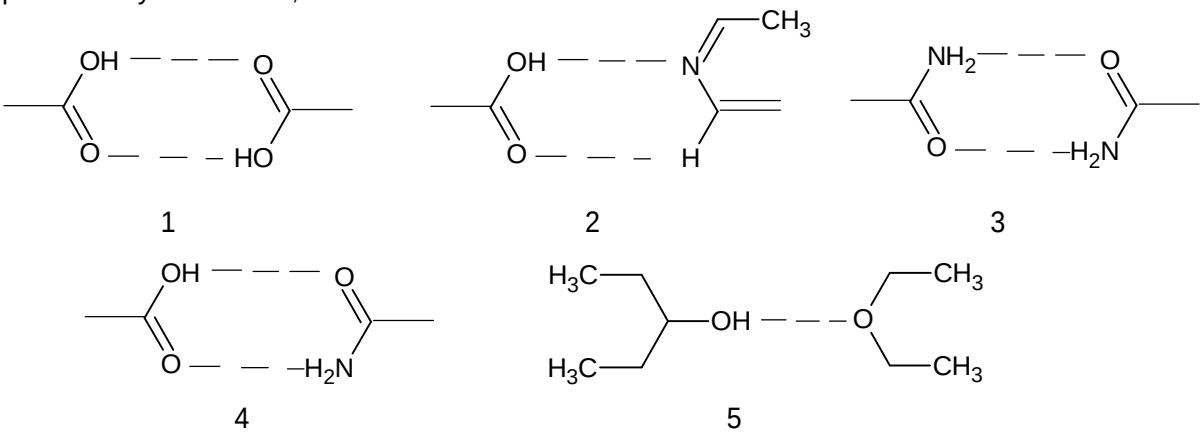

Fig. 3: Typical hydrogen bonds utilised in crystal engineering

PHYSICOCHEMICAL PROPERTIES OF COCRYSTALS

Physical and chemical properties of cocrystals are of great importance to the development of APIs. The overall motivation for investigating pharmaceutical cocrystals as an alternative approach during drug development is the adjustment of the physiochemical properties to improve the overall stability and efficacy of a dosage form [9]. Physicochemical properties, such as crystallinity, melting point, solubility, dissolution, and stability, have been studied extensively by researchers. Some key physicochemical properties of pharmaceutical cocrystals are summarised as following.

1. Melting point

Melting point is the temperature at which the solid phase is at equilibrium with the liquid phase. It is a fundamental physical property and an important consideration during solid drug development. There are complex correlations between the melting point of pharmaceutical product and its processability, solubility and stability. Much research work has been carried out to investigate if the melting point of a cocrystal changes with respect to the individual components and if the melting points can be estimated and modulated within a series of cocrystals. For example, the melting points of cocrystals to the API AMG517 (an insoluble small molecule VR1 (vanilloid receptor 1) antagonist) and their respective coformers showing that all these cocrystals have a melting point that fell between the melting point of the API and their correspondent conformers [10]. In another example, it is hypothesised that the melting point and aqueous solubility of an API may be able to be finely tuned by cocrystallising this API with a series of conformers which have similar structure but show different melting points. This hypothesis was demonstrated by cocrystallisation of hexamethylenebisacetamide, an anticancer drug, and five different even-numbered aliphatic dicarboxylic acids, in which a series of cocrystals with the desired structural consistency were successfully synthesised, showing that the melting points of these five cocrystals were directly related to the melting points of the dicarboxylic acids. Although the solubility of the five cocrystals did not produce a linear correlation as the melting points did, the trend in physicochemical properties of the cocrystals can certainly be rationalised in terms of the properties of the dicarboxylic acids. From these results, it can be concluded that cocrystals may therefore offer unique opportunities for developing new solid forms of drugs in which a variety of desired physicochemical properties can be tuned in a predictable manner [11].

2. Stability

Stability is a very important parameter when evaluating the properties of a pharmaceutical cocrystal. Usually, the stability testing of a

newly developed cocrystal includes four aspects: relative humidity stress, thermal stress, chemical stability, and solution stability. The relative humidity stress test is used to identify the best storage conditions for the product because the amount of water present in the cocrystal can lead to quality deterioration [12]. It was found that better performance of the cocrystals was displayed during water sorption/desorption experiment. For example, negligible amount of water was sorbed by indomethacin saccharin cocrystals in dynamic vapour sorption and desorption experiments [13]. Cocrystals of glutaric acid and 2-[4-(4-chloro-2-fluorphenoxy) phenyl] pyrimidine-4-carboxamide sorbed less than 0.08% water up to 95% relative humidity over repeated sorption/desorption cycles [14]. Results showed that these cocrystals are stable with respect to moisture under normal processing and storage conditions. Thermal stress and chemical stability are relatively less studied areas about cocrystal properties. Very few reports were found and these limited studies showed that thermal stress studies can provide valuable information about physicochemical stability. Meanwhile, assessing chemical stability of cocrystals is important when developing of these materials.

3. Solubility

Solubility is another important parameter for evaluating the properties of a pharmaceutical cocrystal. Traditional methods for improving solubility of poorly water-soluble drugs include salt formation, solid dispersion (emulsification), and particle size reduction (micronisation). However, there are practical limitations with these techniques [15]. Researcher tried to improve the solubilities of two APIs, exemestane (EX) and megestrolacetate(MA), in which two novel cocrystals, exemestane/maleic acis (EX/MAL) and megestrol acetate/saccharin (MA/SA), were prepared from organic solutions with different particle sizes. Cocrystallisations of the EX and MA improved initial dissolution rates compared to the respective original crystals. Cocrystal EX/MAL showed a high dissolution rate even with large particles. Cocrystal MA/SA showed supersaturation with fine particles. The dissolution profiles of the fine MA and MA/SA in the fasted-state simulated fluid at 37^0C are shown in Fig. 4. The supersaturated concentration of MA from MA/SA cocrystal at 15 min was about six times greater than the saturated concentration of fine MA and was two times greater within 4 h [16].

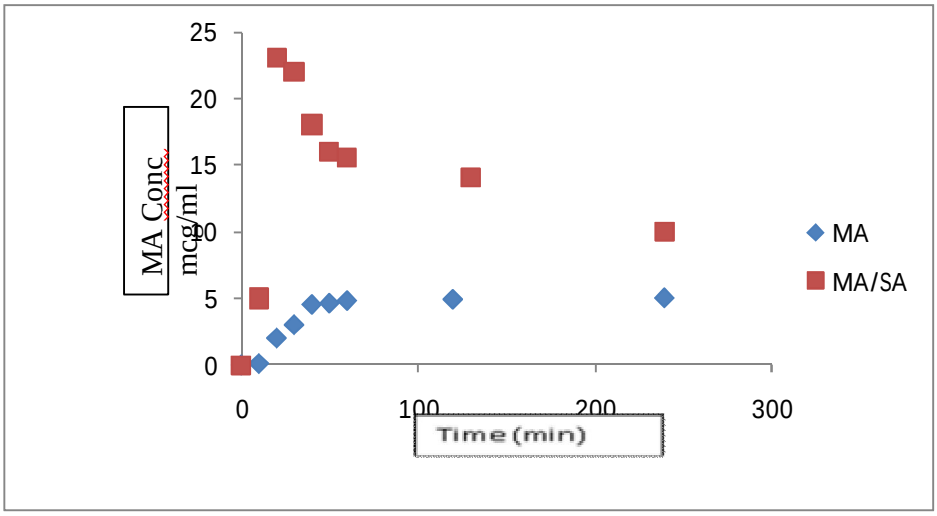

Fig. 4: Dissolution profiles of MA and MA/SA cocrystal[16]

The transformation from cocrystal EX/MAL to EX was observed within 1 min in suspension. Cocrystal MA/SA was transformed to MA within 2–4 h, indicting the mechanisms of dissolution enhancement for the two drugs were different. With cocrystal EX/MAL, a fine particle formation resulted in enhancement, whereas with cocrystal MA/SA, enhancement was due to the maintenance of the cocrystal form and rapid dissolution before transformation to the original crystal. Although pharmaceutical cocrystals have emerged as a potential solution to improve the solubility of poorly soluble APIs and extensive work has been undertaken to explore new cocrystals, less research and fewer results have been published on the theoretical aspects in this area. It was found that cocrystal eutectic constants (Keu), the ratio of solution concentrations of cocrystal components at the

eutectic point, were valuable to guide cocrystal selection, synthesis, and formulation without the material and time requirements of traditional methods. Moreover, Keu values can be used to predict the cocrystal solubility in pure solvent and phase behaviour as a function of solvent, ionization, and solution complexation. Understanding how cocrystal solubility-pH dependence is affected by cocrystal components is important to engineer cocrystals with customised solubility behaviour. In one study, equations that describe cocrystal solubility in terms of product solubility, cocrystal component ionization constants, and solution pH are derived for cocrystals with acidic, basic, amphoteric, and zwitterionic components [17].

4. Intrinsic dissolution

Intrinsic dissolution measures the rate of dissolution of a pure drug substance from a constant surface area, which is independent of formulation effects and measures the intrinsic properties of the drug as a function of dissolution media, e.g. pH, ionic strength and counter-ions. The sample used in the intrinsic dissolution test is pressed into a disk or pellet, which should be no form change upon pressing and the disk, needs to remain intact during the experiment. Most of the APIs studied for cocrystallisation are classified as BCS (Biopharmaceutics Classification System) class II drugs, which have high permeability and low solubility. Thus, intrinsic dissolution rate is a good indicator for in vivo performance of APIs. Although the intrinsic dissolution rate is an important parameter to be investigated, it may become more complicated with cocrystals. Several studies were reported about the intrinsic dissolution rates of cocrystals [18]. One cocrystal example, a low solubility API, 2-[4-(4-chloro-2 fluorophenoxy) phenyl] pyrimidine-4-carboxamide, was cocrystallised with glutaric acid to achieve 18 times higher intrinsic dissolution rate [14].

5. Bioavailability

In pharmacology, bioavailability is a measurement of the extent to which a drug reaches the systemic circulation. The ultimate goal for cocrystal investigation is to improve the bioavailability of an API. Animal bioavailability is an important parameter to consider when preparing new forms of a compound. There are limited numbers of animal bioavailability studies on cocrystals. The cocrystal of glutaric acid and 2-[4-(4-chloro- 2 fluorphenoxy) phenyl]-pyrimidine-4-carboxamide (PPPA) was used to demonstrate an improvement in the oral bioavailability of the API in dogs [14]. Single dose dog exposure studies confirmed that the cocrystal increased plasma AUC (area under the plasma concentration time curve) values by three times at two different dose levels, the mean pharmacokinetic metrics calculated from the dog study data are summarised in Table 1. Another pharmacokinetic study on the indomethacin-saccharin cocrystal also shows an improved bioavailability of the cocrystal over the pure API, indomethacin [19].

Table 1: Comparison of mean pharmacokinetic parameters for PPPA and PPPA-glutaric acid cocrystal[19]

Dose Group	T_{max} (hr)	C_{max} (ng/ml)	AUC (ng h/ml)
5 mg/kg PPPA	13 ± 12	25.4 ± 11.4	374 ± 192
5 mg/kg PPPA Glutaric acid Cocrystal	6 ± 9	89.2 ± 57.7	1234 ± 634
50 mg/kg PPPA	13 ±14	89.2± 68.7	889 ± 740
50 mg/kg PPPA Glutaric Cocrystal	2 ± 0	278 ± 70.5	2230 ± 824

DESIGN STRATEGIES OF PHARMACEUTICAL COCRYSTAL

Pharmaceutical cocrystal design and preparation is a multi stage process. In order to get a desirable cocrystal product of an API with limited aqueous solubility, the first step is to study the structure of the target API molecule and find out the functional groups which can form intermolecular interaction with suitable coformers. As explained before, these intermolecular interactions include van der Waals contacts, π-π stacking interactions, and the most common interaction in cocrystal structure of the hydrogen bonding. The next step is to choose a cocrystal former. The primary request for a coformer is to be pharmaceutically acceptable, for example, pharmaceutical excipients and compounds classified as generally as safe (GRAS) for use as food additives. Coformer selection is the crucial step for designing a cocrystal. During the design process, there are lots of worthwhile reference resources, including both empirical and theoretical resources, such as Cambridge Structural Database (CSD), hydrogen bond theories, and many empirical conclusions. CSD is valuable tool to study intermolecular interactions in crystals [20]. It can

be utilised to identify stable hydrogen bonding motifs, through referring to structural property relationships present in classes of known crystal structures contained in the CSD. A supramolecular library of cocrystal formers has been developed based on the information of CSD, within this library a hierarchy of guest functional groups is classified according to a specific contribution to a crystal packing arrangement, which is dependent on the functionalities contained on the host molecule [21]. As a general guideline, the hierarchy of the supramolecular synthons within a range of common functional groups can be utilised [22]. According to these studies, certain functional groups, such as carboxylic acid, amides, and alcohols are particularly amenable to the formation of supramolecular heterosynthons.

COCRYSTAL FORMATION METHODS

The most common formation methods are based on solution and grinding [23]. The solution method is of great importance due to most of the cocrystals which qualify for single X-ray diffraction (SXRD) testing can only be prepared through this method. Solution methods include evaporation of a heterometric solution method, reaction crystallisation method, and cooling crystallisation. Grinding methods include neat grinding and solvent drop grinding. Apart from solution and grinding methods, there are also many newly emerging methods, such as cocrystallisation using supercritical fluid, hot stage microscopy, and ultrasound assisted cocrystallisation.

1. Solution methods

In practice, solution cocrystallisation is based on the following two strategies [24]:

(1) Use of solvents or solvent mixtures where the cocrystal congruently saturates and thus the components have similar solubility, or

(2) Use of nonequivalent reactant concentrations in order to reach the cocrystal stability region in noncongruently saturating solvents, which can be illustrated by isothermal ternary phase diagrams (TPDs) as shown in Fig. 5. [25]. In Fig. 5(1), two cocrystal components X and Y have similar solubilities in solvent and solution cocrystallisation with equimolar components will lead to the formation of the 1:1 cocrystal from solvent evaporation. Cocrystal components X and Y have nonequivalent solubilities shown in Fig. 5(2) and solution cocrystallisation through evaporation of an equimolar solution may result in the formation of single component crystal.

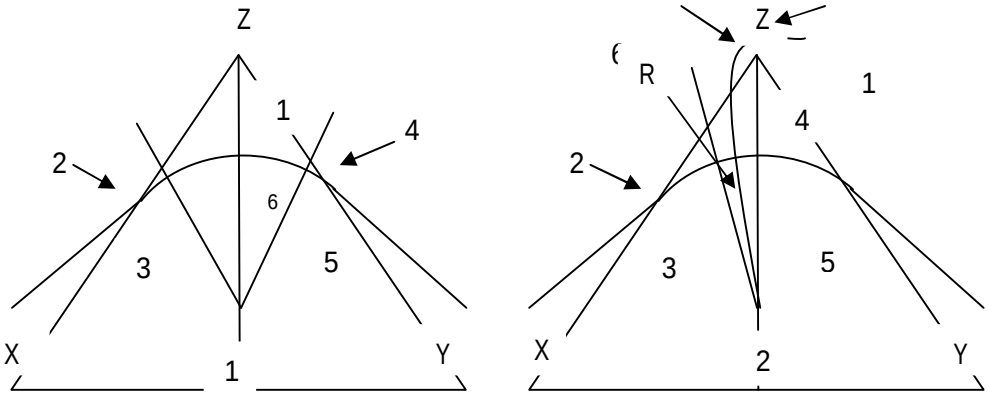

Fig. 5: Isothermal ternary phase diagrams (TPDs) with two components having similar (1) or dissimilar solubilities (2). Region: 1: solution; 2: X + solvent; 3: X + cocrystal; 4: Y + solvent; 5: Y + cocrystal; 6: cocrystal. Path R indicates the evlution of solution composition as a result of adding reactant Y to solutions at close to saturation with Y.

1.1. Evaporation cocrystallisation

Cocrystallisation by evaporation of stoichiometric solutions is based on strategy and it is the most important tool for cocrystal screening. In order to design successful cocrystal screening experiments, it is very important to consider reactant solubilities. As shown in Fig. 5 (1), in which two cocrystal components X and Y have similar solubilities in solvent Z and the 1:1 pure cocrystal can be formed when equimolar components are dissolved in the solvent by evaporation. To date, many successful cocrystal examples were obtained by this method [13].

1.2. Reaction crystallisation

If cocrystal components X and Y have nonequivalent solubilities as shown in Fig. 5 (2), solution cocrystallisation through evaporation of an equimolar solution 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 cocrystal. There is a risk of crystallising a single reactant or a mixture of individual reactant and cocrystal. The reaction cocrystallisation (RC) approach has been adopted for this situation. RC experiments are performed by adding reactant Y to a saturated or close to saturated solution of reactant X and then the solution become supersaturated with respect to cocrystal XY, where cocrystallisation proceeds along the route R as shown in Fig. 5 (2). This method is more effective with nonequivalent solution concentrations and when solutions are saturated with respect to reactants. In one study, RC experiments were performed by adding carbamazepine to saturated or nearly saturated solutions of 18 coformers separately and several pure carbamazepine cocrystals were obtained [24].

1.3. Cooling crystallisation

Another solution method called cooling crystallisation involves varying the temperature of the crystallisation system, which has recently attracted much more attention for potential of a large scale of cocrystal production. First, large amounts of reactants and solvent are mixed in a reactor typically a jacketed vessel, and then the system is heated to a higher temperature to make sure all solutes are totally dissolved in the solvent and is followed by a cooling down step. Cocrystals will precipitate when solution becomes supersaturated with respect to cocrystal as the temperature drops down [14]. Cocrystals of caffeine and p-hydroxybenzoic acid were obtained through cooling crystallisation experiments [26]. The intermolecular interactions of caffeine and p-hydroxybenzoic acid at different concentration ratios in a methanol solvent have been investigated by cooling crystallisation, showing that by understanding the details of the intermolecular interactions it not only enhances the effectiveness on cocrystal screening but also serves as a qualitative and predictive indicator for the final crystalline products. The cooling crystallisation approach can be also used in conjunction with the TPDs in depicting the regions of thermodynamic stability in a multicomponent crystal system and in predicting for the potential formation of cocrystals. In another research, cooling crystallisation of concentrated CBZ/NCT slurry was monitored by using an in situ ATR-FTIR spectroscopy probe, in which the evolution of the CBZ and NCT concentration showed the kinetic pathways of the cocrystallisation process providing useful information on nucleation and growth of the cocrystals and on the proportion of each solid phase present in suspension. Through analysing the kinetic pathways and supersaturation levels of the components, it is possible to determine the optimal operating conditions for a cooling cocrystallisation process [27].

2. Grinding method

It has been witnessed a great progress in cocrystal formation via grinding method over the past few years. There are two different techniques for cocrystal formation via grinding. The first method is neat grinding, which is also called dry grinding, consisting of mixing the stoichiometric cocrystal components together and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill. This method requires one or both reactants exhibiting significant vapour pressures in the solid state [28]. To date many kinds of pharmaceutical cocrystals have been successfully synthesised by neat grinding [29]. Various mechanisms have been utilised to describe the process of neat grinding, involving a different types of intermediate phases, such as molecular diffusion, eutectic formation, and amorphous phase, in which one of the three distinct intermediate bulk phases (a gas, a liquid, or an amorphous solid) should exhibit enhanced mobility and/or higher energy of reactant molecules with respect to their starting crystalline forms [28].

COCRYSTAL CHARACTERISATION TECHNIQUES

Cocrystal characterisation is an important constituent part within cocrystal research. The basic physicochemical properties of cocrystal can usually be characterised by powder X-ray diffraction (PXRD), single crystal X-ray diffraction (SXRD), infrared spectroscopy (IR), Raman spectroscopy, differential scanning calorimetry (DSC), solid state nuclear magnetic resonance spectroscopy (SSNMR), scanning electron microscopy (SEM), and terahertz spectroscopy.

1. Single crystal X-ray Diffraction

SXRD is a basic characterisation technique for determination of the solid state structure of cocrystals at an atomic level. However, the problem is that a single pharmaceutical cocrystal which is qualified for SXRD testing cannot always be produced. Therefore, PXRD are utilised more frequently to verify the formation of cocrystals [30].

2. Raman Spectroscopy

Raman spectroscopy is a spectroscopic technique used to study vibrational, rotational, and other low frequency modes in a system, which has been demonstrated to be a powerful tool for distinguishing isostructural phase. There are many applications using Raman spectroscopy to identify characteristic peaks of cocrystal products [31].

3. Scanning Electron Microscope

SEM is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals which provide information about the sample's surface topography. It is applied to determine the cocrystal micrograph and particle size in many examples [13].

4. Terahertz time-domain-spectroscopy (THz-TDS)

Terahertz time-domain-spectroscopy (THz-TDS) has emerged as a versatile spectroscopic technique, and an alternative to powder X-ray diffraction in the characterisation of molecular crystals. It has been demonstrated that terahertz spectroscopy has the ability to distinguish between chiral and racemic hydrogen bonded cocrystals that are similar in molecular and supramolecular structure. The investigation of the cocrystal of theophylline with chiral and racemic forms of coformers using PXRD and Raman spectroscopy suggested that THz-TDS is comparable in sensitivity to diffraction methods and more sensitive than Raman to changes in cocrystal architectures [32].

CASE STUDIES OF PHARMACEUTICAL COCRYSTALS

They studied complex formation between macromolecules and certain pharmaceuticals. For example, complexes of polyvinylpyrrolidone (PVP) with sulfathiazole, procaine hydrochloride, sodium salicylate, benzylpenicillin, chloramphenicol, mandelic acid, caffeine, theophylline, and cortisone were isolated [33]. However, these would not be classified as pharmaceutical cocrystals according to the criteria applied herein. Perhaps the first application of crystal engineering to the generation of pharmaceutical cocrystals was a series of studies concerning the use of substituted barbituric acid, including barbital and melamine derivatives, to generate supramolecular 'linear tape', 'crinkled tape', and 'rosette' motifs sustained by robust supramolecular synthons with three point hydrogen bonding. Despite their success in cocrystal formation, the focus of these studies was not so much the physical properties of the resulting cocrystals but rather the supramolecular functionality of barbitals and their complementarities with melamine [34]. Nevertheless, these studies illustrated very well the potential diversity of forms that can exist for a particular API as more than 60 cocrystals were structurally characterized in this series of studies. Clearly, such a diversity of forms could offer an exciting opportunity to novel and improved crystalline forms of APIs. Herein, we have chosen to focus upon several case studies that involve the formation of pharmaceutical cocrystals with altered physical properties of clinical relevance.

Pharmaceutical cocrystals of carbamazepine (Tegretol1) P

Carbamazepine (CBZ) is an important anti-epileptic drug that has been in use for over three decades. Oral administration of CBZ encounters multiple challenges, including low water solubility with high dosage required for therapeutic effect (i.e. >100 mg/ day), dissolution-limited bioavailability and autoinduction for metabolism. In contrast to its simple molecular structure, CBZ exhibits complexity in its crystal forms [35].To date, four anhydrous polymorphs, a dihydrate, an acetone solvate, and two ammonium salts of CBZ have been identified. It is noted that, in the crystal structures of all these forms, the self-complementary nature of the amide group manifests itself in a predictable manner. Therefore, CBZ has been used as an ideal candidate to demonstrate how APIs can be converted to pharmaceutical cocrystals, and how these cocrystals could offer optimized physicochemical properties over existing forms of an API. Two strategies have been adopted for cocrystal formation of CBZ. One crystal engineering strategy is to employ the peripheral hydrogen bonding capabilities that are not engaged in the pure form of CBZ. A second strategy for cocrystallization of CBZ involves breakage of the CBZ amide– amide dimer and formation of a supramolecular heterosynthon between CBZ and a cocrystal former [36]. Both strategies are successful and have afforded a number of CBZ cocrystals that exhibit improved physicochemical properties. For example, the CBZ:saccharin cocrystal shows significantly improved physical stability (i.e. only one cocrystal form with equivalent chemical stability to the anhydrous polymorph has been identified after sophisticated form screening). In addition, the CBZ:saccharin

cocrystal possesses favorable dissolution properties, suspension stability, and pharmacokinetics using dog models. The pharmacokinetic study reveals that the CBZ:saccharin cocrystal exhibits a higher Cmax and comparable Tmax when compared with the marketed form, Tegretol. In short, the CBZ: saccharin cocrystal appears to be superior to existing crystal forms of CBZ in the following respects: stability relative to the anhydrous polymorph of CBZ; favorable dissolution and suspension stability; favourable oral absorption profile in dogs.

Pharmaceutical cocrystals of fluoxetine hydrochloride (Prozac1)

The availability and marketability of a variety of APIs as chloride salts is well recognized, and, recently, an approach to utilize such chloride salts, specifically fluoxetine hydrochloride (fluoxetine HCl), to generate cocrystals of an amine hydrochloride salt via a chloride-mediated carboxylic acid supramolecular synthon has been reported. Fluoxetine HCl is the active pharmaceutical ingredient found in the common antidepressant drug Prozac1. It is a solid under ambient conditions, only one crystalline phase is known, and it is available in the salt form. It has been demonstrated that cocrystallization of this API modifies the physical properties of fluoxetine HCl while still retaining the hydrochloride salt of the API. Fluoxetine HCl was cocrystallized with benzoic acid (1:1), succinic acid (2:1), and fumaric acid (2:1) via traditional evaporation techniques. For all three cocrystals, the carboxylic acid was found to hydrogen bond to the chloride ion, which in turn interacted with the protonated amine, thus generating, in all three cases, amine hydrochloride salt hydrogen bonding to an additional neutral molecule. Powder dissolution experiments were carried out in water for the three novel cocrystals resulting in a spread of dissolution profiles (Fig 6). The fluoxetine HCl: benzoic acid cocrystal was found to have a decrease in aqueous solubility by ca. 50%, and the fluoxetine HCl:fumaric acid cocrystal had only a slight increase in aqueous solubility. However, the fluoxetine HCl:succinic acid cocrystal exhibited an approximately two fold increase in aqueous solubility after only 5 min. The complex formed between succinic acid and fluoxetine HCl falls apart in solution to generate its pure components after about 1 h. An intriguing aspect of this study is that by simply hydrogen bonding a hydrochloride salt of an API with similar cocrystal formers one can generate distinctively different dissolution profiles [37].

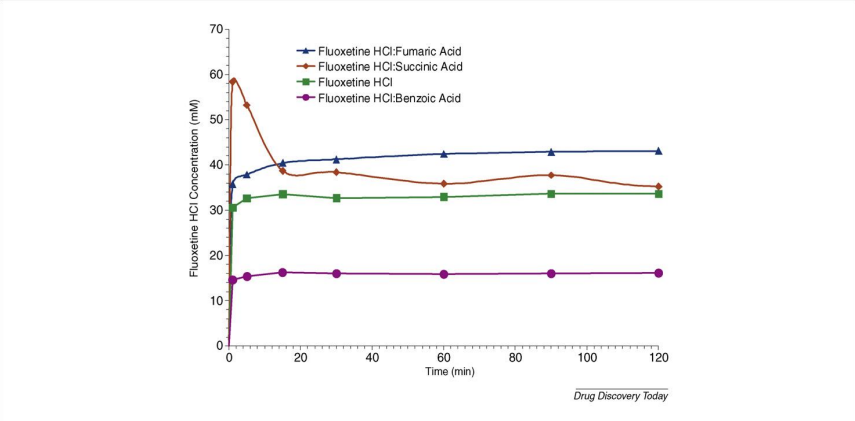

Fig. 6: Dissolution profiles for novel cocrystal forms of fluoxetine HCl reveal how intrinsic dissolution can be modified through cocrystallization

Pharmaceutical cocrystals of itraconazole (Sporanox1)

Itraconazole is a triazole antifungal agent that is prescribed to patients with fungal infections. Itraconazole is extremely water insoluble and administered both orally and intravenously. In order to achieve the required oral bioavailability, the oral formulation of itraconazole is the amorphous form coated on the surfaces of sucrose beads, and marketed as the Sporanox1 capsule. In addition, co-administration of acidified HP-b-cyclodextrin beverages with Sporanox1 capsules is required to achieve the maximal absorption of the API, even though such a co-administration can cause diarrhea. Interestingly, no crystalline salt of itraconazole has been reported in the patent literature, even though

salt formation using itraconazole and an acidic salt former would seem to be a logical approach to improve the absorption properties of the API. In order to improve the absorption of the API and maintain the form crystallinity and stability, the pharmaceutical cocrystal approach has been evaluated in the formulation of itraconazole.

Pharmaceutical cocrystals of sildenafil (Viagra1)

Sildenafil is a drug used in the treatment of pulmonary arterial hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency and peripheral vascular disease, as well as male erectile dysfunction and female sexual disorders. Sildenafil selectively inhibits cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 that is responsible for degradation of cGMP in the corpus cavernosum, leading to smooth muscle relaxation in the corpus cavernosum, and resulting in increased inflow of blood and an erection. Sildenafil citrate, with moderate water solubility, has been commercially developed and marketed by Pfizer and is available under the trademark Viagra. It has been observed that sildenafil in a pharmaceutical cocrystal form could provide an improved solubility of the API under acidic conditions. In addition, such an improvement of solubility of sildenafil could be particularly advantageous for its orally administrable formulation. Sildenafil has been successfully cocrystallized with acetylsalicylic acid (1:1 molar ratio) by slurry or under reflux conditions. The crystal structure of the cocrystal of sildenafil and acetylsalicylic acid has been determined by single crystal X-ray diffraction, and in addition, the composition of matter was confirmed by powder X-ray diffraction and infrared spectrometry. Moreover, the differential scanning calorimetry and thermogravimetric analyses indicate that the melting point of the cocrystal is approximately 143^0C, and it remains thermodynamically stable up to ca. 165^0C. An intrinsic dissolution study in simulated gastric body fluid (pH 1.2) shows that the sildenafil:acetylsalicylic acid cocrystal exhibits an intrinsic dissolution rate (IDR) of ca. 11.75 mg min^{-1} cm^{-2} vs. 6.64 mg min^{-1} cm^{-2} for sildenafil citrate under the same conditions [38].

CONCLUSION

Pharmaceutical cocrystal becoming increasingly important for increasing solubility of poorly soluble drug. Many of researchers putting their attention for developing cocrystal of API. This contribution highlights how crystal engineering can afford opportunities to diversify the number of crystal forms known for an API and to improve their physical properties of clinical relevance. A future challenging aspect is related to the development of efficient cocrystals screening technologies. This can be achieved by implementation of solid based techniques need grinding and liquid assisted grinding. A key advantage of cocrystal as a solid form of API is possibility of achieving the high dissolution rate comparable to that of amorphous form.

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