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Review

Pharmaceutical cocrystals: An overview

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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. In this paper a brief and systematic overview of pharmaceutical cocrystals is provided, with particular focus on cocrystal design strategies, formation methods, physicochemical property studies, characterisation techniques, and recent theoretical developments in cocrystal screening and mechanisms of cocrystal formations. Examples of pharmaceutical cocrystals are also summarised in this paper.

1. Introduction

In the pharmaceutical industry, it is the poor biopharmaceutical properties rather than toxicity or lack of efficacy that are the main reasons why less than 1% of active pharmaceutical compounds eventually appear into the marketplace (Aakeröy et al., 2009; PhRMA, 2006; Ramanathan, 2009). Among these biopharmaceutical properties, solubility remains a key issue (Blagden et al., 2007), 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 (Cho et al., 2010; Li et al., 2006a; Rasenack et al., 2003), salt formation (Umeda et al., 2009), emulsification (Hong et al., 2006; Torchilin, 2007), solubilisations using co-solvents (Amin et al., 2004), and the use of polymer drug vehicles for delivery of poorly soluble drugs (Yue et al., 2010). 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 (Blagden et al., 2007; Huang and Tong, 2004; ter Horst et al., 2009; Vishweshwar et al., 2006). 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.

To start with, it is necessary to know two important definitions: cocrystal and pharmaceutical cocrystal. Cocrystals can be defined in a number of ways (Schultheiss and Newman, 2009; Shan and Zaworotko, 2008). A restrictive definition utilised by Aakeröy and Salmon (2005) is that cocrystals are structurally homogeneous crystalline materials containing two or more components present in definite stoichiometric amounts. The cocrystal components are discrete neutral molecular reactants which are solids at ambient temperature. Based on this definition of cocrystals, a pharmaceutical cocrystal means a cocrystal with one of the cocrystal components as an Active Pharmaceutical Ingredient (API) and the other components are called coformers. From the definition, it is clearly shown that an API hydrate is not a cocrystal, however a solid-state API hydrate can cocrystallise with a solid coformer to form a cocrystal (Chieng et al., 2009). Currently cocrystal approach is a method of great interest for the pharmaceutical industry. Apart from offering potential improvements in solubility, dissolution rate, bioavailability and physical stability, pharmaceutical cocrystals can enhance other essential properties of the APIs such as flowability, chemical stability, compressability and hygroscopicity (Lu and Rohani, 2009).

To date, several literature reviews focusing on pharmaceutical cocrystals have been published (Aakeröy and Salmon, 2005; Blagden et al., 2007, 2008; Friščić and Jones, 2009, 2010; Miroshnyk et al., 2009; Schultheiss and Newman, 2009; Sekhon, 2009; Shan and Zaworotko, 2008; Vishweshwar et al., 2006). A general introduction to pharmaceutical cocrystals was provided by Miroshnyk et al. (2009). Blagden's articles covered the basic knowledge of crystal engineering and discussed preparation methods of cocrystals and the potential influence of pharmaceutical cocrystallisation

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on its dissolution and oral absorption (Blagden et al., 2007, 2008). Another review (Vishweshwar et al., 2006) addressed how crystal engineering has been applied to make APIs, with emphasis upon how pharmaceutical cocrystals can be generated in a rational way. Pharmaceutical cocrystals were addressed from the perspective of design by Shan and Zaworotko (2008). Aakeröy and Salmon (2005) provided an overview of some strategies for the synthesis of cocrystals based upon a hierarchy of intermolecular interactions, notably hydrogen bonds. A review focusing on the mechanistic aspects of cocrystal formation through grinding was given by Friščić and Jones (2009). An article published by Schultheiss and Newman (2009) highlighted and discussed the improvements of physicochemical properties, such as melting point, solubility, dissolution, and stability, made through pharmaceutical cocrystals. A recent review by Friščić and Jones (2010) pointed out that the potential of cocrystallisation for modification of API solid forms is well recognised by summarising the recent applications of cocrystals which improve the physicochemical and materials properties of APIs and the research is now moving towards the rationalisation of cocrystal structure-property relationships. From the above analysis, it is clearly seen that most of the recent reviews focused only on one or two specific issues regarding pharmaceutical cocrystals.

The aim of this article is to provide a brief and systematic overview of pharmaceutical cocrystals, focusing on all key issues of pharmaceutical cocrystals including cocrystal design strategies, formation methods, physicochemical properties studies, characterisation techniques, and recent theoretical development in cocrystal screening and mechanisms of cocrystal formations. It is hoped that this review will provide an appreciation for an overview of understanding of pharmaceutical cocrystals and will prove a good starting point for readers for further study.

2. 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 (Almarsson and Zaworotko, 2004; Khan et al., 2010; Padrela et al., 2010; Walsh et al., 2003). 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 non-covalent bonds, such as hydrogen bonding, van der Waals force, π-stacking, electrostatic interactions, and halogen bonding (Aakeröy et al., 2007; Cinčić et al., 2008; Miroshnyk et al., 2009; Saha et al., 2005).

The term supramolecular synthon is frequently used in the research field of cocrystals. It is defined by Desiraju (1995) as structural units within supramolecules which can be formed and/or assembled by known conceivable synthetic operations involving intermolecular interactions. 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 (Blagden et al., 2007).

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. 1.

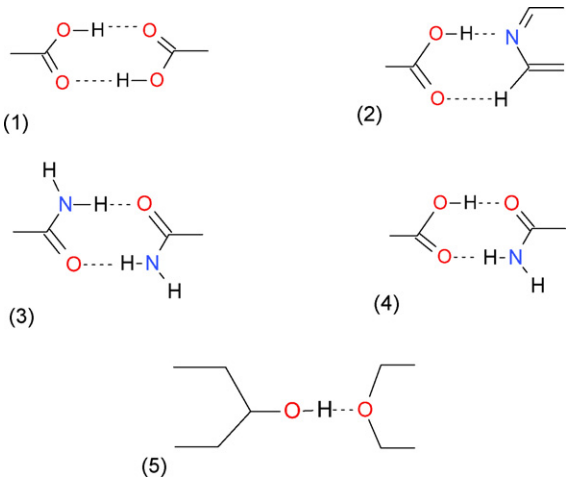


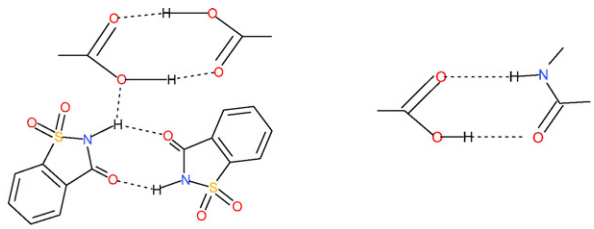
Fig. 1. Typical hydrogen bonds utilised in crystal engineering.

Existing widely in drugs, carboxylic acid functional group has been extensively studied in the pharmaceutical cocrystal research area. With self-complementary hydrogen bond donor and acceptor, the formation of carboxylic acid homosynthon in Fig. 1(1) through C=O···H–O hydrogen bond is very common (Basavoju et al., 2008). Another widely studied homosynthon is amide homodimer in Fig. 1(3), forming a cocrystal through C=O···H–N hydrogen bond. Apart from homosynthons, some favourable heterosynthons are also shown in Fig. 1, such as carboxylic acid-pyridine in Fig. 1(2), carboxylic–amide in Fig. 1(4), and alcohol-ether in Fig. 1(5).

Recently, studies of hydrogen bonds competition have attracted increasing interest from a number of researchers (Aakeröy and Salmon, 2005; Bis et al., 2007; He et al., 2008; Steiner, 2001). Generally, heterosynthons are more robust than homosynthons, e.g., the acid–amide heterosynthons favoured over both carboxylic acid and amide homodimer (Vishweshwar et al., 2006). Through analysis of the Cambridge Structural Database (CSD) by Bis et al. (2007), it is revealed that the hydroxyl–pyridine and hydroxyl–cyano heterosynthons are strongly favoured over the competing hydroxyl–hydroxyl homosynthon. Among all the heterosynthons, one of the most widely used synthons has contained an O–H···N hydrogen bond, formed by carboxylic acid and a suitable N-containing heterocycle (Aakeröy and Salmon, 2005; Weyna et al., 2009), such as carboxylic acid–pyridine heterosynthon shown in Fig. 1(2). The CSD study indicated carboxylic acid–pyridine heterosynthons more favoured over carboxylic acid homodimer (Steiner, 2001). These empirical conclusions on hierarchy of supramolecular synthons are particularly useful for cocrystal design. However, there is not always a case in reality. The indomethacin and saccharin (IND–SAC) cocrystal structure was revealed that the indomethacin carboxylic acid dimer interacts with the saccharin imide dimer synthon through a weak N–H···O bond in Fig. 2(1) rather than an indomethacin carboxylic acid···saccharin imide heterosynthon in Fig. 2(2) which is more favourable according to the empirical rules (Basavoju et al., 2008). Therefore, these empirical conclusions can only provide a supplementary guidance for cocrystal design.

3. 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



(1) acid dimer connected with weak N-H···O interaction

(2) acid···imide dimer synthon

Fig. 2. IND–SAC cocrystal structure.

during drug development is the adjustment of the physiochemical properties to improve the overall stability and efficacy of a dosage form (Blagden et al., 2008). Physicochemical properties, such as crystallinity, melting point, solubility, dissolution, and stability, have been studied extensively by researchers. A systematical review of these properties was given by Schultheiss and Newman (2009). Some key physicochemical properties of pharmaceutical cocrystals are summarised as following.

3.1. 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 10 cocrystals to the API AMG517 (an insoluble small molecule VR1 (vanilloid receptor 1) antagonist) (Bak et al., 2008) and their respective coformers were compared by Stanton and Bak (2008), showing that all these cocrystals have a melting point that fell between the melting point of the API and their correspondent coformers. In another example (Aakeröy et al., 2009), 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. More cocrystalline samples were analysed by Schultheiss and Newman (2009) showing that the melting points of APIs can be altered through forming cocrystals, which were usually in between that of the APIs and coformers or lower than that of the APIs or coformers.

The impact of crystal packing on the melting points of cocrystals were investigated by Fleischman et al. (2003), in which four cocrystals with the same fundamental heteromeric O–H···N hydrogen bond but different overall packing arrangements had different melting points. In addition, it was also shown that there were some correlations between a compound's melting point and its solubility, which was that high melting points may contribute to poor solubility of cocrystals. Because all of the results obtained are based on small number of samples, further study within this area is required.

3.2. 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 (Reutzel-Edens and Newman, 2006). It was found that better performance of the cocrystals was displayed during water sorption/desorption experiments (Basavoju et al., 2008; McNamara et al., 2006; Padrela et al., 2010; Trask et al., 2006). For example, negligible amount of water was sorbed by indomethacin–saccharin cocrystals in dynamic vapour sorption and desorption experiments (Basavoju et al., 2008). 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 (McNamara et al., 2006). 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 (Oswald et al., 2002; Variankaval et al., 2006) 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. Solubility stability is defined by Schultheiss and Newman (2009) as the ability of the cocrystal components to stay in solution and not readily crystallise. Solution stability is an important parameter during drug development. Stability experiments accompany solubility or dissolution experiments to provide a more complete understanding of the behaviour of cocrystals in release media.

3.3. 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 (Blagden et al., 2007). Pharmaceutical cocrystallisation as a novel way to improve the physicochemical properties of a drug such as solubility, which has attracted great interests from researchers (Aakeröy et al., 2009; Blagden et al., 2007; Childs et al., 2004; Cho et al., 2010; McNamara et al., 2006; Miroshnyk et al., 2009; Remenar et al., 2003; Shiraki et al., 2008). Shiraki et al. (2008) 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 °C are shown in Fig. 3. 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.

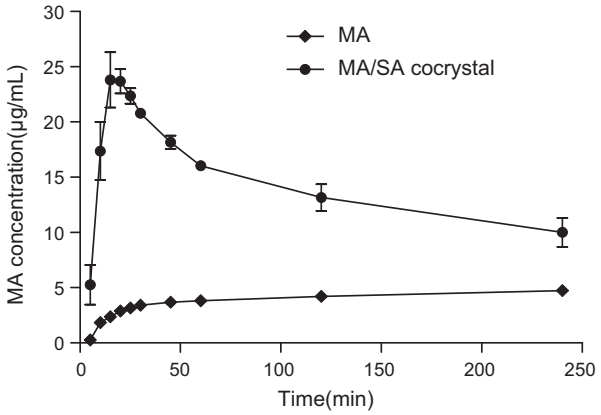


Fig. 3. Dissolution profiles of MA and MA/SA cocrystal (Shiraki et al., 2008).

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. Recently, a theoretical analysis was published by Good and Rodriguez-Hornedo (2010), focusing on how to predict pharmaceutical cocrystal solubility and its influential factors. It was found that cocrystal eutectic constants (K_{eu}), 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, K_{eu} values can be used to predict the cocrystal solubility in pure solvent and phase behaviour as a function of solvent, ionization, and solution complexation. The applicability of K_{eu} towards describing the cocrystal solubility ratio and solution chemistry has been demonstrated by Serajuddin (1999) with a set of more than 40 cocrystals and solvent combinations. Understanding how cocrystal solubility-pH dependence is affected by cocrystal components is important to engineer cocrystals with customised solubility behaviour. In one study (Bethune et al., 2009), 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.

3.4. 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.

Table 1
Comparison of mean pharmacokinetic parameters for PPPA and PPPA-glutaric acid cocrystal (McNamara et al., 2006).

Dose group	T_{max} (h)	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 ± 613
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

Various factors need to be considered and extra experiments may be needed to obtain and interpret intrinsic dissolution data on cocrystals correctly (Schultheiss and Newman, 2009). The static disk method for intrinsic dissolution rates testing was elaborated by Kobayashi et al. (2000). Several studies were reported about the intrinsic dissolution rates of cocrystals (Lee et al., 2010; McNamara et al., 2006). 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 (McNamara et al., 2006).

3.5. Bioavailability

In pharmacology, bioavailability is a measurement of the extent to which a drug reaches the systemic circulation (Shargel and Yu, 1999). 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 (McNamara et al., 2006). 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 (Jung et al., 2010).

4. Pharmaceutical cocrystal design strategies

Pharmaceutical cocrystals have rapidly emerged as a new class of API solids demonstrating great promise and numerous advantages. Much work has focused on exploring the crystal engineering and design strategies that facilitate formation of cocrystals of APIs and cocrystal formers. Pharmaceutical cocrystal design and preparation is a multi-stage process, as schematically illustrated in Fig. 4 (Miroshnyk et al., 2009). 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, $\pi\cdots\pi$ stacking interactions, and the

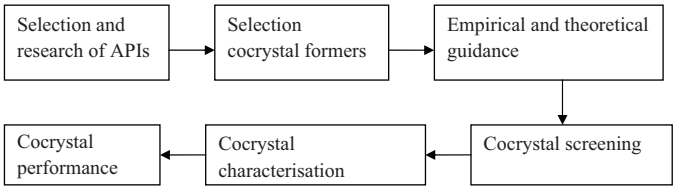


Fig. 4. Steps for cocrystal design and preparation (Miroshnyk et al., 2009).

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 (Orpen, 2002). It can be utilised to identify stable hydrogen bonding motifs (Blagden et al., 2008), 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 (Blagden et al., 2007). As a general guideline, the hierarchy of the supramolecular synthons within a range of common functional groups can be utilised (Bis et al., 2007). According to these studies, certain functional groups, such as carboxylic acid, amides, and alcohols are particularly amenable to the formation of supramolecular heterosynthons.

For most pharmaceutical cocrystal structures, hydrogen bonds take an important role in directing intermolecular recognition between an API and a coformer molecule (Desiraju, 1995; Etter, 1991; Etter and Reutzel, 1991). A graph-set notation system introduced by Etter et al. (1990) was used widely to describe and label hydrogen bond motifs. In the graph-set system four principal motifs are used: chains (C), dimers (D), rings (R), and intramolecular hydrogen bonds (S), as descriptors of hydrogen-bonded molecular solids. Additionally, the following guidelines were proposed to facilitate the design of hydrogen bonded solids (Dale et al., 2004): (1) all good proton donors and acceptors are used in hydrogen bonding; (2) if six-membered ring intramolecular hydrogen bonds can form, they will usually do so in preference to forming intermolecular hydrogen bonds; (3) the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation, form intermolecular hydrogen bonds to one another.

Recently pKa has been used to predict the possibility of cocrystal formation between two cocrystal components (Weyna et al., 2009). In the pharmaceutical industry the pKa difference between two reactants is used as, typically $\Delta pKa > 3$, a criterion for selecting counter ions for salt formation. The same criterion has been used for selection of a cocrystal former (Dhumal et al., 2008b). However, many problems using this pKa evaluation method are found and the criterion is not always applicable. In the meantime, there are many exceptions, such as Johnson and Rumon (1965) reported that $\Delta pKa < 3.75$ can produce neutral COOH···N interactions and therefore further study is needed. In a newly published research work (Mohammad et al., 2011), miscibility of a drug and coformer, as predicted by Hansen solubility parameters, can indicate cocrystal formation and guide cocrystal screening. The results show that the drug and coformer should be miscible for cocrystal formation, thus, predicting the miscibility of cocrystal components using solubility parameters can guide the selection of potential coformers prior to exhaustive cocrystal screening work.

Cocrystal screening is an experimental process to determine if a particular coformer candidate is able to cocrystallise with a targeted API. After a small scale screening exercise, proper coformers could be selected to do scale up experiments. Various screening methods have been developed for cocrystal screening. A solution method is usefully utilised for screening, in which small amounts of stoichiometric cocrystal components are dissolved in solvent and then the products are obtained through slow evaporation for testing. Zhang et al. (2007) extended the established physical stability treatment for hydrates/solvates to cocrystals with solid coformers to improve the screening efficiency. Based on the proposed treatment, a suspension/slurry cocrystal screening technique was developed and tested in sixteen pharmaceutical cocrystal systems. Recently, a hot-stage thermal microscopy method, which is also called Kofler technique, has been frequently utilised in the initial cocrystal screening (Berry et al., 2008; Lee and Wang, 2010; McNamara et al., 2006). This method allows elucidation of the thermodynamic landscape within the binary phase diagram in which the melting profile of a two-component system can be visualised and mapped. It provides a quick preliminary test by observing the occurrence of a new phase on the interface of two reactants under hot-stage microscope. In another research work (Habgood et al., 2009), computed crystal energy landscapes were successfully adopted to explain why carbamazepine can cocrystallise with isonicotinamide but not with picolinamide, which could provide useful complement information to experimental cocrystal screening.

The aim of cocrystal characterisation is to investigate the physical, chemical, and crystallographic properties of cocrystals. Usually, characterisation includes the chemical structural conformation and crystallographic analysis of the newly formed supramolecular synthon, its thermal features, stability and solubility. Details of different cocrystal characterisation techniques will be given in section 6 of this paper. The final step of cocrystal design and preparation is the performance tests of newly formed compounds, which includes both *in vitro* and *in vivo* tests. *In vitro* tests focus on intrinsic dissolution and dissolution tests, while *in vivo* tests refer to animal bioavailability measurements, the measurement of the rate and extent of an API that reaches systemic circulation (Bermejo and Gonzalez-Alvarez, 2007).

5. Cocrystal formation methods

To date, many ways of producing cocrystals have been reported. The most common formation methods are based on solution and grinding (He et al., 2008). 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.

5.1. Solution methods

In practice, solution cocrystallisation is based on the following two strategies (Childs et al., 2008): (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 (Ainouz et al., 2009; Blagden et al., 2008; Miroshnyk et al., 2009). In Fig. 5(1), two cocrystal components A and B 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 A and B 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.

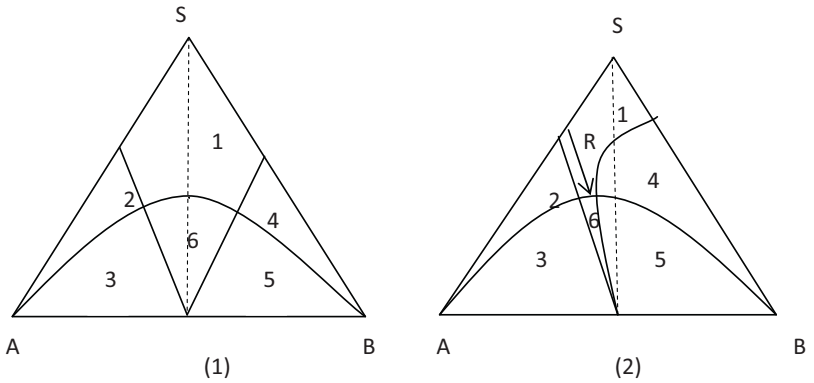


Fig. 5. Isothermal ternary phase diagrams (TPDs) with two components having similar (1) or dissimilar solubilities (2). Region: 1: solution; 2: A + solvent; 3: A + cocrystal; 4: B + solvent; 5: B + cocrystal; 6: cocrystal. Path R indicates the evlution of solution composition as a result of adding reactant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

5.1.1. Evaporation cocrystallisation

Cocrystallisation by evaporation of stoichiometric solutions is based on strategy 1 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 A and B have similar solubilities in solvent S 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 (Basavoju et al., 2008; Bis et al., 2007; Weyna et al., 2009).

5.1.2. Reaction crystallisation

If cocrystal components A and B 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 B to a saturated or close to saturated solution of reactant A and then the solution becomes supersaturated with respect to cocrystal AB, 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 (Childs et al., 2008), RC experiments were performed by adding carbamazepine to saturated or nearly saturated solutions of 18 coformers separately and several pure carbamazepine cocrystals were obtained.

5.1.3. 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 (McNamara et al., 2006).

Cocrystals of caffeine and p-hydroxybenzoic acid were obtained through cooling crystallisation experiments (He et al., 2010). 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. Cocrystallisation of carbamazepine and nicotinamide (CBZ/NCT) were carried out by Gagniere et al. (2009b), in which the evolution of the solid phases during the cooling cocrystallisation process were monitored by an *in situ* video probe. For kinetic reasons of nucleation and growth, both metastable and stable solid phases were temporarily observed, even though only the stable phase remained at the end of the process. These results demonstrate the importance of the initial conditions on the pathway of crystallisation. In another research (Gagniere et al., 2009a), 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.

5.2. Grinding method

It has been witnessed a great progress in cocrystal formation via grinding method over the past few years. Several reviews focusing on this area have been published. Examples and methodologies of cocrystal formation using grinding have been summarised by Braga and Grepioni (2004) and Braga et al. (2006). A brief and systematic overview focusing on the mechanistic aspects of cocrystal synthesis via grinding is given by Friščić and Jones (2009).

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 (Friščić and Jones, 2009). To date many kinds of pharmaceutical cocrystals have been successfully synthesised by neat grinding (Jayasankar et al., 2006; Lu and Rohani, 2009; Myz et al., 2009). 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 (Friščić and Jones, 2009).

The second technique for cocrystal synthesis via grinding is that of liquid-assisted grinding (also referred to as kneading, solvent-drop, wet cogrinding). Significant improvements in kinetics of cocrystal formation by grinding can be achieved by the addition of minor amounts of an appropriate solvent (Shan et al., 2002). The improvements in kinetics might be rationalised by the additional degrees of orientational and conformational freedom open to molecules at the various interfaces as well as the enhancement of opportunities for molecular collisions (Trask et al., 2004). In addition, tiny cocrystal seeds may be envisaged to form within the solvent during the grinding process so that the rate of cocrystallisation can be increased. Besides increasing the cocrystallisation rate, the method of solvent-drop grinding (SDG) can control over the polymorphic outcome of cocrystallisation. The nature of solvents using in grinding may have a profound effect on the process of the mechanochemical reaction. The SDG method has been demonstrated to be a novel means of obtaining a particular caffeine–glutaric acid cocrystal polymorph (Trask et al., 2004). The choice of solvent used in grinding is important and one basic requirement is that it should be able to dissolve at least part of the original components. Comparing this method to the slow evaporation cocrystallisation method, little solvent is used in SDG, which therefore appears to be a cost-effective, environmentally friendly, and reliable method for the discovery of new cocrystals as well as for the preparation of existing cocrystals (Basavoju et al., 2008; Braga and Grepioni, 2005; Trask et al., 2004; Weyna et al., 2009).

5.3. Other formation methods

Recently several novel methods have appeared in the area of pharmaceutical cocrystallisation. The application of a supercritical fluid (SCF) technology into cocrystal formation has been carried out by Padrela et al. (2009, 2010). The feasibility of SCF technologies in the screening and design of cocrystals was studied. The utilisation of SCF is based on its three fundamental properties: solvent power, miscibility with organic liquids (anti-solvent), atomisation enhancement. In Padrela's work (2009), indomethacin–saccharin cocrystals with different morphologies and sizes (nano-to-micron) were produced using supercritical fluid techniques, demonstrating the potential of SCF technologies as screening method for cocrystals.

Ultrasound has been used to prepare cocrystals from solution or suspension/slurry (Dhumal et al., 2008a,b, 2009). Ultrasound assisted solution cocrystallisation (USSC) has been studied using a noncongruently soluble pair of caffeine and maleic acid in methanol (Aher et al., 2010), in which pure caffeine/maleic acid 2:1 cocrystal was obtained. It is suggested that ultrasound applications in USSC must have altered supersaturation conditions of caffeine and maleic acid in solution, favouring generation of caffeine/maleic acid 2:1 cocrystal nuclei. Further investigations need to be carried out for understanding the nucleation mechanisms during USSC.

6. 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.

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. While, PXRD cannot distinguish solvates, hydrates or polymorphs from cocrystals, to make things worse, pharmaceutical cocrystals are prone to forming isostructural phases (Miroshnyk et al., 2009). In order to gain a better understanding about the solid structure, the integration of more advanced methods of solid-state analysis is necessary. 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 (Aher et al., 2010; Childs et al., 2008; Lu and Rohani, 2009; McNamara et al., 2006; Porter Iii et al., 2008).

IR is a very common spectroscopic technique in determining the chemical conformation of compounds. It can be a very powerful tool in distinguishing cocrystals from salts when a carboxylic acid is involved in hydrogen bond formation (Aakeröy et al., 2006). A neutral carboxylic group (–COOH) has a strong carbonyl (C=O) stretching peak around 1700 cm^{-1} and a weak C–O stretch around 1200 cm^{-1}; however, if deprotonation has occurred, a carboxylate anion ($–COO^-$) has only a single C–O stretch in the fingerprint region of 1000–1400 cm^{-1}.

SSNMR is another complementary technique to XRD, which is often used to characterise solid phases that cannot be studied by SXRD (He et al., 2008; Li et al., 2006b). Recently, high-resolution SSNMR has shown to be a versatile and powerful tool for characterisation of pharmaceutical cocrystals. Notably, NMR not only allows for non-invasive, element-specific observation of different nuclei, but also facilitates the identification of chemically distinct sites based on NMR chemical shifts. Additional structural insights may be obtained from double-quantum ^1H MAS NMR. The application of different kinds of NMR methods in pharmaceutical cocrystal characterisation were introduced by Khan et al. (2010), including ^1H or ^2H MAS NMR, ^{13}C or ^{15}N CPMAS NMR, and two dimensional ^1H–^1H or ^1H–^{13}C, ^1H–^{15}N, NMR.

DSC is the most widely used technique for the thermal property testing of cocrystals. DSC is the preferred technique for obtaining comprehensive melting point data and additional thermal data, such as the enthalpy of melting, can also be obtained simultaneously. In addition to being a characterisation technique, DSC has recently been used as a screening tool for rapid cocrystal screening (Lu et al., 2008; Mohammad et al., 2011).

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 (Basavoju et al., 2008; Johnson and Rumon, 1965; Jung et al., 2010; Padrela et al., 2009).

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 (Parrott et al., 2009).

It is important to stress that no single technique is adequate to completely characterise the properties of a cocrystal. Integration of various characterisation techniques could help elucidate a better understanding of samples when analysing cocrystalline materials.

7. Pharmaceutical cocrystal examples

Although, there is no commercial pharmaceutical cocrystal has been approved for use in the market, much work has been done focusing on drugs with poor water solubility, such as carbamazepine, indomethacin and ibuprofen, as shown in Fig. 6. Herein, we list several case studies which aim to investigate the formation of pharmaceutical cocrystals and/or improve the physicochemical properties of APIs.

7.1. Pharmaceutical cocrystals of carbamazepine

Carbamazepine (CZP) [5H-dibenz (b, f) azepine-5-carboxamide], as shown in Fig. 6(1), is a widely prescribed anticonvulsant antiepileptic drug and has at least four polymorphic forms, a dihydrate, an acetone solvate, and two ammonium salts (Etter, 1990; Kaneniwa et al., 1987; Kobayashi et al., 2000; McMahon et al., 2005; Meyer et al., 1998). Extensive research has been done into the formation, properties and bioavailability of CZP cocrystallisation. Generally, two strategies have been adopted for CZP cocrystallisation: one strategy is to employ the peripheral hydrogen bonding capabilities that are not engaged in the pure form of CZP; the second strategy involves breakage of the CZP amide–amide dimer and formation of a supramolecular heterosynthon between the CZP and a coformer (McMahon et al., 2005; Shan and Zaworotko, 2008; Vishweshwar et al., 2006). In one study (Hickey et al., 2007), preparation of 1:1 cocrystals of CZP and saccharin (SAC) was achieved on a 30 g scale with a conventional cooling crystallisation process from alcohol solution without seeding. Through comparison of the 1:1 CZP/SAC cocrystals with marketed products, the CZP/SAC cocrystal exhibits improved bioavailability in dogs. The study investigated the preparation of CZP cocrystals through four different methods (Childs et al., 2008), in which twenty-seven unique solid phases utilising eighteen carboxylic acid coformers were generated. This study demonstrated that CZP cocrystals can be formed in aqueous media and the coformer solution concentration and solubility are important factors for the formation and stability of CZP cocrystals. Another example focused on solvent drop grinding (SDG) as a method for CZP cocrystallisation (Weyna et al., 2009), and results revealed that all the CZP cocrystals that were grown from solution can also be prepared by SDG. The formation kinetics and stability of the CZP and nicotinamide (NIC) cocrystals prepared by neat grinding with different initial polymorphic forms of CZP (form I, III and dihydrate) were studied by Chieng et al. (2009), showing that water molecules appeared to have a significant effect on the formation and stability of CZP–NIC cocrystals in which CZP dihydrate formed cocrystals faster than the anhydrous forms when co-milled with NIC, and high humidity promoted cocrystal formation and stability during storage.

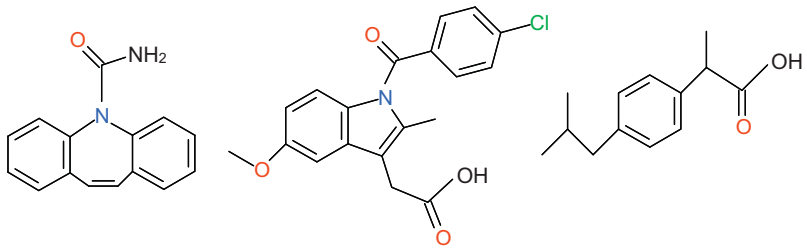
7.2. Pharmaceutical cocrystals of indomethacin

Indomethacin (IND) [1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid] is a BCS class II drug with anti-inflammatory, antipyretic and analgesic properties, and its molecular structure is shown in Fig. 6(2). Indomethacin exists in polymorphic forms α and γ, and the latter of which is thermodynamically stable at room temperature and is practically insoluble in water. The poor solubility of IND is claimed to be responsible not only for its low and erratic oral bioavailability but also for gastric irritation associated with the drug. In fact, IND has been a classic model compound for demonstrating the ability of cocrystallisation method to improve solubility and dissolution rate.

The cocrystals of indomethacin and the FDA-approved sweetener saccharin were prepared through both the slow evaporation method and liquid-assisted cogrinding method (Basavoju et al., 2008). Cocrystal IND–SAC displayed improvement of the physical properties compared to the stable indomethacin γ-form. Dissolution studies showed that IND–SAC prepared in this work was more soluble and associated with a significantly faster dissolution rate than IND (γ-form). The intrinsic dissolution rate of IND–SAC cocrystals was determined and a bioavailability study for the IN-SAC cocrystals was performed in beagle dogs. The study indicates that the improved aqueous solubility of the IND–SAC cocrystals lead to improved bioavailability of IND. A scale up study of the IND–SAC cocrystals was undertaken using cooling batch crystallisation by (Jung et al., 2010). IND–SAC cocrystals have also been prepared using supercritical fluid technology (SCF) (Padrela et al., 2009, 2010).

7.3. Pharmaceutical cocrystals of ibuprofen

Ibuprofen, (RS)-2-(4-(2-methylpropyl) phenyl) propanoic acid, as shown in Fig. 6(3), is a non-steroidal anti-inflammatory drug. It is used for the relief of arthritis, fever, as an analgesic, and additionally it possesses an antiplatelet effect. There are two possible enantiomers of ibuprofen, (R)-ibuprofen and (S)-ibuprofen. Ibuprofen is only very slightly soluble in water, less than 1 mg of ibuprofen dissolves in 1 mL water. Some studies have been undertaken to improve the properties of ibuprofen (Berry et al., 2008; Oberoi et al., 2005; Walsh et al., 2003). For example, 2:1 ibuprofen/4,4′-bipyridine cocrystal was formed with a melting point higher than pure individual components (Walsh et al., 2003). Ibuprofen and nicotinamide cocrystals were obtained for both the racemic form and the S-enantiomer of ibuprofen by Berry et al. (2008).



(1) carbamazepine (2) indomethacin (3) ibuprofen

Fig. 6. Molecular structures of three model drugs.

7.4. Other pharmaceutical cocrystals case studies

The API theophylline (TP) and cocrystal former nicotinamide (NCT) were employed to prepare TP–NCT cocrystals through solid-state grinding and slow evaporation from ethanol (Lu and Rohani, 2009) and the product was characterised and its pharmaceutically relevant properties were evaluated. The results showed that the TP–NCT cocrystals, obtained with a 1:1 molar ratio of TP and NCT, possessed unique thermal, spectroscopic, and X-ray diffraction properties. In addition, the solubility and hygroscopicity of the TP–NCT cocrystals are considerably higher than those of anhydrous TP.

The stable cocrystals of thiocarbamides and bipyridine with the molar ratio of 2:1 were successfully produced (Ellis et al., 2009), in which five cocrystals were isolated as a single crystal by slow evaporation methods and fully characterised by spectroscopic and X-ray crystallographic methods. Uniformly, trimeric molecules aggregates were formed where each pyridine-N was connected to an amide-H via $N_{pyridine}\cdots H–N_{amide}$ hydrogen bond. The results showed that the homosynthon found in the thiocarbamides is readily disrupted in the presence of bipyridine-type molecules to enable the formation of the stable heterosynthon.

Cocrystallisation studies of API acetazolamide (ACZ) were performed by Arenas-Garcia et al. (2010), in which twenty coformer candidates were chosen for the screening and two cocrystals were obtained: ACZ–4HBA (cocrystal of acetazolamide and 4-hydroxybenzoic acid) and ACZ–NA–H_2O (cocrystal of acetazolamide and nicotinamide hydrate). Both co-crystals can be prepared through neat grinding and the reaction crystallisation method. The dominant hydrogen bonding patterns in the co-crystals show that 4HBA (4-hydroxybenzoic acid) binds to the thiadiazole acetamide fragment of ACZ via C(N)NH···HOOC and O–H···N interactions, while NA (nicotinamide) is linked through N–H···N and N–H···O contacts. In ACZ–NA–H_2O, the components are connected further by crystal lattice water molecules through N–H···O_w and O_w–H···N hydrogen bonds. This is a typical multi-site hydrogen bond interaction example.

8. Conclusion

Pharmaceutical cocrystals are becoming increasingly important as an alternative way to improve the bioavailability of poorly water-soluble drugs, especially for these neutral compounds or those having weakly ionizable groups. Researchers have been putting much of their attention into exploring new cocrystals of an API. It is expected that many other pharmaceutical cocrystal systems will be explored in the near future. Meanwhile, there is an increasing need for a better understanding of the mechanism of the cocrystallisation process and theory for how pharmaceutical cocrystal improve the bioavailability of APIs.

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