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INVITED REVIEW PAPER

Solid forms of pharmaceuticals: Polymorphs, salts and cocrystals

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Abstract−Control and selection of the properties of active pharmaceutical ingredients is a crucial part of the drug development process. One major part of this process is the selection of an appropriate solid form. This review will discuss three major types of crystalline solids, polymorphs, salts and cocrystals and processes used to develop and find these forms.

Key words: Solid Forms, Polymorphs, Pharmaceutical Salts, Cocrystals, Design, Screening, Scale-up

INTRODUCTION

The development of small molecule pharmaceutical products requires an early decision on the solid form of the active pharmaceutical ingredient (API) and hence the dosage form that will be used to make a drug product with this API. The properties of the pharmaceutical solid such as solubility, dissolution rate and chemical stability are crucial as is the ability to manufacture this solid form at scale. Attempting to find a solid with the desired properties and manufacturability, companies spend significant effort looking for polymorphs, salts and cocrystals of their API's. This review will discuss each of these areas.

POLYMORPHISM

Polymorphism is the ability of a solid material to exist in more than one crystal structure while retaining the same chemical composition [1]. The molecules in polymorphs of organic molecular crystals are held together by weak interactions, such as hydrogen bonds, van der Waals forces and π-π interactions. The two main types of polymorphism are packing and conformational. In packing polymorphism, molecules are usually quite rigid and are arranged differently in the unit cell of each polymorph while keeping more or less the same molecular conformation. In conformational polymorphs, molecules are more flexible and exist as distinctly different conformers. In practice, mixed types of polymorphs are often encountered. Other crystal forms, which include solvent in the crystal structure, are known as solvates and hydrates and are often referred to as pseudo-polymorphs.

Polymorphism is very common among active pharmaceutical ingredients (APIs). A well studied molecule 5-Methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, commonly known as ROY, has ten known polymorphs, seven of them with solved structures [2]. Different polymorphs differ in their thermodynamic, kinetic, spectroscopic, surface, packing and mechanic properties, among which the solubility and the dissolution rate are the most important. This continues to pose a challenge to scientists and engineers in developing a robust process to produce crystal products of consistent quality. An undesired polymorphic form of the drug product, for instance, can lead to different bioavailability in the target organism, which could render the drug useless, or increase its potency to a dangerous limit [3]. One well-known example is the case of antiviral drug Ritonavir, an inhibitor of HIV-protease [4-6]. A more stable polymorphic form discovered after the drug was commercialized led to the withdrawal of the drug product from the market and required reformulation to account for the reduced solubility of the more stable form. In pharmaceuticals, 70% of barbiturates, 60% of sulfonamides and 23% of steroids exist in different polymorphic forms [7,8]. Hence, understanding and control of the polymorphism of active APIs is one of the most important considerations in crystallization process design.

If a compound has polymorphs, only one polymorph is thermodynamically stable at a given temperature. The stable polymorph is characterized by the lowest Gibbs free energy and hence the lowest solubility in any solvent. In a monotropic system, the stability ranking of all polymorphs does not change with temperature before they all melt. In other words, free energy curves of the various polymorphs against temperature do not cross. For an enantiotropic system, the free energy curves change with temperature and show a crossing point before the various melting points. The stable form at one temperature can become metastable at another temperature. Uncontrolled polymorph transitions of metastable polymorphs into more stable forms can present a significant challenge in the pharmaceutical industry. It may happen during the crystallization of API, during tablet manufacturing, or even in the tablet during storage. Therefore, for a drug formulation the most stable polymorph is generally preferred. Developing robust manufacturing processes for both API and drug product requires a thorough understanding of all the potential polymorphs, their relative stability and possible transitions.

Crystallization, which is the key experimental technique for polymorph screening, occurs in two distinct steps known as nucleation and crystal growth. The resulting polymorphic form is the consequence of the kinetic relationship between these two elementary processes. The Ostwald rule of stages [9] says that for a dipoly-

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morphic system, the metastable form has the lower free energy of nucleation and usually nucleates first. It will transform into the more stable form during the growth process. The polymorph eventually obtained from a crystallization process is determined by the combination of the relative nucleation rates and the relative crystal growth rates. There are a number of techniques that can be used for polymorph screening. In general, crystallization from solution and recrystallization from a neat compound are the commonly used methods for polymorph screening [10,11]. The key process parameters in solution crystallization include the choice of solvent or solvent mixture, the method of generating supersaturation (cooling, evaporation of solvents, anti-solvent addition), the rate of generating supersaturation, the use of additives and the temperature employed. Slurry conversion, as part of the solution crystallization, is a widely used method to discover the most stable form, since metastable polymorphs will convert into the most stable form through solution mediated transformation in principle if given enough time. Solution crystallization is also used to examine solvates and hydrates and their stability at various temperatures and solvent conditions. Solvates and hydrates can either be used as the final form of the API for formulation into a drug product or can be further processed by dehydration/desolvation sometimes yielding additional new forms [12,13]. The common methods used in recrystallization from a neat compound include sublimation, thermal treatment, crystallization from melt and dry/wet grinding. These crystallization methods allow the discovery of polymorphs that are hard to form from solution crystallization and are often neglected. For example, the form III crystal of acetaminophen was only generated by melt crystallization [14]. Recently, several other innovative methods, such as capillary crystallization [15], laser-induced crystallization [16], sonocrystallization [17] and heterogeneous crystallization [18], were reported to be able to aid in the discovery of new polymorphic forms. For example, a fourth polymorph of carbamazepine, which appears to be more stable than any of the previously found forms, was obtained using the polymer heterogeneous approach [18].

Due to the complexity of both the pharmaceutical compounds and the crystallization process, the discovery of all the potential polymorphs requires extensive experimentation. A variety of factors changing the relative nucleation and growth rates of different polymorphs need to be examined. The use of technology to assist in parallel experimentation and polymorph screening is becoming increasingly common. A high-throughput screening method utilizing automation to carry out experiments and to investigate several factors (e.g., level of supersaturation and solvent composition) systematically can help reducing the time and labor required. In a recent review paper by Aaltonen et al., they summarized the conditions and the results of a series of high throughput polymorph screening studies of seven pharmaceutical compounds [10]. Recently, our group has developed patterned substrates of self-assembled monolayers (SAMs), which can be used to carry out a large number of independent crystallization trials with a minimal amount of material [19]. We have used this method to perform polymorph screening experiments with

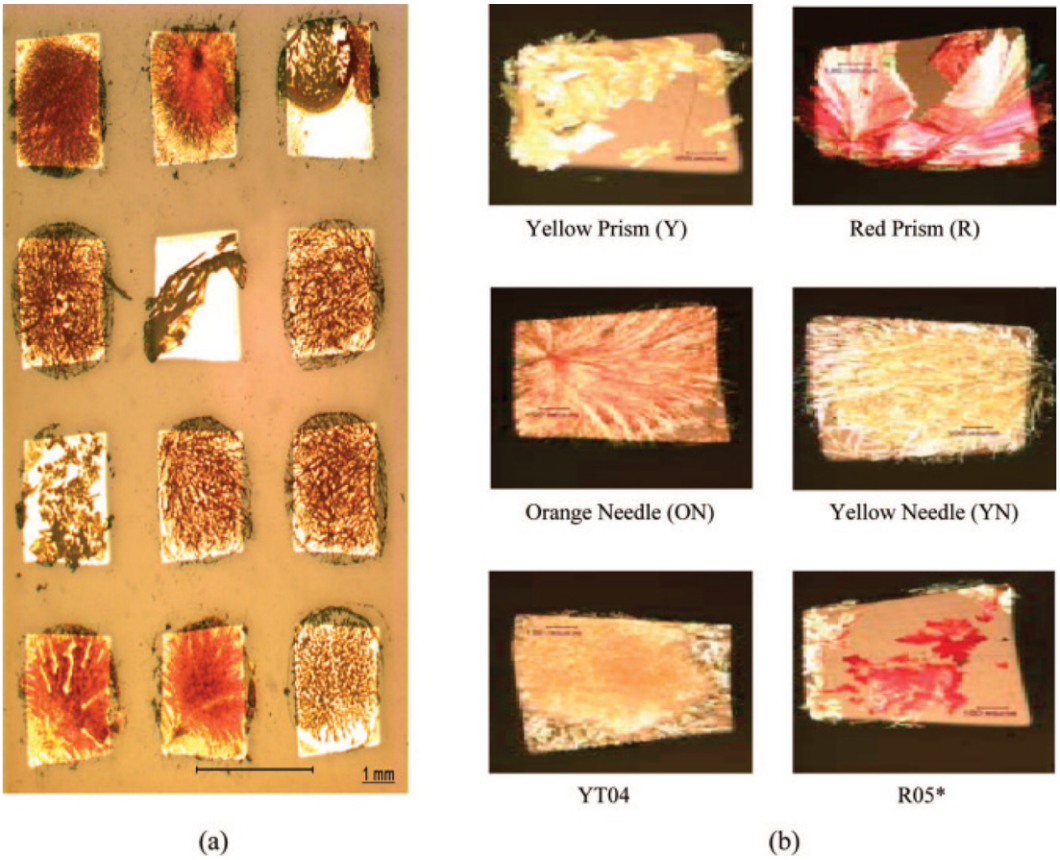


Fig. 1. Crystallization of ROY on self-assemble monolayer on gold substrate. (a) A microscope image showing an array of gold islands with a dimension of 725 μm with ROY crystals on them and (b) different forms of ROY crystallized on 725 μm islands.

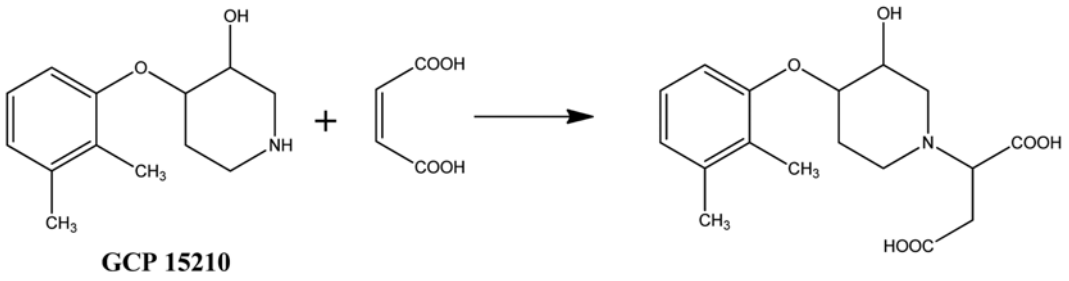


Fig. 2. Reaction of CGP15210 with fumaric acid yields a tertiary amine as contaminant.

sulfathiazole [20] and ROY [21]. We were able to crystallize all four of the five polymorphs of sulfathiazole and six of the seven stable polymorphs of ROY using this method, as shown in Fig. 1. As target drug materials are often available in limited quantities in the development phase, methods that utilize minimal amount of material are particularly useful. The amount of material required in our approach is significantly less than other common high-throughput methods.

PHARMACEUTICAL SALTS

Salt formation is an established means for the isolation and purification of substances. Alkaloids are generally extracted from plant as crystalline salts because of the easy formation of salt with available nitrogenous base. Most of the drugs contain nitrogenous functionality that opens up an opportunity for salt formation with improved physiochemical properties. Drugs containing -COOH group like aspirin, dichlofenac, ibuprofen etc. can also be considered for salt formation. An estimated more than 50% drugs are administered as salts. Therefore, salt formation has become an essential step in pharmaceutical development [22,23]. Molecules that do not carry suitable functionality for salt formation can be considered as candidates for cocrystals or amorphous solids if a crystalline polymorph of desired properties cannot be found.

There has been a long standing and lively debate on the nomenclature issues, starting from what is cocrystal and salt, to the definition of pseudopolymorph, solvate, host-guest compounds etc. A salt is a multicomponent system where protons are transferred from acid to base in the ionic state [24]. The transfer from neutral to ionic hydrogen bond can be as a continuum of intermediate X···H···Y bond state. The ΔpK_a value (pK_a of base - pK_a of acid) in solution and the crystalline environment determines the extent of proton transfer. For a carboxylic acid and pyridine system, the carbonyl stretch frequencies are the preliminary confirmation whether the complex is a cocrystal or salt. The monomeric C=O stretching band of a carboxylic acid, when on an aromatic ring, appears at around 1,760 cm^{-1}, while the acid dimeric C=O stretching mode absorbs at a lower frequency in the region of 1,720-1,706 cm^{-1}. The carboxylate ion also displays a strong asymmetrical stretching band around 1,650-1,550 cm^{-1} and a weaker symmetric stretch ~1,400 cm^{-1}.

Neat drug substances are rarely applied for therapeutic uses. Thus the design, development and manufacture are intended to the availability of administered amount and concentration of the drug to the site of action of individual active substances. The selection of suitable salt form [25] for pharmaceutical development is dependent on pharmaceutical technological aspects, manufacturing and biopharmaceutical effects. Solubility and/or partition of the drug dosage form with pH, absorption and chelation with metal ions are some of the biopharmaceutical aspects which must be considered. It is also important for the solid form of an API to maintain the same physical state in the drug product (morphology, particle size distribution etc.) and to be chemically stable on storage. A loss of more than 10% of the drug substance is not tolerable. For an example, antidepressive CGP15210 is a free nitrogenous base. Based on modulated properties it was clear that the tablets should be developed with the fumarate salt. However an accelerated chemical stability test confirmed formation of a tertiary amine as a contaminant when the drug mixed with fumaric acid (Fig. 2).

A salt selection strategy for a new drug candidate involves the selection of chemical forms of salts, selection of physical forms of salts, time and composition. Feasibility assessment for salt formation requires the pKa value of conjugate acid be smaller than the pKa value of the conjugate base to ensure sufficient proton transfer from the acidic to basic species [26]. Another important scale in determining which salt can be synthesized for a particular free acid or base is pH-solubility interrelationship and the location of pH_{max} in the pH scale. A schematic representation of the pH-solubility profile of monobasic compound (Fig. 3(a)) and monoprotic acid (Fig. 3(b)) is illustrated. Fig. 3(a) shows that a salt will not formed unless the pH of the saturated salt solution is raised above the pH_{max}. For a monoprotic acid, the free acid would be the equilibrium species at a pH below pH_{max} and salt formation is possible only if the pH is raised above the pH_{max} by using suitable counter ions [27]. Serajuddin and co-workers [28,29] and many others confirmed the application of the pH-solubility relationships in determining under which pH conditions salts of particular acidic and basic drugs can be formed. Similarly, pH-solubility profile of a dibasic compound can be expressed by three independent curves corresponding to three independent equations comprised of two pH_{max} points.

One important criterion that affects salt solubility and dissolution is the counter ion effect. When a basic drug forms a salt with relatively strong acid such as HCl, the aqueous solubility of the salt is strongly influenced by common ion-effect [29]. An organic solvent influences the solubility of a salt in several ways: (i) increase solubility of non-ionized species, (ii) decrease protonation, and (iii) decrease solubility of salt formed. Morris et al. reported [23] a multitier approach whereby salts can be screened for their optimal physical form (Scheme 1). Similarly, Gross et al. also predicted [30] a salt-screening flow diagram for the optimal selection of a drug salt to be processed. The characterization of pharmaceutical salts, critical

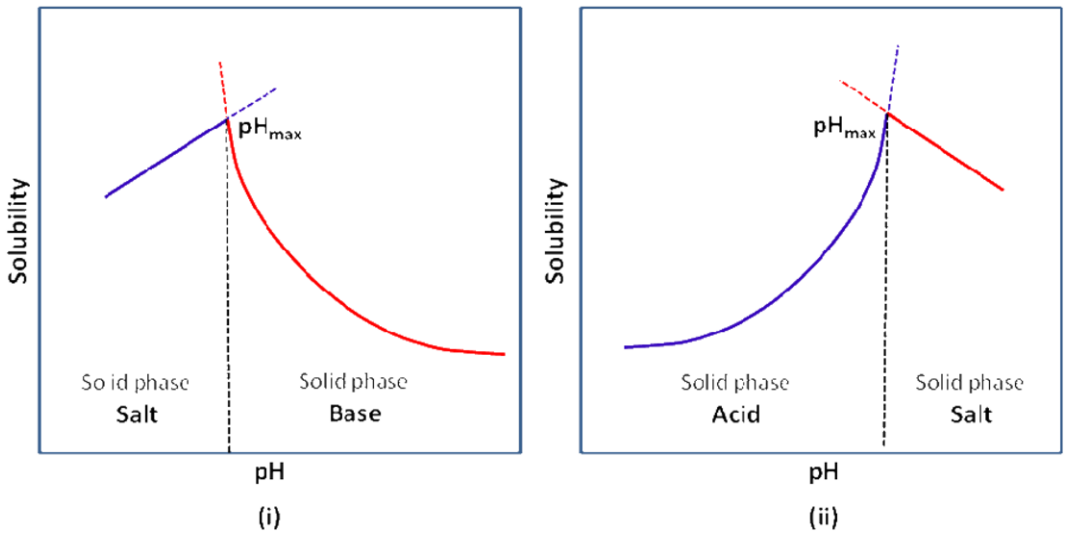
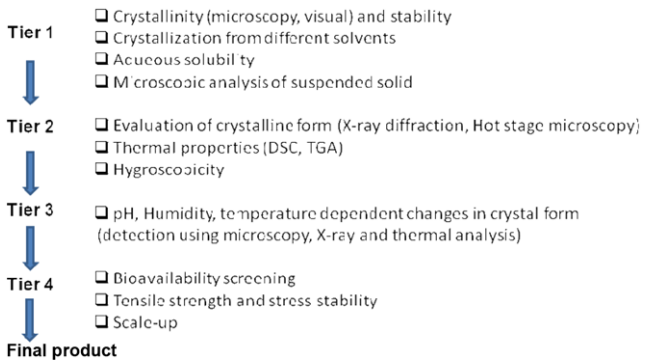


Fig. 3. Schematic representation of the pH-solubility profile of (i) a monobasic compound and (ii) a monoprotic acid [27].



Scheme 1. Flow chart of multi-tier approach for the selection of optimized pharmaceutical salts [23].

to the drug development process, examines appropriate salt selection, confirmation of stoichiometry, and the detection of impurities. Multiple analytical techniques are often required to address the diverse nature of analytes such as inorganic/organic, anionic/cationic, chromophoric/non-chromophoric, hydrophobicity/polarity etc.

In the gastro-intestinal tract, the administered drug dose encounters various and changing environmental conditions after dissolution. For a basic drug (7<pKa<10) there is no complication as the dissolution can readily take place and protonate in the acidic stomach [31]. However, a sufficient amount could be left for the non-ionized or lipophilic form in the intestine which provides neutral to weakly basic condition. Thus, to achieve rapid *in-vivo* dissolution basic drugs are preferably administered in their salt form. For weak bases the pH condition prevailing in the intestine is the less soluble free base, and salt formation is not beneficial. For a weakly acidic drug [32] the dissolution in acidic stomach contents will result in the precipitation of the free acid making the free form preferable [33]. To improve solubility, salt formation has been employed to increase the melting point, in particular for converting low molecular weight bases and acids into solids. The Gould approach [34] for salt selection of basic drugs shows the significance of melting points of the salt-forming acids and the resulting salt of a base and their relationship with solubility, stability and mechanical processing. Substances with melting point above 100 °C are stable and suitable for mechanical processing that allows easy sintering and milling for particle size reduction. Sun and Grant [35] discussed the mechanical properties relevant for tableting of drug salt is a function of the anion and their compact tensile strength. The melting point of each salt correlates the maximum tensile strength of its compacted form. Hydrates of drug substances whether salt or other formulations can readily be used provided their state of hydration is maintained under all the climatic conditions.

A pH dependent adducts formation often become apparent during drug-excipient testing at the preformulation stage. Therefore, it is necessary to find an optimal pH range in the formation of adduct during development and processing [36]. Salts can also be used for solution dosage forms and in these cases should have chemical stability in solution, sufficient solubility for the needed drug load, should not transform and precipitate into a solid form and should have an acceptable taste. Often sweeteners and other flavor components are added to these formulations.

Powerful and improved modeling techniques are now being employed to save time, cost and man-power in the salt-selection process associated with drug-product formulation development. Roberts recently reported [37] a systematic grid-based search method to predict the host/counter-ion binding for a simple and representative organic salt 3,4,6,7,8,9-hexahydro-2H-pyrimido (1,2-a) pyrimidinium acetate.

In general, food additives including acids and bases of interest for salt formation are of GRAS (generally regarded as safe) status. The World Health Organization (WHO) assigned an acceptable daily intake (ADI) to food additives and processing aids even if consumed for a lifetime. Practically, the classification of salt formers is of three kinds: (i) First class salt formers are those which can be used without restriction because they form physiologically ubiquitous ions, or because they occur as intermediate metabolite in biochemical pathways. For example, hydrochloride, chlorides and sodium salts. (ii) Second class salt formers comprised of those molecules that show low toxicity. (iii) Third class salt-formers are intro-

duced to achieve special effects such as ion-pair formation. Counter ions influence an API's solubility, stability, and hygroscopicity, so appropriate counterion selection is an important part of the drug development process. The most common pharmaceutical counterions include chloride, sodium, sulfate, acetate, phosphate, potassium, maleate, calcium, citrate, bromide, nitrate, ammonium, tosylate, phosphate, tartrate, and ethylenediamine. A wide range of common pharmaceutical salt formers are tabulated below [38].

Salt formers	Examples
Anions	
Inorganic acids	Hydrochloride, hydrobromide, sulphate, nitrate, phosphate
Sulfonic acid	Mesylate, Esylate, Tosylate, Napsylate, Isethionate, Besylate
Carboxylic acid	Acetate, Propionate, Maleate, Benzoate, Salicylate, Fumerate
Anionic amino acid	Glutamate, Aspartate
Hydroxy acids	Citrate, Lactate, Succinate, Tartrate, Glycolate
Fatty acids	Hexanoate, Octanoate, Decanoate, Oleate, Stearate
Acids or insoluble salts	Pamoate, Resinate
Cations	
Metallic	Sodium, Potassium, Calcium, Magnesium, Zinc
Organic amines	Triethylamine, Ethanolamine, Triethanolamine Meglumine, Ethylene diamine, Choline
Cationic amino acids	Arginine, Lysine, Histidine
Bases for insoluble salts	Procaine, Benzathine

The cumulative information from the preliminary crystallization and characterization is must for a chemical engineer to investigate possible manufacturing routes and scale-up for each of the candidates. A salt screening and selection [38] program aims to deliver a number of developable salt forms that could be based on the studies: (i) the pKa of the API, (ii) the market precedence of each counterion, (iii) the available toxicology data of each counterion, (iv) past salt-screening experience, (v) formulation plans and (vi) case studies. In a process [39] the chemist usually manufactures 50-200 g scale of one or two candidates to verify the consistency of properties found during pre-formulation. These candidates may remain in progress towards initial clinical evaluation; however, the manufacturing route is usually significantly different. This is because both the process chemistry and pre-formulation groups have to ensure a viable synthetic route and choose the right formulation of the drug substance. Often 3-4 g of a drug salt is produced and compared with free the base/acid. A number of tests are performed during salt selection including (i) structural analysis, (ii) measurement of physiochemical properties, (iii) physical properties, (iv) level of impurity studies and removal, and (v) chemical stability. The results obtained from each of these tests are tabulated for the free acid/base, together with each of the salts, and the decision-making process results in the proposal of a single salt for further study and scale-up. The second phase of a drug substance for clinical development requires a minimum amount of 20 g. As large quantities of drug substance and samples from different batches become available, it is imperative that the variation in basic physical and solid state properties (crystal size and shape, surface area, powder flow properties, bulk and tapped density etc.) are studied and documented for each batch. The final step is to obtain approval of the health authorities before the product is commercially available for therapeutic application. It is therefore essential to know the regulatory processes and requirements regarding drugs in general and drug salts of approved substances. Diclofenac [40,41], Ranitidine [42], Cimetidine [43], Famotidine [44] are some of the classic examples of drug salts associated with regulatory issues.

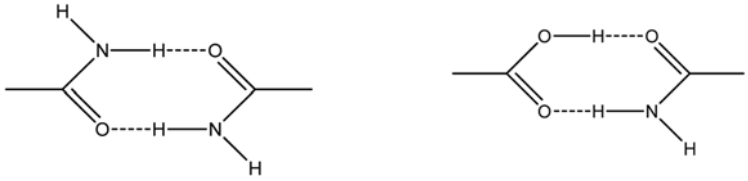
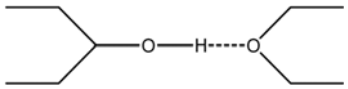
COCRYSTALS

While the definition of cocrystals can be debated, in this review we defined cocrystals as homogeneous crystalline materials composed of a neutral target and a neutral coformer held together through noncovalent bonds. For pharmaceutical applications it is essential that the coformers have GRAS status. Pharmaceutical companies are interested in cocrystals for two main reasons. First, the physiochemical properties of active pharmaceutical ingredients (APIs) can be modified while the intrinsic activities of these drug molecules remain the same. Second, product life for existing APIs can be extended by employing cocrystals [45] in drug products. As a relatively new technique, cocrystal formation is not only important for drug property modulation but also useful in designing extended supramolecular architecture, synthesis of NLO materials, solid-state photodimerization reactions, enantioseparation of racemic compounds etc. It is essential to understand the basics behind cocrystal formation so cocrystals can be designed with the desired properties. From a thermodynamic point of view pharmaceutical cocrystals are stable and high energy forms. Therefore, they can have impact on solubility and dissolution rate of the drug. The strategy involves drug :coformer combinations that have the potential of forming energetically and structurally robust interactions.

A typical cocrystal design process involves three steps: coformer selection, computational analysis, and cocrystal characterization [46]. Pharmaceutical cocrystals often rely on hydrogen-bonded assemblies between an active pharmaceutical ingredient (API) and conformer with well-defined stoichiometries. For a target API, we are interested in coformers with functional groups that can interact (i.e., form H-bonds) with the functional groups on the API. Common functional groups, such as carboxylic acids, amides, and alcohols, are typically found to interact with one another in cocrystals (Table 1) [46]. The most common intra/intermolecular interaction found in cocrystals is hydrogen bonding. Etter has studied hydrogen bonds in cocrystals and uses them as design elements [47]. Instead of studying hydrogen bonds from an energy viewpoint, she analyzed the cocrystal patterns as a result of intra/intermolecular interactions and established general rules for hydrogen bonding.

The hydrogen bond general rules [47] are the following: (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, and (3) the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular hydrogen bonds with one another. In addition, Etter demonstrated

Table 1. Common functional groups found in cocrystals [46] and their formation of supramolecular hydrogen bond synthons

Functional groups	Typical supramolecular synthons used in crystal engineering
Carboxylic acid (e.g., acetic acei, adipic acid, benzoic acid, fumaric acid, maleic acid, malonic acid)	
Amides (e.g., nicotinamide and urea)	
Alcohols	

the selectivity of hydrogen bonding in cocrystals by using pyridines as an example [47]. Cocrystal of 4-phenylpyridine and ethyl isonicotinate from a mixture of two carboxylic acids with different pKa were prepared and found that they only selectively formed cocrystals with the carboxylic acid with the smaller pKa. The selectivity is demonstrated with a mixture of 3, 4-dinitro-and 3, 5-dinitrobenzoic acids where the difference of their pKa is only 0.04. Similarly, Seaton et al. [48] used Hammett constants to design the acid/acid cocrystals. Hammett constants are used to describe the electron withdrawing ability of the substituents on the benzoic acid derivatives. The more acidic the hydrogen, the larger the Hammet constant. This study found that the greater the difference in Hammett constants, the greater the chance these two acids form cocrystals. By understanding hydrogen bonding, we can select coformers for a target API. After potential coformers are selected, we can search the target API in the Cambridge Structural Database (CSD) and see if it has known cocrystals or has formed cocrystals with the functional groups on the selected coformers. With this list of selected coformers, we can perform experiments to confirm if they can form cocrystals with the target API, and finally, characterize the cocrystals for their physical and chemical properties. With this cocrystal design process, we can design cocrystals for a target API efficiently. High throughput crystallization and screening technologies have potential application on form discovery and characterization in the pharmaceutical development. This minimizes the time and efforts during screening active molecules, selection of preclinical candidates, final form optimization and process chemistry development [49].

Different methods have been used to produce cocrystals: solution crystallization, solid state and solvent drop grinding [50], and crystallization from melt. For scale-up purposes, solution crystallization is the most popular. Producing cocrystals by solution crystallization requires knowing the condition (temperature and concentration of the API and the coformer) of the process. Traditionally, ternary phase diagrams have been used to study the composition of API in its pure state and in its cocrystal state at a constant temperature. To study the temperature effect on the cocrystal system, phase solubility diagrams have been adopted as a graphical tool to present the ternary phase diagram in an x-y format. A typical phase solublity diagram is shown in Fig. 4 where [A] and [B] represent the concentration of the API and the coformers, respectively [51]. The solid line is the solubility of the cocrystal at various concentration of B and the dotted line is the solubility of A at various concentration of B. Four regions are separated by the solubility curve of A and A/B cocrystal. In region I, A is supersaturated but A/B cocrystal is undersaturated. Hence, we have pure A solid in this region. If the concentration of B is increased, then both A and A/B cocrystals become supersaturated in region II. In region III, both A and A/B cocrystal are undersaturated, while in region IV A is undersaturated and A/B cocrystal is supersaturated. Pure A/B cocrystal can be obtained in this region. The intersection of the two solubility curves is $[B]_{tr}$ where the solubility of A equals the solubility of A/B cocrystal. The path x to y shows the phase transition when the concentration of B is increased. The point x represents the starting point where both A and A/B cocrystal are undersaturated. After the concentration of B is increased to the point y, the chemical potential difference between point y and z drives the equilibrium to point z′ by forming A/B cocrystals. With the phase solubility diagram, we can plot multiple solubility curves at different temperature in the same diagram.

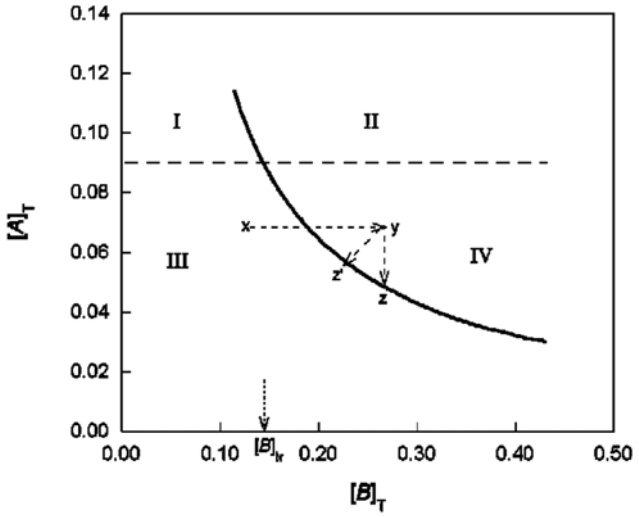


Fig. 4. A typical phase solubility diagram (PSD) [52] of cocrystal formation.

This method helps us to envision the temperature effect. In addition, it is simple to calculate the amount of coformer needed to add to the solution to produce the cocrystal. The temperature effect on the cocrystal system can be presented and the heating/cooling path can be illustrated.

With the understanding of hydrogen bonding and the use of phase solubility diagrams, we can produce cocrystals for a specific API. In the future, general rules to aid in cocrystal design will be needed to help yield materials with the desired properties.

Several reports show that cocrystals can increase solubility and dissolution rate on the basis of supramolecular design of pharmaceutical materials. Celecoxib with nicotinamide [53], caffeine with theophylline [54]; aspirin, rac-ibuprofen, and rac-flurbiprofen with 4,4′-bipyridine [55]; fluoxetine hydrochloride with pharmaceutically acceptable carboxylic acids [56]; Vanilloid receptor AMG 517 with sorbic acid [57]; itraconazole with 1,4-dicarboxylic acids [58], carbamazepine with saccharin were the well known strategies to deal with inadequate solubility, dissolution rate, absorption, physical stability of APIs. A recent study [59] demonstrated the solubility and pharmacokinetics of several cocrystals of drug lamotrigine with methylparaben and nicotinamide. Novel cocrystalline composition of drug tenofovir disoproxil with fumaric acid (2 : 1) was formulated for antiviral medicines. The carbamazepine : saccharin, carbamazepine : nicotinamide cocrystal were studied in terms of scale-up. These formulations exhibit modulated physical and chemical properties as a direct result of hydrogen-bonding interactions between the binary components. A detailed understanding about the molecular assemblies for cocrystal formation [60,61] surely correlates between structure and function, which is yet to be explored. Chemical engineers and scientists offer laboratory to industry leading understanding of design and development of materials for a new generation of medication.

CONCLUSION AND FUTURE PROSPECTS

The pharmaceutical industry has greatly expanded its efforts in solid form selection and development in recent years. This is the result of the low solubility of many new drug candidates, which has resulted in significant efforts in finding more soluble forms such as cocrystals. In addition, product lifetime extension through the patenting of solid forms has played a significant role in this expansion. Improvements in polymorph, salt and cocrystal screening methods have led to the discovery of important forms at earlier stages in development. This in turn has challenges in scale-up and manufacturing as solid forms which are more difficult to make at scale such as metastable polymorphs and cocrystals. This will provide challenges to academic and industrial researchers and practitioners in future.

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