African Journal of Pharmacy and Pharmacology Vol. 6(9), pp. 581-891, 8 March, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP12.044
ISSN 1996-0816 ©2012 Academic Journals

Review

Crystallization and transformation of pharmaceutical solid forms

Jie Lu

National Engineering Laboratory for Cereal Fermentation Technology, School of Chemical and Material Engineering, Jiangnan University, Wuxi 214122, China. E-mail: lujie6742@sina.com. Tel: 86-510-85919779. Fax: 86-510-85917763.

Accepted 23 February, 2012

In the past decades, a great progress has been made in the discovery, identification and control of various solid forms of active pharmaceutical ingredients (APIs), including polymorphs, solvates, hydrates, co-crystals, salts and amorphous solids. It is expected that new solid forms with novel properties of pharmaceutical molecules will explosively expand with further understanding of the formation mechanisms of different solid forms. This mini-review briefly introduces the concept, crystallization, characterization, transformation and controlling of various pharmaceutical solid forms by use of exampling some cases.

Key words: Pharmaceutical technology, forms, crystallization, transformation.

INTRODUCTION

In the last decade the global pharmaceutical market has expanded at an average annual growth rate of 9.1% (Figure 1), with an estimated $ 919 billion in sales in 2011 (IMS, 2010). No matter how pure drug substances or in formulated products, active pharmaceutical ingredients (APIs) can exist in varieties of distinct solid forms, such as polymorphs, solvates (hydrates), salts, co-crystals and amorphous solids (Figure 2). Each form normally displays its own unique thermal, mechanical, physical and chemical properties that can profoundly influence the solubility, dissolution rate, bioavailability, hygroscopicity, melting point, stability, compressibility and other performances of the drug (Byrn et al., 1999). Crystallization has been already employed as the last chemical purification step in the production of active pharmaceutical ingredients but also as an effective means to control the formation of above solid forms in terms of crystal structure, size and shape (Shekunov and York, 2000). Hence, a thorough understanding of the relationship between the particular solid form of an API and its crystallization process is critical to prepare the most suitable form of the API for development into a drug product. In this contribution, we will introduce the concepts, properties and perspectives of various solid forms of pharmaceutical molecules, and example of some cases to illustrate their different properties.

POLYMORPHS

Polymorphism can be defined as a substance which can exist in two or more crystalline forms in which the molecules have different arrangements (packing polymorphism) and/or conformations (conformational polymorphism) in the crystal lattice. In short, polymorphs have the same chemical composition, different lattice structures and/or different molecular conformations. Actually polymorphism has been found to be a widespread phenomenon for most pharmaceutical molecules (Datta and Grant, 2004; Yang et al., 2008), even for those medicinally active substances can be considered for practical purposes to be non-polymorphic for example, aspirin (Payne et al., 1999), there still is a theoretical possibility that those non-polymorphic organic compounds may have potential polymorphs (Morissette et al., 2004). Different polymorphs of a pharmaceutical molecule generally have different physical and chemical properties such as solubility, dissolution rate, bioavailability, melting point, stability, etc (Sirota, 1982). One of the most well-known examples of the evolution of polymorphic molecules into the marketed drug products is Ritonavir (Abbott Laboratories).

Since the original Norvir® capsule formulated by form I entered into the market, a previously unknown, but

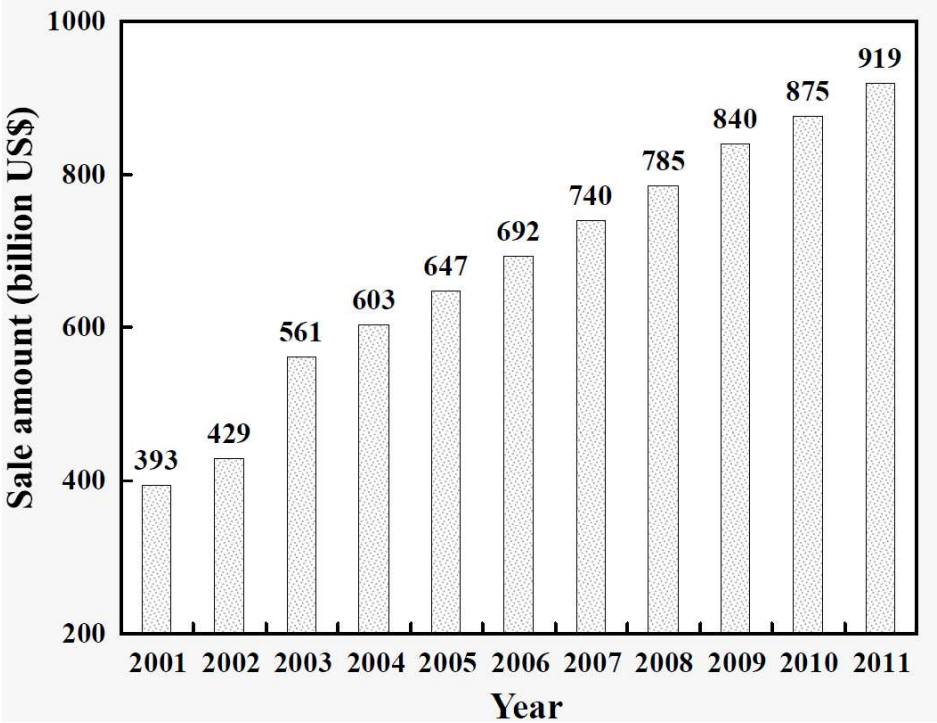

Figure 1. Annual sale amount of global pharmaceutical market since 2001.

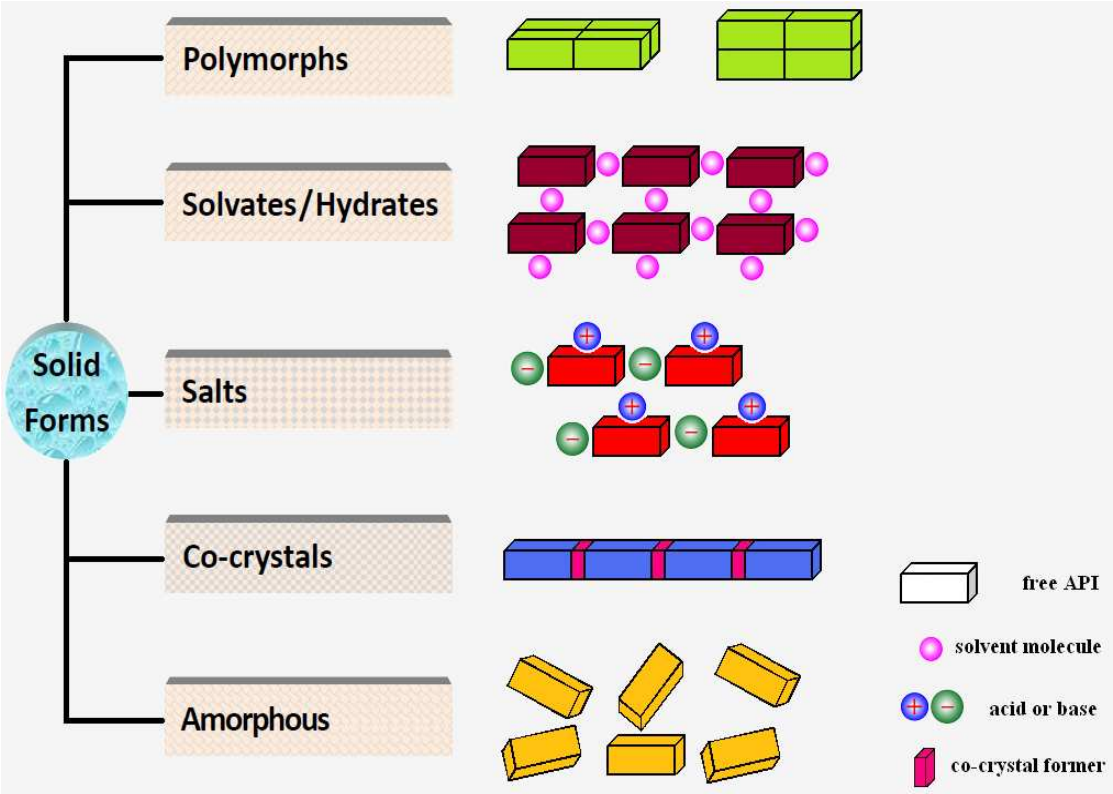

Figure 2. Schematic representation of the structures of solid forms of APIs.

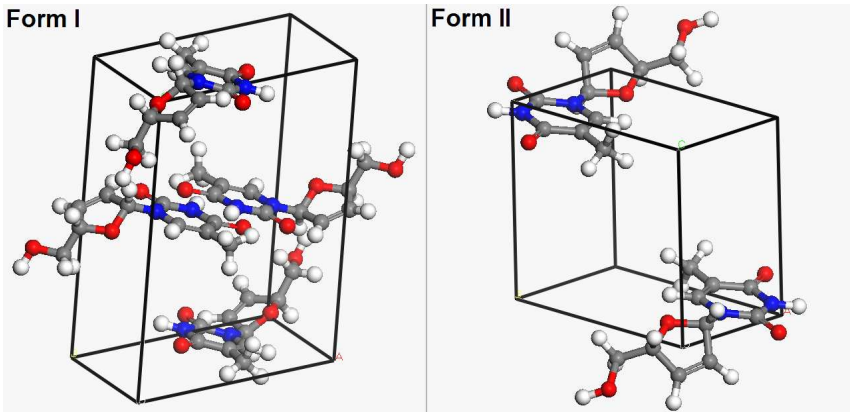

Figure 3. Crystal packings for the two polymorphs of stavudine.

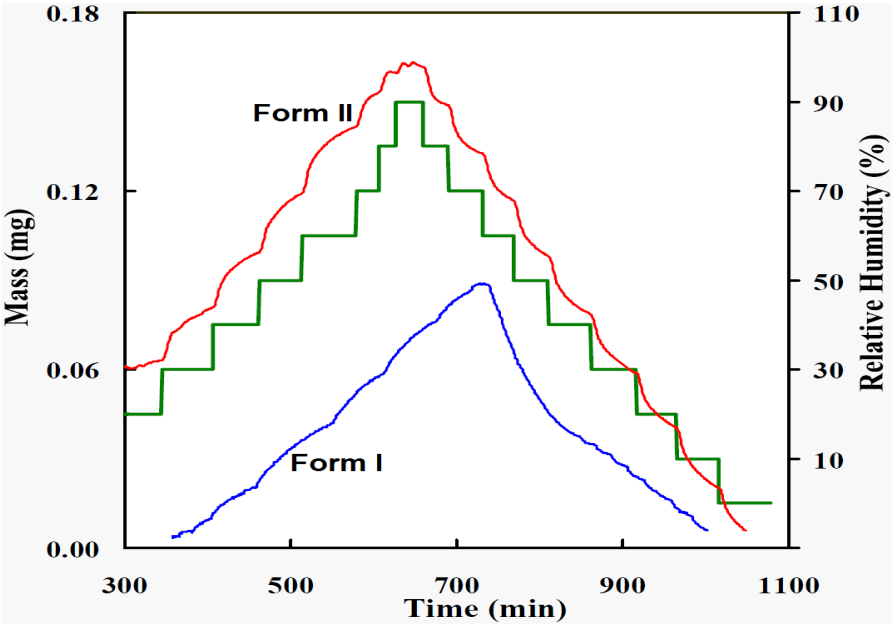

Figure 4. Moisture sorption and desorption behaviors of polymorphs I and II of stavudine at 25℃.

thermo-dynamically more stable polymorph (form II) of Ritonavir was discovered. This new form was approximately 50% less soluble in the hydroalcoholic formulation vehicle. Then the original Norvir® capsule was eventually withdrawn from the market (Chemburkar et al., 2000), and a new formulation of Norvir® using form II was launched (Bauer et al., 2001). Nicergoline, a potent blocking agent for α1-adrenoreceptors, exists in two different polymorphic forms: triclinic form I and orthorhombic form II. Polymorph I is stable up to its melting temperature of 134℃, whereas polymorph II melts at about 120 to 122℃ and then can recrystall ize to form I at low heating rate (Malaj et al., 2011). Stavudine, a thymidine nucleoside with inhibitory activity against reverse transcriptase of the human immunodeficiency virus, has been found to have two polymorphic forms I (monoclinic) and II (Triclinic) (both packing polymorphism and conformational polymorphism), as shown in Figure 3. Polymorph II has a higher hygroscopicity than polymorph I (Lu and Rohani, 2009a), as shown in Figure 4.

SOLVATES AND HYDRATES

Pseudopolymorphism can be defined as crystalline forms of a compound in which solvent molecules are included

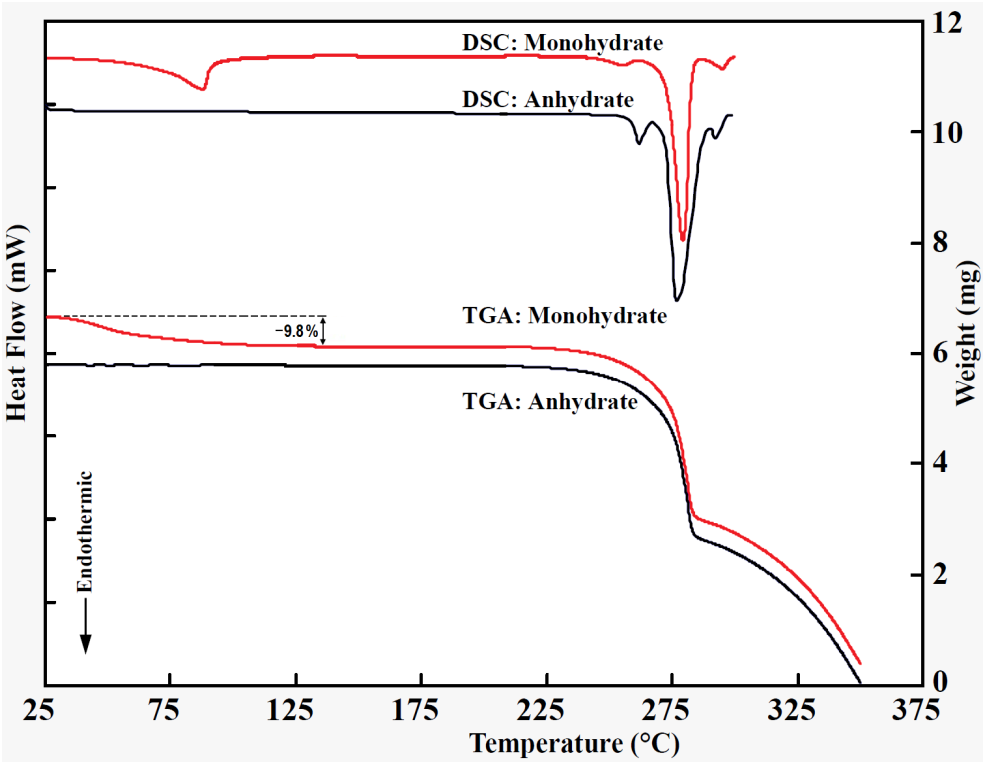

Figure 5. Thermograms show the formation of a monohydrate of L- phenylalanine.

as an integral part of the structure (Pedireddi and Reddy, 2003)http://www.sciencedirect.com/science?_ob=RedirectURL&_method=outwardLink&_partnerName=655&_targetURL=http%3A%2F%2Fwww.scopus.com%2Fscopus%2Finward%2Frecord.url%3Feid%3D2s2.00042671124%26partnerID%3D10%26rel%3DR3.0.0%26md5%3D4fa344ab97a465fd34 View Record in Scopus | HYPERLINK. Solvates or hydrates can be stoichiometric or nonstoichiometric in nature (Morris, 1999). Generally solvates and hydrates may have different solubility, dissolution rate, mechanical behavior, stability and bioavailability from their unsolvated counterparts (Bechtloff et al., 2001). For example, L-phenylalanine, an essential amino acid for human nutrition and widely used in pharmaceutical industry, has been found to be able to form monohydrate (Figure 5). Our experiments have shown that the monohydrate form and the anhydrous form are enantiotropically related and the transition point between them is about 35.8℃ (Figure 6), that is, the anhydrous form is the thermodynamically favored form (stable form) above 35.8℃, whereas the monohydrate is the thermodynamically favored form (stable form) below 35.8℃ (Lu et al., 2010).

Sodium risedronate, marketed as Actonel®, is used to inhibit calcium phosphate precipitation in human bone matrix. Although risedronate is administered orally, it is poorly absorbed due to its numerous complexation reactions. To minimize these, several approaches have been conducted to increase absorption of oral bisphosphonates from the gastrointestinal tract and to avoid side effects. One option for modifying aqueous solubility behavior and dissolution rate is to form a solvate. Brüning et al. (2011) have prepared an acetic acid disolvate of sodium risedronate, and its solubility in physiological buffers differed significantly from that of sodium risedronate, with delayed dissolution under simulated esophageal and gastric conditions, but rapid and complete dissolution under simulated intestinal conditions. On one hand, the propensity of an API molecule to form solvates or hydrates has been related to molecular structures, hydrogen bond patterns, and crystal packing (Gillon et al., 2003).

On the other hand, the propensity of solvent molecules to be included in molecular crystals depends on their ability to effectively participate in hydrogen bonding, and that multi-point recognition via hydrogen bonds between solvent and solute molecules facilitates solvate formation (Nangia and Desiraju, 1999). Because of its small size, activity and ability to act as both a hydrogen bond donor and acceptor, the water molecule is found to be more capable of linking to drug molecules to form new crystal structures (that is, hydrates) than any other solvent. Approximately one-third of active pharmaceutical substances have been found to be able to form crystalline

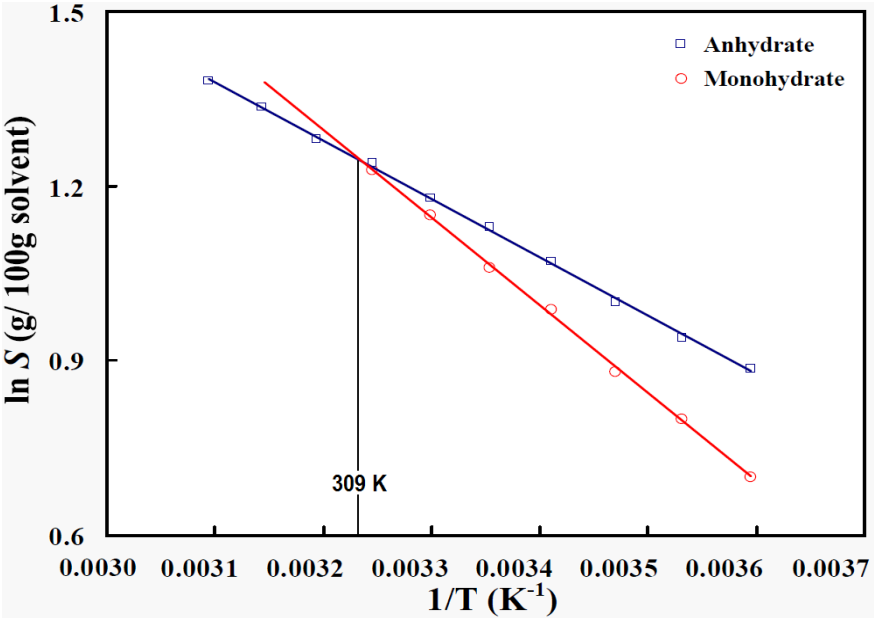

Figure 6. Solubility of the two forms of L- phenylalanine illustrate the transition temperature is about 35.8℃.

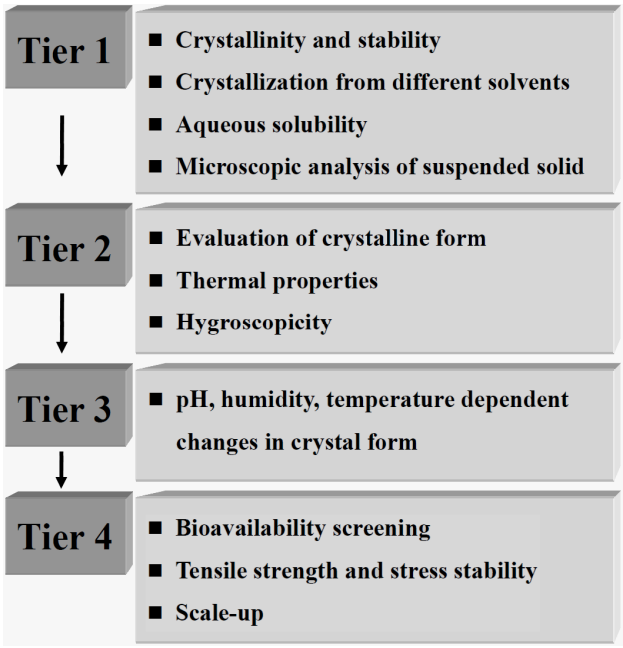

Figure 7. Flow chart of multi-tier approach for the selection of pharmaceutical salts.

hydrates (Stahl, 1980). It is worth noting that solvates or hydrates represent either final or intermediate products of crystallization, and can transform into higher (or lower) solvates or anhydrous "desolvated" forms. For an instance, L-phenylalanine monohydrate will transform to its anhydrous form when the temperature is above the transition point 35.4℃ (Lu et al., 2012a). General ly choice of development of solvated or unsolvated form is dependent upon its pharmaceutical properties.

PHARMACEUTICAL SALTS

A salt refers to a multi-component system where protons are transferred from acid to base in the ionic state (Sarma et al., 2011). In case an API is ionizable, preparation of its salts using pharmaceutically acceptable acids or bases is a common strategy to modulate its solubility (or dissolution rate), to increase chemical stability, to improve bioavailability or to enhance manufacturability (Stahl and Nakano, 2002; Gould, 1986). It is estimated that more than 50% drugs are administered as salts. The selection strategy for a new drug candidate' salts involve the selection of chemical forms of salts, and the selection of physical forms of salts.

Till now, several strategies have been employed to conduct salt selection, such as *in-situ* salt screening technique for ranking the solubility of salts (Tong and Whitesell, 1998), the multi-tier approach developed by Morris et al. (1994) (Figure 7) for the selection of optimal salt form for a new drug candidate, etc. A pioneer work using a microfluidic platform comprised of multi-wells to screen pharmaceutical salts has been developed by

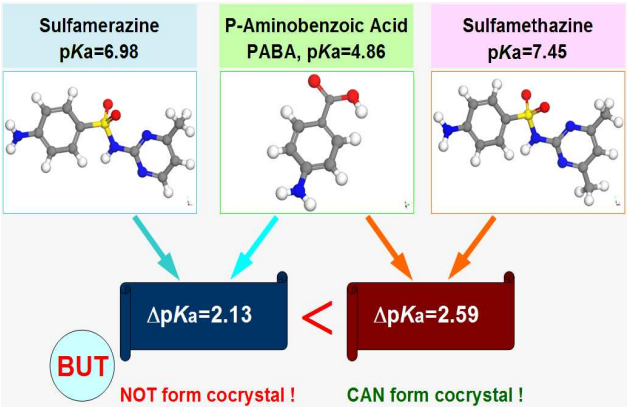

Figure 8. An exception of the rule of ΔpKa in the co-crystal design.

Thorson et al. (2011). In their method, solutions of pharmaceutical parent compounds (PCs) and salt formers (SFs) are mixed on-chip in a combinatorial fashion in arrays of nanolitre wells. Nucleation and growth of salt crystals is induced by diffusive and/or convective mixing of solutions containing, respectively, PCs and SFs in a variety of solvents. Crystals were visualized using bright field polarized light microscopy, followed by the on-chip analyses using Raman spectroscopy to identify different salts.

The presence of ions strongly influences the physicochemical properties of the crystals of formed salts, including solubility, dissolution rate, hygroscopicity, crystallinity, crystal habit, stability, etc (Reddy et al., 2011; Neau, 2000). Generally an organic solvent can influence the solubility of a salt in the following ways: (i) increasing solubility of non-ionized species, (ii) decreasing protonation, and (iii) decreasing solubility of salt formed. Like their parent compounds, pharmaceutical salts may also exist in several polymorphic, solvated and/or hydrated forms (Pudipeddi et al., 2002). For example, ranitidine hydrochloride, frequently used to block acid production in the stomach, has been found to have two polymorphic forms and tautomerism was considered as the main reason of structural differences in the solid state of ranitidine hydrochloride (Mirmehrabi et al., 2004).

Solvents are strong hydrogen bond donors such as methanol and water interact with nitro group of nitroethenediamine moiety and favor the formation of nitronic acid tautomer, and nitronic acid is the predominant tautomer of form 2 crystals. On the other hand, form 1 contains the enamine tautomer, and weak hydrogen bond donor solvents or aprotic solvents favor formation of enamine tautomer and subsequently form 1 (Mirmehrabi and Rohani, 2005). Another example of a salt form that is highly polymorphic and prone to solvate formation is sertraline hydrochloric acid (HCl), which has been found to have 28 forms, including 17 polymorphs, 4 solvates, 6 hydrates and the amorphous solid. Almarsson et al. (2003) and Remenar et al. (2003a) have suggested that minor differences in salt former can have profound effects on the number of polymorphs and solvates that can be found in the corresponding salts.

CO-CRYSTALS

A restrictive definition of co-crystals is that they are structurally homogeneous crystalline materials containing two or more components present in definite stoichiometric amounts, and the co-crystal components are discrete neutral molecular reactants which are solids at ambient temperature (Aakeroy and Salmon, 2005).

The main difference between co-crystals and solvates is the physical state of the isolated pure components: if one component is a liquid at room temperature, the crystals are designated as solvates; if both components are solids at room temperature, the crystals are designated as co-crystals. The primary difference between co-crystals and salts is that in salts a proton is transferred from the acidic to the basic functionality of the crystallization partner, or vice versa if applicable, whereas in co-crystals no such transfer occurs (Aakeroy et al., 2007). Generally co-crystal screening will occupy a lot of time and will consume a large quantity of materials, thus it is great to introduce predictable structural motifs to APIs by design.

One widely used approach to predicting whether a co-crystal or a salt will form between individual components is based on the consideration of p*K*a, as a p*K*a difference of at least three units (between an acid and a base) is required to form a salt, otherwise a co-crystal will form (Remenar et al., 2003b). However, Lu et al. (2011b) have compared the reactivity of *p*-aminobenzoic acid (PABA) and sulfamerazine (SMZ) with that of PABA and sulfamethazine (STH) by use of neat cogrinding and solvent-drop cogrinding, respectively. They found that PABA and SMZ with a Δp*K*a of 2.13 would form a binary eutectic, while PABA and STH with a larger Δp*K*a of 2.59 can form a co-crystal in the ratio of 1:1. The phenomenon further demonstrates that not only the Δp*K*a but also the stereo-hindrance effect (geometric fit) should be considered during the design of pharmaceutical co-crystals, as shown in Figure 8.

A pharmaceutical co-crystal means a co-crystal with one of the co-crystal components as an API and the other components are called coformers (Qiao et al., 2011). Although the utility of the co-crystal formers in pharmaceutical products is limited by their pharmacological and toxicological properties, so far co-crystals have been increasingly recognized as an attractive alternative for solid forms of drug products (Vishweshwar et al., 2006). However, the pharmaceutical co-crystals can be constructed from intermolecular

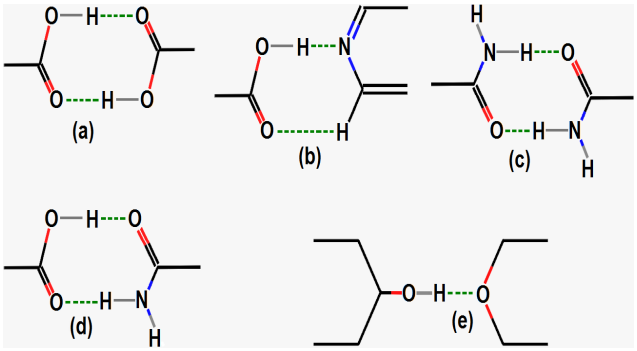

Figure 9. Typical hydrogen bonds existing in pharmaceutical co-crystals.

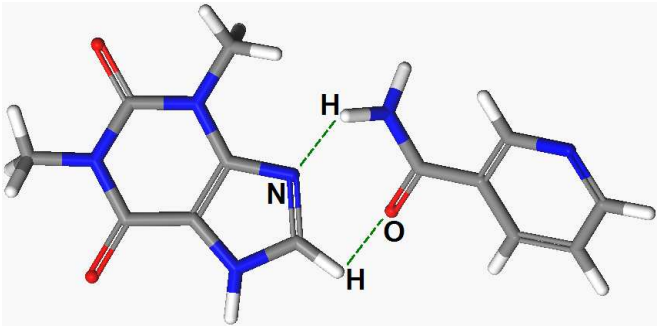

Figure 11. A co-crystal of theophylline and nicotinamide in a molar ratio of 1:1.

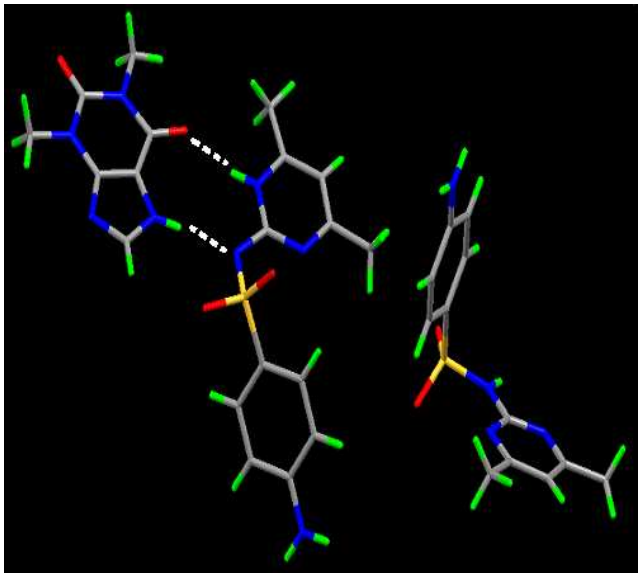

Figure 10. A co-crystal of theophylline and sulfamethazine in a molar ratio of 1:2.

inter-actions such as van der Waals force, π-π stacking, hydrogen bonding, electrostatic interactions, and halogen bonding (Miroshnyk et al., 2009). As shown in Figure 9, typical hydrogen bonds utilized in crystal engineering include those between carboxylic acids (Figure 9a), those between amide homodimers (Figure 9c), those between carboxylic acid and pyridine (Figure 9b), those between carboxylic acid and amide (Figure 9d), and those between alcohol and ether (Figure 9e), etc. Pharmaceutical co-crystals represent a new type of pharmaceutical materials. In addition to potential improvements in solubility, bioavailability, and physical stability, co-crystals may enhance a large number and variety of essential parameters, including hygroscopicity, chemical stability, compressability, and flowability (Trask, 2007).

Theophyllines, often used in the treatment of asthma or chronic obstructive pulmonary disease (COPD), is both weakly acidic and weakly basic, and thus have good possibilities for co-crystal formation due to the presence of O–H and N–H sites in molecule. Sulfamethazine, a sulfonamide drug that has been used to treat bacterial diseases, has been found to format co-crystals with aspirin, benzoic acid, trimethoprim, 4-aminosalicylic acid, etc (Caira, 2007). Nicotinamide, the amide of niacin and one of the vitamin B families (B3), has been used extensively for human consumption and is largely considered to be safe. Lu and Rohani (2009a) have found that theophylline and sulfamethazine can form a co-crystal in a 1:2 molar ratio (Figure 10), and the theophylline-sulfamethazine co-crystal has unique thermal, spectroscopic and X-ray diffraction properties, but higher hygroscopicity than individual components (Lu et al., 2011a; Lu and Rohani, 2010).

On the other hand, the theophylline–nicotinamide co-crystal (Figure 11), obtained in a 1:1 molar ratio, have higher solubility than theophylline (Lu and Rohani, 2009b). In practice, co-crystals can be prepared by neat cogrinding or solvent-drop cogrinding (Chadwick et al., 2007), melt-crystallization (Seefeldt et al., 2007), and slow evaporation from solutions (Vishweshwar et al., 2005). When solution crystallization is utilized, the co-crystals' existence domain can be described by the ternary phase diagram (solvent, molecule, co-crystal former), and the solvent for the co-crystals must dissolve all components, but must not interfere with the interactions necessary for co-crystal formation (Figure 12, Chiarella et al., 2007). It is obvious that co-crystals can also form solvates and exhibit polymorphism.

AMORPHOUS SOLIDS

Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice (Yu, 2001). Amorphous solids lack the three-dimensional long- range order of molecular packing or

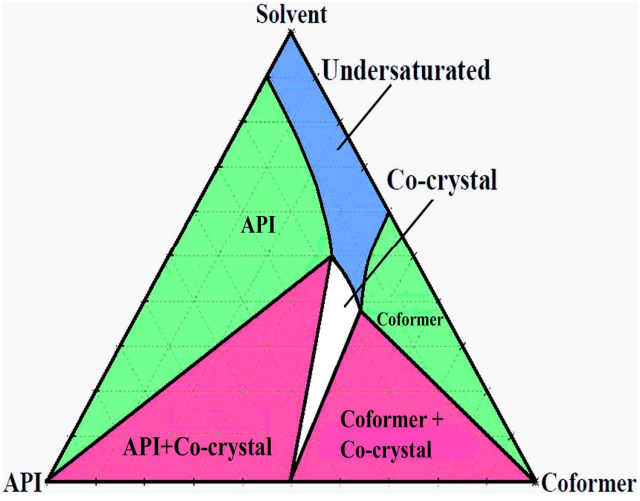

Figure 12. Ternary phase diagram utilized to illustrate the existence domain of co-crystals.

well-defined molecular conformation, but they may have short-range order (Taylor and Zografi, 1997; Hancock and Zografi, 1997). As amorphous solid states of an API are far from equilibrium than its crystalline counterparts, they normally have desirable pharmaceutical properties such as higher solubility (Hancock and Parks, 2000), faster dissolution rate (Pan et al., 2008; Chono et al., 2008) and improved bioavailability (Vasconcelos et al., 2007) compared to their crystalline counterparts. The differences of the solubility between amorphous form and crystalline form have been reported to be between 1.1- and 1000-fold (Huang and Tong, 2004).

It is estimated that over 80% drugs are sold as tablets in which about 40% of marketed drugs have low solubility, and more than 95% of new drug candidates have limited bioavailability (Babu and Nangia, 2011).

Although it has been demonstrated that amorphous pharmaceuticals can provide faster dissolution rates and higher solution concentrations than their crystalline counterparts, (Alonzo et al., 2011), the use of amorphous solids as marketable dosage forms for enhancing oral bioavailability has been limited due to the difficulty in preventing recrystallization from the amorphous state during dissolution (Murdande et al., 2011). When they are introduced to aqueous media, amorphous solids generally have a tendency to crystallize via a form transition. If this form transition takes place rapidly, the observed supersaturation will be much lower than that expected based on theoretical estimates. If the crystallization rate of the solid is extremely rapid, it is possible that no supersaturation will be observed. In order to prevent crystallization of the amorphous phase, polymers are sometimes incorporated into the matrix as stabilizers (Konno and Taylor, 2006). Stabilization of the solid phase during dissolution is equally as important and should be as much of a consideration for formulators as stabilization during storage.

A number of methods have been developed to prepare amorphous solids of APIs, such as rapid precipitation by antisolvent addition (Matteucci et al., 2007), quenching a melt by rapid cooling (Shmeis et al., 2004), freeze-drying (Liu, 2006), spray-drying (Chan et al., 2004), fast evaporation of solvent in liquid solution (Hyvönen et al., 2005), introduction of impurities (Yu et al., 1998), milling or grinding crystalline solids at low temperatures (Gupta et al., 2003), desolvation of crystalline materials (Mirza et al., 2003), and production by solid-dispersion (Chiou and Riegelman, 1971). Amorphous indomethacin can be prepared by use of melt quenching, spray drying, ball milling and cryo-milling. Karmwar et al. (2011) have demonstrated that the amorphous indomethacin prepared using different methods can exhibit different structural and kinetic characteristics, resulted from the variations of molecular conformations and intermolecular interactions. The ranking of the samples with respect to stability was: quench cooled amorphous samples > cryo-milled (alpha-form) > spray dried > ball milled (alpha-form) > ball milled (gamma-form) = cryo-milled (gamma-form).

TRANSFORMATION BETWEEN SOLID FORMS

The knowledge of the transformation kinetics between solid forms is essential to the development of its drug products and to the appropriate storage condition when an active pharmaceutical ingredient have different solid forms. Many APIs are suffering from the transformation of their target forms during processing and formulation which normally will notably degrade the product quality. Till now, there are various methods for identifying the solid forms of APIs, such as powder X-ray diffraction (PXRD), solid-state nuclear magnetic resonance spectroscopy (SS-NMR), differential scanning calorimetry (DSC), thermal gravimetric analysis (TGA), and optical spectroscopy like infrared (IR) spectroscopy, Raman spectroscopy and terahertz pulsed spectroscopy (TPS) (Lu and Rohani, 2009c; Lu et al., 2007). Among these techniques, IR is more economical and more easily available, and thus is more popularly applied to monitor the transformation between different solid forms of APIs. Solid form transformations take place generally via the solid-solid or the solution-mediated mechanism (Sonoda et al., 2006).

The solid-solid transformation is dependent on internal rearrangements or conformational changes of the molecules in solids. Stress-induced transformation refers to that solid-solid transformations of APIs are caused by mechanical stress. This kind of phase transformation is more frequently associated with the formation of metastable forms or amorphous states (Rodríguez-Spong et al., 2004) for example, during grinding or ball milling. Temperature- induced transformation is another wide-

Table 1. Kinetic models for isothermal solid-state reactions.

Kinetic model	Equations*
Prout-Tompkins	$\ln[\alpha/(1-\alpha)] = kt + c$
Avrami-Erofeev (First order)	$-\ln(1-\alpha) = kt$
Avrami-Erofeev (n = 2)	$[-\ln(1-\alpha)]^{1/2} = kt$
Avrami-Erofeev (n = 3)	$[-\ln(1-\alpha)]^{1/3} = kt$
One dimensional phase boundary	$1-\alpha = kt$
Two dimensional phase boundary	$1-(1-\alpha)^{1/2} = kt$
Three dimensional phase boundary	$1-(1-\alpha)^{1/3} = kt$
One dimensional diffusion	$\alpha^2 = kt$
Two dimensional diffusion	$(1-\alpha)\ln(1-\alpha)+\alpha = kt$
Three dimensional diffusion	$[1-(1-\alpha)^{1/3}]^2 = kt$

* k is the reaction rate constant; α is the fraction transformed and t is the transformation time.

spread phenomenon of solid-solid transformation for example, the transformation during heating or cooling. On the other hand, the solution-mediated transformation proceeds through two sequential processes, the dissolution of the metastable form and the recrystallization of the stable form. In this case, the transformation is controlled by differences in solubility of stable and metastable forms, where a metastable form possesses higher solubility. When the temperature is increased and/or the stable form is introduced as "seeds", the transformation process will be greatly accelerated.

Various kinetic models have been used to describe the kinetics of the transformation between solid forms, as shown in Table 1 that is, the relationship between the fraction transformed α and the time t (Brien et al., 2004). It is worth noting that the kinetic models list in the Table 1 is not universal, that is, they are system-dependent. As for the system of L-phenylalanine anhydrous and monohydrate forms, the model of "Three Dimensional Phase Boundary" has been found to be more applicable than others, whereas the model of "Two Dimensional Phase Boundary" is most suitable to simulate the transformation from the form I to the form II of clopidogrel hydrogen sulfate (Lu et al., 2012a, b).

SUMMARY AND OUTLOOK

Most active pharmaceutical ingredients have been demonstrated to have various distinct solid forms (for example, polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids). In past decades, a great progress has been made in the elucidation of the relationship between the particular solid form of a pharmaceutical molecule and its functional properties. With further understanding of the formation mechanisms of different solid forms, it is expected that new solid forms with novel properties will explosively expand by use of molecular level design. Future work may include the development of high-throughput crystallization technology and crystal structure prediction methodology.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 21176102 and 21176215), and the Scientific Research Foundation for Returned Chinese Scholars.

REFERENCES

Aakeroy CB, Fasulo ME, Desper J (2007). Co-crystal or salt: does it really matter? Mol. Pharm., 4: 317-322.
Aakeroy CB, Salmon DJ (2005). Building co-crystals with molecular sense and supramolecular sensibility. Cryst. Eng. Comm., 7: 439-448.
Almarsson Ö, Hickey MB, Peterson ML, Morissette SL, McNulty C, Soukasene S, Tawa M, MacPhee M, Remenar JF (2003). High-throughput surveys of crystal form diversity of highly polymorphic pharmaceutical compounds. Cryst. Growth Des., 3: 927-933.
Alonzo DE, Gao Y, Zhou D, Mo H, Zhang GGZ, Taylor LS (2011). Dissolution and precipitation behavior of amorphous solid dispersions. J. Pharm. Sci., 100: 3316-3331.
Babu NJ, Nangia A (2011). Solubility advantage of amorphous drugs and pharmaceutical co-crystals. Cryst. Growth Des., 11: 2662-2679.
Bauer J, Spanton S, Henry R, Quick J, Dziki W, Porter W, Morris J (2001). Ritonavir: an extraordinary example of conformational polymorphism. Pharm. Res., 18: 859-866.
Bechtloff B, Nordhoff S, Ulrich J (2001). Pseudopolymorphs in industrial use. Cryst. Res. Technol., 36: 1315-1328.
Brüning J, Petereit AC, Alig E, Bolte M, Dressman JB, Schmidt MU (2011). Characterization of a new solvate of risedronate. J. Pharm. Sci., 100: 863-873.
Byrn SR, Pfeiffer RR, Stowell JG (1999). Solid-State Chemistry of Drugs. West Lafayette: SSCI, Inc.
Caira MR (2007). Sulfa drugs as model co-crystal formers. Mol. Pharm., 4: 310-316.

Chadwick K, Davey R, Cross W (2007). How does grinding produce co-crystals? Insights from the case of benzophenone and diphenylamine. Cryst. Eng. Comm., 9: 732-734.
Chan HK, Clark AR, Feeley JC, Kuo MC, Lehrman SR, Pikal-Cleland K, Miller DP, Vehring R, Lechuga-Ballesteros D (2004). Physical stability of salmon calcitonin spray-dried powders for inhalation. J. Pharm. Sci., 93: 792-804.
Chemburkar SR, Bauer J, Deming K, Spiwek H, Patel K, Morris J, Henry R, Spanton S, Dziki W, Porter W, Quick J, Bauer P, Donaubauer J, Narayanan BA, Soldani M, Riley D, McFarland K (2000). Dealing with the impact of ritonavir polymorphs on the late stages of bulk drug process development. Org. Process Res. Dev., 4: 413-417.
Chiarella RA, Davey RJ, Peterson ML (2007). Making co-crystals - The utility of ternary phase diagrams. Cryst. Growth Des., 7: 1223-1226.
Chiou WL, Riegelman S (1971). Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci., 60: 1281-1302.
Chono S, Takeda E, Seki T, Morimoto K (2008). Enhancement of the dissolution rate and gastrointestinal absorption of pranlukast as a model poorly water-soluble drug by grinding with gelatine. Int. J. Pharm., 347: 71-78.
Datta S, Grant DJW (2004). Crystal structures of drugs: advances in determination, prediction and engineering. Nat. Rev. Drug Discov., 3: 42-57.
Gillon AL, Feeder N, Davey RJ, Storey R (2003). Hydration in molecular crystals - a Cambridge Structural Database analysis. Cryst. Growth Des., 3: 663-673.
Gould PL (1986). Salt selection for basic drugs. Int. J. Pharm., 33: 201-217.
Gupta MK, Vanwert A, Bogner RH (2003). Formation of physically stable amorphous drugs by milling with neusilin. J. Pharm. Sci., 92: 536-551.
Hancock BC, Parks M (2000). What is the true solubility advantage for amorphous pharmaceuticals? Pharm. Res., 17: 397-404.
Hancock BC, Zografi G (1997). Characteristics and significance of the amorphous state in pharmaceutical systems. J. Pharm. Sci., 86: 1-12.
Huang LF, Tong WQ (2004). Impact of solid state properties on developability assessment of drug candidates. Adv. Drug Deliv. Rev., 56: 321-334.
Hyvönen S, Peltonen L, Karjalainen M, Hirvonen J (2005). Effect of nanoprecipitation on the physicochemical properties of low molecular weight poly(L-lactic acid) nanoparticles loaded with salbutamol sulphate and beclomethasone dipropionate. Int. J. Pharm., 295: 269-281.
IMS Health Incorporated (2010). Total Unaudited and Audited Global Pharmaceutical Market .
Karmwar P, Graeser K, Gordon KC, Strachan CJ, Rades T (2011). Investigation of properties and recrystallisation behaviour of amorphous indomethacin samples prepared by different methods. Int. J. Pharm., 417: 94-100.
Konno H, Taylor LS (2006). Influence of different polymers on the crystallization tendency of molecularly dispersed amorphous felodipine. J. Pharm. Sci., 95: 2692-705.
Liu JS (2006). Physical characterization of pharmaceutical formulations in frozen and freeze-dried solid states: Techniques and applications in freeze-drying development. Pharm. Dev. Technol., 11: 3-28.
Lu J, Cruz-Cabeza AJ, Rohani S, Jennings MC (2011a). A 2:1 sulfamethazine- theophyllineco-crystal exhibiting two tautomers of sulfamethazine. Acta Crystallogr. C, 67: o306-o309.
Lu J, Li YP, Wang J, Li Z, Rohani S, Ching CB (2011b). Pharmaceutical co-crystals: a comparison of sulfamerazine with sulfamethazine. J. Cryst. Growth, 335: 110-114.
Lu J, Li Z, Jiang XL, Rohani S (2010). Solubility of L-phenylalanine in aqueous solutions. J. Chem. Eng. Jpn., 43: 810-813.
Lu J, Rohani S (2009a). Polymorphic crystallization and transformation of the anti-viral/ HIV drug stavudine. Org. Process Res. Dev., 13: 1262-1268.
Lu J, Rohani S (2009b). Preparation and characterization of theophylline-nicotinamide co-crystal. Org. Process Res. Dev., 13: 1269-1275.
Lu J, Rohani S (2009c). Polymorphism and crystallization of active pharmaceutical ingredients. Curr. Med. Chem., 16: 884-905.
Lu J, Rohani S (2010). Synthesis and preliminary characterization of sulfamethazine - theophylline co-crystal. J. Pharm. Sci., 99: 4042-4047.
Lu J, Wang J, Li Z, Rohani S (2012a). Characterization and pseudopolymorphism of L-phenylalanine anhydrous and monohydrate forms. Afr. J. Pharm. Pharm., 6: 269-277.
Lu J, Wang J, Rohani S (2012b). Preparation and characterization of amorphous, I and II forms of clopidogrel hydrogen sulfate. Cryst. Res. Technol., doi: 10.1002/crat.201200037.
Lu J, Wang XJ, Yang X, Ching CB (2007). Polymorphism and crystallization of famotidine. Cryst. Growth Des., 7: 1590-1598.
Malaj L, Censi R, Capsoni D, Pellegrino L, Bini M, Ferrari S, Gobetto R, Massarotti V, Martino PD (2011). Characterization of nicergoline polymorphs crystallized in several organic solvents. J. Pharm. Sci., 100: 2610-2622.
Matteucci ME, Brettmann BK, Rogers TL, Elder EJ, Williams RO, Johnston KP (2007). Design of potent amorphous drug nanoparticles for rapid generation of highly supersaturated media. Mol. Pharm., 4: 782-793.
Mirmehrabi M, Rohani S (2005). An approach to solvent screening for crystallization of polymorphic pharmaceuticals and fine chemicals. J. Pharm. Sci., 94: 1560-1576.
Mirmehrabi M, Rohani S, Murthy KSK, Radatus B (2004). Characterization of tautomeric forms of ranitidine hydrochloride: thermal analysis, solid-state NMR, X-ray. J. Cryst. Growth, 260: 517-526.
Miroshnyk I, Mirza S, Sandler N (2009). Pharmaceutical cocrystals - an opportunity for drug product enhancement. Expert Opin. Drug Deliv., 6: 333-341.
Mirza S, Miroshnyk I, Heinämäki J, Christiansen L, Karjalainen M, Yliruusi J (2003). Influence of solvents on the variety of crystalline forms of erythromycin. AAPS Pharm. Sci., 5: A12.
Morissette SL, Almarsson Ö, Peterson ML, Remenar JF, Read MJ, Lemmo AV, Ellis S, Cima MJ, Gardner CR (2004). High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Adv. Drug Deliv. Rev., 56: 275-300.
Morris KR (1999). Structural characteristics of crystalline hydrates. In: Polymorphs in Pharmaceutical Solids, Brittain HG (Ed.), New York: Marcel Dekker.
Morris KR, Fakes MG, Thakur AB, Newman AW, Singh AK, Venit JJ, Spagnuolo CJ, Serajuddin ATM (1994). An integrated approach to the selection of optimal salt form for a new drug candidate. Int. J. Pharm., 105: 209-217.
Murdande SB, Pikal MJ, Shanker RM, Bogner RH (2011). Solubility advantage of amorphous pharmaceuticals, Part 3: Is maximum solubility advantage experimentally attainable and sustainable? J. Pharm. Sci., 100: 4349-4356.
Nangia A, Desiraju GR (1999). Pseudopolymorphism: occurrences of hydrogen bonding organic solvents in molecular crystals. Chem. Commun., pp. 605-606.
Neau SH (2000). Pharmaceutical salts. In: Water-Insoluble Drug Formulation, Liu R (Ed.), Denver: Interpharm Press.
Brien LE, Timmins P, Williams AC, York P (2004). Use of *in situ* FT-Raman spectroscopy to study the kinetics of the transformation of carbamazepine polymorphs. J. Pharm. Biomed. Anal., 36: 335-340.
Pan XH, Julian T, Augsburger L (2008). Increasing the dissolution rate of a low-solubility drug through a crystalline - amorphous transition: A case study with indomethicin. Drug Dev. Ind. Pharm., 34: 221-231.
Payne RS, Rowe RC, Roberts RJ, Charlton MH, Docherty R (1999). Potential polymorphs of aspirin. J. Comput. Chem., 20: 262-273.
Pedireddi VR, Reddy JP (2003). Supramolecular pseudopolymorphs: double helix and planar structures with channels. Tetrahedron Lett., 44: 6679-6681.
Pudipeddi M, Serajuddin ATM, Grant DJW, Stahl PH (2002). Solubility and dissolution of weak acids, bases and salts. In: Handbook of Pharmaceutical Salts, Properties, Selection, and Use, Stahl PH, Wermuth CG (Eds.), Weinheim: Wiley.
Qiao, Schlindwein W, Malek N, Davies A, Trappitt G (2011). Pharmaceutical co-crystals: an overview. Int. J. Pharm., 419: 1-11.
Reddy JS, Ganesh SV, Nagalapalli R, Dandela R, Solomon KA, Kumar KA, Goud NR, Nangia A (2011). Fluoroquinolone salts with carboxylic acids. J. Pharm. Sci., 100: 3160-3176.

Remenar JF, MacPhee JM, Larson BK, Tyagi VA, Ho JH, McIlroy DA, Hickey MB, Shaw PB, Almarsson Ö (2003a). Salt selection and simultaneous polymorphism assessment via high-throughput crystallization: the case of sertraline. Org. Process Res. Dev., 7: 990-996.

Remenar JF, Morissette SL, Peterson ML, Moulton B, MacPhee MJ, Guzman HR, Almarsson Ö (2003b). Crystal engineering of novel co-crystals of a triazole drug with 1,4-dicarboxylic acids. J. Am. Chem. Soc., 125: 8456-8457.

Rodríguez-Spong B, Price CP, Jayasankar A, Matzger AJ, Rodríguez-Hornedo N (2004). General principles of pharmaceutical solid polymorphism: a supramolecular perspective. Adv. Drug Deliv. Rev., 56: 241-274.

Sarma B, Chen J, Hsi HY, Myerson AS (2011). Solid forms of pharmaceuticals: polymorphs, salts and co-crystals. Korean J. Chem. Eng., 28: 315-322.

Seefeldt K, Miller J, Alvarez-Núñez F, Rodríguez-Hornedo N (2007). Crystallization pathways and kinetics of carbamazepine-nicotinamide co-crystals from the amorphous state by in situ thermomicroscopy, spectroscopy, and calorimetry studies. J. Pharm. Sci., 96: 1147-1158.

Shekunov BY, York P (2000). Crystallization processes in pharmaceutical technology and drug delivery design. J. Cryst. Growth, 211: 122-136.

Shmeis RA, Wang ZR, Krill SL (2004). A mechanistic investigation of an amorphous pharmaceutical and its solid dispersions, part I: A comparative analysis by thermally stimulated depolarization current and differential scanning calorimetry. Pharm. Res., 21: 2025-2030.

Sirota NN (1982). Certain problems of polymorphism (I). Cryst. Res. Technol., 17: 661-691.

Sonoda Y, Hirayama F, Arima H, Yamaguchi Y, Saenger W, Uekama K (2006). Selective crystallization of the metastable form IV polymorph of tolbutamide in the presence of 2,6-di-O-methyl-beta-cyclodextrin in aqueous solution. Cryst. Growth Des., 6: 1181-1185.

Stahl PH (1980). The problems of drug interactions with excipients. In: Towards Better Safety of Drugs and Pharmaceutical Products, Braimer DD (Ed.), Amsterdam: Elsevier / North Holland Biomedical Press, pp. 265-280.

Stahl PH, Nakano M (2002). Pharmaceutical aspects of the drug salt form. In: Handbook of Pharmaceutical Salts: Properties, Selection, and Use, Stahl PH, Wermuth CG (Eds.), New York: Wiley.

Taylor LS, Zografi G (1997). Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm. Res., 14: 1691-1698.

Thorson MR, Goyal S, Schudel BR, Zukoski CF, Zhang GGZ, Gong YC, Kenis PJA (2011). A microfluidic platform for pharmaceutical salt screening. Lab Chip, 11: 3829-3837.

Tong W, Whitesell G (1998). *In situ* salt screening - a useful technique for discovery support and preformulation studies. Pharm. Dev. Technol., 3: 215-223.

Trask AV (2007). An overview of pharmaceutical co-crystals as intellectual property. Mol. Pharm., 4: 301-309.

Vasconcelos T, Sarmento B, Costa P (2007). Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov. Today, 12: 1068-1075.

Vishweshwar P, McMahon JA, Bis JA, Zaworotko MJ (2006). Pharmaceutical co-crystal. J. Pharm. Sci., 95: 499-516.

Vishweshwar P, McMahon JA, Peterson ML, Hickey MB, Shattock TR, Zaworotko MJ (2005). Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. Chem. Commun., pp. 4601-4603.

Yang X, Lu J, Wang XJ, Ching CB (2008). Effect of sodium chloride on the nucleation and polymorphic transformation of glycine. J. Cryst. Growth, 310: 604-611.

Yu L (2001). Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv. Drug Deliv. Rev., 48: 27-42.

Yu L, Mishra DS, Rigsbee DR (1998). Determination of the glass properties of D-mannitol using sorbitol as an impurity. J. Pharm. Sci., 87: 774-777.