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Historical Perspectives

A material science perspective of pharmaceutical solids

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Abstract

This review introduces the basic material science concepts and principles behind some common topics in the development of pharmaceutical solid formulations. The physiochemical properties of small organic pharmaceutical materials are summarized. Common phases, differences in phases, phase transitions, and their relation to pharmaceutical development are reviewed. The characteristics and physical nature of solid phases, including crystalline and amorphous solids, are presented in conjunction with some pharmaceutically relevant phenomena, such as polymorphism, phase transition kinetics, and relaxation. Mesophases, including liquid crystals and condis crystals, are introduced. The potential energy states of different phases are highlighted as the key connection between the physical nature of the materials and their pharmaceutical behavior, and energy landscape is employed to enhance the understanding of this relation.

Keywords: Material science; Physical property; Phase; Solid; Crystalline; Amorphous; Mesophases; Liquid crystals; Energy landscape

Contents

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1. Introduction

In modern drug discovery environment, it is crucial to build "drug-like" properties in the candidate molecules to ensure successful late-stage product development. Nevertheless, this goal has been proven challenging, particularly in many new drug discovery organizations, where pharmaceutical functionalities and procedures have not been well established. The challenge results partly from the lack of understanding among the discovery teams on the basic principles, technologies, and limitations of formulation development. Consequently, the "late-stage concerns" have not been given sufficient consideration at the early compound screening stage. To solve this problem, formulation scientists not only need to provide early formulation support, but also should serve as counselors to the discovery teams and ensure that "late-stage concerns" are well understood and addressed. To help achieve this goal, this article is targeted to provide an educational review on formulation strategies for drug discovery scientists with a diverse set of background.

Formulation of drug products has long been recognized as a multidisciplinary field. Material science is one of the pivotal branches that continuously provide important insights, theories, and technologies to formulation sciences. As an introduction to this broad topic, this article should necessarily be general, selective, and somewhat superficial. The focus is on early-stage solid formulation development strategy. Additionally, mesophases were given considerable attention in the text. This attention, however, highlighted the solid formulation considerations of mesogenic drug substances. The liquid crystalline drug delivery systems, on the other hand, have not been incorporated in this discussion. Although pharmaceutical implications and formulation strategies were underlined as the key topics, they were approached from a material science perspective and the underlying physical nature is the focus of this paper. The emphasis was given to energy states of various phases that are commonly encountered in pharmaceutical field due mainly to the rationale that the energy states impact directly to the pharmaceutical behaviors. Potential energy landscape was introduced to delineate the energy states in a topographic fashion. While maintaining the text straightforward and qualitative, attempt was made to keep the content consistent with the current scientific understanding, insights, and opinions in this broad area. In order to provide a general and broad overview, the literature cited has an emphasis on classical monographs and review papers.

2. Molecules and phases

Molecules are aggregates of atoms that are connected together through strong chemical bonds, most commonly covalent bonds. Molecules can generally be divided into two categories based upon their size: small molecules refer to molecules consisting of less than 1000 atoms or a molecular weight (MW) less than 10,000 Da; while large molecules (or macromolecules) consist of more than 1000 atoms (Wunderlich, 1999). This division is generally correct in many areas. In pharmaceutical environment, however, it may be more appropriate to set the division line at 1500 Da. One of the reasons to make this change is the difference in absorption of the molecules between these two ranges. In fact, Lipinski pointed out that those molecules with MW higher than 500 Da may already see significant reduction in absorption (Lipinski et al., 1997). Currently, most pharmaceutically significant small molecules indeed have MWs below 1500 Da.

Macroscopically, molecules exist in the form of phases. Molecules, either a single type or a mixture of different types, can aggregate together in different macroscopic forms with different states of thermodynamic energies. These macroscopic forms, which are uniform and homogeneous in chemical composition and physical state within the boundary of the forms, are called "phases" (Tilly, 2005).

When defining a phase, a couple of points should be kept in mind:

1. Phases should have well-defined boundaries or interfaces.
2. The boundaries or interfaces should have negligible influence on the phase properties. This requirement restricts the phases at the macroscopic scale because the interfaces will have significant impacts on the properties of "phases" if the size of the "phases" reduces to a sufficiently small scale.
3. The size or scale, within which the homogeneity is maintained, is crucial in defining a phase. In general, the composition and physical state become more and more heterogeneous as the scale goes smaller. For example, a solution consisting of two different types of molecules is homogeneous when observed at a macroscopic scale (e.g., of micrometers or above). It is therefore defined as ONE phase. However, when the scale reduces to one molecule, we either see molecule A or molecule B, which are obviously different and heterogeneity is observed. Therefore, homogeneity, and thereby phases, is really scale-dependent. Sometimes, when the scale reduces to a critical size, a clear definition of a phase is somewhat difficult. An example in pharmaceutical field is the difference between microemulsions and micellar systems containing solubilized oil in the core. Both systems contain dispersed oil "droplets" surrounded by surfactant layers. Microemulsons are viewed as two-phase systems, while micellar systems are generally believed to have only one phase (Attwood, 1994). These phases are sometimes called "microphases" or even "nanophases", with some ambiguity in their meanings.

Phases are one of the most crucial topics in pharmaceutical sciences. This is partly due to the following reasons:

1. Phases are the macroscopic existence of molecules. In practical applications, molecules are always utilized in the form of their phases. Therefore, the phase properties always play a role in the applications.
2. When molecules aggregate together in different ways, e.g. with different intermolecular distances or molecular orientations, different phases are produced, often at different energy levels. These energy differences, although in general are quite "weak", often generate pharmaceutically significant impact on the compound behaviors, including solubility, bioavail-

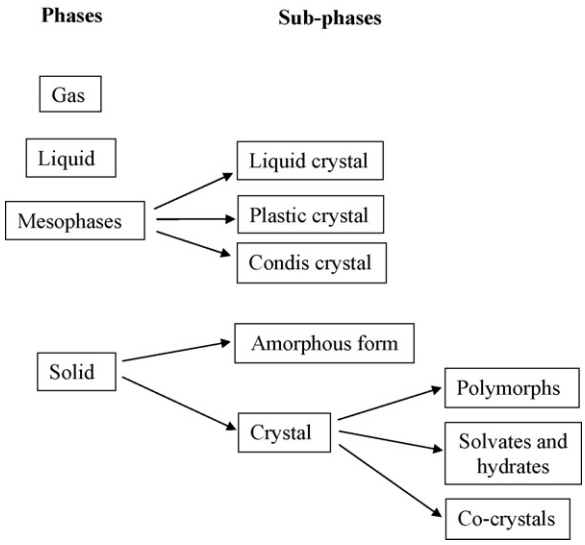

Fig. 1. Categorization of common phases and subphases.

ability, and stability. Therefore, a good understanding about the phase behavior, especially their energy states, of the target compound or delivery systems is crucial.

3. From a different perspective to the same issue, since the intermolecular interactions that are critical in phase formation are generally much weaker than the intramolecular bonding, a change in the state of a phase (phase transition) usually does not involve changes in the chemical structure/bonding of the molecule. This provides pharmaceutical scientists a valuable tool to manipulate the phase changes to achieve their goals without destroying the compound structure. Contrarily, it is easy to see that changes in the chemical structure of a molecule often inevitably result in changes of the phase.

Gas, liquid, and solid are the three most common phases. Mesophases, on the other hand, are relatively rare and their occurrence is highly molecule dependent. Ranked as the fourth class of phases, mesophases include liquid crystals, plastic crystals, and condis crystals (see Fig. 1). They are unique in sharing some properties with both liquid and solid (Wunderlich, 1999). Different from gas and liquid phases, solid and mesophases have multiple distinctive "subphases", which will be discussed in more detail later.

The differences among the phases can be examined from several perspectives: intermolecular distance, molecular motion, order of molecular packing, and potential energy state. In general, these differences are progressive: the most distinctive is the intermolecular distance; then the molecular motion; molecular packing order is the most subtle one. All of these will result in difference in the potential energy. Therefore, energy difference is an inherent feature for different phases. These differences are summarized in Fig. 2. Among these differences, molecular motion merits some additional attention. There are three types of "large-amplitude" molecular motions: translation, rotation, and conformational movement, relative to "small-amplitude" motions, such as vibration. Gas and liquid phases present all three large-amplitude motions, while in a typical crystalline solid these motions are absent or "frozen", only leaving small-amplitude motions active. It is crucial to recognize that these phase differences, particularly the presence or absence of various large-amplitude motions, are the key to differentiate phases and understand their properties. This point will be visited repeatedly throughout the text.

It is interesting to note that "motion" and "lack of order" are often used interchangeably in literature. For example, translational movement is contrary to positional order; rotational movement is absence of orientational order; and conformational motion means lack of conformational order. The term "order" refers to certain ways of molecular arrangement in a phase. It is often true that losing certain type/types of order results in activation of the relevant type/types of molecular motion, and vise versa. However, these two terms are not always interchangeable. For instance, during devitrification of an amorphous solid, molecules gain large-amplitude mobility without changing the order of molecular packing (Wunderlich and Grebowicz, 1984). The same is true for glass transition, where molecular mobility is lost while no molecular ordering is obtained. Here, the difference between these two concepts should be appreciated.

3. Solid phase

Solid is the most commonly encountered phase in pharmaceutical practice. First, most pharmaceutical materials, either the active pharmaceutical ingredients (APIs) or excipients, are in solid phase. Additionally, the most common drug products,

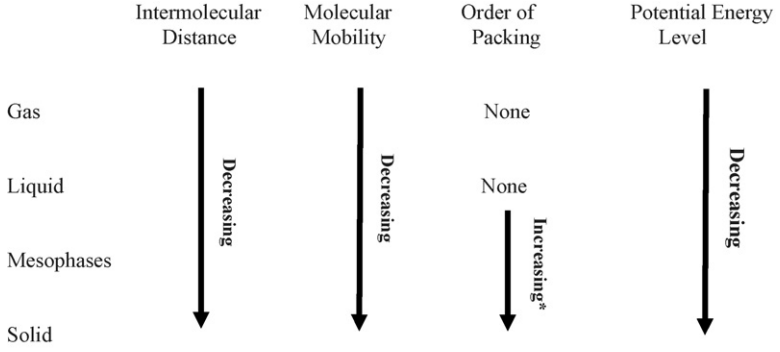

Fig. 2. Differences among the common phases. *Solid phase here refers only to crystalline solid. Another type of solid, amorphous glass, lacks long-range order that exists in mesophases. This will be discussed in more detail in Section 3.

e.g., tablets or capsules, are solids as well. Therefore, solid phase merits a more detailed discussion.

Solid phase can be further classified into two major types of subphases based upon the order of molecular packing. Crystalline form, in which the molecules aggregate together with both short-range and long-range orders, is probably the most well-known solid subphase. Amorphous form (also called "glass"), on the other hand, only presents short-range order but no long-range order in the way of molecular packing. Here, "short-range order" refers to the way (molecular coordination) that the neighboring molecules sit next to each other; while "long-range order" refers to the regularity or periodicity that hundreds and thousands of molecules aggregate, first through "neighboring" (short-range) and then propagate to an "appreciable" distance, to form a phase (Ossi, 2003). Notice here the two "orders" have slightly different meanings, but both are the "rules" (types of spacial arrangements) that molecules follow when they aggregate together and arrange themselves.

The differences between crystalline and amorphous states can be examined from the four perspectives given in Section 2. First, amorphous states demonstrate greater intermolecular distance and molecular mobility than crystals. More fundamentally, in crystalline state molecules arrange in a highly regular fashion both in short-range and in long-range, while in amorphous state only certain level of order is found in neighboring molecules (short-range) and this regularity does not extend beyond the scale of a couple of molecules. In fact, this difference leads to all other differences including greater intermolecular distance and molecular mobility, as well as higher free energy levels for amorphous states relative to crystals.

As shown in Fig. 1, crystalline solids can also exist in multiple subphases, such as polymorphs, solvates, hydrates, and co-crystals (Vippagunta et al., 2001; Vishweshwar et al., 2006). Resulting from different arrangements of molecular packing, polymorphs are different crystalline forms (at different free energy states) of the same molecule or molecules. On the other hand, solvates, hydrates, and co-crystals are similar in that all of them consist of more than one type of molecule. In pharmaceutical environment they are usually made of two types of molecules, one is the API and the other can be either an organic solvent (to form a solvate) or water (to form a hydrate) or another crystalline solid (to form co-crystals) (Vishweshwar et al., 2006). Both types of molecules participate in the short-range and long-range orders of one *single* crystalline form, and the stoichiometric ratios between the two types of molecules and their coordinations in those crystalline forms often are highly regular. Therefore, they are *single* crystalline forms consisting of two types of molecules.

3.1. Why crystals?

This apparently simple question can also be rephrased as: why is there any order in molecular packing when molecules aggregate together? Or, what does the order of molecular packing do? Surprisingly, this fundamental question has often been ignored by many authors. It seems that crystalline states and "order" are so ubiquitous around us that an answer to its origin is not necessary. Nevertheless, readers will find that the efforts in answering this question will greatly strengthen our understanding about the solid phases.

First, a straightforward answer is that crystalline states present lower potential energy levels. Therefore, they are thermodynamically more stable than amorphous or other disordered states and there is a tendency that molecules will pack into crystals.

Then, why is it so? Here the order of molecular packing comes into the picture. By arranging in an orderly fashion, the molecules can sit together more tightly and pack more efficiently, and thereby reduce the specific volume. This results in lower energy level. Additionally, molecules or atoms often have directional specific intermolecular or interatomic interactions, such as hydrogen bonding or covalent bonding, which lead to orderly arrangement of neighboring molecules or atoms. For example, SiO_2 has silicon-oxygen bonding which forms tetrahedral short-range order (see Fig. 3A). Disruption or distortion of this short-range order (also called "local order") increases the potential energy of the system (Ossi, 2003).

More importantly, after aggregating into certain short-range spacial arrangements, these arrangements can propagate in three dimensions *continuously* without producing any "fractures" or "voids" between them (Hammond, 1997; Ossi, 2003). This greatly reduces the interfacial area between this molecular aggregate (solid) and the neighboring phases, which thereby greatly reduces the potential energy level of the solid aggregate. In fact, only those molecular arrangements or orders that can continuously propagate themselves in three dimensions have

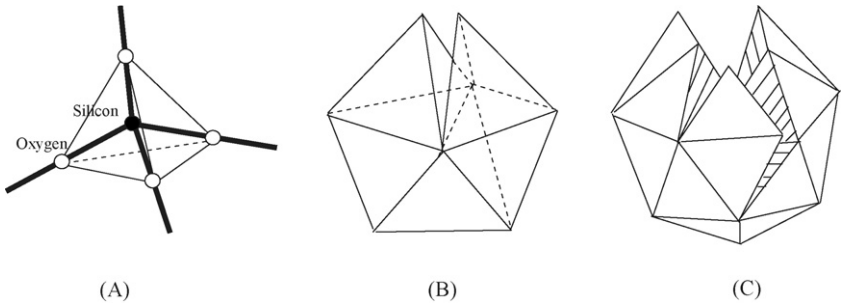

Fig. 3. Tetrahedral local order and its three-dimensional propagation. (A) Tetrahedral local order of silicon dioxide; bold lines are covalent bonding between silicon and oxygen atoms; (B) packing of five tetrahedra about one common edge; a fracture of 7°35′ is produced; (C) packing of 20 tetrahedra into an icosahedron with a fracture produced.

been found in various crystals. Other arrangements, albeit they are also in "orders", do not exist in crystalline solids. An example of such arrangements is the tetrahedral local order shown in Fig. 3A. When tetrahedra are packed together to fill the three-dimensional space, fractures are inevitably produced as exemplified in Fig. 3B and C. This phenomenon is called "structural frustration" (Ossi, 2003). A "frustrated" structure may be viewed as a "crystalline" state with a maximum level of "defects". This defective structure is highly energetic and cannot propagate into long-range. On the other hand, those local molecular arrangements that can continuously propagate themselves to fill the space, when reduced to their very basic forms, are called "unit cells" in crystallography. Geometrically crystallographers have found that there are only 14 types of qualified unit cells in three-dimensional space (obviously, tetrahedral structure is not one of them). In reality it has been proven by thousands and thousands of crystals that these 14 unit cells are indeed the only possible packing orders in crystals. Here an amazing harmony is achieved between mathematics and the real world (Hammond, 1997).

3.2. A topological view of condensed phases

The energy state of condensed matter, including liquid, crystalline and amorphous solids, can be presented more clearly using the concept of energy landscape (Stillinger, 1995; Debenedetti and Stillinger, 2001). An example is given in Fig. 4.

As mentioned earlier, the potential energy of a phase is determined by several factors including intermolecular distance and order of molecular packing. These two factors can be represented by molecular coordinations (position, orientation, and conformation). For example, intermolecular distance can be manifested by molecular positions, while molecular packing orders are just certain particular types of molecular coordinations. An energy landscape is produced when the potential energy of the phase is plotted against molecular coordination, as shown in Fig. 4.

First, in gas phase the intermolecular distance is so large that the interactions among the molecules are very weak. Consequently, changes in molecular coordinations do not impact the potential energy state of the phase. In liquid state, however, the situation changes slightly. With reduced intermolecular distance, the intermolecular interaction strengthens and therefore small fluctuations in potential energy state occur upon changing molecular coordinations. This can be illustrated by Fig. 4A and B.

When temperature further reduces to below the melting point, the liquid enters the supercooling stage, where the intermolecular distance further reduces and intermolecular interactions further strengthen. This increases the energy fluctuation with molecular coordinations because changes in molecular coordination now need to overcome a stronger hindrance and accordingly cause more energy perturbation to the system. At this stage the liquid starts to show structural heterogeneity, where at certain "preferred" coordinations the potential energy is lower than that at other coordinations (Fig. 4C) (Debenedetti and Stillinger, 2001). It is reasonable to believe that the initial heterogeneity is due to some sort of local order, resulting from directional intermolecular interactions. This heterogeneity becomes apparent when temperature goes further down and the liquid approaches glass transition (Fig. 4D). Given enough time at this stage, energy fluctuations in supercooled liquid may generate certain spots with higher local energy level than the bulk liquid, which will create stable tiny crystals, called "nuclei". The nuclei are shown in Fig. 4D as sharp dips (Y and Z). The for-

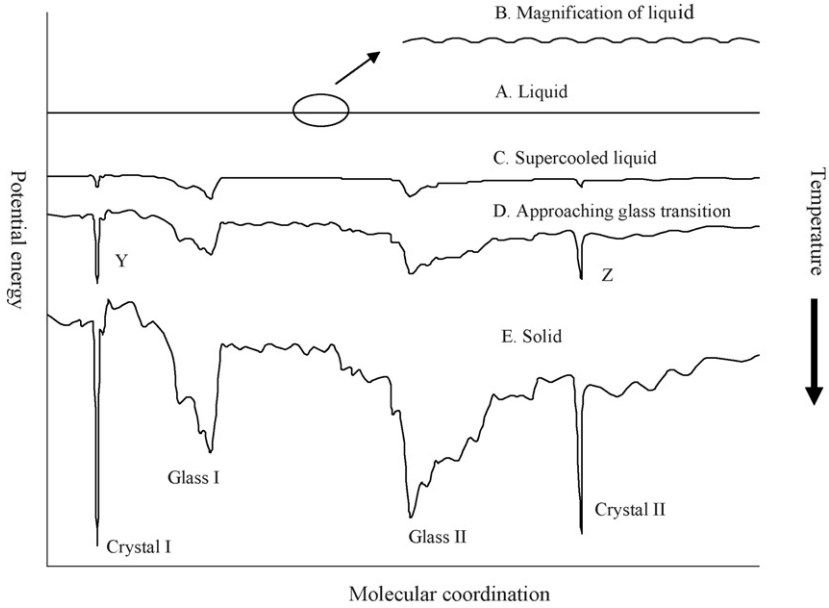

Fig. 4. Energy landscape of liquid and solid phases. (A) Isotropic liquid phase at higher temperature. The energy fluctuation with molecular coordination is small; (B) magnified view of isotropic liquid, the small energy fluctuation can be observed; (C) supercooled liquid at temperature slightly below the melting point. Certain degree of heterogeneity is depicted as energy basins; (D) deeply supercooled liquid at temperature approaching the glass transition temperature. The crystal-forming coordinations are shown as sharp and deeper dips (Y and Z) relative to other energy basins, indicating they are thermodynamically more favorable; (E) solid states. Crystalline polymorphs are shown as sharp dips and amorphous states are broad basins.

mation of nuclei requires higher kinetic energy to overcome the energy barrier entailed with the additional interfacial energy of the newly generated nuclei (this energy barrier is not directly shown in Fig. 4) (Mullin, 2001). Once the stable nuclei are formed, other molecules can change to the "crystal-forming" coordinations and add on the surface of the nuclei, causing the crystals to grow. Schematically, crystal growth can be understood as the flow of molecular coordinations into crystalline energy dips Y or Z. This process presents a lower energy barrier than nucleation therefore it is usually not the rate-limiting step.

It should be noted that all crystalline forms are shown in energy landscape as sharp narrow dips (see Fig. 4E Crystals I and II). This is because all crystalline states exhibit highly ordered molecular packing. Only those particular "crystal-forming" coordinations can form and exist in crystals and no other coordination are involved. Additionally, the crystalline states present low potential energy levels than other disordered states. Therefore, crystalline states are always shown as sharp dips in energy landscape.

The difficulty of crystallization may be understood from the perspective of dynamic redistribution of molecular coordinations along the energy landscape. Since the supercooled liquid starts to show structural heterogeneity, the molecules tend to change their coordinations to those preferred coordinations (e.g., W, X, Y, and Z in Fig. 5A). However, in slightly supercooled liquid the thermodynamic driving force for crystallization (i.e., degree of supercooling) is weak. This may be manifested in the energy landscape as a relatively small energy difference between the crystal-forming coordinations (Y and Z) and other energy basins (W and X). Moreover, crystal-forming coordinations are always very narrow, while other energy basins can be quite broad. This leads to a higher probability for molecules to distribute to those wide energy basins (W and X) rather than to crystal-forming coordinations (Y and Z). A dynamic picture is given in Fig. 5A, where molecular coordinations (represented by solid dots) "flow" to the minima W and X as indicated by the arrows.

When the liquid further cools down, the degree of supercooling increases, which is shown in Fig. 5B as an increased energy difference between the crystal-forming coordinations (Y and Z) and other energy basins (W and X). Thermodynamically, molecular coordinations tend to flow from energy basins W and X to Y and Z as shown by the arrows in Fig. 5B. However, redistribution of coordinations needs molecular mobility and kinetic energy to overcome the energy barrier between the energy basins. Since kinetic energy is dictated by temperature, in deeply supercooled liquid the kinetic energy is relatively low and molecular movement becomes sluggish. As a result, the redistribution of molecules to the crystal-forming coordinations is a somewhat "time-consuming" process. To achieve successful crystallization, it relies on energy fluctuation throughout the supercooled liquid to generate certain local spots with higher kinetic energy, which may push the molecule coordinations "climb" over the energy barriers and fall into the crystal-forming coordinations. This time-consuming nucleation process may present challenges to the crystallization of some compounds. The pharmaceutical implication of crystallization difficulty will be discussed further in Section 3.6 together with the properties of amorphous forms.

One question worth noting is why the energy difference between the crystal-forming coordinations and other energy basins increases upon further cooling of the supercooled liquid. This is mainly because the crystal-forming coordinations have to be those that can propagate three dimensionally. Recall that the initial structural heterogeneity in slightly supercooled liquid is due primarily to certain local orders, resulting from directional intermolecular interactions. These local orders are shown as basins in energy landscape (Fig. 5A, W, X, Y, and Z). However, some of these local orders (e.g., W and X) may not be able to continuously propagate in three dimensions, meaning that they will move to higher energy levels due to structural

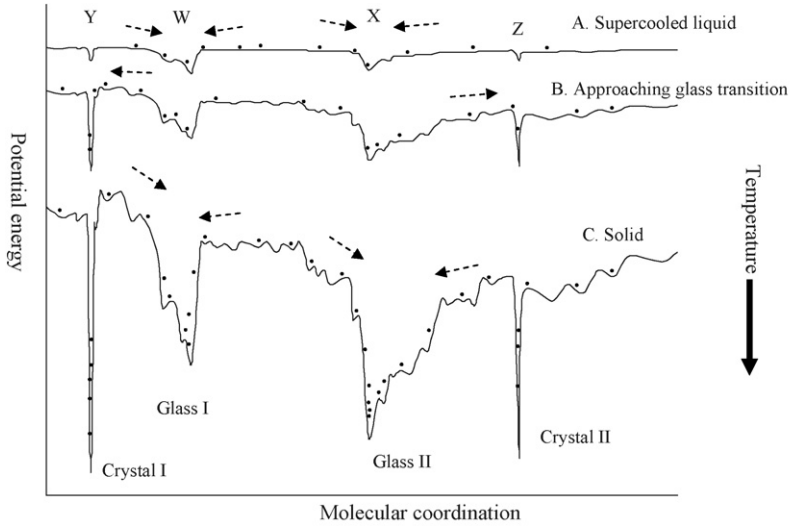

Fig. 5. Dynamic redistribution of molecular coordination in different stages. Solid dots represent molecular coordinations. (A) Supercooled liquid at temperature slightly below the melting point. Molecular coordinations tend to distribute to wide energy basins W and X; (B) deeply supercooled liquid approaching the glass transition. The molecular coordinations "slowly" redistribute to the sharp crystal-forming dips; (C) solid states. The arrows indicate the structural relaxation of the amorphous forms with molecular coordinations moving towards the minima of the energy basins representing glasses.

frustration once the local orders start to propagate to long-range upon further cooling. On the other hand, those crystal-forming coordinations (Y and Z) will continue moving to lower energy levels because they can continuously propagate. Therefore, the energy gap will enlarge between these energy basins when the liquid further cools.

Potential energy landscape has advanced gradually from a qualitative concept to a quantitative description of condensed matter. Originated from the projection by Goldstein (Goldstein, 1969), Stillinger and Weber formulated the initial theory of energy landscape (Stillinger and Weber, 1982). Quantitative construction of energy landscape is currently under intensive research and is progressing rapidly (Sciortino, 2005). The success of this endeavor will have fundamental impacts in many fields, particularly in amorphous solids and supercooled liquids. Angell and co-workers commented that ". . .Although complex, it is ultimately the only correct way to deal with the many-body disordered systems. . ." (Angell et al., 2000). This comment certainly applies to crystalline solids as demonstrated in this section. Nevertheless, the progress is contained by the available computational power, which is needed to process the formidably huge number of molecular coordinations for complex molecules (Debenedetti and Stillinger, 2001). Despite that the compound-dependent energy landscape is not readily available at this point; its quantitative and complex nature can be appreciated for small organic compounds (Stillinger, 1998).

3.3. Polymorphism and pseudopolymorphism

Now we should consider why one compound, with only one type of molecule, can arrange into different crystalline forms or "polymorphs". From Fig. 5C it is clear that polymorphs all occupy the lowest dips on energy landscape relative to other molecular coordinations. This happens when one type of molecule can stay at multiple coordinations and each can arrange the molecules into a different unit cell (including different dimensions of a same type of unit cell). All of these unit cells can propagate continuously in three dimensions, therefore forming multiple crystalline forms with different energy levels. This is how polymorphism occurs. On the other hand, for some molecules there may be only 1 coordination that allows them pack into 1 of the 14 types of unit cells. In these cases, only one crystalline state can be produced. It is easy to understand that polymorphic phenomenon is compound dependent because the energy landscape is specific for each compound. The detailed structural origin of polymorphism can be found in literature (Grant, 1999; Lahani and Grant, 2006).

Since the molecular packing orders are different for polymorphs, the potential energy levels for polymorphs are also different (see Fig. 5C Crystals I and II). A natural question associated with this phenomenon is whether one compound can stay stable in different polymorphs under a given condition. Thermodynamically, the answer is no because the polymorph with higher potential energy will sooner or later convert to the one with a lower potential energy. Kinetically, however, the conversion rate is variable and can be affected by many factors. According to Arrhenius law, the conversion rate is determined by the magnitude of activation energy, which is essentially the energy barrier between the two polymorphs. The higher the energy barrier and the lower the storage temperature, the slower the conversion is. However, the energy barrier can be affected by many factors, such as seeding and impurities (Giron, 2005). An implication of variable polymorph conversion kinetics is the uncertainty associated with searching for the potential polymorphs, particularly thermodynamically most stable polymorph (McCrone, 1957; Guillory, 1999). Occasionally, the most stable polymorph can emerge tens of years after the compound was first made and produced in a metastable crystalline form, which often causes turmoil if the compound is in a marketed drug product. The reasons, again, are related to the different energy levels of polymorphs.

It is well recognized now that polymorphs, due to the difference in their potential energy levels, can have significant impact on the pharmaceutical behaviors of a compound, e.g., stability, solubility, and bioavailability (Haleblian and McCrone, 1969; Brittain and Grant, 1999). Typically, a metastable polymorph presents higher molecular mobility and therefore worse chemical stability relative to the more stable polymorph. On the other hand, solubility of a metastable polymorph is higher and therefore its bioavailability often exceeds the more stable polymorph (the difference in solubility is determined by the difference in energy levels of the involved polymorphs and can be estimated thereafter (Pudipeddi and Serajuddin, 2005)). These differences in compound behaviors are often pharmaceutically significant. Therefore, the conversion from a metastable to a more stable polymorph can impact the pharmaceutical performance of a drug product, sometimes resulting in the failure of a marketed product. To control the risk, the thermodynamically most stable crystalline form is always preferred in current pharmaceutical practice. Occasionally, the most stable polymorph cannot yield a sufficient bioavailability, while a metastable form can. Under these circumstances the metastable polymorph may be attempted, often temporarily, to support certain non-clinical or clinical studies. However, it has often been found that once the more stable polymorph is generated the consistent production of the metastable polymorph is difficult, if not impossible, which presents a great challenge to supply chain management. Therefore, avoiding using metastable polymorph seems to be the current industrial trend. In any case, the searching and evaluation of polymorphs and their thermodynamic relations are the key activities in the selection of the appropriate polymorph for drug development. Unfortunately, there is always a risk that due to the variable kinetics of polymorph conversion "the most stable polymorph" found so far may be a metastable one and a more stable polymorph may emerge in the future. Therefore, besides polymorph screening a consistent monitoring of the crystalline forms is crucial in drug development.

Similar to polymorphs, occurrence of hydrates, solvates, and co-crystals may also impact the development strategy of a drug candidate. Nevertheless, the situation with hydrates or solvates can be more complex. Before getting into more details, it should be noted that although hydrates, solvates, and co-crystals are formed by two compounds, which is different from polymorphs, they are also distinct physical phases that an API may exist

in. Thus, they are called "pseudopolymorphs", in a sense to show their similarity to the "real" polymorphs (Bechtloff et al., 2001). These phases are often encountered in pharmaceutical development process. For example, water and moisture are often involved in the processing and storage of drug substances and drug products, which may lead to formation of hydrates. Solvents are commonly used in the manufacturing of drug substances, during which solvates may be generated.

The impact of hydrates, solvates, and co-crystals to pharmaceutical development strategy stems from the fact that these new phases may offer different, sometimes better, physical and chemical properties than their original crystalline forms (Khankari and Grant, 1995). As a result, the pharmaceutical behaviors, including solubility, stability, bioavailability, and processibility, of the APIs can be improved. Similar to polymorphs, these different properties can also be understood from the energy landscape. For example, if a hydrate stays at a lower potential energy dip than the anhydrate crystalline forms, it will display a better stability. From the structural perspective, it has been found that the inclusion of certain "guest" molecules, such as water or solvent molecules, may help build more stable crystalline structures by forming stronger intermolecular interaction networks or filling some "voids" in the crystalline lattices of some APIs (Morris, 1999). This generates a lower potential energy state and thus a better stability.

The impacts of these new phases to the properties of compounds are compound specific. For solubility, the general rule is that solvates (including hydrates) usually is the thermodynamically most stable form in its own solvents. Thus, solvates often enhance aqueous solubility (Griesser, 2006), while hydrates often decrease it. The latter is usually to a few folds (Pudipeddi and Serajuddin, 2005). Co-crystals, in general, enhance aqueous solubility if the guest molecules are water-soluble. For stability, processibility, and other properties, there are hardly any general rules. These properties and their potential value in pharmaceutical development need to be assessed on a case-by-case basis.

The implication of hydrates, solvates, and co-crystals are discussed sequentially below. First, co-crystals are rarely seen during pharmaceutical development unless being made intentionally. Co-crystals are formed by the APIs with guest compounds through strong intermolecular interactions, particularly hydrogen-bonding (Aakeroy et al., 2006). In pharmaceutical development a very limited number of crystalline small molecules are applied, which leads to a quite low chance of forming intermolecular hydrogen-bonding between the APIs and these additives. Nevertheless, this should not derogate the importance of co-crystals, especially when the APIs have certain undesirable properties, such as low aqueous solubility. In these cases, formation of co-crystals may provide valuable opportunities to improve the physical and chemical properties of the APIs. To achieve this goal, co-crystals usually need to be purposely designed and searched (Aakeroy et al., 2006). Recently co-crystals have attracted considerable attention due primarily to their potentials in improving the API properties (Vishweshwar et al., 2006). Despite of the growing interests, it should also be recognized that application of co-crystals can be restricted by the limited number and safety of the available guest molecules, scale-up difficulty, and stability issues. Extensive studies are often needed to assess the feasibility of this approach.

Solvates basically are co-crystals formed by the APIs with solvent molecules. They are frequently encountered due to the wide application of solvents in API manufacturing. Although solvates may also offer better physical and chemical properties than the unsolvated crystalline forms, the toxicities of most solvents (except a couple of alcohols such as ethanol (Griesser, 2006)) present a serious regulatory concern. Consequently, avoiding formation of solvates is the goal of discovery and evaluation of solvates.

Comparing to solvates and co-crystals, hydrates play a much more important role in drug development. A survey conducted in 1999 indicated that more than 90 hydrates were included in USP monographs (Guillory, 1999). Similar survey with Pharmacopoeia European indicated that about 29% of 808 organic compounds can form hydrates (Griesser, 2006). Several reasons should account for this situation. First, some hydrates are somewhat "unavoidable" or more stable than the anhydrates under conventional pharmaceutical processing and storage conditions. These hydrates are formed upon contact with water or with moisture at low relative humidity. Preventing the formation of hydrates in these cases is difficult. Furthermore, inclusion of water molecules sometimes is necessary to stabilize the crystalline structures of some APIs, and dehydration results in amorphorization of the compounds. Azithromycin and fenoprophen calcium are two examples. The amorphorization presents other challenges to pharmaceutical development, which will be discussed in Section 3.4. Finally, hydrates usually do not raise regulatory concerns comparing to solvates (with toxicities) and metastable polymorphs (with potential phase transitions). Despite that proper strategies have been recommended (Byrn et al., 1995), the importance of this last point probably has not been fully recognized. In industrial practice it actually means that hydrates could have greater value in intellectual property than other physical forms. From a practical standpoint, if certain metastable polymorphs or solvates or amorphous forms have been discovered by other industrial competitors, they may not present a serious threat to the original inventor of the most stable polymorph because these new physical forms have various issues if used in development. Contrarily, hydrates, if patented first by other competitors, can be a real threat. An example is topiramate sodium (Stuart, 2004). Therefore, searching for potential hydrates is a critical step that warrants more effort.

3.4. Amorphous state

Amorphous state, also called glass, is another commonly encountered solid subphase. Despite that amorphous materials have many important applications and lots of intensive studies have been devoted to this area throughout the past century, the structural elucidation of amorphous materials is still incomplete. As pointed out earlier, the molecular arrangement of the amorphous state lacks long-range order, which is the unique feature of crystals. Short-range order, though, has been found to widely exist in inorganic amorphous materials. Using SiO_2 again as an

example, it was found in amorphous SiO_2 the tetrahedral local order preserves (see Fig. 3A) but the long-range propagation of the order is missing (Ossi, 2003). Obtained from studying inorganic glasses such as SiO_2, this conclusion has been extrapolated to other amorphous materials, such as organic small molecules, without vigorous experimental evidence. In fact, up to this point most structural studies in amorphous state have been focused on inorganic materials due mainly to its simplicity. The lack of appropriate experimental techniques and the complexity of data analysis for other amorphous systems should account for this unsatisfactory situation. When discussing the existence of local order in organic small molecule glasses, it should be noted that this is truly a projection, although with reasonable basis.

The discussion on amorphous state can be organized by following the energy landscape. In fact, the initial theory of energy landscape was proposed to describe glass and glass transition (Stillinger and Weber, 1982; Stillinger, 1995). This approach will be employed below.

3.5. Why amorphous state?

Before a liquid turns into a glass, a question we need to answer is why it turns into a glass rather than a crystal? As we know, crystalline states present lower potential energies than glasses and therefore should be thermodynamically more favorable. Then why still glasses? The short answer is that glasses are formed due to kinetic reasons. More specifically, crystallization of supercooled liquids often "needs some time" and may fail if "insufficient" time is given. If this happens, a supercooled liquid may turn into a glass upon cooling.

As presented earlier, potential energy of isotropic liquid barely varies when molecules change their coordinations. Under supercooling, where the temperature is between the melting point and glass transition temperature, a liquid is thermodynamically unstable, meaning that the kinetic energy that is dictated by temperature cannot sustain the system in a stable liquid state. Consequently, the supercooled liquid has a thermodynamic tendency to form a crystalline solid. However, crystallization needs to overcome an energy barrier entailed with the interfacial energy of a newly generated crystal–liquid interface. To overcome this energy barrier a significantly higher kinetic energy is needed, which is absent in the bulk liquid under supercooling. The low kinetic energy is manifested by the increasing viscosity and sluggish molecular movement in the supercooled liquid. Given sufficient time, however, a local high kinetic energy state may be created by energy fluctuation in the supercooled liquid and this will lead to successful nucleation and crystallization (Mullin, 2001). If, before the stable nuclei have sufficient time to form, the temperature sharply decreases, the viscosity may become so high that all large-amplitude molecular movements are "frozen" and the liquid completely loses its mobility and turns into a solid glass. This is the most common way that glasses are generated. As a result, glasses are also considered "frozen liquids" due to their structural similarity. Here the word "frozen" has a relative meaning. It means that the large-amplitude molecular movement in a glass may still exist, but at a much slower pace, e.g., days to years, relative to the experimental time scale, which is usually seconds to hours. Consequently, in most experimental observations the glasses behave more like solids than liquids in many aspects, although structurally they are liquid-like.

This kinetic view of glass formation can be demonstrated in an energy landscape. In Fig. 5, with decreasing temperature, structural heterogeneity emerges in the supercooled liquid (Fig. 5A and B). As a result, molecules start to redistribute and flow to those preferred coordinations with local energy minima. If temperature reduces at a sufficiently slow rate, molecules may have sufficient time to sample the energy minima, within which there are crystal-forming coordinations. This will lead to successful nucleation and crystallization. On the other hand, if temperature drops quickly, the viscosity of the liquid increases accordingly and molecules do not have sufficient kinetic energy to change their coordinations in the time given. They are therefore "frozen" at their initial coordinations as they were in liquid state and this state is maintained when the system turns into a glass.

In addition to temperature quenching, amorphous form can also be produced by fast evaporation of solvents, lyophilization, vapor condensation, mechanical stress, etc. Although these pathways are different, they are somewhat in common in kinetically avoiding crystallization (except for mechanical stress) and keep the molecules in the coordinations as they were in liquid state.

3.6. Properties of glass—high potential energy, structural heterogeneity, and relaxation

3.6.1. High potential energy

Amorphous solids present many special and intriguing properties that have found various important applications. One of the most fundamental properties of amorphous solid is its high potential energy state relative to crystalline forms. It is clear now that amorphous forms, due to their low packing efficiency and lack of long-range order, present higher potential energy than their crystalline counterparts (Yu, 2001). What does the high energy state mean to pharmaceutical scientists? Similar to the metastable polymorphs, it can impact the properties of pharmaceutical products in several aspects: physical and chemical stability, solubility, and bioavailability (Hancock and Zografi, 1997).

First, higher potential energy means physical instability and potential conversion to a thermodynamically more stable crystalline form may occur over time. Again, the conversion rate is dictated by kinetics. If the kinetics is sufficiently slow relative to the pharmaceutically significant time frame, the amorphous states may still be utilized in drug products (Dannenfelser et al., 2004).

Secondly, due to their higher molecular mobility, amorphous forms often exhibit stronger chemical reactivity and thereby faster chemical degradation rate. More specifically, the chemical degradation rate is dependent on the energy state of the glass and the scale of the molecular movement that is involved in the particular degradation reaction. As mentioned earlier, in amorphous states certain types of large-amplitude molecular movement are still active under the given temperature but at a slower pace. If these active modes of movement are involved in the particu-

lar chemical degradation of the compound, the degradation rate is certainly faster than it is in a crystalline state (Xiang and Anderson, 2004).

Finally, amorphous forms often present higher solubility. This offers a great tool for pharmaceutical scientists to enhance bioavailability for those sparsely water-soluble compounds. In fact, recently amorphous forms have attracted increasing interests in the pharmaceutical field due mainly to this valuable property. The solubility increment of amorphous forms over crystalline states depends on the potential energy difference between these physical states. In a study involving limited number of model compounds it was estimated that 10–1600 folds of solubility increment can be achieved by applying amorphous glasses (Hancock and Parks, 2000). Of course, the trade-off for solubility enhancement is the risk of aggravating chemical stability and potential conversion of the amorphous forms to crystalline states. Therefore, the benefits and risks of this strategy need to be carefully evaluated during pharmaceutical development process.

We may compare the strategies of applying a metastable polymorph versus using an amorphous glass in drug development. Both strategies, as discussed separately earlier, aim at enhancement of solubility and bioavailability of the compound. Since the energy difference between a metastable polymorph and the most stable polymorph is relatively small, the increase in solubility is usually just a couple of folds (Pudipeddi and Serajuddin, 2005). On the other hand, manufacturing of a metastable polymorph in a consistent manner often encounters difficulty, especially after the most stable polymorph has been generated. This approach has been proven to be risky and its benefit is often limited. Application of amorphous forms usually does not have too much trouble in manufacturing, but often has a higher tendency to convert to a crystalline state due to the fact that the energy difference between the amorphous and the crystalline state is much larger. Of course, the benefit is that solubility enhancement is greater, sometimes up to several orders of magnitude. This is also a strategy with considerable risk. However, the magnitude of the risk is compound specific. Some compounds exhibit a stronger tendency to convert to the crystalline form than others, which can be explained by the difference in their energy landscapes. Theoretically, greater energy barriers may exist between the amorphous and crystalline states for some compounds, which will therefore lead to better physical stability of their amorphous states. For these compounds the risk may be manageable for pharmaceutical applications.

The higher solubility of amorphous state may have another important impact to pharmaceutical development. This occurs when a compound has difficulty to crystallize, a phenomenon that is not uncommon in drug development environment. In current industrial practice, compounds are often lyophilized at early discovery stage, which frequently yield amorphous forms. The solubility and bioavailability of these forms are hence often "acceptable". Once compounds are selected for late-stage development, the risk may rise if crystallization of these compounds is not readily achievable. In these cases, due to the tight timeline, it may be necessary to conduct some pre-clinical or clinical studies using an amorphous form of the compound. If crystallization occurs later at certain unpredicted point, solubility and bioavailability may drop significantly, which often threatens the formulation strategy and timeline. This risk needs to be addressed as early as possible by an extensive crystallization effort involving a variety of approaches. Additionally, the amorphous materials should be carefully monitored in each study for unpredicted crystallization.

In this strategy there are two points worth mentioning. First, the multiple crystallization approaches provide numerous different crystallization conditions. Based upon the energy landscape, these different conditions create new pathways through which the molecular coordinations can "flow" from one point to another. Some of these pathways may happen to present lower energy barriers so that the molecular coordinations can flow readily into the crystal-forming coordinations. Hence, the more comprehensive the crystallization effort, the better the chance for success.

Another important point is time. As discussed earlier, crystallization kinetics can be variable and successful crystallization could be "time-consuming". Therefore, time is a key factor for success. For this reason it is always a good idea to start crystallization effort early. This includes constant monitoring of the physical state of the compound in each study because crystallization can take a long time and often occur unexpectedly.

3.6.2. Structural heterogeneity and relaxation

Some insights in the structural features of amorphous forms will lead us to a better understanding of this solid subphase. We have learned that molecular arrangement in amorphous forms lacks long-range order. Moreover, as pointed out earlier, when a supercooled liquid is converted into a glass, either by quenching or fast evaporation or lyophillization, the molecules are frozen at various coordinations and these different molecular coordinations are brought into the glass. Recall that crystalline forms always have highly uniform molecular coordinations, this heterogeneity in molecular coordination is unique in amorphous solids. From the energy perspective, different molecular coordinations represent different potential energy levels, suggesting that in an amorphous system the energy levels of molecules are not uniform. Some molecules may present higher potential energy than others and there is an energy distribution for all molecules (Shamblin et al., 2000). This is a significantly different feature for amorphous forms relative to their crystalline counterparts.

The heterogeneity in potential energy state has a profound influence on the interpretation of physical and chemical properties of amorphous solids. Due to the heterogeneity, some molecules are at higher energy levels than the bulk average, which result in, for example, worse-than-average physical and chemical stability for this subset of molecules. From a pharmaceutical standpoint, unfortunately, it is the molecules with the worst stability in the systems that eventually determine the stability of amorphous products. This is because drug products can only tolerate a small percentage of physical or chemical changes (instability) before their quality is fatally affected. Therefore, an accurate projection of some pharmaceutical behaviors (e.g., stability) of amorphous systems demands the characterization of

certain subset of the molecules rather than of the bulk average. This presents a formidable task because most modern characterization techniques, including thermal, spectroscopic, and other methods, aim at detecting various bulk properties. The projection based upon these bulk properties may therefore introduce systemic inaccuracy. For instance, in recent years numerous studies have been devoted to characterization of molecular mobility of pharmaceutical amorphous systems in order to predict their physical stability (Shalaev and Zografi, 2002). These studies rely largely on the measurement of bulk properties, such as relaxation enthalpy or heat capacity. As a result, the predicted physical stability of the amorphous systems could be more optimistic than they actually are (Shamblin et al., 2000). This potential risk should be recognized in the characterization and assessment of amorphous solids.

Furthermore, the energy landscape suggests that different distributions of molecules over the whole energy landscape can be obtained upon varying temperature quenching rate. Specifically, when quenching at a slower rate, the molecules in the supercooled liquid have more time to redistribute to those preferred coordinations, which are the minima on the energy landscape. Consequently, the resulting amorphous system may present lower overall potential energy. On the other hand, a faster quenching allows less time for molecules to redistribute into the energy minima and a glass with higher overall potential energy will be obtained. Similarly, this energy difference in amorphous forms can also be observed by applying different processes to generate amorphous forms. Therefore, the structural features and energy levels of an amorphous state are in fact *process dependent*, which means that we are generating "different" amorphous states by applying different process parameters. This feature is further complicated by structural relaxation of the amorphous systems, which will be discussed below.

"Relaxation" is a word commonly used in material science and technology. To put in a simple way, relaxation can refer to any process that occurs over a longer time period relative to the common experimental observation time frame. For example, a highly viscous liquid may flow very slowly, or a plastic sheet may deform gradually by its own weight. For amorphous solids, molecules are distributed over different coordinations and some present higher potential energies than those at energy minima (see Fig. 5C). Since the large-amplitude molecular movements in glasses still exist at a slower pace, over time the molecules at higher energy levels can change their coordination through molecular movements and gradually move to the energy minima. This process is called "structural relaxation" (Angell et al., 2000). As indicated by the arrows in Fig. 5C, molecular coordinations will flow towards the megabasins of Glasses I and II over time. During this process the extra energy will be released out in the form of heat. So, from the energy perspective, structural relaxation results in a gradually decreasing energy level of the amorphous system until the system falls completely into the energy megabasins (Glass I or II in Fig. 5C), which are sometimes called "ideal glasses". Consistent with this decreasing energy level, the molecular mobility is gradually slowing down. From the structural perspective, the molecular arrangement in amorphous systems gradually becomes more uniform through relaxation, as indicated by the narrower distribution in molecular coordination in ideal glasses, but certainly will never be as uniform as the crystalline forms.

Structural relaxation is one of the most unique features of amorphous solids (Angell, 1991). What does this mean to pharmaceutical scientists? First, it means that amorphous states do not stand still. They are constantly changing in structure and more importantly, in their energy level. Together with the conclusion obtained earlier, we can see that the structure and energy level of amorphous systems are both *process* and *time* dependent. As we know, the potential energy level is related to physical and chemical stability, solubility, and bioavailability. Thus, one relevant question is whether the time and process dependency of the amorphous forms will impact the pharmaceutical performance of the systems. Logically, the answer should be yes. With the decreasing energy level caused by relaxation, the amorphous system should exhibit better physical and chemical stability but somewhat lower solubility. Experimentally, however, this question has not been well addressed so far. It seems that not many people in pharmaceutical filed have been bothered by this issue yet, which might be a good or bad sign.

3.7. Polyamorphism

Since there are polymorphs in crystalline state, an interesting question is whether there are multiple amorphous forms for a single compound. Based on the energy landscape, the answer should be positive. Fig. 5C gives an example of two energy megabasins representing two different amorphous forms (Glasses I and II) for one compound. Experimentally, this phenomenon was first discovered by Mishima and his colleagues, who found polyamorphism of water in 1984 (Mishima et al., 1984). Following that, polyamorphism has been discovered for a few inorganic materials (Poole et al., 1997). So far, however, little evidence has unequivocally shown that small organic molecules demonstrate this behavior (Shalaev and Zografi, 2002). Occasionally mesophases or defected crystalline structures could be mistakenly treated as polyamorphism (Ha et al., 1996; Hedoux et al., 1999). One of the reasons is probably due to the difficulty in structural elucidation of organic glasses. Generally, as pointed out earlier, glasses show structural heterogeneity, which are process and time dependent. Strictly speaking, this can be considered as polyamorphism because the glasses are not structurally identical. But this heterogeneity is still at the molecular scale, not at a macroscopic scale. In other words, they are not in separate phases. The latter remains to be discovered for organic materials.

4. Mesophases

Mesophases are intermediate states between crystalline solid and liquid. The term "mesophase" originates from the Greek word "meso", which means "in the middle". Recall the properties of liquid and crystalline solid: molecules in liquid exhibit all large-amplitude mobility, including translational, rotational, and conformational mobility, while in crystalline solid the mobility is virtually absent. If restrictions on molecular mobility in

crystalline solid are partially lifted, the intermediate states are produced. Depending on the types of existing molecular mobility, these states can be categorized into liquid crystals (with positional and if applicable conformational mobility), plastic crystals (with orientational mobility), and condis crystals (with conformational mobility). Among them, liquid crystals and plastic crystals are well-known mesophases for a long time (Kleman and Lavrentovich, 2003; Sherwood, 1979), while condis crystals are relatively new. The term "condis crystal" was coined in 1984 from a contraction of "conformationally disordered crystal" (Wunderlich and Grebowicz, 1984). However, the existence and properties of conformationally disordered crystals have been recognized and studied from a much earlier time (Smith, 1975). Due to the fact that conformationally disordered crystals are most commonly seen in partially crystalline polymers, it has long been viewed as part of polymeric crystals rather than a type of mesophase (Wunderlich, 1989). Nevertheless, condis crystals have also been found in small organic molecules (Wunderlich and Grebowicz, 1984). Although hardly seen in publications, condis crystals have appeared in developmental drug candidates based upon the knowledge of the author. However, they were often treated mistakenly as crystalline polymorphs with imperfection or with weak lattice energy. For the purpose of this work, the mesophase concept of condis crystals is adopted to emphasize their intermediate nature and to differentiate them from crystalline polymorphs.

To better understand the general properties of these three mesophases, it is useful to compare their thermodynamic states against the isotropic liquid and crystalline solid. The comparison can be conducted by determining the phase transition entropy among these phases (Wunderlich and Grebowicz, 1984). It was found that liquid crystals are fairly close to the isotropic liquid phase in their free energy states, indicating that the orientational order in liquid crystals is quite imperfect in addition to the absence of the positional and conformational order. Condis crystals, on the contrary, are rather close to crystalline solid, although the difference in their energy states varies with the number of conformationally flexible bonds in the molecules. In fact, the properties of condis crystals, which maintain positional and orientational order, deviate only slightly from the fully ordered crystalline solid. This is the major reason that condis crystals are often treated mistakenly as crystalline polymorphs. Finally, plastic crystals are between these two mesophases despite that they display a high positional order. In short, liquid crystals, plastic crystals, and condis crystals are increasingly more solid (Wunderlich, 1989).

Another important feature of mesophases is their intermediate mechanical properties between liquid and solid, which is often ignored by many people. From a mechanical perspective, an "ideal" liquid is completely plastic, meaning that the deformity of an "ideal" liquid under stress is completely unrecoverable by itself after the stress is withdrawn. Contrarily, an "ideal" solid is completely elastic; meaning its deformity under stress is completely recoverable by elasticity once the stress is withdrawn. Mesophases usually are either viscous liquid or semi-solid or soft solid, whose deformity under stress is partially and/or slowly recoverable. Therefore, the mechanical behaviors of mesophases are between a typical liquid and solid. This property differentiates in one way the mesophases from the amorphous solid. The latter is also an intermediate state both structurally and energetically between liquid and crystalline solid. However, amorphous glass behaves more like crystalline solid mechanically, while typical mesophases are either viscous liquid or soft solid. Of course, structurally mesophases presents a certain degree of long-range order, which is absent in amorphous solid (Dierking, 2003).

The intermediate mechanical strength of mesophases results from the physical nature of the material. First, the mesophases are formed by organic molecules bound by weak intermolecular interactions (Kleman and Lavrentovich, 2003). Additionally, the phases are partially ordered and thereby no strong crystalline lattice energy is present. This physical nature leads to phase transition temperatures of mesophases often close to room temperature and relatively small transition enthalpies are frequently seen. For pharmaceutical scientists the low-temperature phase transitions often mean stability or quality control issues which warrant special care.

The capability of forming different mesophases stems largely from the structure and geometry of the molecules. In condis crystals the molecules have flexible structures and conformational changes do not encounter a high activation energy. Liquid crystals always have a rigid rod- or disc-like core molecular structure, which causes a high activation energy for rotational reorientation and thereby certain degree of orientational order is maintained (see Section 4.1 for more details). Plastic crystals, in contrast, are more globular in their molecular shape, so that the energy barrier for reorientation is low. As a result, molecules can rotate readily within the crystalline lattice at certain temperature, indicating that the orientational order is lost, while the crystalline structure is retained. The globular molecular shape of plastic crystals also results in cubic unit cells. Due to the lack of strong intermolecular interactions, plastic crystals are often easy to deform (Kleman and Lavrentovich, 2003). Plastic crystals have rarely been reported in pharmaceutical field, possibly because few pharmaceutically related molecules have spherical shapes.

Liquid crystals and condis crystals are discussed further below.

4.1. Liquid crystals

Liquid crystals (LC) are liquids featuring a certain level of orientational order. Specifically, molecules in LCs tend to point to a certain direction, while they still have translational (positional) freedom. Based on the ways that LCs are generated, they can be categorized into two classes: thermotropic and lyotropic. The former is generated by temperature variation in the liquid state, while the latter is formed by dissolving the compound in certain solvents. Either way offers the systems sufficient large-amplitude molecular mobility so that molecules can change positions and reorient themselves forming LC phases. Obviously, thermotropic LCs usually are one-compound systems, while lyotropic LCs are always solutions consisting of multiple compounds (i.e., solvent and solute).

First, let's see how a thermotropic LC phase is usually generated. At temperatures much higher than the melting point, the system is a stable isotropic liquid phase. No directional alignment of molecules can occur due to the high kinetic energy. Upon cooling, the molecular mobility decreases accordingly. When temperature falls into a certain range above the melting point, the LC-forming molecules present an appropriate mobility so that they start to reorient and "stably" point to a certain direction. A liquid crystal is then generated. Upon further cooling to below the melting point, the molecular mobility reduces to the level that the translational movement is not sustainable. As a result, the LC either crystallizes into a fully ordered crystal or a condis crystal or is frozen into a LC glass (obtained when the LC phase vitrifies instead of crystallizes upon cooling, the directional molecular alignment is retained (Wunderlich and Grebowicz, 1984)).

The above cooling process is no different from the process discussed in Section 3.2. Thus, an immediate question is why some compounds can form thermotropic LCs, while others cannot. The answer is in molecular geometry and intermolecular interaction. First, the molecules need to be "directional" in order to align toward certain direction, which in most cases means the molecular shapes are either rod-like or disc-like. As a general rule, most thermotropic LC formers have a rigid core scaffold, such as phenyl or biphenyl groups, and some flexible outer groups, such as aliphatic chains. This general structure induces a high activation energy for rotational reorientation so that the molecules tend to maintain certain orientations, while keeping the fluidity and translational mobility (within certain temperature range). An example is given in Fig. 6A.

The lyotropic LC formers, on the other hand, have different molecular features. Although elongated shape is still necessary, a rigid core scaffold is not required. Instead, the lyotropic LCs are often amphiphilic (surface active), in which a hydrophilic head and a hydrophobic tail occupy the two ends of the elongated molecule. When dissolved in water, the molecules align themselves to hide the hydrophobic tails away from the aqueous media and leave the hydrophilic heads in contact with the media (see Fig. 6B). This often results in anti-parallel double layers which lead to smectic LC phases (Kleman and Lavrentovich, 2003).

In addition to molecular geometry, molecular interactions also play a key role in pushing the molecules to align. Amphiphilic molecules orient into anti-parallel double layers due to hydrophobic interactions. Fig. 6A represents an example of thermotropic LC former whose terminal cyano group causes strong dipole–dipole interaction among the molecules. This interaction induces alignment of the molecules into anti-parallel layers at certain temperature. The chemical structure features of LC formers are detailed in a monograph (Dunmur et al., 2001).

The LC phase often presents multiple subphases. Nematic and smectic phases are the most common subphases. Fig. 7 provides examples of some common LC subphases. The nematic phase presents only linear orientational order in which molecules point towards one direction (see Fig. 7A), while smectic phase shows two-dimensional orientational order, in which the molecules assemble into layers (see Fig. 7B and C). Within the class of smectic phase, many distinct subphases can form due to different arrangements of the molecules. For example, a Smectic A phase is generated when the molecular direction is normal to the layer where the molecules reside (Fig. 7B), while a Smectic C phase is when the molecule direction presents certain angle against the normal of the layer (Fig. 7C) (Dierking, 2003). All these subphases have been proven to be truly distinct phases. Specifically, they are macroscopic in size and have defined boundaries between each other, meaning that they are immiscible. Moreover, one molecule may exhibit multiple LC subphases depending on external conditions, which include but not limited to, temperature variation. When they change, transitions between these subphases can occur. For example, nematic phase may form at a higher temperature, and turn into Smectic A phase at a lower temperature. LC phases are further complicated by chiral compounds (Collings and Hird, 1997). Due to the steric effect, chiral LC formers orient in a helical fashion rather than pointing toward one direction when they form nematic phases (see Fig. 7D), which are called "chiral nematic" phases, or "cholesterol" phases.

For pharmaceutical purposes, it is important to recognize that multiple phases and subphases are often displayed by LC formers. It was pointed out that LC formers can have five possible pure phases, which are fully ordered crystals, LC glass, amorphous glass (no orientational order is maintained), liquid crystal, and isotropic melt (Wunderlich and Grebowicz, 1984). In fact, this number is often higher if LC subphases are also counted. Additionally, condis crystals can be another possible low temperature phase if the LC formers have conformationally flexible structures (such as many lyotropic LCs). The transitions among these phases are often first-order, which can be shown by thermal analysis. This feature is important for formulation scientists because multiple thermal transitions are often the first sign suggesting the potential formation of LCs. To confirm and further characterize the LC phases, polarized light microscope and special sample preparation techniques are necessary. This is

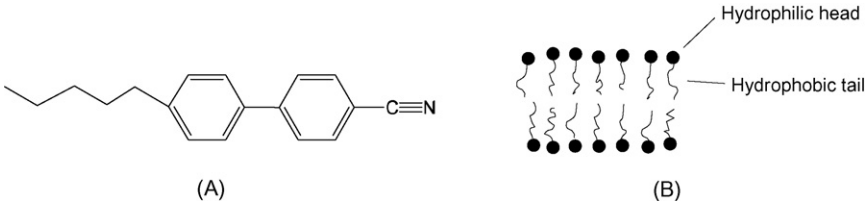

Fig. 6. Examples of thermotropic and lyotropic liquid crystals. (A) 4-Cyano-4-*n*-pentylbiphenyl (5-CB) and (B) anti-parallel double layer formed by amphiphilic molecules.

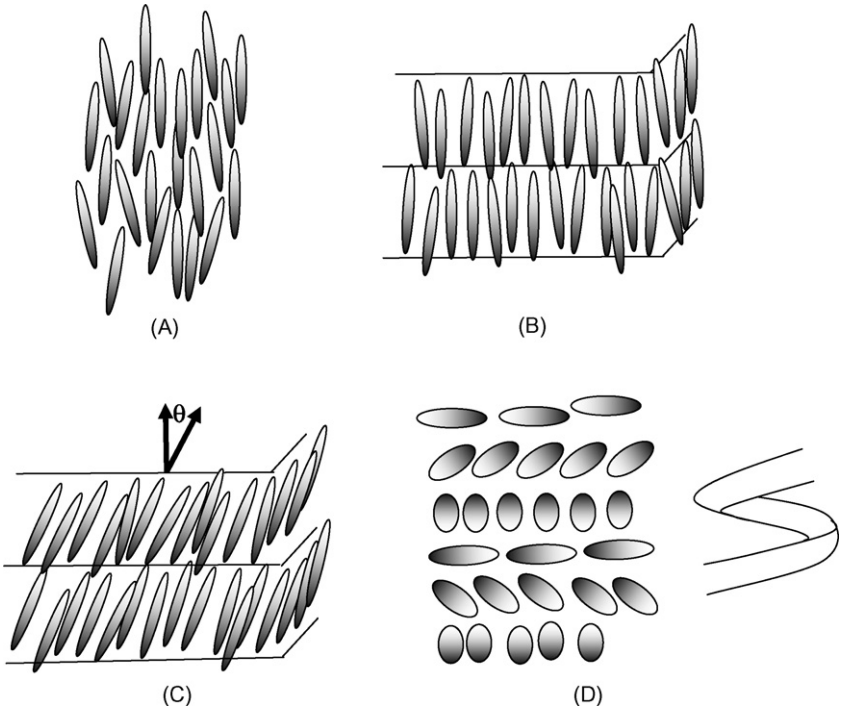

Fig. 7. Liquid crystal subphases (redrawn from Dierking, 2003). (A) Nematic phase; (B) smectic A phase; (C) smectic C phase; (D) chiral nematic (cholesterol) phase; the helix on the right illustrates the rotation of the chiral molecules.

because LC phases present unique optical properties, which can be exploited to identify, characterize, and structurally elucidate various LC subphases. The details are beyond the scope of this text and the readers can refer to another monograph (Dierking, 2003).

When discussing pharmaceutical applications, the energy states of the systems should not be forgotten. Fig. 8 demonstrates the potential energy landscape of LC phases. With temperature decreasing, the isotropic liquid first turns into a nematic phase, which is represented as an energy basin in Fig. 8. The molecular coordination then "flows" into this basin forming nematic phase. When temperature reduces further, the uni-directional molecules may aggregate into layers and the nematic phase turns into a Smectic A phase, where a deeper energy basin is shown (see Fig. 8). It should be noted that the energy basins for LC phases are wider and shallower than crystalline solids. This is because LC phases still retain many modes of large-amplitude molecular mobility. The molecular coordinations in the LCs are not as restricted as they are in crystalline solids.

The LC behaviors, if displayed by development candidates, can have significant impact on the development strategy. First, due to the higher energy level of LCs relative to crystalline solids,

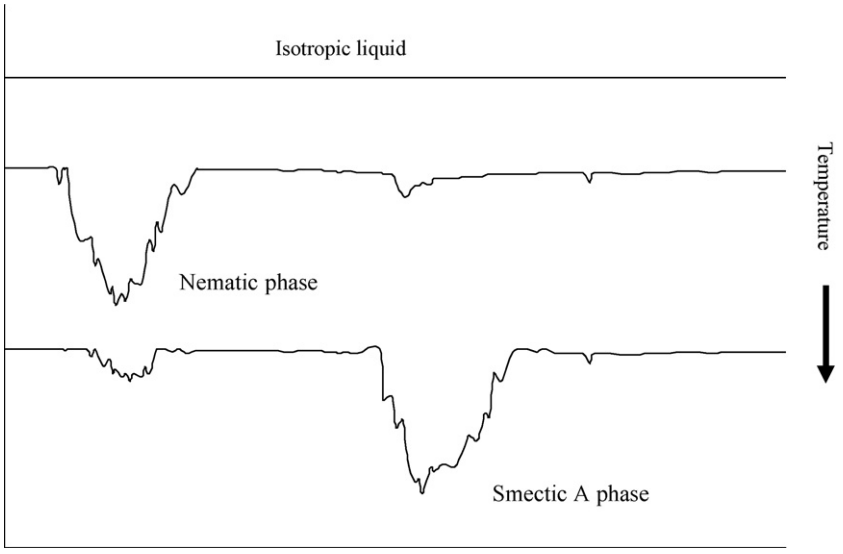

Fig. 8. Energy landscape of liquid crystal phases.

it is reasonable to speculate that the pharmaceutical behaviors should be affected. Unfortunately, little work has been found so far to address this issue. Furthermore, due to the existence of multiple phases and the relatively low phase transition temperatures, selection and control of the appropriate physical form are great challenges. For instance, the LC phases generated by high process temperatures may turn into LC glasses rather than reverse back to the fully ordered crystals upon cooling. Many LC formers, particularly lyotropic LC formers, have multiple flexible bonds in their structures, which leads to a high probability of condis crystal formation at ambient conditions (the issues associated with condis crystals will be discussed in the next section). The generation of these new phases in an uncontrolled manner raises quality and regulatory concerns. Finally, lyotropic LC formers can introduce additional problems in liquid formulation development, such as hemolysis and opalescence.

Although application of LC systems in pharmaceutical areas has a long history, most of the attention has been given to LC drug delivery systems rather than to the APIs. Historically, surfactants, cholesterol derivatives, phospholipids and many lipid families are the common LC formers applied in various liquid delivery systems. More recently, some cellulose derivatives, which are typically used in solid dosage forms, were also found to display LC phases (Ambrosino and Sixou, 1989; Sixou, 1999). These excipients include hydroxypropylcellulose (HPC), ethylcellulose (EC), and cellulose acetate (EA). In the past several years, LC forming APIs started to draw the attention in pharmaceutical field (Bunjes and Rades, 2005; Stevenson et al., 2005). Although the interests of pharmaceutical scientists in LC systems are growing, it appears that the development strategy has not been fully addressed for this class of APIs.

4.2. Condis crystals

In condis crystals molecules or part of the molecules are conformationally flexible. Many chemical structures can have conformational isomers. The formation of condis crystal depends on the magnitude of the activation energy involved in conformational changes. A low activation energy leads to a high conformational freedom and therefore a high probability of condis crystal formation. For example, linear aliphatic chains with small substitute groups encounter low resistance in conformational motion about the chain axis. Some polymers, such as polyethylene and polytetrafluoroethylene, feature this structure and condis crystal phases are displayed by them at elevated temperature (Wunderlich, 2006; Wunderlich, 1999). Many LC formers, especially lyotropic LCs, present condis crystal phase at low temperature when they turn into solids or plastic solids. These molecules, such as soaps and surfactants, often contain flexible long-chain aliphatic groups. In fact, flexible chains are the most common structures that induce the formation of condis crystals, although other structural features, such as boat/chair ring conformations, have also been reported (Glaser et al., 1990; Wunderlich and Grebowicz, 1984).

Condis crystals merit more attention in pharmaceutical areas particularly because they are in general rather close to crystalline solids. This characteristic, as discussed earlier, often causes condis crystals to be confused with crystalline polymorphs. The challenges of condis crystals in solid formulation development result mainly from their low crystallinity and weak mechanical strength. The compounds that show condis crystal phase, when crystallized, often display low or imperfect crystallinity due to the conformational flexibility of their molecules. When water or heat is involved in the processes, certain portion of compounds may be left in amorphous state upon recrystallization. Moreover, condis crystals are easy to deform mechanically, which is often accompanied by certain degree of amorphorization. The uncontrolled amorphorization raises concerns to the quality control of the drug products. In many occasions it could mean that development of a tablet formulation is nearly impossible. In some companies, it actually leads to the termination of an oral delivery candidate. Therefore, it is important to identify condis crystals and differentiate them from fully ordered crystalline polymorphs. This can be achieved in most cases through conventional thermal analysis (Wunderlich, 1989). Additionally, the potential crystalline form changes upon water and mechanical stresses should be examined before a compound is elected for development.

5. Concluding remarks

There is a growing interest among the drug discovery scientists in formulation strategies and considerations. This paper aimed at providing some background and insights in this area by addressing the physical nature of the pharmaceutical solid systems. It is obvious that this text is by no means complete. For instance, liquid and colloidal systems are commonly applied in early drug discovery support, which demand a detailed discussion. Due to the size limitation, this paper is unable to address these important topics. The readers are encouraged to refer to other literature on the interested topics.

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