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Review Article

Theme: Develop Enabling Technologies for Delivering Poorly Water Soluble Drugs: Current Status and Future Perspectives
Guest Editors: Ping Gao and Lawrence Yu

Stability of Amorphous Pharmaceutical Solids: Crystal Growth Mechanisms and Effect of Polymer Additives

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Abstract. We review recent progress toward understanding and enhancing the stability of amorphous pharmaceutical solids against crystallization. As organic liquids are cooled to become glasses, fast modes of crystal growth can emerge. One such growth mode, the glass-to-crystal or GC mode, occurs in the bulk, and another exists at the free surface, both leading to crystal growth much faster than predicted by theories that assume diffusion defines the kinetic barrier of crystallization. These phenomena have received different explanations, and we propose that GC growth is a solid-state transformation enabled by local mobility in glasses and that fast surface crystal growth is facilitated by surface molecular mobility. In the second part, we review recent findings concerning the effect of polymer additives on crystallization in organic glasses. Low-concentration polymer additives can strongly inhibit crystal growth in the bulk of organic glasses, while having weaker effect on surface crystal growth. Ultra-thin polymer coatings can inhibit surface crystallization. Recent work has shown the importance of molecular weight for crystallization inhibitors of organic glasses, besides "direct intermolecular interactions" such as hydrogen bonding. Relative to polyvinylpyrrolidone, the VP dimer is far less effective in inhibiting crystal growth in amorphous nifedipine. Further work is suggested for better understanding of crystallization of amorphous organic solids and the prediction of their stability.

KEY WORDS: amorphous solid; crystal growth; crystallization; crystallization inhibitor; glass; glass transition; polymer additive; surface molecular mobility.

INTRODUCTION

Amorphous solids can be produced by cooling liquids, evaporating solutions, and condensing vapors while avoiding crystallization. Other routes are known that lead to amorphous solids; for example, mechanically damaging crystals (1) and removing water from hydrated crystals (2). Amorphous solids produced by cooling liquids are commonly called glasses. In this process of glass formation, molecular motions become increasingly slower with cooling until finally, at the so-called glass transition temperature T_g, the system can no longer reach internal equilibrium with each decrease of temperature and becomes kinetically frozen. With respect to molecular packing, amorphous solids are usually envisioned as having significant local order (*e.g.*, each molecule having similar number of nearest neighbors), but lacking long-range order that characterizes molecular packing in crystals.

Amorphous solids are generally more soluble and faster dissolving than their crystalline counterparts, which makes them potentially useful for delivering poorly soluble drugs whose bioavailability is limited by their low solubility. For indomethacin, the solution concentration reached by dissolving an amorphous solid has been found to be 5–17 times higher than by dissolving a crystalline solid (3–5). Amorphous ritonavir was found to dissolve ca. ten times faster than crystalline ritonavir (6).

Amorphous drugs must resist their thermodynamic tendency to crystallize, for crystallization negates their solubility advantages. The past two decades have seen active research on amorphous pharmaceutical solids and their stability against crystallization, and several reviews have appeared (7–11). Some questions studied in this context are:

(1) Can the crystallization rate of an organic glass be predicted by extrapolating that of the corresponding liquid? This question is studied to learn whether the crystallization of organic glasses can be treated as the

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low-temperature version of liquid-state crystallization. Because crystallization involves nucleation and crystal growth, this question is posed for each step.

(2) What molecular motions in amorphous solids are associated with crystallization?
(3) How do free surfaces affect crystallization in organic glasses?
(4) How does the crystallization of an amorphous solid depend on the method of preparation (melt-cooling, solution-drying, vapor-condensation, cryo-milling, and others) and its thermal history?
(5) How do excipients (especially polymers) affect the crystallization of amorphous drugs, both during storage and dissolution? What attributes of a polymer make it a good crystallization inhibitor?
(6) How soluble are crystalline drugs in polymers? (12–14), This question is studied to learn the maximal drug loading in a polymer matrix without risk of crystallization.
(7) What is the effect of moisture on the stability of amorphous drugs and formulations? (15)

We will focus this review on crystal growth in organic glasses. We do so because of recent progress in this area and because crystal growth in organic glasses has properties unknown for (and thus unpredictable from the behaviors of) other materials. We also discuss recent work to understand the role of polymer additives in stabilizing amorphous drugs against crystallization. The materials covered are relevant to Questions 1, 2, 3, and 5.

FAST MODES OF CRYSTAL GROWTH IN ORGANIC GLASSES

Many studies have observed that the linear velocity u of crystal growth in a one-component liquid typically increases and then decreases with supercooling. Figure 1 illustrates this pattern for crystal growth in liquid *o*-terphenyl (OTP), a well-studied small-molecule organic liquid. The u *vs.* temperature plot is a bell-shaped curve between the melting point T_m and the glass transition temperature T_g (triangles). This pattern exists because at small supercooling, the growth rate is limited by thermodynamic driving force, and at larger supercooling, the growth rate is limited by molecular mobility in the liquid. For OTP, u closely tracks the self-diffusion coefficient D (open symbols) at large enough supercooling (T<285 K), over several orders of magnitude of change (16–18). This relation justifies the description of the crystal growth process as diffusion-controlled, and is consistent with the common view that molecular diffusion in the liquid defines the kinetic barrier for crystal growth (19,20).

Diffusion-controlled growth serves as a reference point for fast modes of crystal growth that can emerge as organic liquids are cooled to become glasses. These growth modes lead to crystal growth rates orders of magnitude faster than expected for diffusion-controlled growth. One such growth mode happens in the interior of a glass, and another occurs at the free surface. These phenomena are unknown or uncommon for other classes of glass-forming liquids. We review below key observations concerning these growth modes and their current explanations.

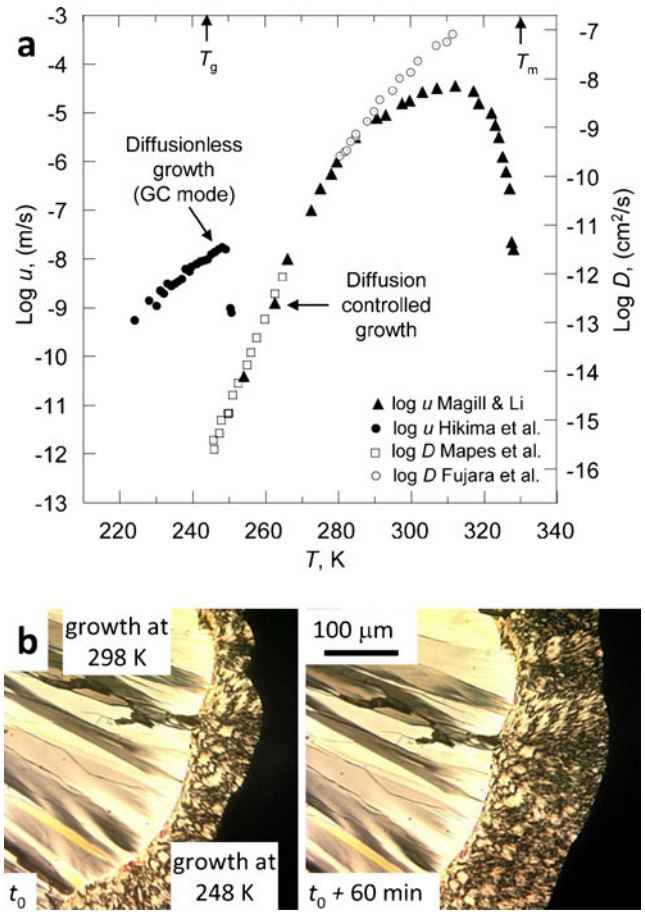

Fig. 1. **a** Crystal growth rate u and self-diffusion coefficient D of liquid and glassy *o*-terphenyl. Tg=246 K. **b** Photomicrographs of GC growth at 248 K

GLASS–CRYSTAL GROWTH MODE

Figure 1 shows that while the crystal growth rate u tracks the diffusion coefficient D above T_g, u becomes orders of magnitude faster with a temperature drop of a few K (filled circles) (21,22). This growth mode, termed GC (glass-to-crystal), is so fast that it is not limited by molecular diffusion in the bulk liquid. This phenomenon was apparently first noted by Greet and Turnbull in 1967 (21) and then studied systematically by Oguni and coworkers since 1995 (22,23). The phenomenon is remarkable because on cooling, the loss of liquid-like mobility activates fast crystal growth, and on heating, the gain of liquid-like mobility disrupts the fast crystal growth that occurs in the glass state. To our knowledge, the abrupt activation of fast crystal growth has not been reported for non-organic liquids. Since there is no corresponding increase in the diffusivity at the onset of GC growth, this growth mode has been called “diffusionless”, in contrast to diffusion-controlled growth.

To date, GC growth has been reported for more than ten organic liquids (23–26), including nifedipine (NIF), a poorly water soluble calcium channel blocker drug (24). For NIF, the rate of crystal growth shows an abrupt tenfold increase as the temperature is decreased from above to below T_g (315 K).

GC Growth Favors Certain Crystal Structures

Sun *et al.* studied GC growth using the polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile, named ROY for its numerous red, orange, and yellow polymorphs and the top system for the number of coexisting polymorphs of known structures in the Cambridge Structure Database (27,28). Because polymorphs share the same liquid and glass, which polymorph grows and which polymorph shows GC growth can reveal the dependence of the phenomenon on crystal structure. Of seven polymorphs of ROY whose crystal growth can be studied near T_g (T_g= 260 K), four polymorphs show GC mode, while the other three do not (25). The polymorphs that show the GC growth have more isotropic molecular packing and greater densities than those that do not. For a molecule in a polymorph showing GC growth, the closest neighbors are at approximately the same distance, as one expects for the packing in the liquid state, whereas a molecule in a polymorph not showing GC growth has the closest neighbors at very different distances. Similar isotropic packing characterizes other crystal structures showing GC growth, including OTP, toluene, and salol. This finding suggests that fast crystal growth may occur if sufficient similarity exists between molecular packing in the liquid and the crystalline state.

GC Growth has Precursor in the Equilibrium Liquid

Sun *et al.* reported that GC growth is not truly a growth mode suddenly emerging near T_g but already existing in the form of fast-growing fibers in the equilibrium liquid up to about 1.15 T_g (29). If the growth rates of these fibers are plotted against temperature, they fall smoothly in line with rates of the fully activated GC growth near and below T_g. It is also observed that the actively growing tips of the fibers are the preferred site for activation of the compact, spherulitic GC growth upon cooling below the onset temperature for GC growth. Figure 2 shows such an example. The spherulitic GC growth of YT04 (a polymorph of ROY) was interrupted by a 3-K temperature increase from 267 K to 270 K. During holding at 270 K, the compact GC growth appeared to cease, but close examination revealed fiber-like crystals extending into the liquid. After the temperature is returned to 267 K, new GC growth was initiated predominately on the tips of the actively growing, far-reaching fibers. Xi *et al.* reported a similar observation for GC growth in OTP (30).

Models for GC Growth

Three models have been proposed for GC growth: homogeneous nucleation-based (HNB) crystallization (22), tension-induced interfacial mobility (31,32), and solid-state crystal growth by local mobility (25). The HNB model assumes that GC growth occurs via the coalescence of homogeneous crystal nuclei onto an existing crystal surface at a rate defined by the β relaxation (33). The model of tension-induced interfacial mobility hypothesizes that molecular mobility is enhanced at the crystal–glass interface because of tension created by the crystal–glass density difference. This model suggests that the tension thus created "should provide the free volume to the particles surrounding the crystal, increase their mobility, and help further crystallization" (31). The model of solid-state crystal growth by local mobility views GC growth as a new mode of crystal growth distinct from diffusion-controlled growth. This model assumes that the molecular motion responsible for GC growth is not the α relaxation or bulk diffusion of the liquid (which is associated with the diffusion-controlled growth), but local molecular motions native to the glassy (solid) state. According to this model certain crystal structures can grow by local molecular fluctuations because their formation requires relatively minor rearrangements of the structure of the liquid. The model makes an analogy between crystal growth in the glass and crystal growth in other solids (*e.g.* from another polymorph) (25). Sun *et al.* evaluated the current models for GC growth against known features of GC growth and concluded that "while none of these three explanations satisfactorily accounts for all of the features, the model of solid-state crystal growth by local mobility comes the closest" (25).

FAST SURFACE CRYSTAL GROWTH

Wu and Yu observed that if crystal growth occurs at the free surface of an indomethacin (IMC) glass (T_g= 315 K), the linear velocity of growth is orders of magnitude faster than in the bulk (Fig. 3). (34) This phenomenon results in a thin surface layer of crystals around a slower-crystallizing interior. The fast surface crystal growth can be halted by an ultra-thin coating (*e.g.*, 10 nm of gold and 3–20 nm of polymer) (35), which suggests that surface molecular mobility is an enabler for the phenomenon. The finding also suggests a way to stabilize amorphous drugs against crystallization (see later). It was established by other studies that the linear velocity of crystal growth in the interior of an IMC liquid is approximately proportional to the diffusion coefficient as temperature approaches T_g (36,37), a relation expected for diffusion-controlled growth. Thus, fast surface crystal growth is another mechanism by which crystal growth rate exceeds that expected for diffusion-controlled growth.

The significant difference between surface and bulk crystallization rates leads to an unusual crystallization kinetics of amorphous IMC (34). The degree of crystallinity rises initially and then stabilizes at levels well below 100 % crystallinity. The initial rise is due to surface crystallization, and the subsequent leveling off to slower bulk crystallization. This phenomenon also causes a particle-size dependence of crystallization kinetics: the crystallinity "plateau" increases with decreasing particle size (increasing surface/volume ratio). Fast surface crystallization is consistent with the observation that mechanical damages of organic glasses accelerate their crystallization (9).

Nifedipine (NIF) and griseofulvin (GSF, an antifungal drug) also exhibit fast surface crystal growth in the glassy state (38,39). At the same temperature relative to T_g, the surface crystal growth rate u_s of NIF is ca. 10 times faster than that of IMC, and the u_s of GSF is ca. 100 times faster than that of IMC (39). Surface-enhanced crystal growth of organic glasses contrasts the comparable rates of crystal growth at the free surface and in the interior of metallic and silicate glasses (40–43).

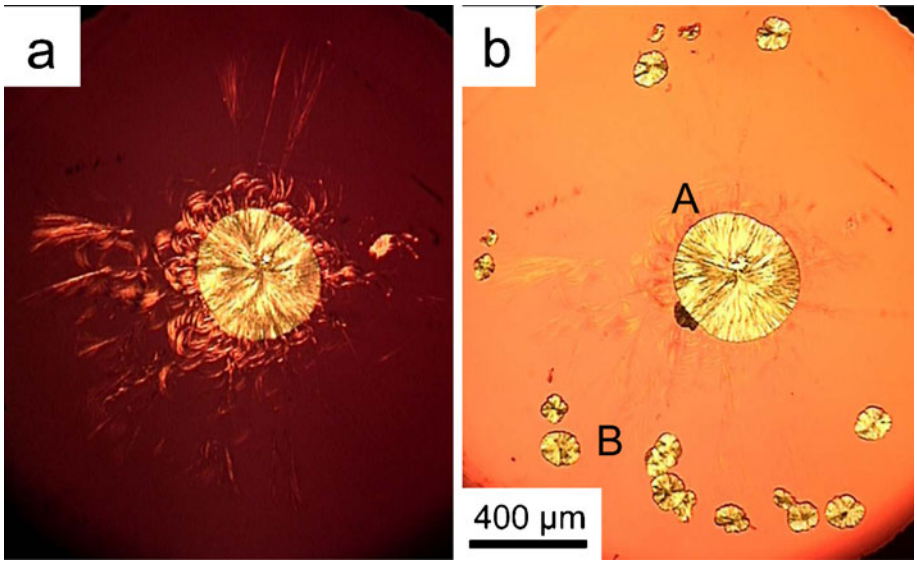

Fig. 2. **a** Fibers of YT04 (a ROY polymorph) emerging at 270 K in 250 min from a spherulite previously grown at 267 K. Crossed polarizers were used to reveal the fibers and resulted in dark background. **b** Same as **a**, but after returning to 267 K for 30 min, allowing GC growth to occur. One polarizer was used, resulting in bright background and low visibility of the fibers seen in **a**

Surface Crystals Grow Upward (Toward Free Space)

Sun *et al*. reported that surface crystals rise substantially above the glass surface while growing laterally, without penetrating deep into the bulk. (44) For the two polymorphs of IMC (α and γ) studied, the growth front can be hundreds of nanometers above the glass surface. Figure 4 shows typical images collected by light microscopy (LM) and atomic force microscopy (AFM) of α IMC grown at the surface of an IMC glass film at T_g–2 K. The AFM height image shows that surface crystals at the growth front rise significantly above the flat glass surface.

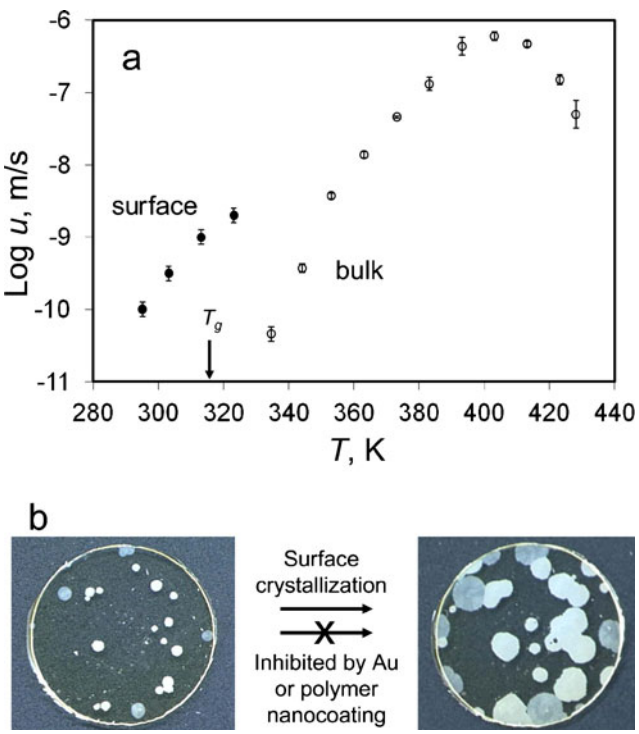

Fig. 3. **a** Crystal growth rates of γ IMC in the bulk and at the free surface. **b** Photographs of γ IMC growing at the free surface. The sample is on a circular cover glass. The fast surface crystal growth can be inhibited by a thin coating of gold (10 nm) or polymer (3–20 nm) (34,35)

Sun *et al*. also studied surface crystal growth in films with different thicknesses, from 50 nm to 15 μm, to assess how the phenomenon depends on the amount of bulk material underneath. Films thinner than 500 nm were prepared by spin-coating. For α IMC, the crystal growth rate near T_g changes little with film thickness until it decreases below ca. 300 nm; the surface growth of γ IMC shows no dependence on film thickness down to 180 nm, the thinnest film in which growth of γ IMC could be observed. These results argue that surface crystal growth on IMC glasses is not perturbed by reducing the glass thickness to a few hundred nanometers, and that the surface crystal layer is approximately a few hundred nanometers thick.

Models for Fast Surface Crystal Growth

Current views differ on how crystal growth rate should change on going from the interior of a glass to the free surface. Schmelzer and coworkers hypothesize that growing high-density crystals in low-density glass causes elastic strain and lowers the thermodynamic driving force (45), and that on going from the bulk to the surface, the elastic strain diminishes and crystallization becomes faster. Analyzing the same process of growing denser crystals in less dense glasses, however, Tanaka concludes that the stress around a crystal growing in a glass "should provide the free volume to the particles surrounding the crystal, increase their mobility, and help further crystallization." (31,32) Based on this model, crystal growth rate at the free surface would be slower than that in the bulk. In another view, the different packing of molecules at the surface is thought to be

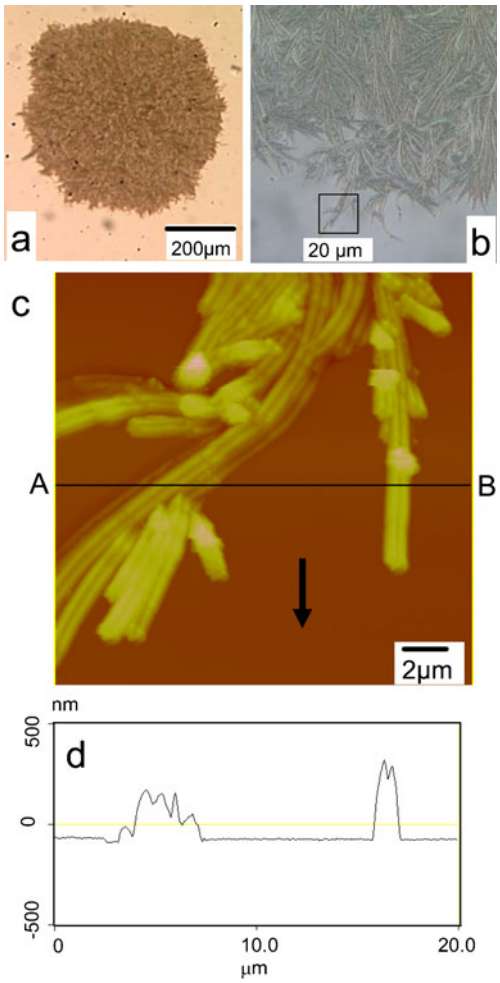

Fig. 4. Light microscopy (LM) **a** and **b** and atomic force microscopy (AFM) **c** images of α IMC crystals grown at the surface of a 15 μm thick glass at 40°C. The AFM scan in **c** covered the square in **b**. *Arrow* indicates advance direction of crystal growth front. **d** Height profile along line *AB* in **c**. The crystals can be hundreds of nanometers above the glass surface

responsible for the faster crystallization (46). This scenario seems unlikely considering the fact that the surface crystal layer can be hundreds of nanometers thick, much thicker than the mobile surface layer typically envisioned (a few nanometers). Another type of model emphasizes the greater molecular mobility at the surface (35,44), reasoning that if crystal growth rate is limited by molecular mobility, the enhanced mobility of surface molecules can accelerate crystal growth. This model is consistent with the upward-lateral growth of surface crystals. In this scenario, crystallizing molecules would be drawn to the crystal, climb up, and deposit at the growth sites. This model is also consistent with the inhibitory effect of surface crystal growth by nanocoating (35), which presumably reduces the high surface mobility to bulk level.

Gunn *et al.* tested the models of Schmelzer and coworkers and of Konishi and Tanaka using the polymorphs of carbamazepine (CBZ), an anticonvulsant drug (47). CBZ has four known polymorphs with different densities, three polymorphs of which were observed to grow at the surface and in the bulk of CBZ glasses. The model of Schmelzer and coworkers predicts that u_s/u_b (the ratio of surface and bulk crystal growth rates) increases with crystal density, whereas the model of Konishi and Tanaka predicts the opposite. Gunn *et al.* found that there is no consistent increase or decrease of u_s/u_b with crystal density (Fig. 5), indicating that crystal density has no controlling effect on the difference between surface and bulk crystal growth rates.

To test whether surface diffusion can support surface crystal growth, Zhu *et al.* determined the surface self-diffusion coefficient of IMC glasses (48). Surface diffusion has been well studied for metals and semiconductors (49), but no data existed on organic solids before Zhu *et al.*'s work. To determine the self-diffusion of IMC glass, the classic method of surface smoothing (50) was used. Driven by surface tension, an initially corrugated surface flattens over time by various mechanisms, among which surface diffusion dominates the kinetics at short length scales and low temperatures. The smoothing of surface gratings was followed at a constant temperature in dry nitrogen with an atomic force microscope, which measured the grating's amplitude, or an optical microscope, which measured the grating's diffraction intensity. It was found that surface diffusion on IMC glasses is at least one million times faster than bulk diffusion, indicating the existence of a highly mobile surface (Fig. 6). This finding is consistent with recent reports of surface mobility for polymer glasses (51–54), and a small-molecule glass-forming liquid (55). The finding that exceptionally stable organic glasses can be prepared by vapor deposition is also linked to enhanced surface mobility (56,57). At T_g-2 K, the surface crystal growth front of IMC advances 1 nm or one molecular layer per second; during this time, an average molecule in the bulk diffuses $(2D_vt)^{0.5}=$ 0.1 nm and a surface molecule could diffuse $(2D_st)^{0.5}=100$ nm. This analysis suggests that surface diffusion is fast enough to sustain observed surface crystal growth while bulk diffusion is not.

POLYMER INHIBITORS OF CRYSTALLIZATION OF AMORPHOUS SOLIDS

Macromolecules can be inhibitors of crystallization. Antifreeze proteins suppress ice formation in arctic fish to enable their survival in subzero waters (58), presumably by binding to small ice crystals to inhibit their growth (59,60). Polymer additives can prevent diesel fuels and crude oils from crystallizing in cold climates (61,62). Amorphous calcium carbonate, though crystallizing readily if chemically pure,

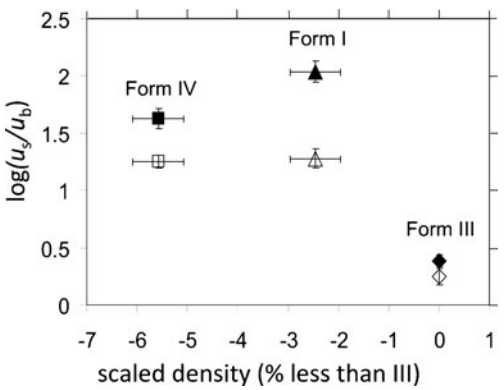

Fig. 5. u_s/u_b *vs.* crystal density for three CBZ polymorphs at 303 and 313 K (*open* and *closed symbols*, respectively)

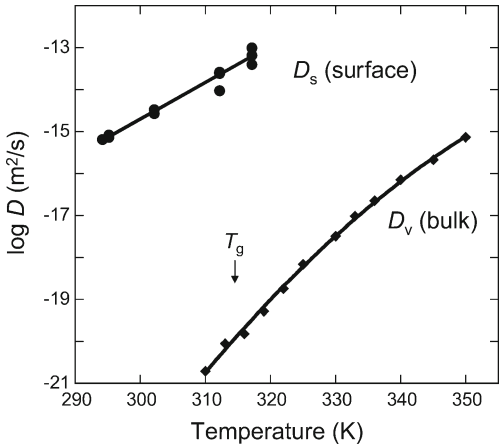

Fig. 6. Surface and bulk diffusion coefficients of IMC liquid and glasses

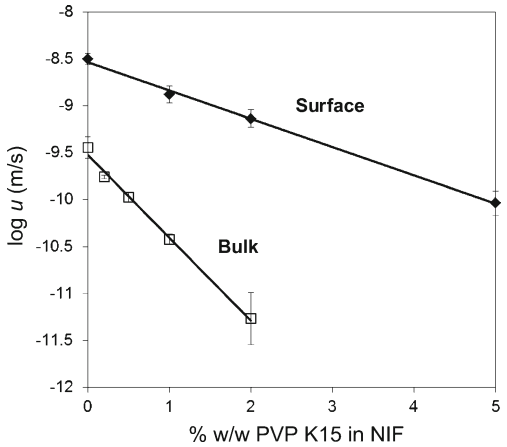

Fig. 7. Different dependences of bulk and surface crystal growth rates in an NIF glass on PVP-K15 concentration

exists in many organisms (63), and can be stabilized by dendrimers (64) and proteins (65,66). In pharmaceutical science, polymers are known to inhibit the crystallization of amorphous drugs (24,67–69). Aso *et al.* observed that the presence of 10 % PVP slows the rate of total crystallization of amorphous NIF by a factor of 300 (67).

Although amorphous pharmaceutical formulations may contain polymers as the major component, recent studies have examined the use of low-concentration polymers as crystallization inhibitors (24,68,69). Such studies are a necessary first step for understanding more complex formulations, and could discover effective polymer additives that significantly improve the properties of amorphous drugs. In these studies, the light doping of polymers (a few wt %) does not significantly change the thermodynamic driving force of crystallization and the dynamics of the glasses, allowing a close examination of other factors affecting crystallization.

Polymer Additives can Have Different Effects on Bulk and Surface Crystal Growth

Ishida *et al.* observed that doping an NIF glass with 1 wt % of Polyvinylpyrrolidone (PVP) K15 can slow crystal growth in the bulk by a factor of 10 at 313 K (T_g−12 K) (24). This inhibitory effect is remarkable and suggests that low-concentration polymer additives can substantially stabilize amorphous drugs against crystallization. Their finding was substantiated by Cai *et al.* (69), who showed that the logarithm of the bulk crystal growth rate decreases linearly with the concentration of PVP in weight percent (Fig. 7). At 2 wt % PVP K15, the bulk crystal growth rate is slowed from 0.2 mm/week to 0.1 mm/year. Kestur *et al.* observed a similar linear relation between log u and w/w % PVP for crystal growth in liquid felodipine containing PVP at temperatures substantially above T_g (68). They reported a weaker inhibitory effect of PVP on crystal growth in liquid felodipine than the effect observed by Cai *et al.* for crystal growth in PVP-doped NIF glasses (Fig. 7, the line labeled "bulk"). This difference probably reflects the greater power of a polymer dopant to inhibit crystal growth in a glass than in a low-viscosity liquid.

It is noteworthy that the strong inhibitory effect of PVP is lost if its molecular weight is reduced to that of a dimer. Whereas PVPs of different molecular weights have comparable performance as crystallization inhibitors, the VP dimer has virtually no inhibitory effect. This observation indicates the importance of high molecular weight for an effective crystallization inhibitor. Because the VP dimer and the PVPs have similar interactions with NIF molecules, the analysis of "direct" intermolecular interactions alone is insufficient for predicting their effectiveness as crystallization inhibitors.

Although PVP additives can strongly inhibit bulk crystal growth in NIF glasses, their effect on surface crystal growth is much weaker (69). Figure 7 shows that both log u_s and log u_b decrease linearly with increasing concentration of PVP K15 in weight percent, log u_b decreases approximately three times faster than log u_s. As a result of the stronger inhibition of bulk crystal growth, the thickness of the propagating surface crystal layer is substantially thinner in the presence of PVP additives (Fig. 8).

Cai *et al.* (69) considered several explanations for the weaker inhibition of surface crystal growth by polymer additives than bulk crystal growth: (1) lower polymer concentration at the surface than in the bulk; (2) upward growth of surface crystals making the process less sensitive to polymer impurities; and (3) surface molecular mobility making polymers less effective as crystal growth inhibitors. Further work is needed to determine which explanation accurately accounts for the effect observed. Regardless of the explanation, the effect observed argues that it might be profitable to complement bulk doping with surface stabilization in developing technologies to stabilize amorphous solids with polymer additives.

Polymer Nanocoating for Inhibiting Surface Crystal Growth

Wu *et al.* demonstrated that surface crystal growth on organic glasses can be inhibited with a coating only a few nm thick (34,35). Coatings of very different materials and thicknesses have been found effective; for example, 10 nm of gold and 3–20 nm of polymer deposited layer-by-layer through electrostatic assembly. Under a coating, the rate of surface crystal growth is decreased to that of bulk crystal growth. Even the growth of existing surface crystals is halted.

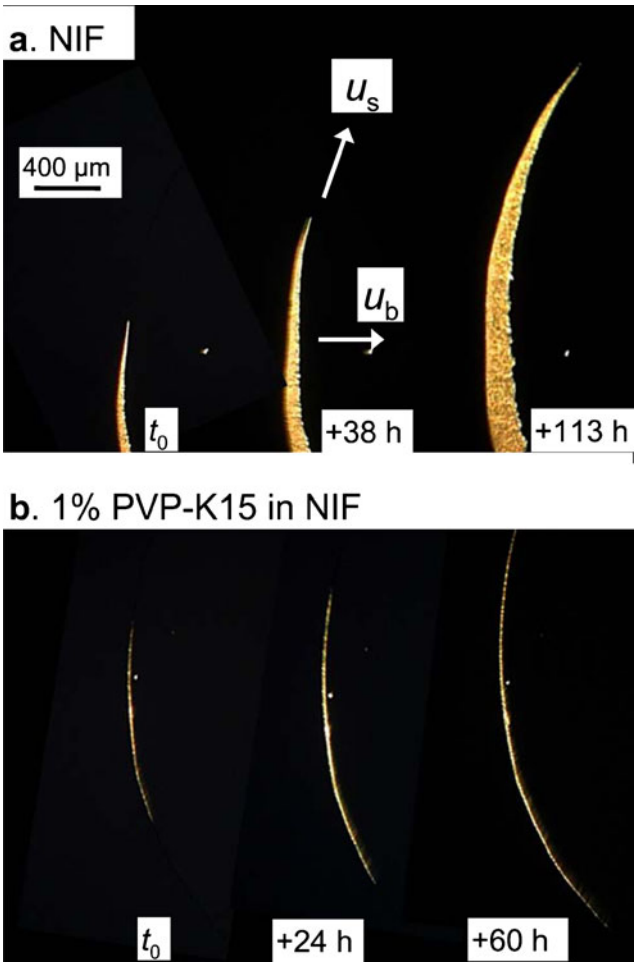

Fig. 8. Effect of PVP on crystal growth in an NIF glass at 313 K. **a** Pure NIF. **b** NIF containing 1% *w/w* PVP-K15. u_b: bulk growth rate; u_s: surface growth rate. t_0 is the time to start tracking crystal growth. **a** and **b** share the same *scale bar*

Although multiple layers of polyelectrolytes can be deposited, a single layer proves sufficiently effective for inhibiting crystallization on IMC glasses. The ultra-thin polymer coating still permitted fast dissolution of amorphous IMC, while improving its wetting and flow.

The finding of Wu *et al.* (35) supports the view that fast surface crystal growth of amorphous IMC is enabled by the mobility of a thin layer of surface molecules, and that this mobility can be suppressed by a coating of only a few nanometers thick. The effectiveness of ultra-thin polymer coatings for halting surface crystallization suggests a general way to stabilize amorphous drugs with the addition of only a small amount of polymers. The aqueous coating solutions used in electrostatic deposition of polymers are compatible with drugs of low aqueous solubility. Such hydrophobic amorphous drugs may dissolve and crystallize during a coating process that uses organic solvents.

CONCLUSIONS

We have reviewed some recent progress toward understanding the crystallization of amorphous organic solids. Fast modes of crystal growth can emerge as organic liquids are cooled to become glasses. One such growth mode, the glass-to-crystal or GC mode, occurs in the bulk, and another fast growth mode exists at the free surface, both leading to crystal growth rates orders of magnitude faster than predicted by theories that assume diffusion defines the kinetic barrier of crystallization. These findings indicate that such "molecular mobility" measures as diffusivity, viscosity, and structural relaxation time are poor indicators of crystallization rates in organic glasses, and new theories are needed to account for these phenomena. With the aid of polymorphs, recent studies have found that GC growth favors more isotropically packed and denser crystal structures and is kinetically similar to polymorphic conversion. Among the explanations proposed for GC growth, we favor the view that the process is solid-state transformation enabled by local mobility in glasses.

It is noteworthy that free surfaces of organic glasses can enhance not only crystal nucleation (a well anticipated effect) but also crystal growth. Surface crystals on organic glasses rise upward as they grow laterally, a growth mechanism that is unavailable to bulk crystals and that effectively utilizes higher surface molecular mobility. Studies with crystal polymorphs established that the degree to which crystal growth rate is enhanced on going from the bulk to the surface is not controlled by the crystal–glass density difference as predicted by the models of Schmelzer and coworkers and of Konishi and Tanaka. We attribute fast surface crystal growth to surface molecular mobility.

The emergence of fast modes of crystal growth near the glass transition temperature makes it invalid to predict the rates of crystallization in organic glasses by extrapolating the corresponding rates in the liquid state. The importance of free surfaces in accelerating the crystallization of amorphous drugs demonstrates that searches for molecular motions responsible for crystallization must not be limited to bulk motions, and must include surface mobility. There has been recent progress in measuring surface diffusion on organic glasses, and the results indicate that surface diffusion can be orders of magnitude faster than bulk diffusion and fast enough to support the surface crystal growth observed.

Recent work has found that low-concentration polymer additives can be remarkably effective in slowing bulk crystal growth in organic glasses, but their effect on surface crystal growth is much weaker. It was also discovered recently that ultra-thin polymer coatings can inhibit surface crystallization, as well as improving the flow and wetting of a hydrophobic drug. These results suggest the possibility of using low-concentration polymer additives to stabilize amorphous drugs; for example, a bulk additive to inhibit bulk crystallization and an ultra-thin surface coating to halt surface crystallization.

In searches for effective polymers as crystallization inhibitors, attention has been paid to "direct" intermolecular interactions such as hydrogen bonding between drugs and polymers. Recent work, however, has highlighted the importance of the molecular weight of the inhibitor. Relative to polyvinylpyrrolidone, the VP dimer has little effect on crystal growth in nifedipine glasses. Because the dimer and the polymer have similar "direct" interactions with the drug, this finding argues that molecular weight is an important factor for an effective crystallization inhibitor.

Important questions remain concerning the stability of amorphous drugs against crystallization. The mechanistic details are still lacking for fast crystal growth in the bulk and at the surface of organic glasses, and for the emergence of fast modes of crystal growth as organic liquids are cooled to become glasses. It is unclear what factors define the degree to which crystal growth rate is enhanced on going from the interior to the surface of an organic glass, and why fast surface crystal growth seems more prevalent for organic glasses. The molecular motions responsible for crystallization in glasses remain to be better understood. It is unknown how different factors combine to define effective crystallization inhibitors for amorphous drugs: strength of "direct" intermolecular interactions, molecular weight, miscibility, and perhaps others. We still do not know whether the mechanism of crystal growth changes with increasing concentrations of polymer additives. With better understanding of crystallization in organic glasses, more accurate models may be formulated and more informative experiments be conducted to design amorphous pharmaceutical formulations with good physicochemical stability.

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