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RESEARCH PAPER

Crystallization of Organic Glasses: Effects of Polymer Additives on Bulk and Surface Crystal Growth in Amorphous Nifedipine

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ABSTRACT

Purpose To study the influence of polymer additives on bulk and surface crystal growth in organic glasses (amorphous solids), which are being investigated for delivering poorly soluble drugs and in this role must resist crystallization. Recent studies have discovered new modes of crystal growth that emerge as organic liquids are cooled to form glasses: one existing in the bulk (GC growth) and another at the surface, both leading to crystal growth much faster than predicted by standard theories.

Methods Bulk and surface crystal growth rates were measured in nifedipine glasses doped with polyvinylpyrrolidone (PVP) of different molecular weights. AFM enabled observation of the microstructure of surface-growing crystals.

Results Polymer additives influence bulk and surface crystal growth differently. For every weight percent of PVP added, surface crystal growth of nifedipine slows by two times at 12°C below T_g, whereas bulk crystal growth slows by 10 times. In contrast to the polymers, the VP dimer had little effect on crystal growth.

Conclusions Polymer additives inhibit crystal growth in nifedipine glasses more strongly in the bulk than at the surface. The effectiveness of crystallization inhibitors depends not only on intermolecular interactions but also on molecular sizes.

KEY WORDS amorphous solid · bulk · crystal growth · glass · polymer dispersion · surface

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INTRODUCTION

Glasses are amorphous solids formed by cooling liquids, drying solutions, or condensing vapors without crystallization. For many applications, amorphous solids are advantageous over crystals (1). While better known amorphous materials are inorganic (e.g., window glass), there is a growing interest in developing organic or molecular glasses as vehicles for delivering poorly soluble drugs (2), as photo- and electro-active materials (3,4) and as matrices for preserving proteins and cells (5). For an amorphous material, stability against crystallization is essential because crystallization negates its advantages.

Recent studies have discovered different modes of crystal growth that emerge as organic liquids are cooled to become glasses. One such growth mode (the glass-to-crystal or GC mode) exists *in the bulk* and can cause an increase of crystal growth rate by orders of magnitude with a temperature drop by a few K (6–10). Another growth mode occurs *at the surface* and can lead to crystal growth substantially faster at the surface than in the interior (11–14); this surface growth mode can be halted by a coating only a few nm thick (12). Owing to these growth modes, crystal growth in some organic glasses is much faster than predicted by standard models that assume diffusion defines the kinetic barrier for crystal growth (15,16). At present, these crystal growth phenomena remain imperfectly understood. Explanations proposed for GC growth include change of crystal growth mechanism from molecule-by-molecule to cluster-by-cluster (7), tension-enhanced molecular mobility at crystal/glass interfaces (17), and solid-state transformation through local mobility (8). Explanations for fast surface crystal growth in glasses include release of crystallization-induced tension at surfaces (18,19) and surface molecular mobility (11–14).

Macromolecules can be inhibitors of crystallization. Antifreeze proteins suppress ice formation in arctic fish to enable their survival in subzero waters (20), presumably by binding to small ice crystals to inhibit their growth (21,22). Polymer additives can prevent diesel fuels and crude oils from crystallizing in cold climates (23,24). Amorphous calcium carbonate, though crystallizing readily if chemically pure, exists in many organisms (25) and can be stabilized by dendrimers (26) and proteins (27,28). In pharmaceutical science, polymers are known to inhibit the crystallization of amorphous drugs (10,29).

Despite many examples of macromolecules as crystallization inhibitors, it remains poorly understood what attributes are important for an effective crystallization inhibitor. Do intermolecular interactions such as hydrogen bonding play a controlling role? (30,31) Is the inhibitor's molecular weight significant? Since organic glasses can grow crystals at different rates at the surface and in the bulk, does a polymer have the same effect on the two modes of crystal growth? In this work, we studied how polyvinylpyrrolidone (PVP), a common pharmaceutical polymer, affects crystal growth in the organic glass nifedipine (NIF). NIF is a model amorphous drug (32–35) and well suited for this study because fast crystal growth has been observed both in the bulk (10) and at the surface (13). By using PVPs of different molecular weights, including the dimer, we hoped to learn the relative importance of intermolecular interactions and the sizes of inhibitor molecules in retarding crystallization.

We report here that despite its strong inhibition of crystal growth in the bulk of an NIF glass, PVP has a much weaker effect on crystal growth at the surface. For every weight percent of PVP added, surface crystal growth slows by 2 times at 12°C below the glass transition temperature, whereas bulk crystal growth slows by 10 times. We find that PVP's power to inhibit crystal growth greatly diminishes upon lowering its molecular weight to that of a dimer, indicating that the effectiveness of crystal growth inhibitors depends on their molecular sizes. These findings are relevant for understanding the mechanisms of surface and bulk crystal growth in organic glasses and the effectiveness of crystallization inhibitors.

MATERIALS AND METHODS

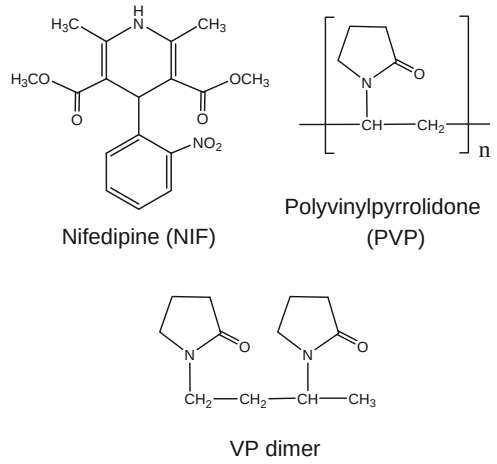
Nifedipine (1,4-dihydro-2,6-dimetyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylate; NIF) was obtained from Sigma (St. Louis, MO) and used as received. PVP-K15 ($M_w \approx 8$ kg/mole) was obtained from ISP Technologies, Inc. (Texas City, TX); PVP-K12 (Kollidon 12PF, $M_w = 2$–3 kg/mole) and PVP-K30 (Kollidon 30, $M_w = 44$–54 kg/mole) from BASF; and PVP-K90 ($M_w = 1{,}000$–2,000 kg/mole) from GAF Chemicals. The VP dimer (1,3-bis(2-pyrrolidione-1-yl)-butane, $M = 224$ g/mole) was obtained from Abbott Laboratories. See Scheme 1 for the structures of NIF, PVP, and VP dimer.

Mixtures of NIF and PVP were prepared by cryogenic milling (SPEX CertiPrep model 6750), a procedure found to be effective for making uniform drug-polymer mixtures (36). In a typical procedure, 2 g of NIF and PVP mixture in an airtight tube was cryomilled at 10 Hz for 5 cycles. Each cycle of milling was 2 min, followed by a 2-min cool-down. Liquid nitrogen was used as coolant. A two-step dilution was used to achieve uniform mixing for NIF containing low-concentration PVP. In this procedure, NIF and PVP were first mixed at the ratio of 9:1 or 8:2, and the resulting mixture was mixed with NIF at the ratio of 1:9 to yield the mixtures containing 1 and 2% w/w PVP in NIF. The mixture of 5% w/w PVP in NIF was prepared by diluting a mixture containing 20% w/w PVP in NIF.

A sample for studying crystal growth was prepared by melting 2.5–3.0 mg of NIF (pure or doped) at 183°C for 3 min on a clean microscope cover slip. The liquid was covered with another cover slip to yield a film 12–15 μm thick and was cooled to room temperature by contact with an aluminum block. Samples prepared in this way were confirmed to contain no crystals by observation through a light microscope between crossed polarizers. Crystal growth was studied at 30±1°C (ca. 12°C below T_g). During growth, samples were protected from moisture by storage in desiccators loaded with Drierite®; during observation, they were exposed for less than 10 min to the ambient atmosphere. No significant difference in growth rate was noticed with slightly different exposure times and with more or less frequent observations.

Bulk crystal growth was measured with a sample sandwiched between two 15-mm diameter round cover slips (Fig. 1a). Crystals formed spontaneously or around previously formed crystal seeds. In the latter procedure, a sample was partially crystallized at 60°C and cooled to 30°C. There was no difference between growth rates observed at 30°C of crystals spontaneously nucleated at 30°C and previously grown at 60°C. The procedure of forming crystals first at 60°C saved time and ensured observation of crystal growth in a freshly made glass. In NIF glasses doped with PVP, spontaneous bulk nucleation was substantially slower, and crystal growth was always studied by following the growth of seed crystals formed at 60°C in 6–12 h.

To observe crystal growth at a free surface, an NIF sample was melted between a clean 22-mm square cover slip and a 15-mm diameter round cover slip. After quenching to room temperature, the square cover slip was removed by gently bending it toward the sample to expose a free surface (Fig. 1b). The sample was allowed to crystallize partially at 40°C and transferred to 30°C to



Scheme 1 Structures of nifedipine, PVP and VP dimer.

observe further crystal growth. This procedure was used because the surface crystal growth rate decreased with glass age, and we would like to measure the growth rate in a freshly made glass. A special side-view experiment was performed to simultaneously track surface and bulk crystal growth (Fig. 1c). Here the same sandwiched sample as used for bulk growth measurements was prepared, but the site of observation was the sample's perimeter, where a free surface is exposed. In this way, we could follow both surface crystal growth along the edge and bulk growth into the interior.

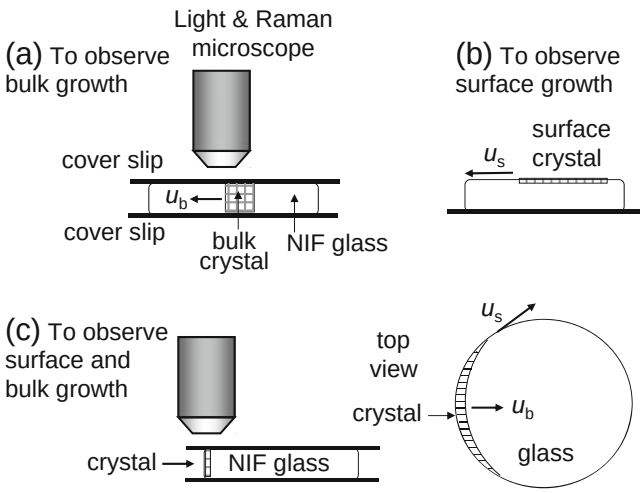


Fig. 1 Various experiments for observing crystal growth in an NIF glass. (**a**) A sandwiched sample for observing bulk crystal growth. An NIF liquid is spread between two cover slips and vitrified by cooling to below T_g. Crystals form spontaneously or grow from pre-formed seeds at $T > T_g$. (**b**) An open-surface sample for observing surface crystal growth. It is prepared in the same way as described in (**a**), but the top cover slip is subsequently removed. (**c**) A perimeter-surface sample for observing surface and bulk crystal growth simultaneously. It is prepared in the same way as described in (**a**), but the site of observation is the exposed side surface.

Polarized light microscopy was performed with a Nikon Optiphot Pol 2 microscope equipped with an Olympus video camera. The growth rate of NIF was measured by tracking the radius of NIF spherulite. Each reported growth rate was the average of several measurements with two or three independently prepared samples. Morphologies of NIF surface crystals were examined with an Atomic Force Microscope (AFM) (Veeco Multimode IV Scanning Probe Microscope). The AFM was operated in the tapping mode at 1 s per line; a typical scan covered a $10 \times 10\ \mu m^2$ area. Differential Scanning Calorimetry (DSC) was conducted in crimped aluminum pans using a TA Instruments DSC Q2000 under 50 ml/min N_2 purge.

Polymorphs were identified using Raman microscopy (Thermo Scientific DXR Raman microscope with a 10 mW 532 nm laser) and x-ray diffraction (Bruker D8 Advance powder diffractometer). Raman microscopy could be conducted directly for samples prepared for our crystallization studies, either with or without the top cover slips. X-ray diffraction was performed in the Bragg-Brentano geometry from 2 to 40° (2-theta) at 0.02°/step. Surface-crystallized samples were analyzed as grown; bulk-crystallized samples were analyzed after removing the top cover slips.

RESULTS

State of Mixing of NIF and PVP

To understand the effect of a polymer additive on crystal growth, it is necessary to determine the state of mixing of the components. We prepared a PVP-doped NIF glass by cryo-milling the components, heating the mixture above the NIF melting point, and cooling the mixture to temperatures of crystallization studies (typically 30°C). A previous study has established that NIF and PVP are miscible at 110–170°C (36); the corresponding Flory-Huggins interaction parameter χ is negative, indicating NIF is a "good solvent" for PVP. Assuming χ does not depend strongly on temperature, thermodynamic miscibility is expected between NIF and PVP at the temperatures of our crystallization studies.

The state of mixing of NIF and PVP was also assessed from the glass transitions of their mixtures. Figure 2 shows that an NIF-PVP glass prepared in this study had a single glass transition when analyzed by DSC, and the glass transition temperature T_g increased slightly with PVP concentration (by ca. 2°C at 5% PVP K15) above the pure NIF T_g (42°C). A previous study found that this increase of T_g with PVP concentration continues over the entire range of concentrations (36). These observations would be unexpected if PVP were phase separated from NIF. It is possible in theory that an NIF-PVP glass solution was

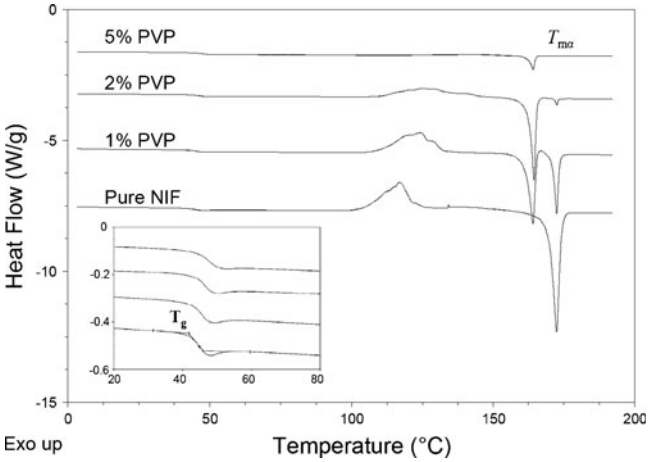


Fig. 2 DSC traces of NIF and NIF doped with PVP-K15 (scan rate 10°C/min). Inset: enlarged view of the glass transition region in the same order as in the full figure. The T_g increases slightly with polymer concentration, by 2°C at 5%. For pure NIF, the exotherm at 100–130°C is attributed to crystallization of an unstable polymorph and conversion to the α polymorph (T_m = 171°C) (37,38). The presence of PVP retards liquid crystallization and allows the observation of the fusion of a lower-melting polymorph at 163°C.

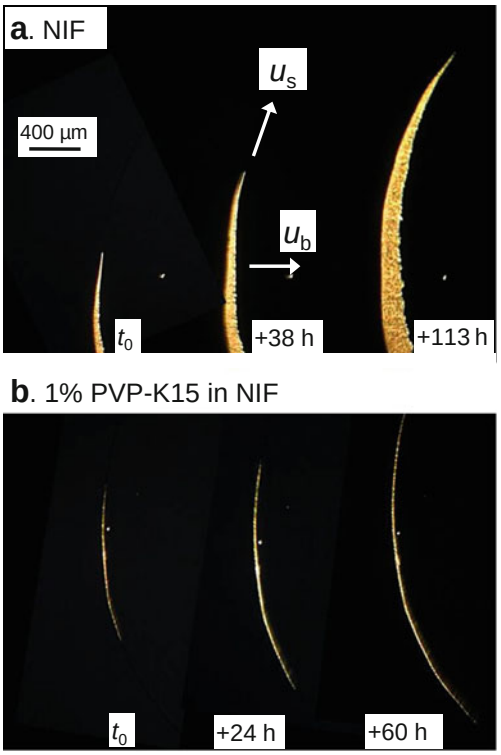


Fig. 3 Effect of PVP on crystal growth in an NIF glass at 30°C. (**a**) Pure NIF. (**b**) NIF containing 1% w/w PVP-K15. u_b: bulk growth rate; u_s: surface growth rate. t_0 is the time to start tracking crystal growth. (**a**) and (**b**) share the same scale bar.

trapped in a single phase but could separate to two phases over time. This possibility was tested by annealing an NIF-PVP-K90 glass solution containing 10% PVP-K90 at 50°C for 1 h. (PVP-K90 was chosen because it was the highest molecular weight PVP used and would have the greatest tendency to separate from NIF if such a tendency existed; 50°C was chosen because it is slightly above T_g and changes due to glass relaxation could be avoided.) We observed no change in the glass transition of this sample after annealing.

Finally, we note that the presence of PVP elevated the crystallization temperature of NIF (see the exotherms in Fig. 2). This result would again be unexpected if the two components were phase separated. Taken together, these results are consistent with the notion that our preparation yielded single-phase glass solutions of NIF and PVP.

Effects of PVP on Bulk and Surface Crystal Growth in NIF Glass

All crystal growth experiments were performed at 30°C. Because of the low polymer concentrations (<5%), our NIF samples, pure or polymer-doped, had comparable glass transition temperatures (5% PVP K15 raised the NIF T_g by 2°C). Our crystallization temperature was 12–14°C below T_g. Figure 3 shows the results of a "perimeter-surface experiment" (Fig. 1c), which followed the progress of NIF crystals growing simultaneously along the glass perimeter, where a free surface is exposed, and into the interior that is sandwiched between cover slips. It is evident that crystal growth in a pure NIF glass was substantially faster along the exposed surface than into the interior, yielding a layer of surface crystals that traced the glass perimeter. The thickness of the surface crystal layer is determined by the ratio of bulk and surface growth rates, u_s/u_b. The observed aspect ratio of the surface crystal layer implies $u_s > u_b$, which agrees with the previously measured crystal growth rates in the bulk (10) and at the surface (13) of NIF glasses. Figure 3b shows that doping an NIF glass with 1% PVP-K15 strongly inhibited crystal growth in the bulk, but had a much weaker effect on crystal growth at the surface. As a result, the spreading layer of surface crystals was significantly thinner. Since NIF is polymorphic (37–41), we note that in this study, only one polymorph was observed to crystallize at 30°C. This polymorph has a distinct Raman spectrum and X-ray diffraction pattern, both of which are given in Ref. (10). There this polymorph is designated β on the basis of its Raman spectrum and the naming of Chan et al. (41).

Figure 4 shows the effect of doping NIF with PVP K15 on *bulk* crystal growth at 30°C. Using a setup illustrated in Fig. 1a, we observed the growth of NIF crystals as compact circular patches (spherulites) whose radii increased over time (Fig. 4a). Figure 4b shows the advance distance of a

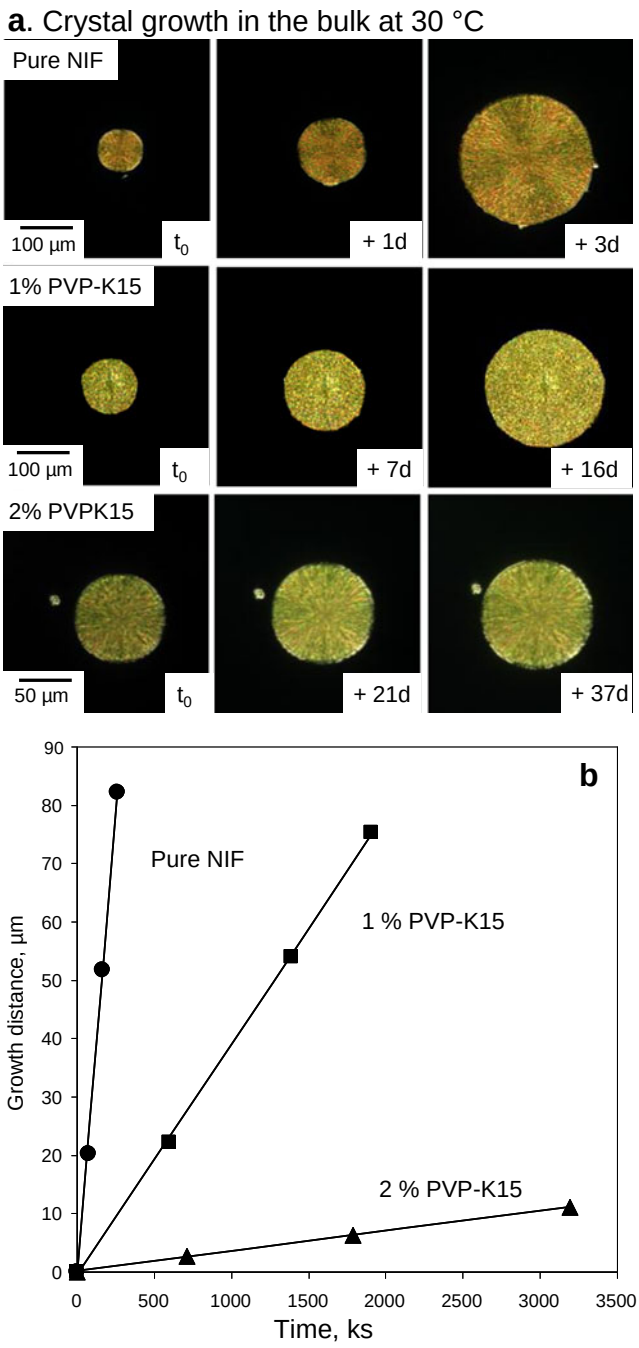


Fig. 4 Effect of PVP-K15 on bulk crystal growth in an NIF glass at 30°C. **a** Photomicrographs of crystal growth. t_0 is the time to start tracking crystal growth, chosen arbitrarily because crystal growth rate was independent of time. **b** Typical data of growth distance *vs.* time. The data are shifted vertically to coincide at the origin for better comparison.

crystal growth front *vs.* time for the samples in Fig. 4a, from which the rate of crystal growth was calculated. It is evident that the crystal growth rate decreased substantially with increasing polymer concentration. No significant growth was observed for NIF containing 5% w/w PVP K15 in 6 months at 30°C.

Figure 5 shows the corresponding results for *surface* crystal growth in pure and polymer-doped NIF glasses at 30°C. Similar to bulk crystals (Fig. 4a), surface crystals

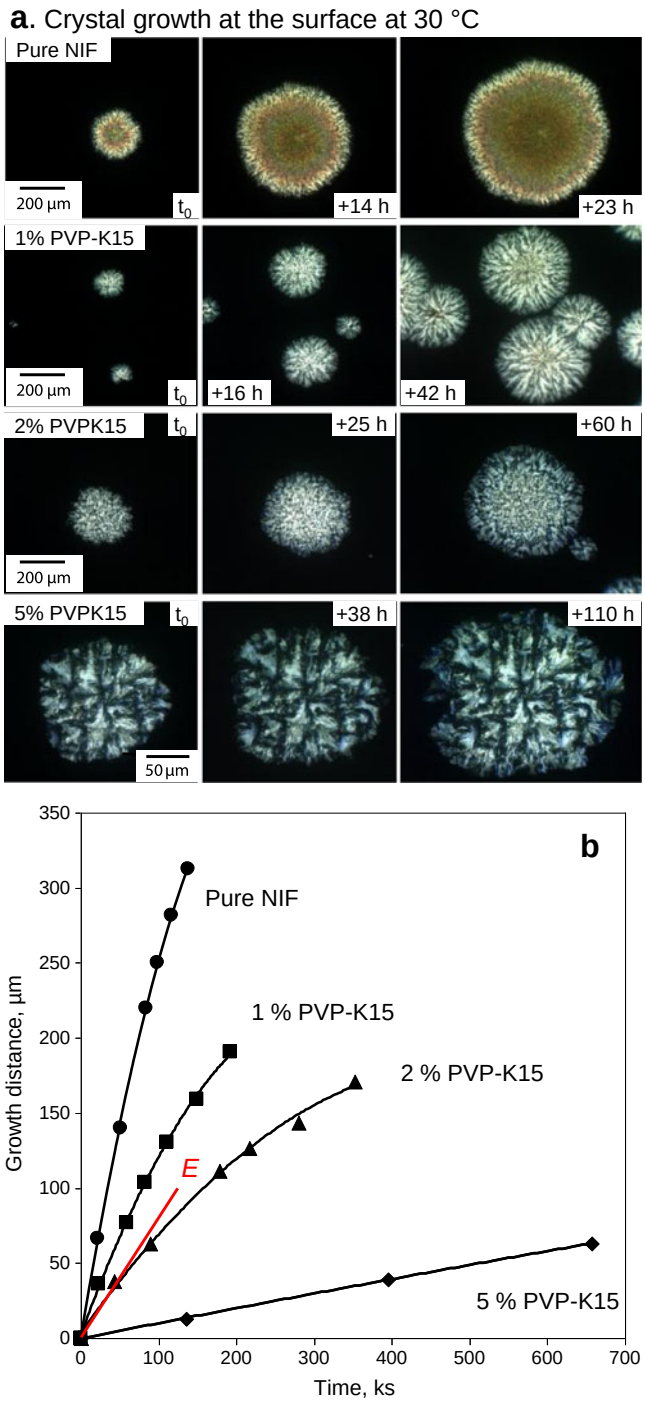


Fig. 5 Surface crystal growth in pure and PVP-doped NIF glasses at 30°C. (**a**) Photomicrographs of crystal growth. t_0 is an arbitrarily chosen time to start tracking crystal growth. (**b**) Typical data of growth distance *vs.* time. The zero time (not to be confused with t_0 in (**a**)) is the time at which a sample was cooled from 40 to 30°C to begin the observation of surface crystal growth at 30°C; at this time the glass age is zero. Line E illustrates the calculation of the early-stage growth rate reported.

formed circular polycrystalline patches ("cylindrites") (Fig. 5a). Surface crystals, however, appeared more transparent, especially at the growth front; between crossed polarizers, they appeared less colorful. Surface crystals, moreover, could change appearance over time, a feature especially noticeable for crystals grown in pure NIF glasses. As shown in Fig. 5a (first row), the center of a crystal patch became more opaque over time, while the edge (site of new growth) transformed from a light-colored "corona" to a denser, more opaque texture. At higher PVP concentration, the textural change of the surface crystal layer over time was less noticeable.

The changing appearance of surface crystals (Fig. 5) is in contrast with the "fixed" appearance of bulk crystals (Fig. 4). We interpret this difference as follows: the growing crystalline domain in the bulk is in contact with the top and the bottom cover slips, whereas the crystal layer propagating at the surface is so thin that its growth front is not in contact with the bottom cover slip; over time, the surface crystal layer thickens because of growth into the bulk. In the presence of PVP, the bulk growth is suppressed, slowing down the changes observable of the surface crystal layer.

Figure 5b shows the advance distance of a surface crystal growth front *vs*. time for the four samples in Fig. 5a. It is evident that crystal growth slowed over time. With the slowdown of surface crystal growth in the pure NIF glass, the width of the light-colored "corona" became smaller. These features are in contrast to the constant advance rate (Fig. 4b) and consistent appearance of the growth front (Fig. 4a) for crystal growth in the bulk. A similar slowdown has been reported for the surface crystallization in the organic glass indomethacin (11). The origin of this phenomenon is still not understood. In reporting the surface crystal growth rates, we used the growth rate at the early stage (illustrated by Line E for one of the samples in Fig. 5b).

Figure 6a shows the NIF surface and bulk crystal growth rates, u_s and u_b, *vs*. the PVP-K15 concentration at 30°C (T_g – 12°C). While both decreased with increasing polymer concentration, u_b decreased much faster than u_s. For every weight percent of PVP added, u_s decreased by a factor of 2, whereas u_b decreased by a factor of 10. Figure 6b compares the effects of PVPs of different molecular weights on the bulk and surface growth in an NIF glass. From PVP-K12 (2 kg/mole) to PVP-K90 (1,000–2,000 kg/mole), the molecular weight changes by ca. 1,000 times. Figure 6b shows that at a fixed concentration of 1% w/w, the various grades of PVP had similar effects on the bulk or surface crystal growth in an NIF glass. It is noteworthy, however, that the VP dimer, a small molecule, had little effect on either mode of crystal growth, indicating the importance of high molecular weight for an effective crystallization inhibitor.

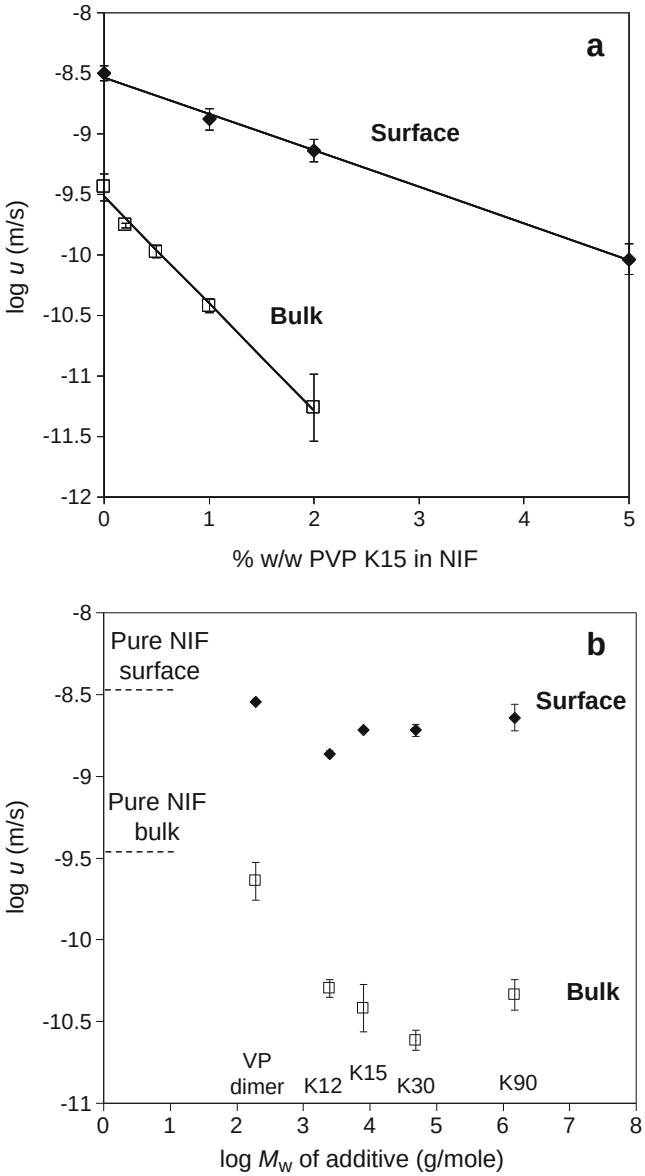


Fig. 6 (**a**) Different dependences of bulk and surface crystal growth rates in an NIF glass on PVP-K15 concentration. (**b**) Effect of PVP molecular weight on the power to inhibit bulk and surface crystal growth in an NIF glass. PVP concentration = 1% w/w. For pure NIF, log *u* (m/s) = −9.4 (bulk) and −8.5 (surface). All growth rates at 30°C (T_g – 12°C).

Real-Time AFM Observation of Surface Crystal Growth

To aid the interpretation of the polymer effect on the crystal growth in NIF glasses, AFM was used to observe the microstructure of growing surface crystals at higher resolution. Figure 7 shows a series of images recorded while crystals grew at the surface of a 15 μm thick NIF glass at 22°C. These images reveal that the growth front of NIF surface crystals consisted of fibers, which lengthened and branched as the growth front advanced. It is noteworthy

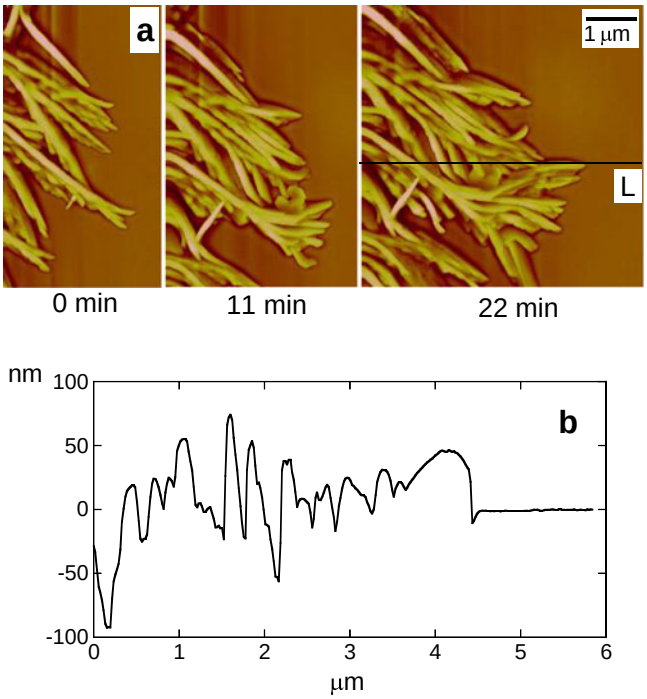


Fig. 7 (**a**) Real-time AFM images of crystals growing at the surface of a 15 μm thick NIF glass film at 22°C. (**b**) Height profile along line L.

that at the growth front, surface crystals were higher than the glass surface by tens of nanometers. A similar feature has been observed for the surface crystal growth of indomethacin glasses (42). The fiber growth rate measured from the AFM images is log u (m/s) = − 8.81, which agrees with that measured from light microscope images (13).

DISCUSSION

This study has found that a polymer additive can have significantly different effects on the crystal growth in the bulk and at the surface of an organic glass. Doping the organic glass nifedipine with PVP inhibited bulk crystal growth much more strongly than surface crystal growth. Because of this phenomenon, the ratio of surface and bulk crystal growth rates, u_s/u_b, at T_g − 12°C increases from 10 for the pure NIF glass to more than 100 for the NIF glass doped with 2% w/w PVP-K15. The PVPs of various molecular weights had similar influence on crystal growth in NIF glasses, but the small-molecule VP dimer had a much weaker effect under the same conditions.

Why Does a Polymer Additive Inhibit Surface Crystal Growth Less Strongly Than Bulk Crystal Growth?

We consider below a few possible explanations. At present, none of them is sufficiently developed or tested to explain the phenomenon.

Lower Polymer Concentration at the Surface Than in the Bulk

The relation between the surface crystal growth rate and PVP concentration (Fig. 6a) would be expected if the PVP concentration at the surface were lower than its bulk concentration and if an increase in the PVP concentration at the surface would slow crystal growth by the same factor as in the bulk. A lower polymer concentration at the surface could be a result of minimizing surface energy or could be simple geometric effects. Viewing NIF and PVP molecules as spheres of smaller and larger radii, one concludes that the top surface monolayer of NIF molecules would contain fewer centers of mass of polymer molecules than the bulk concentration implies. The lower polymer concentration at the surface (in the sense just defined) could in turn lead to weaker inhibition of surface crystal growth. It seems unlikely, however, that this geometric effect can explain our observations. If the effect existed, smaller PVP molecules should inhibit surface crystal growth more strongly. But we observed that the surface crystal growth rate depends weakly on PVP's molecular weight (2–2,000 kg/mole) (Fig. 6b).

We note a different geometric effect related to the lower dimensionality of the surface. Let there be one polymer molecule for every N NIF molecules in the bulk. If there is w% of the polymer by weight in NIF, $N = [(100 - w)/w](M_2/M_1)$, where M_1 and M_2 are the molecular weights of NIF and PVP, respectively. The average volume that contains one polymer molecule is $NV_1 + V_2$, where V_1 and V_2 are the molecular volumes of NIF and PVP, respectively. For a dilute PVP solution, $NV_1 >> V_2$ and the average center-of-mass distance between two adjacent polymer molecules is $(NV_1)^{1/3}$. For Poisson-distributed polymer molecules, this distance is also the average distance d_b between an NIF molecule and its nearest polymer neighbor. We now conduct the same analysis for molecules *at the surface*. Assuming that the polymer has the same number concentration at the surface (one in N NIF molecules), the average area that contains one polymer molecule is $NA_1 + A_2$, where A_1 and A_2 are the areas occupied by an NIF molecule and a PVP molecule on a glass surface, respectively. For a dilute PVP solution, $NA_1 >> A_2$ and the average distance between two adjacent polymer molecules is $(NA_1)^{1/2}$. For Poisson-distributed polymer molecules, this distance is also the average distance d_s between an NIF molecule and its nearest polymer neighbor on the surface. It follows that $d_s/d_b \approx N^{1/6}\ (V_1^{1/3}/A_1^{1/2})$. Noting that $V_1^{1/3}$ and $A_1^{1/2}$ are both approximately the "size" of an NIF molecule, we have $(V_1^{1/3}/A_1^{1/2}) \approx 1$ and $d_s/d_b \approx N^{1/6} > 1$. For 1% w/w PVP in NIF, N= 600–600,000 for the PVP grades used and d_s/d_b = 3–9. A larger distance between NIF and PVP at the surface could lead to weaker inhibition of NIF crystallization.

Upward Growth of Surface Crystals Making the Process Less Sensitive to Polymer Impurities

Our AFM data (Fig. 7) show that NIF surface crystals rise substantially above the glass surface as they grow laterally. This upward growth of surface crystals (toward free space) has been observed for another organic glass, indomethacin (14). This growth mechanism is unavailable to bulk crystals. The upward growth of surface crystals is consistent with the view that fast crystal growth at surfaces is enabled by surface molecular mobility. In this mechanism, the crystallizing molecules originate from the glass surface, are drawn to the crystals by their lower chemical potential, and deposit at growth sites. It is conceivable that the upward growth of surface crystals can better evade polymer molecules and be less affected by them than bulk crystal growth.

Surface Molecular Mobility Making Polymers Less Effective as Crystal Growth Inhibitors

It has been observed that PVP's power to inhibit the bulk crystal growth in liquid NIF is relatively weak at temperatures well above T_g, but much stronger near T_g: at 90°C (T_g+48°C), the bulk crystal growth rate is not strongly affected by 1% w/w PVP-K15, but reduced 100 times at 51°C (T_g+9°C) (10). A similar effect has been observed with liquid felodipine, for which 4.5% PVP-K29/32 reduces the crystal growth rate by a factor of 6 at 110°C but by a factor of 35 at 70°C (29). These observations argue that the inhibitory effect of a polymer additive on crystal growth depends on the mobility of molecules in the system: the effect may be relatively small if the molecules are highly mobile. For glasses, molecular mobility is low in the bulk, but may be much higher at the surface (42–44). Thus, crystal growth at a glass surface could be analogous to crystal growth in a low-viscosity liquid and be less perturbed by polymer impurities.

It is still unclear which explanation accurately accounts for the different effects of polymer additives on surface and bulk crystal growth of organic glasses. Further progress could benefit from measuring surface concentrations of polymer additives and learning the mechanism of crystal growth and the mobility of molecules at the surface. To test the possibility of surface depletion of polymer molecules, different polymers could be introduced that differ in the strength of interaction with the host molecules and in mobility.

Why Does the VP Dimer Inhibit Crystal Growth Less Strongly Than PVP?

In studies of crystallization inhibitors, attention has been paid to specific interactions between inhibitor molecules and host molecules (e.g., hydrogen bonding) (30,31). There has been less attention to the molecular weight of the inhibitor. This study has found that at the same weight fraction, the VP dimer has much weaker effect on crystal growth in NIF glasses than the PVPs (Fig. 6b). There is a smaller difference between the PVPs of various molecular weights (2–2,000 kg/mole) in their effects on NIF crystal growth. Because the VP dimer and the PVPs have similar interactions with NIF molecules, this finding demonstrates that analysis of intermolecular interactions alone is insufficient for predicting the effectiveness of crystallization inhibitors. The molecular weight and mobility of inhibitor molecules may also play an important role.

CONCLUSIONS

Doping the organic glass nifedipine with the polymer PVP can strongly inhibit crystal growth in the interior but has much weaker effect on crystal growth at the free surface. PVP's power to inhibit bulk crystal growth greatly diminishes upon lowering its molecular weight to that of a dimer, which indicates the importance of molecular size for crystallization inhibitors. These findings are relevant for understanding the mechanisms of surface and bulk crystal growth in glasses, predicting the stability of amorphous materials against crystallization, and developing effective crystallization inhibitors.

Among the possible causes for the relative insensitivity of surface crystal growth to polymer additives are (1) polymer concentration is lower at the surface than in the bulk, (2) upward growing surface crystals avoid encounters with polymer molecules, and (3) high mobility of surface molecules makes the process of crystal growth less sensitive to polymeric impurities. It is still unclear which explanation accurately accounts for the phenomenon. Further understanding could benefit from measuring surface concentrations of polymer molecules and learning the mechanism of crystal growth and surface molecular mobility of organic glasses.

For an organic glass such as NIF, polymer doping can strongly inhibit bulk crystallization, while having weaker effect on surface crystallization. For such systems, polymer doping alone is insufficient for preventing crystallization and could be complemented with polymer coating (12) to inhibit surface crystallization. Meanwhile, selective suppression of bulk crystallization could create glasses with thin crystalline coatings and useful properties.

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