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Probing the Interplay between Amorphous Solid Dispersion Stability and Polymer Functionality

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Abstract

Amorphous solid dispersions containing a polymeric component often impart improved stability against crystallization for a small molecule relative to the pure amorphous form. However, the relationship between side chain functionalities on a polymer and the ability of a polymer to stabilize against crystallization is not well understood. To shed light on this relationship, a series of polymers were functionalized from a parent batch of poly-(chloromethylstyrene-*co*-styrene) to investigate the effect of functionality on the stability in amorphous solid dispersions without altering the physical parameters of polymers, such as the average molecular weight or backbone chain chemistry. The kinetics of the crystallization of the nonsteroidal anti-inflammatory drug nabumetone from amorphous solid dispersions containing each functionalized polymer were interpreted on the basis of two interactions: hydrogen bonding between the drug and the polymer and the solubility of the polymer in the amorphous drug. It was found that hydrogen bonding between functionalized polymers and nabumetone can impart stability against crystallization, but only if the polymer shows significant solubility in amorphous nabumetone. Methylation of a protic functionality can improve the ability of a polymer to inhibit nabumetone crystallization by increasing the solubility in the drug, even when the resulting polymer lacks hydrogen bonding functionalities to interact with the pharmaceutical. Furthermore, factors, such as the glass transition temperature of pure polymers, were uncorrelated with isothermal nucleation rates. These findings inform a framework relating polymer functionality and stability deconvoluted from the polymer chain length or backbone chemistry with the potential to aid in the design of polymers to inhibit the crystallization of hydrophobic drugs from amorphous solid dispersions.

Graphical Abstract

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Supporting Information

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Details on polymer synthesis, functionalization, and characterization, including GPC, NMR, and Raman, and IR spectroscopy; complete list of induction time data from crystallization experiments; T_g prediction using the Fox equation; and powder X-ray diffraction of crystallized nabumetone from amorphous dispersions and nabumetone melting temperature by DSC (PDF)

Time-lapse photography of crystallization events under polarized filters (MPG)

The authors declare no competing financial interest.

Keywords

crystallization inhibition; physical stability; polymer pharmaceutical interaction; polymer-induced heteronucleation; polymorphism; amorphous solid dispersion

INTRODUCTION

The amorphous form of a pharmaceutical can display dramatically improved solubility compared to crystalline forms.^{1,2} However, the amorphous state is metastable,³ and additives are often necessary to delay crystallization and reap the benefits of this high energy state in pharmaceutical formulations.⁴ Polymers have shown promise as crystallization inhibitors, yet there is no consensus on the most relevant chemical factors that dictate the ability of a polymer to slow crystallization.^{5,6} It has been proposed that polymers restrict crystallization by decreasing the molecular mobility of pharmaceuticals in the amorphous state.⁷ A decrease in mobility could stem from an antiplasticizing effect where the polymer raises the glass transition temperature of a pharmaceutical dispersion.⁸ In practice, there is not a direct relationship between the glass transition temperature of a polymer and its ability to inhibit crystallization.^{9–11} Strong intermolecular interactions (e.g., hydrogen bonding) between drug molecules and polymer chains have been shown to occur in systems showing low mobility and slow kinetics of crystallization.^{12–16} However, these functional group trends derive from a few examples, and although the ability of specific polymers to stabilize against crystallization has been studied for a number of drug molecules, such studies employ a diverse set of polymeric materials in order to draw broad chemical conclusions; the validity of such structure–function relationships may be convoluted with parameters, such as polymer molecular weight and backbone chain chemistry.

In order to elucidate the relationship between functional groups within a polymer and the ability of a polymer to inhibit amorphous form crystallization, a series of polymers was synthesized on a common scaffold. This was accomplished via functionalization of a single batch of poly-(chloromethylstyrene-*co*-styrene), such that the average degree of polymerization and backbone chemistry could all be held constant. As shown in Figure 1, functionalities were selected to explore the impact of hydrogen bonding on the stability of dispersions and test, without influencing other structural parameters, how modulating the interaction strength between the polymer and the drug alters the kinetics of crystallization. Nabumetone, a Biopharmaceutics Classification System (BCS) class II nonsteroidal anti-inflammatory drug,¹⁷ was selected as a model pharmaceutical for this study because of its fast crystallization kinetics at room temperature and lack of degradation upon melting. This latter point is particularly critical for establishing generalizable conclusions, because

individual drugs will have characteristic decomposition products that may vary depending on the polymer and will almost certainly influence crystallization kinetics. By comparing polymers with protic functionalities (which can donate a hydrogen bond to nabumetone) and their methylated counterparts (which cannot), the prevailing theory that hydrogen bonding imparts stability to an amorphous dispersion was tested for a set of otherwise equivalent polymers.

EXPERIMENTAL SECTION

Poly(chloromethylstyrene-*co*-styrene) was synthesized by free radical polymerization in ethylbenzene, resulting in a parent polymer with a molecular weight of 10 kDa which contains 80% chloromethylstyrene repeat units (see the Supporting Information for additional details on all experimental procedures). Functionalization was achieved by reacting a linear polymer with a substituted phenol and cesium carbonate in dimethylacetamide, and functionalization was verified with both Raman and NMR spectroscopies. All functionalized polymers in this study came from a single poly-(chloromethylstyrene-*co*-styrene) batch to ensure a consistent polymer length for each sample. Molecular weights were measured using a Shimadzu GPC equipped with a diode array UV–vis detector. Glass transition temperatures were measured by differential scanning calorimetry (DSC) at a 20 °C/min scanning rate in a Q2000 from TA Instruments in hermetically sealed aluminum pans containing pinholes, where T_g was taken as the inflection point along a glass transition. Onset crystallization temperatures were measured at 20 °C/min in a Q20 DSC after quench cooling melts from 105 °C to –20 °C in pans containing pinholes.

Amorphous solid dispersions were prepared by dissolving equal amounts of drug and polymer in dichloromethane (10 mg/mL each) and evaporating 0.25 mL of solution among six regions on a glass slide.¹⁸ The material was heated to 105 °C for at least 1 min before quench cooling to 30 °C, yielding amorphous islands which were monitored by time lapse photography for crystallization events. Quench cooling occurred within 19 ± 2 s as measured by an FLIR TG165 Spot Thermal Camera. The few crystallites which appeared after only 1 min were discarded from statistical analysis, as these represent samples where drug was not adequately mixed with polymer. Crystallizations were run in duplicate with two glass slides for each run to give a minimum of 20 induction times for each polymer sample. Nabumetone displays rapid crystal growth rates relative to its nucleation rate at 30 °C; complete crystallization of amorphous droplets occurred within minutes of the initial crystal appearance (Figure 2) and was verified to be crystalline nabumetone by polarized light microscopy and PXRD (see SI 6 and the attached video for PLM images and SI 7 for PXRD in Supporting Information). Therefore, the recorded induction time was approximated to be the induction time to nucleation without a considerable delay due to slow growth rates, obviating the need to detect nanometer sized nuclei and their associated difficulties.^{19,20}

RESULTS

Figure 3 shows a probability plot of nabumetone crystallization in 50 wt % dispersions in the polymer at 30 °C. In this plot, the percent of amorphous samples containing each polymer that has undergone crystallization is plotted against time to give a curve

representing the nucleation rate of nabumetone from each amorphous solid dispersion (see the Supporting Information for information on statistical significance). Without the added polymer, nabumetone is a rapid crystallizer, and nucleation was recorded to occur on average in 13 min. The addition of unfunctionalized polyCMS extends induction times, but in order to dramatically inhibit crystallization, it is necessary to attach more strongly interacting functional groups to the polymer. A general ranking of the polymers in their ability to stabilize against crystallization is shown in Figure 3. Side chain functionality on a polymer plays a crucial role in dictating the kinetics of nabumetone crystallization, apparent by the diversity of the nucleation rates of the amorphous solid dispersions, and in this series of polymers of equal size, structure–function relationships can be established without the influence of other polymer parameters. Although the strongest inhibitors of nucleation, polyBA and polyMACM, both contain polar functionalities, the presence of a polar side group on a polymer is not required for strong inhibition. PolyPH, a nonpolar polymer, outperforms both polyACM and polyCMS in stabilizing against crystallization. Many of the polymers which have been investigated in the literature as crystallization inhibitors are water-soluble and polar. However, these results hint that nonpolar polymers may rival or outperform many of the previously studied polymers to inhibit devitrification of a nonpolar drug, such as nabumetone. Furthermore, complementary hydrogen bonding accepting and donating groups on the drug and the polymer are not sufficient to ensure the inhibition of crystallization. Nabumetone is a hydrogen bond acceptor, yet the presence of a hydrogen bond donating functionality does not reliably predict which polymers inhibit the nucleation of nabumetone. Both polyBA and polyACM contain hydrogen bond donating functionalities, yet polyACM is not a particularly strong inhibitor, and methylation of polyACM (and removal of its ability to hydrogen bond with nabumetone) does not result in a polymer with a reduced ability to inhibit crystallization. Neither the presence of a polar functionality nor a hydrogen bond donating side group are necessary to inhibit nucleation in these amorphous solid dispersions.

The nucleation rates of dispersions were modeled after a Poisson distribution, where $P(t)$, the percent probability of nucleation in each sample after t minutes, is a function of time t and J , a fitted parameter representing the nucleation rate.²¹

$$P(t) = 100 - 100 \times \exp(-Jt)$$

Table 1 shows the fitted nucleation rates from each sample. Dispersions were also characterized by differential scanning calorimetry. Glass transition temperatures of each pure polymer are shown in Table 1. Using the Fox equation, which predicts the glass transition temperature of miscible blends, the T_g of nabumetone was calculated and used to approximate the T_g of each dispersion containing 50 wt % polymer. These T_g values were not directly measured due to devitrification at slow cooling rates but are proportional to the glass transition temperature of the pure polymer.²² Comparing experimental T_g and the fitted nucleation rates shows that the glass transition temperature of the pure polymer is a poor predictor of the crystallization behavior. Although, for nonpolar polymers (polyBME and polyPH), a higher glass transition temperature corresponds with stronger inhibition, for polymers with polar functionalities, there is no trend relating the glass transition temperature

and inhibition behavior. Such a discrepancy between T_g and the crystallization inhibition has been observed in amorphous solid dispersions of water-soluble polymers;^{10,11} however, this represents the first time the relationship has been established in a series of polymers of equivalent size, indicating a robust finding. Furthermore, although the onset crystallization temperature has been proposed as a gauge for the stability of dispersions against crystallization,^{14,23} it is apparent that the ability of a polymer to inhibit isothermal nucleation is not well approximated by extrapolating this parameter. The onset crystallization temperature was measured by cooling dispersions to $-20\text{ }^{\circ}\text{C}$ from $105\text{ }^{\circ}\text{C}$ and recording the temperature of nabumetone crystallization upon heating. Comparing this parameter with the nucleation rate for dispersions, it is clear that the onset crystallization temperature does not approximate isothermal stability against nucleation at $30\text{ }^{\circ}\text{C}$. For instance, the onset crystallization temperature of unfunctionalized polyCMS dispersions is over $10\text{ }^{\circ}\text{C}$ higher than that of polyPH dispersions, in spite of the fact that nabumetone dispersed in polyPH has a nucleation rate 30 times slower than when dispersed in polyCMS. Accelerated aging techniques, such as this, thus should be interpreted with care and are not replacements for isothermal nucleation rate measurements.

IR Spectroscopy.

Hydrogen bonding between the polymer and the drug will cause peak shifts in the vibrational spectrum of dispersed pharmaceuticals.²⁴ Pure amorphous nabumetone contains a carbonyl stretch at 1713.1 cm^{-1} . The transmission IR spectra of nabumetone dispersions in polymers with hydrogen bond donating functionalities show shifting to a lower frequency for this carbonyl stretch (see Figure 4). This region in the IR does not contain significant peaks from the pure polymer (see the Supporting Information), thus such shifts can be attributed to intermolecular interaction. The extent of peak shifting, and presumably hydrogen bonding strength, between the polymer and the drug does not directly correlate with stability in the amorphous state. While benzyl alcohol functionalities on polyBA donate a hydrogen to the carbonyl group on nabumetone (red-shifting the carbonyl peak frequency to 1711.1 cm^{-1}) and stabilize the dispersion against crystallization, a similar interaction originating from the amide hydrogen on polyACM does not result in lengthened induction times, although the presence of this hydrogen bond can be inferred from IR peak shifting (at 1712.7 cm^{-1}). That being said, the interaction strengths of these hydrogen bonds are weak; spectroscopic investigation of other amorphous pharmaceuticals have shown larger peak shifts when dispersed in the polymer,¹⁶ and it is possible that the presence of stronger hydrogen bond donating functionalities would strongly bind to pharmaceuticals and restrict crystallization. Furthermore, interactions between the polymer and other functionalities on nabumetone might account for improved stability against nucleation, although such interactions did not result in dramatic peak shifts of other vibrational modes. From a practical standpoint, although hydrogen bonding correlates with peak shifting in the infrared spectra of nabumetone dispersions, such peak shifting from hydrogen bonding between the drug and the polymer fails to predict the relative ability of the polymer to inhibit the crystallization of nabumetone.

DISCUSSION

Hydrogen bonding between the polymer and pharmaceuticals is a feature often cited to interpret the relative ability of polymers to inhibit crystallization.^{10,14,15} It was found that the rate of nucleation of nabumetone from polymeric dispersions depends on the character of hydrogen bond interactions between the drug and the polymer, and methylation of the protic polymer functionalities leads to divergent effects on the stability of dispersions. For a hydroxy functionality, methylation resulted in a weaker inhibition of crystallization. Comparing the performance of polyBA and polyBME (Figure 1), the replacement of a hydroxy group with a methoxy in the polymer dispersion decreases the stability (Table 1). It is proposed that the hydrogen bonds formed between the hydroxy groups on polyBA and the carbonyl on nabumetone impart stability to the amorphous phase, in line with the classic framework correlating hydrogen bond strength and stability in amorphous solid dispersions.²⁵ However, polymers with hydrogen bond donating amide functionalities did not form dispersions with a long-term stability against crystallization; polyACM (containing hydrogen bond donating secondary amide functionalities) is a less potent inhibitor of nucleation compared to polyMACM (containing tertiary amide functionalities which cannot donate a hydrogen bond). We consider two possible reasons for this observed deviation from expectations: limited polymer solubility in the drug and polymer-induced heteronucleation from the amorphous phase.

First we examine the possibility that weak stability of dispersions containing polyACM stems from low polymer solubility in nabumetone. The solubility of small-molecule pharmaceuticals in a polymer carrier is regularly considered when addressing the stability of an amorphous dispersion,^{26,27} high supersaturations of the drug in the polymer will lead to phase separation of the drug and devitrification.^{28–30} However, the solubility of the polymer in the drug also plays an important role.³¹ Although increasing the polymer concentration in a solid dispersion can decrease molecular mobility and crystallization rates,^{32,33} high concentration may lead to polymer phase separation or crystallization within the amorphous dispersion.^{31,34} If polyACM has limited solubility in nabumetone at 50 wt % compared to other dispersed polymers, it would limit its ability to restrict crystallization. Evidence for this solubility discrepancy can be seen by DSC, where nabumetone (Form I) crystallized from polyACM shows less significant melting point depression compared to that of the crystalline material in polyMACM (see the Supporting Information for the DSC trace). To further investigate this phenomenon, amorphous solid dispersions containing 16 wt % polymer relative to nabumetone were prepared, and their nucleation rates were measured (Figure 5). At this lower concentration, polyACM is a stronger inhibitor of nucleation than polyMACM, in contrast to at higher weight loadings. We hypothesize that for 50 wt % dispersions of nabumetone in polyACM, the polymer shows incomplete solubility in the drug, while at a lower concentration, polyACM is fully dissolved in the amorphous phase. The enhanced stability of polyACM dispersions relative to polyMACM at 16 wt % polymer could then be attributed to intermolecular hydrogen bonding between nabumetone and the polymer, and at higher weight percent loadings, because polyACM is not soluble in the drug, it is less effective than other polymers to stabilize the amorphous phase. Furthermore, dispersions containing 16 wt % polyMACM show dramatically weaker stability than those

containing 50 wt % polyMACM, suggesting that the more incorporated polymer (when dissolved) corresponds to a higher barrier to nucleation of nabumetone from the amorphous phase.³⁵ As seen in these experiments, polymer solubility in the drug plays a salient role in dictating the relationship between polymer functionality and stability of an amorphous dispersion at high weight percent polymer loadings. This point is particularly relevant when designing amorphous formulations for long-term stability, dispersions containing 50 wt % polyMACM show far slower nucleation rates than those containing either 16 or 50 wt % polyACM. One explanation for why polymer solubility in the drug is rarely evoked to interpret the relative inhibitory ability of polymers is that many of the commercially available polymers employed in amorphous solid dispersions contain side chains with weaker homomeric interaction strength (carboxylate,^{36,37} lactam,^{27,38,39} and hydroxy⁴⁰) than those explored here, and the solubility of the polymer in amorphous drug is seldom a limiting parameter in such systems. However, in this study, extending the scope of polymers to include those with stronger homomeric hydrogen bonding interactions gives rise to examples where the solubility of the polymer in the drug may be a limiting parameter on the ability of a polymer to inhibit crystallization. As a result, stability is difficult to predict from accelerated aging or spectroscopic data because it depends on both local drug–polymer interactions and global polymer solubility.

A second possible origin of the anomalously fast nucleation kinetics of nabumetone dispersed in polyACM is polymer-induced heteronucleation. Phase separation in an amorphous dispersion will lead to polymer-rich regions in contact with drug-rich regions, and this polymer-rich phase might provide a surface to seed the crystallization of pharmaceuticals. Heterogeneous nucleation on a polymer substrate, also known as polymer-induced heteronucleation, is a well-studied crystallization technique which can result in polymorphic phase direction and enhanced nucleation rates.^{41–47} Although polymer-induced heteronucleation typically employs cross-linked polymers as heteronuclei, there is evidence that linear polymers can display the same effect to speed nucleation in both solution and in the amorphous phase.^{48–52} Nabumetone is a compound with two known polymorphs.^{53,54} On glass, the thermodynamic polymorph (Form I) nucleates from the supercooled state; in the presence of stabilizing polymers, the metastable form (Form II) was found to appear as well. However, dispersions with polyACM often resulted in crystallizations containing only the thermodynamic form, hinting at the possibility that this polymer preferentially nucleates Form I (see Supporting Information for PXRD data). A common approach in the design of stable amorphous solid dispersions is to encode strong hydrogen bonding interactions between the polymer and the drug to restrict molecular mobility. However, these same functionalities may template nucleation upon phase separation, promoting more rapid crystallization than less strongly interacting functionalities.^{41,43} Such a mechanism likely contributes to the weak stability in polyACM dispersions, phase separation in other dispersions may not result in such fast nucleation kinetics due to a weaker interaction and weaker propensity to organize molecules from the amorphous phase.

CONCLUSION

This study stands out as the postulated relationships between polymer functionality and stability in amorphous solid dispersions have been probed in the absence of other physical

differences between polymers, allowing testing of a number of hypotheses in the field.^{5,55,56} Two critical findings are that (1) the thermal properties (T_g , onset crystallization temperature) are not strong predictors of the isothermal nucleation rate of nabumetone from dispersions, and that (2) hydrogen bond donating functionalities are not necessary to stabilize the amorphous state of nabumetone, and, at times, they lead to dispersions with reduced induction times to crystallization. This failure to inhibit crystallization by polymers containing strongly interacting hydrogen bonding groups is attributed to the limited solubility of the polymer in the amorphous drug. Such an argument may explain the behavior of other amorphous solid dispersions, especially those composed of polymers intended to strongly interact with the drug to inhibit crystallization. Once deconvoluted from other physical factors, it is clear that the design for the polymers to impart stability to an amorphous dispersion must consider a range of chemical interactions between the polymer and the drug, and that evaluation of these polymers as crystallization inhibitors cannot rely solely on structural predictions or accelerated aging without isothermal nucleation rate experiments. Future work will investigate the influence of chemical functionality on the stability for a broader range of hydrophobic drugs, with the goal of a generalizable framework to predict the ability of a polymer to inhibit the crystallization in any amorphous dispersion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Series of statistical copolymers studied as the crystallization inhibitors in amorphous solid dispersions with (b) nabumetone. Each is given a name corresponding to functional groups on the polymers; polyCMS is the parent poly(chloromethylstyrene-costyrene) polymer, polyPH has a phenyl group, polyACM bears an acetaminophen ligated through the phenol, polyMACM bears a methylated acetaminophen, polyBA has a benzyl alcohol functionality, and polyBME has a benzyl methyl ether moiety.

Figure 2.

Crystal appearance of nabumetone dispersed in polymer (shown here in polyBME). As seen in the sample indicated with a red circle, within 3 min of initial nucleation ($t = 33$ min), crystallization occurs throughout the entire dispersion. Thus, the induction time to nucleation is designated as the time to the first crystal appearance in dispersions, and delays due to growth rates are assumed to be negligible. The two samples at the bottom of the slide remain amorphous over this time period, and the other samples have undergone crystallization earlier in the trial.

Figure 3.

Rate of crystallization for nabumetone dispersed in each of the functionalized polymers at 30 °C. The black trace shows pure nabumetone crystallization from the amorphous state, and each colored trace represents a 50 wt % dispersion of nabumetone in the corresponding colored polymer, ordered left-to-right according to their relative ability to inhibit crystallization.

Figure 4. Overlaid transmission IR spectra of dispersions ranked top-to-bottom by decreasing peak frequency of the nabumetone carbonyl stretch, highlighted in red.

Figure 5. Probability plot of nabumetone nucleation from amorphous solid dispersions containing 16 wt % (dotted lines) and 50 wt % (solid lines) of polyACM (blue) and polyMACM (purple). Pure nabumetone crystallization is shown in black.

Table 1.

Glass Transition Temperatures for Pure Functionalized Polymers, Predicted T_g of Polymeric Dispersions from the Fox Equation, and Onset Crystallization Temperature of Nabumetone Dispersions (Measured by DSC) Compared with the Nucleation Rate of Dispersions^a

	polyCMS	polyBME	polyACM	polyPH	polyMACM	polyBA
$J \times 10^3 \text{ (hr}^{-1}\text{)}$	783.1 $\pm$ 13.1	338.7 $\pm$ 9.7	72.2 $\pm$ 0.7	25.8 $\pm$ 0.3	8.24 $\pm$ 0.1	7.48 $\pm$ 0.1
T_g pure polymer ($^{\circ}\text{C}$)	107 $\pm$ 0.6	47.3 $\pm$ 2.7	105 $\pm$ 2.5	68 $\pm$ 1.3	94 $\pm$ 4.4	121.5
predicted T_g 50 wt % dispersion ($^{\circ}\text{C}$)	11	-7	11	0	8	15
onset crystallization temperature ($^{\circ}\text{C}$)	14.1 $\pm$ 0.8	-1.9 $\pm$ 0.6	24 $\pm$ 0.4	1.1 $\pm$ 0.5	10.3 $\pm$ 0.1	15.5 $\pm$ 0.2

^aValues recorded by DSC shown with standard errors are the average of two experimental runs.