Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Mol Pharm. Author manuscript; available in PMC 2020 February 04.

Published in final edited form as:

Mol Pharm. 2019 February 04; 16(2): 682–688. doi:10.1021/acs.molpharmaceut.8b00972.

Effect of Polymer Hydrophobicity on the Stability of Amorphous Solid Dispersions and Supersaturated Solutions of a Hydrophobic Pharmaceutical

Derek S. Frank and **Adam J. Matzger***

Department of Chemistry and the Macromolecular Science & Engineering Program, The University of Michigan, Ann Arbor, Michigan 48109, United States

Abstract

Amorphous solid dispersions of pharmaceuticals often show improved solubility over crystalline forms. However, the crystallization of amorphous solid dispersions during storage, or from elevated supersaturation once dissolved, compromise the solubility advantage of delivery in the amorphous phase. To combat this phenomenon, polymer additives are often included in solid dispersions to inhibit crystallization; however, the optimal properties for polymer to stabilize against crystallization are not fully understood, and furthermore, it is not known how inhibition of precipitation from solution is related to the propensity of a polymer to inhibit crystallization from the amorphous phase. Here, polymers of varied hydrophobicity are employed as crystallization inhibitors in supersaturated solutions and amorphous solid dispersions of the BCS Class II pharmaceutical ethenzamide to investigate the chemical features of polymer that lead to long-term stability for a hydrophobic pharmaceutical. A postpolymerization functionalization strategy was employed to alter the hydrophobicity of poly(*N*-hydroxyethyl acrylamide) without changing physical properties such as number-average chain length. It was found that supersaturation maintenance for ethenzamide is improved by increasing the hydrophobicity of dissolved polymer in aqueous solution. Furthermore, amorphous solid dispersions of ethenzamide containing a more hydrophobic polymer showed superior stability compared to those containing a less hydrophobic polymer. This trend of increasing polymer hydrophobicity leading to improved amorphous stability is interpreted by parsing the effects of water absorption in amorphous solid dispersions using intermolecular interaction strengths derived from global structural analysis. By comparing the structure–function relationships, which dictate stability in solution and amorphous solid

***Corresponding Author** Mailing Address: Adam J. Matzger, Department of Chemistry and the Macromolecular Science & Engineering Program, The University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States; Phone: (734) 615-6627; matzger@umich.edu.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information

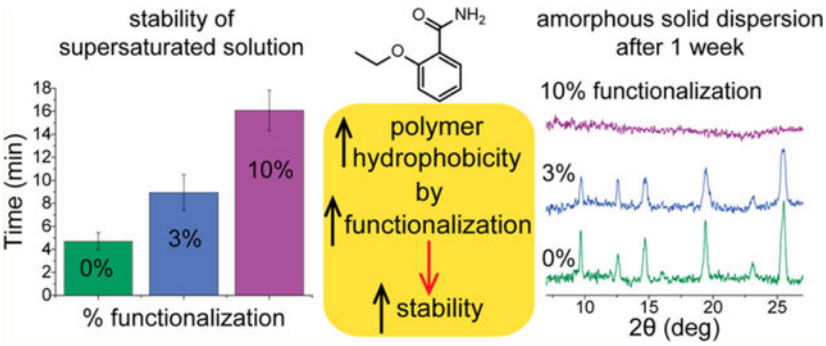
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.molpharmaceut.8b00972. Details on polymer synthesis and characterization by NMR and GPC. DSC trace of glass transition temperatures for ethenzamide dispersions and pure PHEAM polymers. Theoretical amorphous solubility of ethenzamide. Statistical analysis of induction times to precipitation. Raw PXRD of crystallization of ethenzamide amorphous solid dispersions. Details on water vapor sorption experiments and procedure to determine average intermolecular bond distances from CSD (PDF)

The authors declare no competing financial interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

dispersions, the effect of hydrophobicity can be broadly understood for the design of polymers to impart stability throughout the application of amorphous solid dispersions.

Graphical Abstract



Keywords

crystallization inhibition; physical stability; amorphous solid dispersion; supersaturation maintenance; polymer pharmaceutical interaction; postpolymerization functionalization; ethenzamide

INTRODUCTION

The dissolution rate of pharmaceuticals can be enhanced by delivery from an amorphous phase,[1] leading to increased apparent oral bioavailability for many hydrophobic drugs.[2] As a result, there is substantial interest in formulating poorly soluble drugs in amorphous solid dispersions, a mixture of amorphous drug and stabilizing excipients.[3] However, there are two mechanisms by which the theoretical solubility advantage can fail to be delivered experimentally: crystallization of pharmaceutical within an amorphous solid dispersion during storage and crystallization of pharmaceutical from the supersaturated solution generated upon dissolution of the amorphous phase.[3–5] Polymers are particularly well-positioned for use as stabilizers of amorphous drug given their ability to inhibit crystallization when intimately mixed with pharmaceutical in amorphous solid dispersions[6] and when dissolved in solution.[7,8] However, the fundamental structure–function relationships that dictate the stability of amorphous solid dispersions and polymer-stabilized supersaturated solutions are often difficult to deconvolute from effects rising from changes in physical properties of polymers such as differing chain lengths/topology. In this work, a postpolymerization functionalization strategy is used to probe the effect of polymer hydrophobicity on stability without altering other physical parameters of the polymers. The influence of polymer hydrophobicity on precipitation inhibition in supersaturated solutions and crystallization inhibition in amorphous solid dispersions is determined using a set of functionalized polymers for the same model pharmaceutical. There are few studies that correlate the stability of amorphous solid dispersions and the supersaturated state for a given combination of pharmaceutical and polymeric excipient;[9–12] however, effective formulation additives in amorphous solid dispersions must inhibit crystallization in both of these contexts. By controlling for physical differences among polymer and the chemical identity

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

of crystallizing drug, the relationship between polymer hydrophobicity and stability can be understood in order to optimize the properties of polymer for long-term stability of amorphous solid dispersions.

The influence of polymer hydrophobicity on the ability of a class of poly(*N*-hydroxyethyl acrylamide) (PHEAM) polymers to inhibit crystallization of ethenzamide was examined in both aqueous solution and in the amorphous phase. Ethenzamide is BCS Class II analgesic drug (solubility of 8.8 mM in deionized water[13]) commonly coadministered with NSAIDs such as acetaminophen or aspirin.[14,15] Delivery of ethenzamide in its amorphous phase will increase solubility; however, polymer stabilizers are necessary to prevent precipitation in aqueous media at elevated supersaturation.[7] It has been observed in other systems that polymers of moderate hydrophobicity are more potent inhibitors of crystallization from aqueous solution than hydrophobic or hydrophilic polymers.[8,16–20] Completely hydrophilic polymers more favorably interact with solvent over solute, yet fully hydrophobic polymers form insoluble globules in aqueous solution.[8] Partially hydrophobic polymers maintain water solubility while driving strong interactions with dissolved pharmaceutical and tend to be the most effective inhibitors of crystallization from supersaturated solutions.[20,21] To rigorously investigate the effect of increasing hydrophobicity of a watersoluble polymer on the inhibition of precipitation, PHEAM polymers were treated with phenyl isocyanate to transform hydrophilic hydroxy groups on the polymer to hydrophobic phenyl carbamate moieties (see Scheme 1). A single batch of PHEAM was functionalized to ensure that only changes in side-chain functionality, rather than polymer chain length, were probed across crystallization experiments. The induction time to crystallization of supersaturated ethenzamide was measured with equivalent weight loading of this polymer series to determine the effect of hydrophobicity on supersaturation maintenance for a hydrophobic drug.

The effect of functionalization and increasing hydrophobicity of polymer on the ability of PHEAM to stabilize amorphous solid dispersions of ethenzamide was also investigated. Ethenzamide is particularly apt for this study given its lack of degradation upon melting and its strong crystallization propensity during quench cooling (see Supporting Information). To inhibit recrystallization of its amorphous phase, it is necessary to add stabilizing additives.[22–27] However, there is less consensus on the factors that dictate stability in amorphous solid dispersions, and a diverse set of polymer parameters have been shown to influence stability in amorphous solid dispersions of drugs, such as weight percent loading of polymeric stabilizer,[28] molecular weight of polymer,[29,30] hydrogen bonding between polymer and dispersed pharmaceutical,[31] and the solubility of polymer in amorphous pharmaceutical.[32,33] Empirical screening for stable amorphous solid dispersions has a long history,[5] yet design strategies for polymers to ensure long-term stability are still emerging in the field.[34,35] By partially functionalizing hydroxy groups in PHEAM polymers, the effect of hydrophobic residues on amorphous stability was probed and compared to the effect on inhibition in aqueous precipitation to address the overall impact of polymer hydrophobicity to stabilize against solution and amorphous phase crystallization.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

EXPERIMENTAL SECTION

Poly(hydroxyethyl acrylamide) (PHEAM) was synthesized by free-radical polymerization in dimethylformamide to give a polymer with a number-average molecular weight of 38 kDa (Đ = 1.5, molecular weights calculated relative to polystyrene standards). Functionalization was achieved using phenyl isocyanate to form polymers where a portion of backbone chain hydroxy groups are capped with phenyl groups via carbamate linkages (3 and 10% by NMR spectroscopy, here after referred to as PHEAM-3% and PHEAM-10%, respectively) following literature procedures.[36] PHEAM with 20% side-chain functionalization was not soluble in water and thus not used in this study.

Precipitation kinetics were measured in the Technobis CrystalBreeder. Ethenzamide (0.28 mL, 18 mM) dissolved in an aqueous solution containing 300 μg/mL polymer additive (10% the weight of ethenzamide) was pipetted into 0.3 mL vials containing a 5 × 2 mm Teflon stir bar. While stirred at 1200 rpm, vials were heated to 65 °C to allow for complete dissolution of drug and then cooled (5 °C/min) to 30 °C, where the induction time to crystallization was monitored by changes in solution turbidity. Experiments were repeated five times for 24 vials to give a total of 120 induction times to crystallization.

Amorphous solid dispersions of ethenzamide with PHEAM polymers were prepared by quench cooling. Ethenzamide (10 wt %) and polymer (90 wt %) were dissolved (5 mg overall per mL, ratio of ~13 repeat units of polymer per molecule of ethenzamide) in methylene chloride/methanol (1:1 by volume), and 0.3 mL of solution was distributed onto six regions on a glass slide. The material was heated to 140 °C for 1 min and then quench cooled to room temperature to form amorphous dispersions, resulting in a monophasic material with a single glass transition temperature (see Supporting Information for additional details). Dispersions were stored at ambient humidity and temperature and were analyzed by powder X-ray diffraction daily to determine the crystallization propensity of each dispersion over time.

RESULTS/DISCUSSION

Inhibition of Crystallization from Supersaturated Solution.

Functionalizing hydroxy side-chains with hydrophobic phenyl groups improves the ability of PHEAM polymers to inhibit crystallization from aqueous solution. As shown in Figure 1, the number of side-chain phenyl groups on a polymer additive correlates with the induction time to precipitation of ethenzamide. For 18 mM ethenzamide at 30 °C without polymer additives, the average induction time to precipitation is 3.1 ± 0.8 min. Adding 300 μg/mL unfunctionalized PHEAM (10% the weight of dissolved ethenzamide) only weakly inhibits crystallization, extending the induction time to 4.7 ± 0.7 min. However, PHEAM variants functionalized with phenyl isocyanate perform better with increasing degrees of functionalization, with PHEAM-3% lengthening the average induction time to 8.9 ± 1.5 min and PHEAM-10% inhibiting crystallization to 16.1 ± 1.8 min (see Supporting Information for details on statistical significance). This relationship between hydrophobic content on polymers and stability against precipitation is in line with previous work using linear polymers of varying backbone chain chemistry and for polymeric micelles.[8,17,21]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Furthermore, by using a set of otherwise equivalent polymers, this result can said to be robust in relating the hydrophobicity of dissolved polymers and their ability to inhibit aqueous ethenzamide crystallization without the influence of other possibly confounding parameters of polymer additives.

Inhibition of Crystallization from Amorphous Solid Dispersions.

The stability of amorphous solid dispersions of ethenzamide in PHEAM polymers (90 wt % polymer, 10 wt % drug) at ambient temperature and humidity was also quantified. It was found that dispersions containing PHEAM-10% stabilized the amorphous phase far more effectively than either PHEAM-3% or unfunctionalized PHEAM. Changes in the crystalline content of amorphous solid dispersions over time are shown in Figure 2. Similar to trends seen in solution, the addition of phenyl moieties on PHEAM increases stability against crystallization. Dispersions containing unfunctionalized PHEAM undergo devitrification within 2 ± 0.5 days (see Supporting Information for full set of crystallization experiments). Partially functionalizing PHEAM to PHEAM-3% does not result in longer stability for amorphous dispersions. However, at 10% functionalization, PHEAM-10% strongly inhibits ethenzamide crystallization in amorphous dispersions. Throughout all trials, ethenzamide dispersed in PHEAM-10% did not undergo crystallization within a week of preparation, and even up to 4 weeks after preparation, dispersions still lacked any crystalline peaks by PXRD. In some regards, this stability ranking of these dispersions is contrary to an expected result–masking hydroxy functionalities on PHEAM might remove hydrogen bonding sites between polymer and amorphous drug. However, there is reason to expect that replacing hydroxy groups on the dispersed polymer with carbamate functionalities would increase the interaction strength between polymer and ethenzamide. A survey of structures in the Cambridge Structural Database (CSD) containing amide functionalities (the hydrogen bond donor in ethenzamide) interacting with oxygen atoms shows that the average intermolecular bond distance between amide groups and carbamate functionalities (N_{amide}–$O_{carbonyl}$) is shorter than that between amide groups and hydroxy oxygens (N_{amide}–$O_{alcohol}$, see Supporting Information for additional details). This shorter average intermolecular bond distance would imply a greater interaction strength between ethenzamide and carbamate moieties as compared to ethenzamide and free hydroxy groups, which might account for the improved stability of PHEAM-10% dispersions.

In addition to intermolecular interaction strength, the hygroscopicity of amorphous solid dispersions plays a central role in dictating their stability against crystallization. Water absorbed by amorphous materials acts as a plasticizer to increase molecular mobility and crystallization rates as well as can lead to phase separation in otherwise miscible dispersions.[37–43] In fact, this effect of humidity-induced crystallization has been observed in the case of amorphous ethenzamide dispersed in microcrystalline cellulose.[25,26] As a result, amorphous solid dispersions containing hygroscopic polymers tend to be less resistant to crystallization in the presence of moisture than those containing less hygroscopic polymers,[44] and the improved stability of dispersions containing PHEAM-10% over PHEAM-3% or PHEAM may result from the lower hygroscopicity of the host polymer. For this series of PHEAM polymers, capping hydrophilic hydroxy groups with hydrophobic phenyl moieties leads to less ambient water absorbed by amorphous solid dispersions. As shown in Table 1,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

thermogravimetric analysis (TGA) of amorphous dispersions indicates that over 4 times the weight percent of water is absorbed at ambient humidity by unfunctionalized PHEAM as compared to PHEAM-10%. Such differences are reflected in the water vapor sorption isotherms at 25 °C of pure polymer (Figure 3), which show that at 60% RH, PHEAM-10% takes up significantly less water by weight percent (5.8%) as compared to PHEAM-3% (10.0%) or PHEAM (13.2%). Other physical properties of these polymers such as average chain length or glass transition temperatures (shown in Table 1) cannot explain the dramatic differences in their stabilizing ability. We propose that water absorbed in the amorphous dispersions containing hydrophilic polymer increases the molecular mobility of drug, which leads to crystallization. To test this hypothesis, amorphous solid dispersions containing unmodified PHEAM were prepared and stored both in ambient conditions and under dry conditions (in a desiccator). Ethenzamide dispersed in PHEAM under ambient conditions is unstable and undergoes devitrification in ~2 days after preparation. However, dispersions stored under dry conditions show much longer physical stability and do not crystallize within a week of preparation (see Supporting Information). In the absence of atmospheric water, amorphous solid dispersions of ethenzamide in PHEAM are dramatically stabilized, and as a result, the improved stability of PHEAM-10% dispersions can be attributed to their low hygroscopicity. Imparting hydrophobicity through postpolymerization modification restricts PHEAM-10% from absorbing water from the atmosphere, and thus, dispersions with this polymer are less prone to waterinduced plasticization and devitrification during storage.

Another possible effect of postpolymerization modification, independent of the amount of water absorbed by these polymers, is that the interactions between ethenzamide and carbamate functionalities on PHEAM-10% are more stable to disruption by water than ethenzamide interactions with hydroxy groups on PHEAM. This secondary effect is likely the origin of the superior ability of PHEAM-10% to inhibit aqueous precipitation of ethenzamide over unfunctionalized PHEAM (Figure 1); however, it may also play a role in dictating the stability ranking of amorphous solid dispersions. To examine this hypothesis, the relative strength of interactions between polymer and either pharmaceutical or water were approximated by the average intermolecular bond distance between relevant functionalities from a survey of structures in the CSD. The average intermolecular bond distance between primary amide functionalities (representing ethenzamide) or water and primary alcohol or carbamate groups (representing unfunctionalized and functionalized polymer, respectively) are shown in Figure 4 (see Supporting Information for additional details). The average intermolecular bond distance between water and carbamate functionalities (O_{water}–$O_{carbonyl}$, 2.91 ± 0.01 Å) is slightly less than that from amide to carbamate groups (N_{amide}–$O_{carbonyl}$, 2.99 ± 0.02 Å) or roughly equal when accounting for differences in the van der Waals radii of oxygen (1.58 Å) and nitrogen (1.64 Å).[45] However, the average intermolecular distance between water and alcohol groups (O_{water}–$O_{alcohol}$, 2.85 ± 0.004 Å) is far shorter than that from amide to hydroxy functionalities (N_{amide}–$O_{alcohol}$, 3.04 ± 0.02 Å). If one uses these average intermolecular bond distances as a proxy for interaction strength, it follows that water has the potential to easily outcompete ethenzamide to interact with pendant hydroxy functionalities on PHEAM, leading to dispersions and solution complexes with labile interactions with drug and limited stability against

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

crystallization. However, water forms only slightly shorter bonds than primary amides to carbamate groups, which might indicate that the amide–carbamate interaction between ethenzamide and PHEAM-10% is less likely to be disrupted by absorbed water in the amorphous solid dispersion or free water in a solution complex as compared to hydrogen bonding interactions between ethenzamide and the free hydroxy groups in PHEAM. Furthermore, such an effect of protecting polymer–pharmaceutical interactions from ambient water is likely promoted by hydrophobicphenyl groups attached to carbamate functionalities on PHEAM-10%. This general principle of water outcompeting pharmaceutical to bind with polymer functionalities has been observed in the relative kinetics of solution crystallization using polymer additives;[8,46,47] however, such an effect is rarely evoked to explain the relative kinetics of devitrification for amorphous solid dispersions. In the case of amorphous solid dispersions of ethenzamide and functionalized PHEAM polymers, the superior stability of PHEAM-10% over PHEAM-3% may stem from improved resilience to molecular interaction by water. Although pure PHEAM-3% absorbs less water than unfunctionalized PHEAM, dispersions containing PHEAM-3% do not display improved stability relative to amorphous solid dispersions in PHEAM. This instability may be because drug–polymer interactions in amorphous solid dispersions containing PHEAM-3% can be easily interrupted by atmospheric water, and despite a decrease in polymer hygroscopicity, such dispersions do not show an improvement in physical stability against crystallization. PHEAM-10% not only is a less hygroscopic polymer than PHEAM-3%, but its intermolecular interactions with ethenzamide are relatively more stable to disruption from atmospheric water (Figure 4). The same chemical factors that dictate the stability of polymer–pharmaceutical solution aggregates (in the case of precipitation inhibition) might also dictate stability of amorphous solid dispersions given that in both situations, intermolecular interaction between water (either as a solvent or from the atmosphere) and polymer has the effect of displacing pharmaceutical, which leads to crystallization. As a result, the complex polymeric materials, which have been developed to maintain supersaturation of hydrophobic drugs, may also serve well to stabilize amorphous solid dispersions in the case of crystallizations accelerated by water absorption in hygroscopic dispersions. However, it should be noted that increasing the hydrophobicity of amorphous solid dispersions may also impact their kinetics of dissolution and drug release, which in turn could influence the degree to which polymers can stabilize supersaturated solutions.[48,49] Further studies will be necessary to test the validity of the above crystallization assays in predicting the in vivo stability of these amorphous solid dispersions during administration.

CONCLUSION

In this study, we provide evidence that introducing hydro-phobic functionalities on water-soluble polymers via post-polymerization modification improves the stability of amorphous solid dispersions and supersaturated solutions of pharmaceuticals. Optimizing polymer design for amorphous solid dispersions is essential to prevent recrystallization from the amorphous phase and from solution.[50,51] Imparting hydrophobicity to water-soluble polymers has a dual effect of optimizing the performance of amorphous solid dispersions. In the amorphous phase, hydrophobic residues decrease hygroscopicity and protect interactions

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

between polymer and pharmaceutical from interruption by atmospheric water. In aqueous solution, hydrogen bonding between polymer and bulk water competes with bonding between drug and polymer, and tethering hydrophobic functionalities on a water-soluble polymer can preferentially interact to stabilize supersaturated drug from precipitation.[21] A central finding to this study is that many of the same interactions govern stability of solution polymer–pharmaceutical complexes and amorphous solid dispersions in the presence of humidity. This generalization allows for the application of polymers optimized to maintain aqueous supersaturation in amorphous solid dispersions, where strong polymer–drug interactions serve to protect dispersions from atmospheric humidity. Future work will investigate functionalization methodologies to impart hydrophobicity to a broad range of water-soluble polymers and improve their ability to stabilize amorphous and supersaturated phases for efficacious oral delivery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

This work was supported by NIH grant R01 GM106180. D.S.F. gratefully acknowledges research support in the form of a fellowship from PPG.

REFERENCES

(1). Hancock BC; Parks M What is the true solubility advantage for amorphous pharmaceuticals? Pharm. Res 2000, 17 (4), 397–404. [PubMed: 10870982]

(2). Amidon GL; Lennernaš H; Shah VP; Crison JR A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm. Res 1995, 12 (3), 413–420. [PubMed: 7617530]

(3). Serajuddin A Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J. Pharm. Sci 1999, 88 (10), 1058–1066. [PubMed: 10514356]

(4). Rodríguez-hornedo N; Murphy D Significance of controlling crystallization mechanisms and kinetics in pharmaceutical systems. J. Pharm. Sci 1999, 88 (7), 651–660. [PubMed: 10393562]

(5). Chiou WL; Riegelman S Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci 1971, 60 (9), 1281–1302. [PubMed: 4935981]

(6). Yu L Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv. Drug Delivery Rev 2001, 48 (1), 27–42.

(7). Raghavan S; Trividic A; Davis A; Hadgraft J Crystallization of hydrocortisone acetate: influence of polymers. Int. J. Pharm 2001, 212 (2), 213–221. [PubMed: 11165079]

(8). Ilevbare GA; Liu H; Edgar KJ; Taylor LS Maintaining supersaturation in aqueous drug solutions: Impact of different polymers on induction times. Cryst. Growth Des 2013, 13 (2), 740–751.

(9). Chauhan H; Kuldipkumar A; Barder T; Medek A; Gu C-H; Atef E Correlation of inhibitory effects of polymers on indomethacin precipitation in solution and amorphous solid crystallization based on molecular interaction. Pharm. Res 2014, 31 (2), 500–515. [PubMed: 24122167]

(10). Chauhan H; Hui-Gu C; Atef E Correlating the behavior of polymers in solution as precipitation inhibitor to its amorphous stabilization ability in solid dispersions. J. Pharm. Sci 2013, 102 (6), 1924–1935. [PubMed: 23580406]

(11). Blaabjerg LI; Lindenberg E; Löbmann K; Grohganz H; Rades T Is there a correlation between the glass forming ability of a drug and its supersaturation propensity? Int. J. Pharm 2018, 538 (1–2), 243–249. [PubMed: 29341914]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(12). Van Eerdenbrugh B; Baird JA; Taylor LS Crystallization tendency of active pharmaceutical ingredients following rapid solvent evaporation–classification and comparison with crystallization tendency from undercooled melts. J. Pharm. Sci 2010, 99 (9), 3826–3838. [PubMed: 20533435]

(13). Sarmah KK; Boro K; Arhangelskis M; Thakuria R Crystal structure landscape of ethenzamide: a physicochemical property study. CrystEngComm 2017, 19 (5), 826–833.

(14). Kawano O; Sawabe T; Misaki N; Fukawa K Studies on Combination Dosing (III) Aspirin And Ethenzamide. Jpn. J. Pharmacol 1978, 28 (6), 829–835. [PubMed: 745307]

(15). Khatioda R; Saikia B; Das PJ; Sarma B Solubility and in vitro drug permeation behavior of ethenzamide cocrystals regulated in physiological pH environments. CrystEngComm 2017, 19 (46), 6992–7000.

(16). Ting JM; Navale TS; Bates FS; Reineke TM Design of tunable multicomponent polymers as modular vehicles to solubilize highly lipophilic drugs. Macromolecules 2014, 47 (19), 6554–6565.

(17). Johnson LM; Li Z; LaBelle AJ; Bates FS; Lodge TP; Hillmyer MA Impact of polymer excipient molar mass and end groups on hydrophobic drug solubility enhancement. Macromolecules 2017, 50 (3), 1102–1112.

(18). Yin L; Hillmyer MA Preparation and performance of hydroxypropyl methylcellulose esters of substituted succinates for in vitro supersaturation of a crystalline hydrophobic drug. Mol. Pharmaceutics 2014, 11 (1), 175–185.

(19). Xu S; Dai W-G Drug precipitation inhibitors in supersaturable formulations. Int. J. Pharm 2013, 453 (1), 36–43. [PubMed: 23680727]

(20). Tale S; Purchel AA; Dalsin MC; Reineke TM Diblock Terpolymers Are Tunable and pH Responsive Vehicles To Increase Hydrophobic Drug Solubility for Oral Administration. Mol. Pharmaceutics 2017, 14 (11), 4121–4127.

(21). Mosquera-Giraldo LI; Borca CH; Meng X; Edgar KJ; Slipchenko LV; Taylor LS Mechanistic design of chemically diverse polymers with applications in oral drug delivery. Biomacromolecules 2016, 17 (11), 3659–3671. [PubMed: 27715018]

(22). Danjo K; Nakata T; Otsuka A Preparation and dissolution behavior of ethenzamide solid dispersions using various sugars as dispersion carriers. Chem. Pharm. Bull 1997, 45 (11), 1840–1844.

(23). Hanawa T; Ikoma R; Watanabe A; Hidaka M; Sugihara M Preparation and characterization of sealed heated mixture of ethenzamide and porous calcium silicate. Chem. Pharm. Bull 1996, 44 (7), 1367–1371.

(24). Hirasawa N; Okamoto H; Danjo K Lactose as a low molecular weight carrier of solid dispersions for carbamazepine and ethenzamide. Chem. Pharm. Bull 1999, 47 (3), 417–420. [PubMed: 10212391]

(25). Kazuhiro M; Yoshinobu N; Etsuo Y; Toshio O; Keiji Y Physicochemical characteristics of porous crystalline cellulose and formation of an amorphous state of ethenzamide by mixing. Int. J. Pharm 1994, 108 (3), 167–172.

(26). Matsumoto K; Nakai Y; Yonemochi E; Oguchi T; Yamamoto K Effect of pore size on the gaseous adsorption of ethenzamide on porous crystalline cellulose and the physicochemical stability of ethenzamide after storage. Chem. Pharm. Bull 1998, 46 (2), 314–318.

(27). Ozawa M; Hasegawa K; Yonezawa Y; Sunada H Preparation of solid dispersion for ethenzamide–Carbopol and theophylline–Carbopol systems using a twin screw extruder. Chem. Pharm. Bull 2002, 50 (6), 802–807. [PubMed: 12045335]

(28). Marsac PJ; Li T; Taylor LS Estimation of drug–polymer miscibility and solubility in amorphous solid dispersions using experimentally determined interaction parameters. Pharm. Res 2009, 26 (1), 139. [PubMed: 18779927]

(29). Mohapatra S; Samanta S; Kothari K; Mistry P; Suryanarayanan R Effect of Polymer Molecular Weight on the Crystallization Behavior of Indomethacin Amorphous Solid Dispersions. Cryst. Growth Des 2017, 17 (6), 3142–3150.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(30). Pacułt J; Rams-Baron M; Chrząszcz B; Jachowicz R; Paluch M Effect of polymer chain length on the physical stability of amorphous drug-polymer blends at ambient pressure. Mol. Pharmaceutics 2018, 15 (7), 2807–2815.

(31). Kothari K; Ragoonanan V; Suryanarayanan R The role of drug–polymer hydrogen bonding interactions on the molecular mobility and physical stability of nifedipine solid dispersions. Mol. Pharmaceutics 2015, 12 (1), 162–170.

(32). Duong TV; Van Humbeeck J; Van den Mooter G Crystallization kinetics of indomethacin/polyethylene glycol dispersions containing high drug loadings. Mol. Pharmaceutics 2015, 12 (7), 2493–2504.

(33). Frank DS; Matzger AJ Probing the Interplay between Amorphous Solid Dispersion Stability and Polymer Functionality. Mol. Pharmaceutics 2018, 15 (7), 2714–2720.

(34). Baghel S; Cathcart H; O'Reilly NJ Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. J. Pharm. Sci 2016, 105 (9), 2527–2544. [PubMed: 26886314]

(35). Van Duong T; Van den Mooter G The role of the carrier in the formulation of pharmaceutical solid dispersions. Part II: amorphous carriers. Expert Opin. Drug Delivery 2016, 13 (12), 1681–1694.

(36). Biedermann F; Appel EA; Del Barrio J; Gruendling T; Barner-Kowollik C; Scherman OA Postpolymerization modification of hydroxyl-functionalized polymers with isocyanates. Macromolecules 2011, 44 (12), 4828–4835.

(37). Mistry P; Amponsah-Efah KK; Suryanarayanan R Rapid assessment of the physical stability of amorphous solid dispersions. Cryst. Growth Des 2017, 17 (5), 2478–2485.

(38). Hancock BC; Zografi G The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. Pharm. Res 1994, 11 (4), 471–477. [PubMed: 8058600]

(39). Makower B; Dye W Sugar crystallization, equilibrium moisture content and crystallization of amorphous sucrose and glucose. J. Agric. Food Chem 1956, 4 (1), 72–77.

(40). Andronis V; Yoshioka M; Zografi G Effects of sorbed water on the crystallization of indomethacin from the amorphous state. J. Pharm. Sci 1997, 86 (3), 346–351. [PubMed: 9050804]

(41). Mehta M; Kothari K; Ragoonanan V; Suryanarayanan R Effect of water on molecular mobility and physical stability of amorphous pharmaceuticals. Mol. Pharmaceutics 2016, 13 (4), 1339–1346.

(42). Mehta M; Suryanarayanan R Accelerated Physical Stability Testing of Amorphous Dispersions. Mol. Pharmaceutics 2016, 13 (8), 2661–2666.

(43). Marsac PJ; Konno H; Rumondor AC; Taylor LS Recrystallization of nifedipine and felodipine from amorphous molecular level solid dispersions containing poly (vinylpyrrolidone) and sorbed water. Pharm. Res 2008, 25 (3), 647–656. [PubMed: 17846870]

(44). Konno H; Taylor LS Ability of different polymers to inhibit the crystallization of amorphous felodipine in the presence of moisture. Pharm. Res 2008, 25 (4), 969–978. [PubMed: 17520180]

(45). Rowland RS; Taylor R Intermolecular nonbonded contact distances in organic crystal structures: Comparison with distances expected from van der Waals radii. J. Phys. Chem 1996, 100 (18), 7384–7391.

(46). Frank DS; Matzger AJ Influence of Chemical Functionality on the Rate of Polymer-Induced Heteronucleation. Cryst. Growth Des 2017, 17 (8), 4056–4059.

(47). Chen Y; Liu C; Chen Z; Su C; Hageman M; Hussain M; Haskell R; Stefanski K; Qian F Drug–polymer–water interaction and its implication for the dissolution performance of amorphous solid dispersions. Mol. Pharmaceutics 2015, 12 (2), 576–589.

(48). Chen Y; Pui Y; Chen H; Wang S; Serno P; Tonnis W; Chen L; Qian F Polymer mediated drug supersaturation controlled by drug-polymer interactions persisting in aqueous environment. Mol. Pharmaceutics 2019, 16, 205.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(49). Surwase S; Itkonen L; Aaltonen J; Saville D; Rades T; Peltonen L; Strachan C Polymer incorporation method affects the physical stability of amorphous indomethacin in aqueous suspension. Eur. J. Pharm. Biopharm 2015, 96, 32–43. [PubMed: 26092472]

(50). Ullah M; Hussain I; Sun CC The development of carbamazepine-succinic acid cocrystal tablet formulations with improved in vitro and in vivo performance. Drug Dev. Ind. Pharm 2016, 42 (6), 969–976. [PubMed: 26460090]

(51). Qian F; Wang J; Hartley R; Tao J; Haddadin R; Mathias N; Hussain M Solution behavior of PVP-VA and HPMC-AS-based amorphous solid dispersions and their bioavailability implications. Pharm. Res 2012, 29 (10), 2766–2776.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

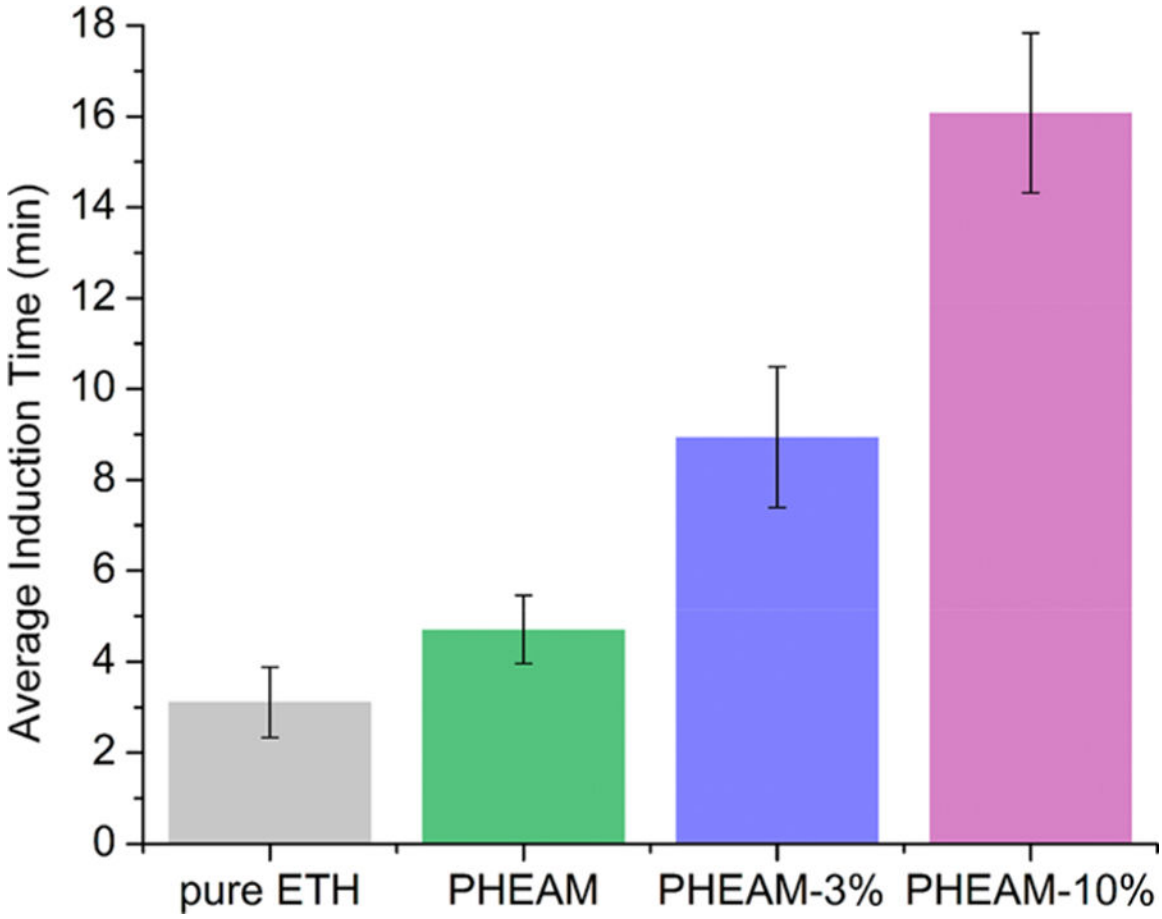


Figure 1.

Average induction time of aqueous ethenzamide (3 mg/mL, 18 mM) crystallization at 30 °C (shown with standard error) with 300 μg/mL poly(hydroxyethyl acrylamide) polymers as crystallization additives.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

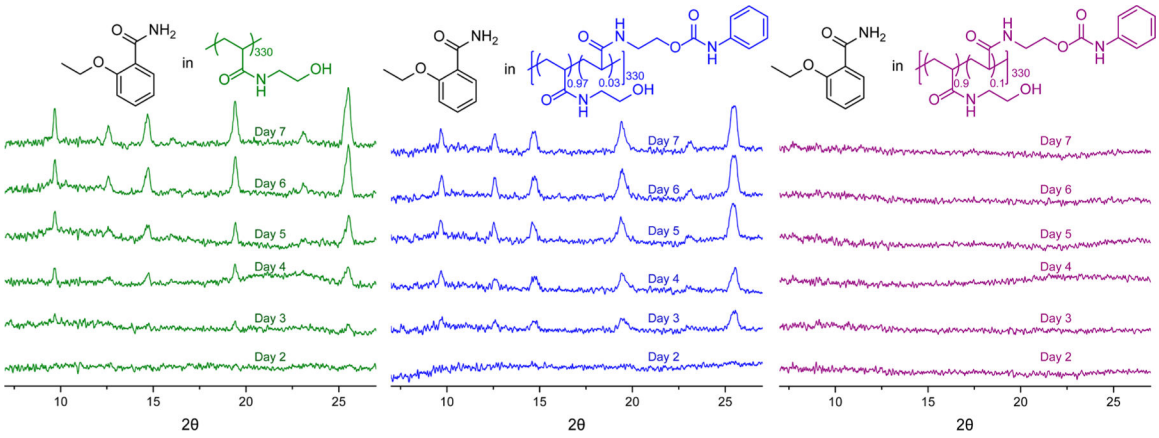


Figure 2.

Powder X-ray diffraction data of amorphous solid dispersions over time. Crystalline content of a dispersion containing 10 wt % ethenzamide in PHEAM over 1 week is shown on the left (in green), as compared to ethenzamide in PHEAM-3% (blue) and ethenzamide in PHEAM-10% (in purple). Diffraction patterns have been background subtracted and baseline corrected to remove signal from amorphous polymer and glass substrate (see Supporting Information for additional details and raw patterns).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

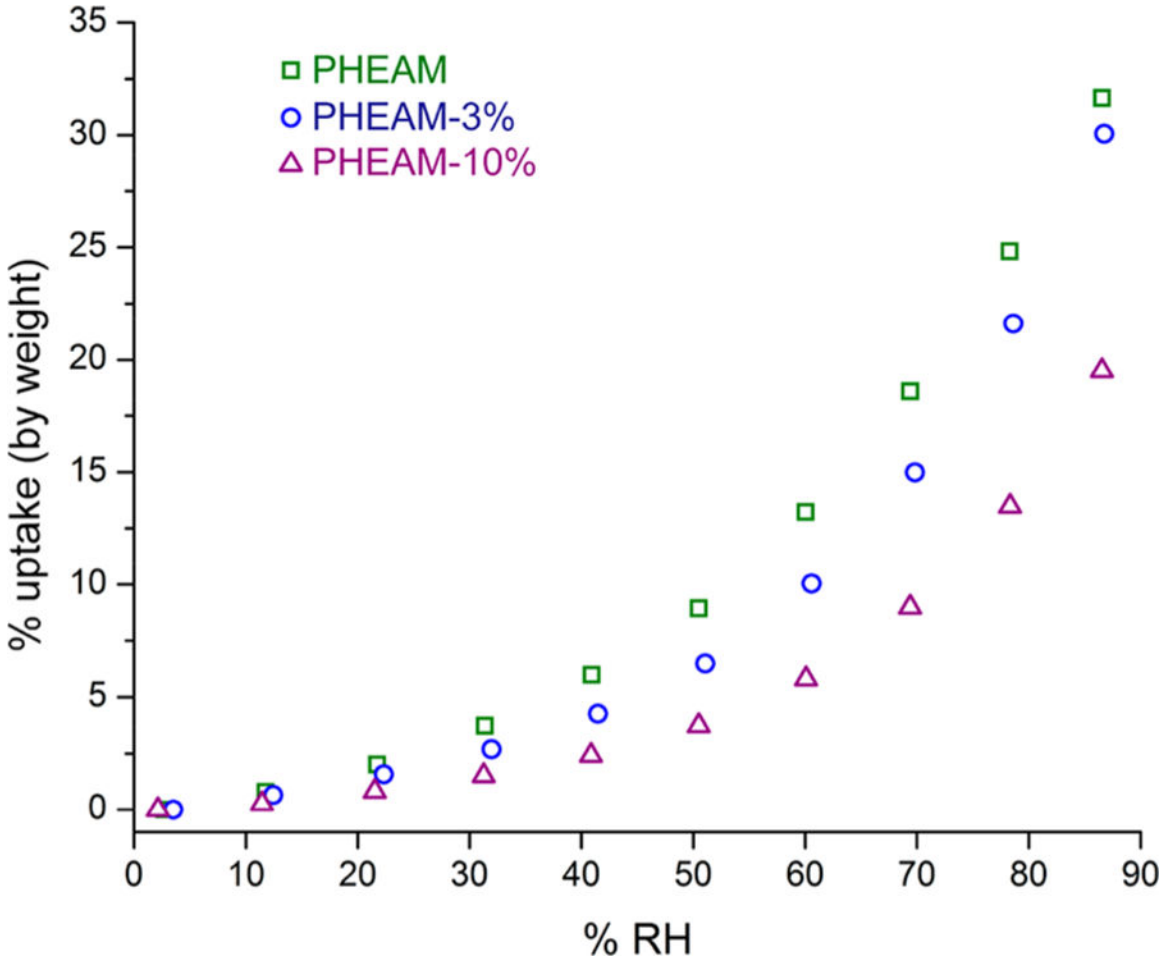


Figure 3.
Percent uptake of water vapor by pure polymeric materials. PHEAM is shown with green squares, PHEAM-3% is shown with blue circles, and PHEAM-10% is shown with purple triangles.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

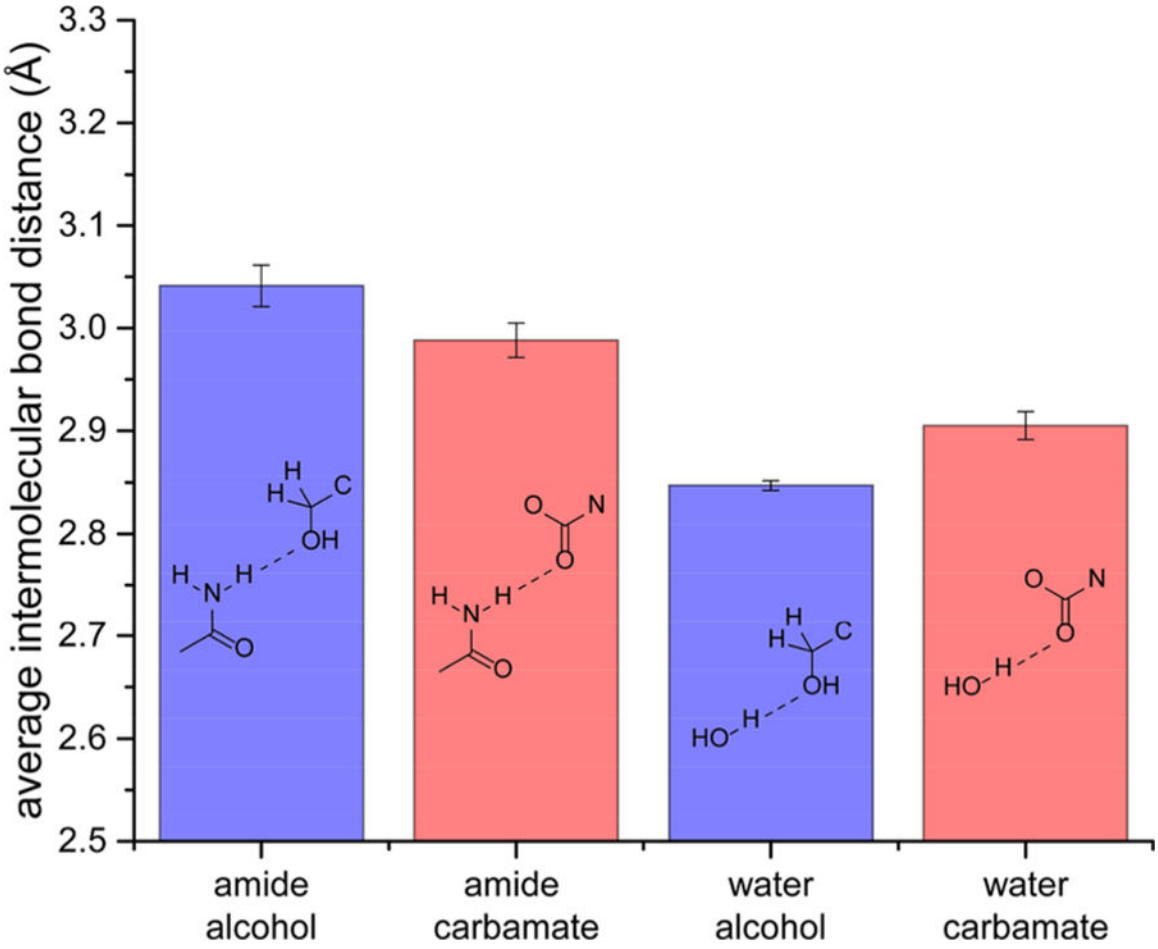
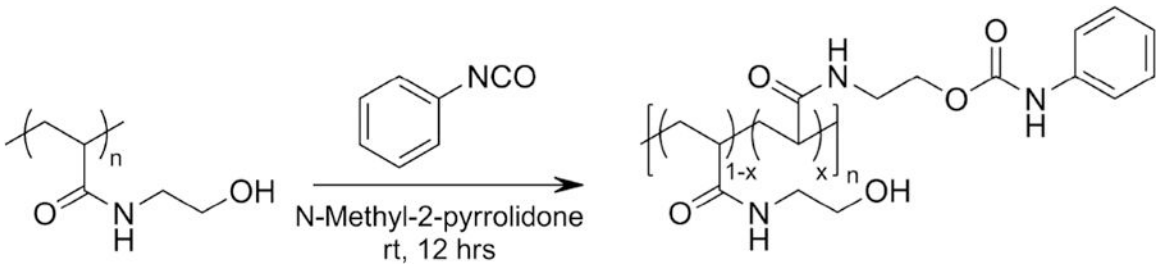


Figure 4.

Average intermolecular bond distance between amide or water groups and carbamate and primary alcohol groups as determined by an arithmetic average of bond distances from crystal structures from the CSD, shown with standard error. Interaction distances with alcohol functionalities are shown in blue, and interaction distances with carbamate functionalities are shown in red.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



Scheme 1.

Functionalization of Poly(N-hydroxyethyl acrylamide) To Tether Hydrophobic Phenyl Groups to Side-Chains on the Polymer

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1.

Glass Transition Temperatures of Pure PHEAM Polymers and Amorphous Solid Dispersions of Polymer and Ethenzamide[a] As Measured by Inflection Points by Modulated DSC[b]

	PHEAM	PHEAM-3%	PHEAM-10%
T_g of pure polymer (°C)	121.5 ± 0.8	123.7 ± 1.3	120.0 ± 0.7
T_g of amorphous dispersion (°C)	98.5 ± 0.8	96.5 ± 0.2	90.9 ± 2.5
water content by TGA (%)	5.6 ± 0.1	3.9 ± 1.2	1.2 ± 0.2

[a]10 wt % drug.

[b]See Supporting Information for additional details. Each value is the average of two measured transition temperatures. Water content was measured as total weight loss by TGA below 125 °C for amorphous dispersions stored at ambient temperature and humidity for 24 h. Dispersions were verified to be amorphous prior to TGA by polarized light microscopy.