Supporting Information for:

*Controlling Pharmaceutical Crystallization with Designed Polymeric Heteronuclei*

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SI 1. Materials. Acetaminophen (ACM) was obtained from Sigma-Aldrich (MO). Mefenamic acid was obtained from Alfa Aesar (MA). The tailor-made additive \(p\)-acetamidostyrene was synthesized by the known literature procedure.\(^1\) \(N\)-hydroxyphenyl methacrylamide was synthesized by the literature procedure.\(^2\) 2-((4-vinylphenyl)amino)benzoic acid was synthesized by a procedure similar to that described by Wolf and coworkers (See SI 8).\(^3\)

SI 2. Raman Spectroscopy. For acetaminophen Raman spectra were obtained using a Renishaw inVia Raman microscope equipped with a RenCam CCD detector, 785 nm diode laser, a 1200 lines/mm grating, and 50 \(\mu\)m slit. Spectra were collected and analyzed using the Wire 2.0 software package. Spectra were collected in extended scan mode with a range of 100-3200 cm\(^{-1}\). For mefenamic acid a Renishaw inVia Raman Microscope equipped with a RenCam CCD detector, 633 nm laser, 1800 lines/mm grating, and 50 \(\mu\)m slit was utilized for collecting data. Spectra were collected in extended scan mode in the range of 100-3500 cm\(^{-1}\) and then analyzed using the Wire 3.4 software package. Calibration was performed using a silicon standard for all experiments.

SI 3. Crystallization of acetaminophen in the presence of the additives. The additive (\(p\)-acetamidostyrene or \(N\)-hydroxyphenyl methacrylamide) was dissolved in a 200 mM aqueous acetaminophen solution at 70 °C in a 20 mL glass vial. Three solutions with different concentrations of additive, 1 mM, 3 mM, and 6 mM, were prepared in addition to a control: a 200 mM aqueous acetaminophen solution.

![Morphology of acetaminophen crystals](image)

**Figure S1.** Morphology of acetaminophen crystals grown in the presence of \(p\)-acetamidostyrene. Clockwise from top left: no additive, 1 mM additive, 3 mM additive, and 6 mM additive.
SI 4. Raman spectra of acetaminophen crystallized in the presence of the additives.

Figure S2. Raman spectra of acetaminophen crystals obtained from crystallizations in the presence of no additive, 1 mol% *N*-hydroxyphenyl methacrylamide, 5 mol% *N*-hydroxyphenyl methacrylamide, and 10 mol% *N*-hydroxyphenyl methacrylamide (from the bottom to the top spectrum).

Figure S3. Raman spectra of acetaminophen crystals obtained from crystallizations in the presence of no additive, 1 mol% *p*-acetamidostyrene, 5 mol% *p*-acetamidostyrene, and 10 mol% *p*-acetamidostyrene (from the bottom to the top spectrum).
SI 5. Polymerization of p-acetamidostyrene/styrene and N-hydroxyphenyl methacrylamide/styrene. Copolymers of p-acetamidostyrene/styrene and N-hydroxyphenyl methacrylamide/styrene with 1 mol%, 5 mol%, and 10 mol% of additive relative to total polymer as well as pure polystyrene were synthesized by free radical polymerization. In all cases 1 mol% of 2,2′-Azobis(2-methylpropionitrile) (AIBN) with respect to monomer was used as the initiator. Solutions of monomer and initiator dissolved in acetone (2:1 v/v acetone to monomer) were heated in glass vials under a nitrogen atmosphere for 24 hours at 75 °C to induce polymerization. Afterwards the polymers were fractionally precipitated once from CH$_2$Cl$_2$ with methanol. The polymer was then ground with a mortar and pestle. This yielded 185 mg of the 1 mol% p-acetamidostyrene/styrene copolymer as a white powder. GPC: $M_n = 45,410$, $M_w = 73,546$. FT-IR (KBr): 3419 (w), 3024 (m), 2921 (m), 1699 (w), 1600 (m), 1514 (w), 1492 (s), 1452 (s), 756 (s), 696 (vs) cm$^{-1}$. This reaction with 5 mol% p-acetamidostyrene relative to the total monomer used yielded 202 mg of the 5 mol% p-acetamidostyrene/styrene copolymer as a white powder. GPC: $M_n = 31,882$, $M_w = 146,111$. FT-IR (KBr): 3406 (w), 3024 (m), 2920 (m), 1695 (m), 1600 (m), 1514 (m), 1492 (s), 1451 (s), 756 (s), 696 (vs) cm$^{-1}$. This reaction with 10 mol% p-acetamidostyrene relative to the total monomer used yielded 168 mg of the 10 mol% p-acetamidostyrene/styrene copolymer as a white powder. GPC: $M_n = 14,982$, $M_w = 35,187$. FT-IR (KBr): 3426 (w), 3023 (m), 2921 (m), 1652 (w), 1600 (m), 1512 (m), 1492 (s), 1451 (s), 756 (s), 697 (vs) cm$^{-1}$. This reaction with 1 mol% N-hydroxyphenyl methacrylamide relative to the total monomer utilized yielded 197 mg of the 1 mol% N-hydroxyphenyl methacrylamide/styrene copolymer as a white powder. GPC: $M_n = 26,725$, $M_w = 74,412$. FT-IR (KBr): 3447 (w), 3024 (m), 2921 (m), 1652 (w), 1600 (m), 1512 (m), 1492 (s), 1451 (s), 756 (s), 696 (vs) cm$^{-1}$. This reaction with 5 mol% N-hydroxyphenyl methacrylamide relative to the total monomer utilized yielded 178 mg of the 5 mol% N-hydroxyphenyl methacrylamide/styrene copolymer as a white powder. GPC: $M_n = 17,474$, $M_w = 110,897$. FT-IR (KBr): 3435 (w), 3024 (m), 2921 (m), 1652 (w), 1600 (m), 1512 (m), 1492 (s), 1451 (s), 756 (s), 697 (vs) cm$^{-1}$. This reaction with 10 mol% N-hydroxyphenyl methacrylamide relative to the total monomer utilized yielded 151 mg of the 10 mol% N-hydroxyphenyl methacrylamide/styrene copolymer as a white powder. GPC: $M_n = 32,698$, $M_w = 67,297$. FT-IR (KBr): 3024 (m), 2921 (m), 1600 (m), 1492 (s), 1451 (s), 756 (s), 696 (vs) cm$^{-1}$.

SI 6. Crystallization of acetaminophen in the presence of additive-containing polymers. Acetaminophen was dissolved in water at 70 °C to produce a 200 mM solution which was subsequently added to the wells of a polypropylene plate containing the ground polymers. The plate was sealed with a Costar 3080 mat and heated for 30 min at 70 °C. The sealed polypropylene plate was removed from the heat source and all crystallizations were monitored by checking each well by optical microscopy every fifteen minutes. Three trials consisting of eight crystallizations in the presence of each type of polymer (1 mol% p-acetamidostyrene/styrene copolymer, 5 mol% p-acetamidostyrene/styrene copolymer, 10 mol% p-acetamidostyrene/styrene copolymer, 1 mol% N-hydroxyphenyl methacrylamide/styrene copolymer, the 5 mol% N-hydroxyphenyl methacrylamide/styrene copolymer, and polystyrene) were performed as well as in the absence of the polymers. The induction time for crystallization was determined to be the moment a crystal appeared in the well.
SI 7. Solubility of \( p \)-Acetamidostyrene/styrene copolymers, \( N \)-hydroxyphenyl methacrylamide/styrene copolymers, and polystyrene in water. \( p \)-Acetamidostyrene/styrene copolymers, \( N \)-hydroxyphenyl methacrylamide/styrene copolymers, and polystyrene were added to separate 4 mL vials, ~3 mg of each polymer, along with 3 mL of water and sealed. These vials were heated at 70 °C for 30 min and cooled to room temperature. The resulting aqueous solutions were filtered and the UV–vis absorbance spectrum of the each was measured. No absorbance was observed from any of the solutions above 220 nm.

SI 8. Synthesis of 2-((4-vinylphenyl)amino)benzoic acid. The procedure used to synthesize 2-((4-vinylphenyl)amino)benzoic acid was similar to that described by Wolf and coworkers. Specifically, a mixture of 4-aminostyrene (9.3 mmol), 2-bromobenzoic acid (8.8 mmol), K\(_2\)CO\(_3\) (13.2 mmol), Cu powder (0.2-0.3 \( \mu \)m, 0.8 mmol), Cu\(_2\)O (<5 \( \mu \)m, 0.4 mmol), and 3 mL of 2-ethoxyethanol was refluxed at 130 °C for 24 hours under nitrogen. The cooled reaction mixture was poured into 30 mL of water to which decolorizing charcoal was added. The mixture was then filtered to remove the charcoal. The crude product was obtained by precipitation upon acidification of the filtrate with 1M HCl. The residue was dissolved in dichloromethane and then purified by column chromatography using a solvent system of 20:1 dichloromethane to ethyl acetate with 0.5 % acetic acid by volume. The resulting yellow needle-like crystals were obtained in 60% yield. mp= 225 °C \( ^1\)H NMR (500 MHz, DMSO-\( d_6\), ppm): \( \delta \) 13.10 (s, 1H), 9.68 (s, 1H), 7.91 (dd, \( J = 1.6 \) Hz, \( J = 8.0 \) Hz, 1H), 7.45 (dt, \( J_d = 8.4 \) Hz, \( J_t = 2.1 \) Hz, 2H), 7.41 (dddd, \( J = 1.7 \) Hz, \( J = 7.1 \) Hz, \( J = 8.6 \) Hz, 1H), 7.27 (dd, \( J = 0.8 \) Hz, \( J = 8.5 \) Hz, 1H), 7.22 (dt, \( J_d = 8.5 \) Hz, \( J_t = 2.3 \) Hz, 2H), 6.80 (dddd, \( J = 1.1 \) Hz, \( J = 7.1 \) Hz, \( J = 8.0 \) Hz, 1H), 6.70 (dd, \( J = 10.9 \) Hz, \( J = 17.6 \) Hz, 1H), 5.73 (dd, \( J = 1.0 \) Hz, \( J = 17.6 \) Hz, 1H), 5.17 (dd, \( J = 1.0 \) Hz, \( J = 10.9 \) Hz, 1H); \(^{13}\)C NMR (125 MHz, DMSO-\( d_6\), ppm): \( \delta \) 169.9, 146.4, 140.3, 136.1, 134.1, 131.9, 131.7, 127.2, 120.8, 117.4, 114.2, 113.1, and 112.5; HRMS (EI) (\( m/z \)) calcd (found) for C\(_{15}\)H\(_{13}\)NO\(_2\): 239.0946 (239.0948).

SI 9. Crystallization of mefenamic acid in the presence of 2-((4-vinylphenyl)amino)benzoic acid. The additive, 2-((4-vinylphenyl)amino)benzoic acid, was dissolved in a 8.1 mg/mL ethanol solution of mefenamic acid at 65 °C in 4 mL vials. Three trials consisting of eight crystallizations with different concentrations of the additive, 1 mol%, 5 mol%, and 10 mol% (relative to the total amount of mefenamic acid), were prepared in addition to a control: a 8.1 mg/mL ethanol solution of mefenamic acid.
Figure S4. Induction time for crystal appearance for mefenamic acid crystallized in the presence of 2-((4-vinylphenyl)amino)benzoic acid in solution.

Figure S5. Morphology of mefenamic acid crystals grown in the presence of 2-((4-vinylphenyl)amino)benzoic acid. (a) no additive, (b) 1 mol% additive, (c) 5 mol% additive, and (d) 10 mol% additive.
Figure S6. Raman spectra of mefenamic acid crystals obtained from crystallizations in the presence of no additive, 1 mol% additive, 5 mol% additive, and 10 mol% additive (from the bottom to the top spectrum).

SI 10. Polymerization of 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene and divinylbenzene. Copolymers of 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene (DVB) with 1 mol%, 5 mol% and 10 mol% of additive to total polymer as well as pure divinylbenzene were synthesized. In all cases 2 mol% of 2,2'-Azobis(2-methylpropionitrile) (AIBN), with respect to the amount of divinylbenzene utilized, was used as the initiator. Solutions of monomer and initiator dissolved in ethanol (1:1 v/v ethanol to monomer) were heated in glass vials under a nitrogen atmosphere for 12 hours at 75 °C to induce polymerization. After polymerization was complete, each of the polymers was ground with a mortar and pestle into a fine powder (≈ 1 µm as measured by optical microscopy). The ground polymers were sonicated in hot ethanol, then in hot acetone, and washed several times with hot ethanol and hot acetone. The polymers were then dried in a vacuum oven at 85 °C for two hours. Additionally, copolymer films comprised of 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene were synthesized by dip coating glass slides into a 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene monomer solution with 2 mol% of AIBN relative to the amount of DVB. The monomer coated slides were then photopolymerized with four 15 W UVA blubs in an N₂ atmosphere, to yield thin polymer films. The polymer films were then washed with ethanol and acetone. The polymer coated slides were then placed in a vacuum oven at 85 °C for two hours.

SI 11. Crystallization of mefenamic acid in the presence of 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymers and divinylbenzene. Solutions of mefenamic acid (8.1 mg/mL) in ethanol were heated at 65 °C for ten minutes in the presence of 1 mg of the 1 mol%, 5
mol%, 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymers, and divinylbenzene. Three trials consisting of eight crystallizations in the presence of each polymer type were performed as well as a control: a 8.1 mg/mL ethanol solution of mefenamic acid. The crystallizations were monitored by time-lapse photography (photos were taken every 60 seconds) with a Canon EOS Rebel SL1 camera with a EF-S 18-55mm f/3.5-5.6 IS STM lens controlled by DSLR Remote Pro for Windows. The induction period for the appearance of crystals was determined by the first moment that a crystal appeared in the vial. The smallest crystal size that was observed using the camera was ~10 µm. In order to determine how the additive copolymer was interacting with the mefenamic acid molecules in solution, mefenamic acid was also crystallized in the presence of 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymer films. A solution of mefenamic acid was prepared by dissolving 1 mg of mefenamic acid in 1 mL of ethanol. The solution was dispensed onto ten distinct 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymer films and allowed to evaporate. The resulting crystals were analyzed by powder X-ray diffraction.

Figure S7. Induction time for crystal appearance for mefenamic acid crystallized in the presence of the 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymers and divinylbenzene.
Figure S8. Raman spectra of mefenamic acid crystals obtained from crystallizations in the presence of no polymer, 1 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymer, 5 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene, and 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene (from the bottom to the top spectrum).

Figure S9. Morphology of mefenamic acid crystals obtained in the presence of the tailor-made additive copolymers.
SI 12. Determining effect of surface energy on induction time for crystal appearance. The 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer, 1 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer, the 10 mol% hydroxyethyl methacrylate/DVB copolymer and 1 mol% hydroxyethyl methacrylate/DVB copolymer were synthesized by the same procedure described in SI 10. The contact angles were measured by using a CAM 100 Optical Contact Meter (KSV Instruments Ltd.). For each type of polymer film ten drops of water were deposited across each type of polymer surface to ensure a consistent advancing water contact angle measurement (see Figure S10). Then following an procedure similar to SI 11 mfenamic acid was crystallized in the presence of the 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer, 1 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer, the 10 mol% hydroxyethyl methacrylate/DVB copolymer and 1 mol% hydroxyethyl methacrylate/DVB (see Figure S11). Five crystallizations in the presence of each polymer type (10 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer, 1 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer, the 10 mol% hydroxyethyl methacrylate/DVB copolymer and 1 mol% hydroxyethyl methacrylate/DVB, and DVB) were performed.

(a) 10 mol% hydroxyethyl methacrylate/DVB copolymer

Average Advancing Water Contact Angle = 32.2° ± 0.82°

(b) 1 mol% hydroxyethyl methacrylate/DVB copolymer

Average Advancing Water Contact Angle = 60.3° ± 0.73°
Figure S10. Average advancing water contact angles and representative photos for the (a) 10 mol% hydroxyethyl methacrylate/DVB copolymer, (b) 1 mol% hydroxyethyl methacrylate/DVB copolymer, (c) 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer, and (d) 1 mol% 2-((4-vinylphenyl)amino)benzoic acid/DVB copolymer.
**Figure S11.** Induction time for crystal appearance for mefenamic acid crystallized in the presence of the 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymers, hydroxyethyl methacrylate /DVB copolymers, and divinylbenzene.

**SI 13. Crystallization of acetaminophen on polymer films.** Solutions of polystyrene, the 10% p-acetamidostyrene containing copolymer, and the 10% N-hydroxyphenyl methacrylamide containing copolymer in toluene (5% w/w) were placed onto glass slides via pipette. The slides were spun at 2000 rpm for 30 seconds. Crystallization was carried out by placing droplets of aqueous acetaminophen solution (200 mM) onto the polymer films via syringe equipped with a 26 gauge needle and allowing the droplets to evaporate at room temperature.

**SI 14. Single crystal face indexing of acetaminophen crystals grown on polymer films.** The orientation matrix for monoclinic acetaminophen was collected on a Bruker SMART CCD-based X-ray diffractometer (MoKα = 0.71073 Å) and determined using the Bruker SMART software package (version 5.054). Using manual control of the goniometer, crystal faces were aligned against the optical axis of a telescope lens used to visualize the mounted crystal. The position of the goniometer was noted and the aligned crystal face indexed according to the orientation matrix determined previously. Monoclinic acetaminophen grown from p-acetamidostyrene/styrene and N-hydroxyphenyl methacrylamide/styrene copolymer films exhibited oriented crystallization from the (001) face in 54% and 46% of crystals, respectively. Monoclinic acetaminophen grown from polystyrene films exhibited oriented crystallization from the (10-1) face in 42% of crystals. Determination of growth orientation of the remaining crystals was complicated by their lack of discernable morphology.
SI 15. Powder X-ray diffraction (PXRD). Powder X-ray diffraction was conducted at room temperature using a Bruker D8 Advance diffractometer operating at 40 kV and 40 mA with Cu-Kα radiation (1.5406 Å). The powder patterns were collected by scanning from 5° to 45° in 2θ using a step size of 0.02° and time of 1.5 seconds/step. Powder patterns were processed using Jade Plus v9.5. The crystals on copolymer films were preferentially oriented along the (100) face.

![Figure S12. Representative PXRD pattern of mefenamic acid crystallized on a 10 mol% 2-((4-vinylphenyl) amino)benzoic acid/divinylbenzene copolymer film.](image)

SI 16. Indexing mefenamic acid crystals formed in the presence of 2-((4-vinylphenyl)amino)benzoic acid and pure mefenamic acid. Pure mefenamic acid and mefenamic acid crystals grown in the presence of 2-((4-vinylphenyl)amino)benzoic acid were indexed (Figures S13, S14) using a Rigaku R-Axis Spider diffractometer with an image plate area detector using graphite monochromated Cu-Kα radiation (λ = 1.54187 Å) operated at 2.0 kW power (40 kV, 44 mA). Both types of crystals were mounted on MiTeGen MicroMounts™, indexed, and then axial images were acquired. It was found that the tailor-made additive was in fact adsorbing onto the (100) face.
Figure S13. (a) View along the a axis of blade-like crystal of mefenamic acid (additive present). (b) View along the c axis of blade-like mefenamic acid crystal.

Figure S14. (a) View along the a axis of native mefenamic acid crystal. (b) View along the c axis of native mefenamic acid crystal.

SI 17. Examining the effect of unground polymer on the induction time for crystal appearance. A copolymer of 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene was synthesized and purified identical to the procedure described in SI 10. However, the polymer was not ground into a fine powder but rather left in large pieces (~ 1 mm) in order to determine how the size of the polymer heteronucleant affected the induction time for crystal appearance. The crystallizations were performed identically to those described in SI 11. The induction time for crystallizations in the presence of the unground 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymer was found to be roughly between that of the ground 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymer and 5 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene.
Figure S15. Crystallization of mefenamic acid in the presence of that 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymers, unground 10 mol% 2-((4-vinylphenyl)amino)benzoic acid/divinylbenzene copolymer, divinylbenzene, and pure mefenamic acid.
SI 18. References

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