Supplementary Information - Methods

1. Materials

Dibucaine, lidocaine, and tolbutamide were obtained commercially from Spectrum Chemical, Gardena, CA, USA. 4-biphenylacetic acid, 4-biphenylcarboxylic acid, 4-biphenylmethanol, 4-phenylphenol, anthranilic acid, benzamide, bifonazole, chlorpropamide, chlorzoxazone, flufenamic acid, flurbiprofen, phenacetin (p-acetophenetidide) and poly(acrylic acid) (PAA, M_v 450.000) were purchased from Sigma-Aldrich Inc, St. Louis, MO, USA. Eudragit® E100 (E100) was obtained commercially from Rohm GmbH, Darmstadt, Germany. Poly(styrene sulfonic acid) [PSSA, 30 % (w/w) solution in water] was purchased from Polysciences, Inc., Warrington, PA, USA. Hydroxypropylmethylcellulose (HPMC, viscosity 6 mPa.s, Hypromellose USP substitution type 2910) and hydroxypropylmethylcellulose acetate succinate (HPMCAS, grade AS-MF) were kindly provided by Shin-Etsu Chemical Co., Ltd., Tokyo, Japan. Dichloromethane (DCM, ChromAR®) and phosphorous pentoxide (powder) were purchased from Mallinckrodt Baker, Inc., Phillipsburg, NJ, USA. Ethyl alcohol (EtOH, 200 proof) was purchased from Pharmco Products, Inc., Brookfield, CT, USA and Aaper, Shelbyville, KY, USA. Poly(vinylpyrrolidone) (PVP, K 12, Ph. Eur., USP) and poly(vinylpyrrolidone-vinyl acetate) (PVPVA, K 28, Ph. Eur.) were kindly provided by BASF Aktiengesellschaft, Ludwigshafen, Germany.

1.1. Preparation and storage of spin-coated samples

Solutions were prepared by dissolving both drug and polymer in EtOH, using drug/polymer weight ratios of 75/25, 50/50, and 25/75 (w/w). For the compounds used in our previous study[14], additional ratios of 90/10, 60/40, 40/60, 20/80 and 10/90 (w/w) were used. The fact that different

sets of ratios were used for different drugs is acceptable as all analysis focuses on differences between polymers for a specific drug and no attempt is made to compare differences between drugs. For solutions with HPMC and HPMCAS, a 1/1 (w/w) EtOH/DCM mixture was used as the solvent. In cases where precipitation was observed (this could be observed for bifonazole-PAA, bifonazole-PSSA, lidocaine-PAA and lidocaine-PSSA in some weight ratios), these samples were mixed vigorously prior to spin coating, using a vortex mixer. Spin-coating was performed using a KW-4A spin-coater (Chemat Technology Inc., Northridge, CA, USA) on 18*18 mm microscope cover slips (Corning Incorporated, Corning, NY, USA). For spin coating, 200 µl of solution was spread out over the cover slip. Subsequently, the sample was spun for 20 sec at 8000 rpm. Each solution was spin coated in triplicate. Following spin coating, the samples were placed in a container under dry conditions, using P_2O_5 as a drying agent.

1.2. Evaluation of crystallization behavior of spin coated samples upon storage

Crystallization of the samples immediately after spin coating and upon storage was evaluated with polarized light microscopy using an Eclipse E600 POL polarizing microscope (Nikon Corporation, Tokyo, Japan), equipped with 4x, 10x, 20x and 40x objectives. Image analysis was performed on the three replicates prepared for each sample. As the spin-coated films are very thin, it is reasonable to assume that when crystallization occurs, it will do so over the complete height of the film. Hence, this 2-dimensional analysis enables a semi-quantitative evaluation of crystallinity based on the relative areas of birefringent and non-birefringent regions. It should be noted that none of the polymers can crystallize, so birefringent regions solely arise from drug crystallites. Spin-coated samples were evaluated for crystallization within 30 minutes after spin coating (‘day 0’ time point). Samples were subsequently placed in a container under dry conditions, using P_2O_5 as a desiccant. Samples were evaluated for crystallinity after 1, 3 and 7 days of storage under dry

conditions. The samples were then semiquantitatively categorized at each time point as being (i) completely amorphous ("AAAA", crystallinity was absent), (ii) slightly crystalline ("AAAC", some crystallinity was observed, but the drug remained predominantly amorphous), (iii) semicrystalline ("AACC", the amounts of crystalline and amorphous drug were comparable), (iv) predominantly crystalline ("ACCC", crystalline drug dominated over amorphous, but crystallization was still incomplete), or (v) completely crystalline ("CCCC", all drug had crystalllized). Further data analysis was done by calculation of the 'amorphicity index' [AI (%)] of each weight ratio of the drug-polymer combinations, to characterize the crystallization inhibiting potential thereof. The latter was defined as the number of A's counted in the categorizations of the different time points, divided by 16 [the number of A's in a sample that remains completely amorphous ('AAAA' at all time points)] and expressed as a percentage. The overall potential of a polymer to inhibit crystallization of a certain drug was determined by calculating the average of the AI values of the different weight ratios for the specific drug-polymer combination.

1.3. Attenuated total reflectance Fourier transform infrared spectroscopy (FTIR)

ATR-FTIR spectra of select pure materials and mixtures of drug and polymers, combined in equimolar concentrations of the drug and polymer functional groups were collected just above the melting point of the drug. Spectra were collected using a Bio-Rad FTS-6000 (Bio-Rad, Cambridge, MA, USA) equipped with an attenuated total reflectance (ATR) accessory (diamond crystal, Golden Gate, Graseby Specac, Inc., Cranston, RI, USA).Samples were scanned over a spectral region of 500 - 4000 cm^{-1} with a resolution of 4 cm^{-1}. 128 scans were co-added for each sample. Dry, CO_2-free air was used to purge the instrument to prevent spectral interference from water vapor and CO_2.

1.4. Evaluation of hydrogen bonding probabilities between functional groups using the Cambridge Structural Database (CSD)

In a number of cases, probable hydrogen bond formation between pairs (A and B) of functional groups was evaluated based on crystal structures found in the CSD (Version 5.31, CCDC, Cambridge, UK). Queries were built in ConQuest (Version 1.12, CCDC, Cambridge, UK), using structures containing the 2 functional groups of interest, combined with a formula query to exclude structures with additional heteroatoms and/or functional groups [e.g. for the $C(O)NC_2$ – COOH pair the formula query would be '$C_{1\text{-}500}H_{1\text{-}500}N_1O_3$', implying only structures within the set having the $C(O)NC_2$ and COOH functional groups having 1 to 500 carbon and hydrogen atoms in combination with one nitrogen and three oxygen atoms would be selected]. Hits were further analyzed using Mercury (CCDC, Cambridge, UK) after exclusion of multiple structures having the same crystal structures (based on their CSD refcode and space group) and structures where intramolecular hydrogen bonding occurred (using the default rule that donor and acceptor atoms have to be separated by at least 3 bonds). Hydrogen bonding was evaluated using the default criteria for hydrogen bond evaluation in Mercury. Based on this, the observed hydrogen bond pattern of the structures with A and B functional groups was classified as (1) 'none' (no hydrogen bonding could be observed), (2) 'A-A' (only), (3) 'A-B' (only), (4) 'B-B' (only), (5) 'A-A & A-B', (6) 'A-A & A-B', (7) 'A-B & B-B', and (8) 'A-A, A-B & B-B'. Probabilities (%) of these different classes were further calculated by dividing the number of cases found in that class by the total number of structures evaluated.

1.5. Computations:

For compounds potentially forming intramolecular hydrogen bonds (flufenamic acid and anthranilic acid), *ab initio* energies of different conformations were evaluated using Density Functional Theory (DFT) calculations. For this purpose, Spartan'08 software was used (Wavefunction Inc., Irvine, CA, USA) and equilibrium geometries were determined at the B3LYP/6-311++G(3d2f, 2p) level, preceded by an equilibrium geometry calculation using the 6-31G* basis set. For anthranilic acid, the O=C–C angle was constrained at 120° and the $C(NH_2)$–C–C–O(H) angle was constrained from 0 to 180°, using steps of 10°. pKa's were determined with ChemAxon calculator plugins using MarvinSketch 5.2.0 (ChemAxon Kft., Budapest, Hungary). Structures of the drugs and that of oligomers of the polymers were used for this purpose. Only pK_a values resulting in ionization (>50%) between 0 and 14 were considered.