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Small Scale Screening To Determine the Ability of Different Polymers To Inhibit Drug Crystallization upon Rapid Solvent Evaporation

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Abstract: In this study, the ability of 7 chemically diverse polymers [Eudragit E100 (E100), poly(acrylic acid) (PAA), poly(vinylpyrrolidone) (PVP), poly(vinylpyrrolidone-vinyl acetate) (PVPVA), poly(styrene sulfonic acid) (PSSA), hydroxypropylmethylcellulose (HPMC) and hydroxypropylmethylcellulose acetate succinate (HPMCAS)] to inhibit the crystallization of 8 readily crystallizable model compounds [benzamide (BD), phenacetin (PH), flurbiprofen (FB), flufenamic acid (FFA), chlorpropamide (CP), chlorzoxazone (CZ), bifonazole (BI) and lidocaine (LI)] was investigated. Films of the different drug−polymer combinations were prepared by rapid evaporation from solution, using a spin coating method. A total of 7 different drug/polymer weight ratios [90/10, 75/25, 60/40, 50/50, 40/60, 25/75 and 10/90 (w/w)] were evaluated for each drug−polymer combination. Crystallization behavior of the films was monitored using polarized light microscopy over 7 days of room temperature storage under dry conditions. It was observed that compounds having a higher crystallization tendency for the pure compound tended to be more difficult to stabilize using the polymeric additives; more polymer was required. In addition, the stabilizing ability of the polymers varied considerably for the individual compounds, with the acidic polymers PAA and PSSA showing the most extreme behavior. The acidic polymers were good stabilizers for the drugs with basic and amide functional groups, but extremely poor stabilizers for acidic drugs. A reasonable correlation between crystallization inhibition in spin coated films versus bulk powders (prepared by rotary evaporation) was observed. The small scale screening method is thus a potentially useful technique to evaluate the role of drug−polymer chemistry in the stabilization of amorphous solid dispersions.

Keywords: Crystallization; amorphous state; spin-coating; solvent evaporation; physical stability; polymeric additives; stabilization

1. Introduction

As a result of recent trends whereby potential new drug candidates are frequently characterized by having low aqueous solubility and/or dissolution rate, the application of solid dispersion technology has become increasingly important as a formulation tool in pharmaceutical development.[1,2] Through application of this technology, a drug product can be obtained where the drug is molecularly dispersed in a suitable carrier, typically a polymer.[2] As a result of the highly dispersed, noncrystalline state of the drug, an increase in apparent solubility and/or a dissolution rate enhancement can be obtained, potentially resulting in higher exposure upon oral administration, relative to the crystalline solid.

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One of the major drawbacks of the solid dispersion approach is the potential for recrystallization during storage. The latter process is driven by the higher energy state of the amorphous drug, relative to the crystalline form.[3] There are numerous examples whereby improved physical stability is achieved through the use of polymers.[4−6] Polymers commonly used to prepare amorphous solid dispersions include, among others, poly(vinylpyrrolidone), poly(vinylpyrrolidone-vinyl acetate), hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate succinate, polyacrylates and polymethacrylates.[1] In studies of solid dispersions, the crystallization of a single model drug, combined with one or more polymers, is typically investigated. While such studies are useful, this focused approach makes it difficult to address important questions such as (i) is the crystallization tendency of the drug in a solid dispersion linked to the crystallization tendency of the corresponding pure amorphous drug, and (ii) can polymers can be ranked in terms of their general tendency to prevent the crystallization of drugs, in other words is a given polymer a better overall stabilizer?

Traditional technologies used to prepare solid dispersions include cooling from the melt (e.g., melt extrusion) and solvent evaporation/sublimation (e.g., spray drying or freeze-drying), although there is increasing interest in alternative methodologies such as mechanical disruption.[7] These methods consume relatively large quantities of drug, and therefore low consumption methods that provide information about the feasibility of solid dispersion formation are of interest. Recent studies by our group have reported the use of miniaturized approaches to screen crystallization tendency of pure drugs either upon cooling from the melt (in situ preparation in DSC pans) or upon rapid solvent evaporation (using spin coating).[8,9] Following evaluation of a set of 51 compounds, clear differences were observed in crystallization behavior, leading to a crystallization classification system where compounds were described as being rapid (class I), intermediate (class II) or slow (class III) crystallizers. Furthermore, a good similarity was found in the classification results obtained by cooling from the melt and solvent evaporation.

The aim of the current study is to investigate the ability of different polymers to inhibit the crystallization of several model compounds upon rapid solvent evaporation. The first hypothesis to be tested is that more polymer will be required to inhibit the crystallization of compounds which have a high propensity to crystallize. The second hypothesis is that the stabilizing ability of different polymers will vary and will depend on the chemistry of the drug and polymer. The model compounds selected for this study have been previously classified as fast or intermediate crystallizers. Spin coating was used as a small scale method to prepare solid dispersions of a test set of 8 compounds, varying in their chemistry and crystallization tendency (classes I and II).[9] These compounds were combined with various proportions of 7 chemically diverse polymers, spin coated and monitored for crystallization. Finally, the relevance of the crystallization data obtained from spin coated films to that of bulk powders was assessed by characterizing a selection of drug−polymer powders prepared by rotary evaporation.

2. Materials and Methods

2.1. Materials. Lidocaine (LI) was obtained from Spectrum Chemical, Gardena, CA. Benzamide (BD), bifonazole (BI), chlorpropamide (CP), chlorzoxazone (CZ), flufenamic acid (FFA), flurbiprofen (FB), phenacetin [(PH), *p*-acetophenetidide] and poly(acrylic acid) (PAA, M_v 450.000) were purchased from Sigma-Aldrich Inc., St. Louis, MO. 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. 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. Trifluoroacetic acid (99%) was purchased from Acros Organics, Geel, Belgium. Dichloromethane (DCM, ChromAR), methanol (MeOH, anhydrous, ChromAR) and phosphorus pentoxide (powder) were purchased from Mallinckrodt Baker, Inc., Phillipsburg, NJ. Ethyl alcohol (EtOH, 200 proof) was purchased from Pharmco Products, Inc., Brookfield, CT, and Aaper, Shelbyville, KY. Acetic acid (glacial, HPLC) was obtained commercially from Fisher Scientific, Fair Lawn, NJ. Benzenesulfonic acid (≥98%) was purchased from Fluka Chemie GmbH, Buchs, Switzerland). 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.

2.2. Preparation and Storage of Spin-Coated Samples. Solutions were prepared by dissolving both drug and polymer in EtOH, using drug/polymer weight ratios of 90/10, 75/25,

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40/60, 50/50, 60/40, 25/75 and 10/90 (w/w). For preparation of drug−polymer solutions containing either HPMC or HPMCAS, a 1/1 (w/w) EtOH/DCM mixture was used as the solvent. In cases where precipitation was observed (this was observed for BI-PAA, BI-PSSA, LI-PAA and LI-PSSA at some weight ratios), the 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) on 18 × 18 mm microscope coverslips (Corning Incorporated, Corning, NY). For spin coating, 200 μL of drug solution was spread out over the coverslip. Subsequently, the sample was spun for 20 s at 8000 rpm. Each solution was spin coated in triplicate. Following spin coating, the samples were placed in a desiccator, using P_2O_5 as a drying agent.

2.3. 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 4×, 10×, 20× and 40× objectives. Crystallinity of the three replicates prepared for each sample was evaluated visually, based on the extent of the observed birefringence. 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 semiquantitative evaluation of crystallinity of the drug based on the relative areas of crystalline/amorphous regions and the drug/polymer ratio. Samples were evaluated for crystallization within 30 min after spin coating ("day 0") and after 1 ("day 1"), 3 ("day 3") and 7 ("day 7") days of subsequent storage under dry conditions. Based on the observations made, the samples were semiquantitatively categorized at each time point as being (i) completely amorphous ("AAAA", no crystallinity could be observed), (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). Representative examples are provided in Figure 1. The data were further evaluated by calculation of the "amorphicity index" [AI (%)] for each weight ratio of the various drug−polymer combinations, to characterize the crystallization inhibiting potential of each of the polymers. The latter was defined as the sum of A's designated for a particular sample for all of the different time points, divided by 16 [the number of A's for a system 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 then determined by calculating the average of the AI values for the different weight ratios of that drug and polymer. Similarly, averages were calculated to characterize the overall potential of a polymer to inhibit crystallization of all drugs (average of the AI's of the different drugs with that polymer) and that of all polymeric additives to inhibit crystallization of a certain drug (average of the AI's of the different polymers with that drug).

2.4. Solubility Determination Using High Performance Liquid Chromatography. The solubility of the drugs in EtOH in the absence and presence of acidic adjuvants was determined with high performance liquid chromatography using ultraviolet spectroscopic detection (HPLC−UV). Measurements were performed using a Waters 2690 separations module equipped with a Waters 996 photodiode array detector and Masslynx V4.1 software (Waters Corporation, Milford, MA). The column used was a LiChrosorb RP-8 column (5 μm, 125 × 4 mm, 1.50432, Merck KGaA, Darmstadt, Germany). For all compounds, a gradient method was employed using an aqueous phase consisting of 0.1% trifluoroacetic acid in water and MeOH as the organic phase. An initial ratio of 90/10 (v/v) was used (0−2 min). Subsequently, the solvent composition was changed to 10/90 (v/v) (linear, 2−14 min) and then kept constant (14−26 min). Finally the solvent composition was returned to the initial 90/10 (v/v) composition (linear, 26−28), which was then kept constant (28−30 min). The flow rate was 1 mL/min, and the injection volume was 10 μL. Standard curves were prepared for the different compounds using concentrations of 10, 25, 50, 75 and 100% of the concentration of the highest standard used [0.54 mg/mL (BD), 0.28 mg/mL (PH), 0.30 mg/mL (FB), 0.47 mg/mL (FFA), 0.34 mg/mL (CP), 0.43 mg/mL (CZ), 1.05 mg/mL (BI), 10.1 mg/mL (LI)]. All standards were prepared in MeOH. For each compound, a suitable wavelength was selected for detection [230 nm (BD), 249 nm (PH), 247 nm (FB), 291 nm (FFA), 230 nm (CP), 282 nm (CZ), 254 nm (BI), 230 nm (LI)].

Samples were prepared by adding an excess of drug compound to a 1.5 mL eppendorf tube (Eppendorf, Hamburg, Germany) containing 1 mL of pure EtOH, a solution of 83.5 mg/mL acetic acid in EtOH or one of 85.4 mg/mL benzenesulfonic acid in EtOH. After 24 h of equilibration at room temperature on an orbit shaking platform (VWR minishaker, VWR International, LLC, West Chester, PA), the saturated solutions were separated from the undissolved drug using centrifugation (16000*g*, 10 min), using an Eppendorf 4515 c centrifuge equipped with a F-45-18-11 rotor (Eppendorf, Hamburg, Germany). Subsequently, 100 μL of supernatant was isolated and further diluted with MeOH into the concentration range covered by the calibration curve. All experiments were performed in triplicate, and average values and standard deviations were calculated.

2.5. Preparation and Storage of Bulk Samples. Solutions with PAA and PVP [50/50 (w/w) drug−polymer] were prepared for all of the drugs with the exception of BI, by dissolving 1 g of both the polymer and the drug in 80 mL of EtOH. As precipitation was again observed for LI-PAA, the suspension was homogenized using a rotor-stator instrument (maximum speed, 10 min, Silverson L4RT, Silverson Machines Ltd., Chesham, U.K.). Solvent was removed by rotary evaporation (Rotavapor R, Büchi Labortechnik AG

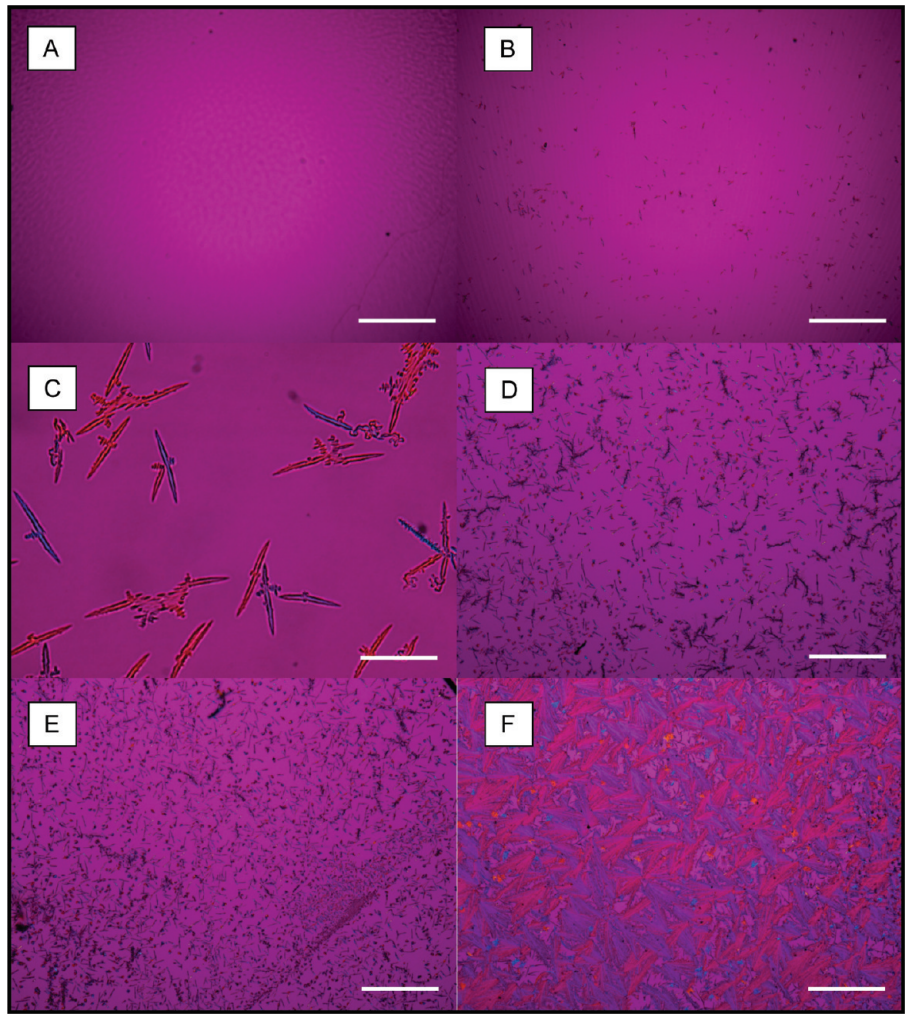

Figure 1. Representative photomicrographs illustrating the semiquantitative categorization of spin coated films (50/50 PH/polymer weight ratios). (A) "AAAA" (PAA, day 0, 4×), (B) "AAAC" (PVPVA, day 0, 4×), (C) "AAAC" (PVPVA, day 0, 40×), (D) "AACC" (PVPVA, day 1, 4×), (E) "ACCC" (PVPVA, day 3, 4×) and (F) "CCCC" (HPMCAS, day 1, 4×). The bar represents 1.25 (4×) or 0.125 (40×) mm.

BÜCHI Labortechnik AG, Flawil, Switzerland) with a water bath temperature of 35 °C. After rotary evaporation, samples were stored under vacuum overnight to remove residual solvent, followed by transfer of the dried powders into 20 mL scintillation vials (Research Products International Corp., Mount Prospect, IL). Subsequently, the vials were stored under dry conditions using P_2O_5 as a drying agent.

2.6. Evaluation of Crystallization Behavior of Bulk Samples upon Storage. Bulk samples were evaluated after 1, 3, and 7 days of storage under dry conditions. At each time point, samples were evaluated using polarized light microscopy (as described above), and differential scanning calorimetry (DSC).

For the DSC measurements, a TA Q2000 instrument, equipped with a refrigerated cooling accessory was used (TA Instruments, New Castle, DE). The instrument was calibrated for temperature using indium and tin and for enthalpic response using indium. Nitrogen gas, 50 mL/min, served as the purge gas. Samples of the pure crystalline drugs and the drug−polymer powders were prepared in aluminum pans with a pinhole lid. Following equilibration at 20 °C, samples were heated above the melting point of the drug, using a heating rate of 5 °C/min. Crystallinity was calculated by comparison of the observed melting enthalpy of the drug in the powder, corrected for drug content, with that of the pure crystalline drug, as described elsewhere.[10] Since no exothermic events, characteristic of crystallization during heating, could be observed for any of the samples, no additional correction was made for cold crystallization upon heating. All samples were analyzed in duplicate and the average values and standard deviations were calculated.

3. Results

3.1. Model Drugs and Polymers. Structures of the model drug selected for this study are shown in Figure 2, together with computed pK_a values and classification results obtained

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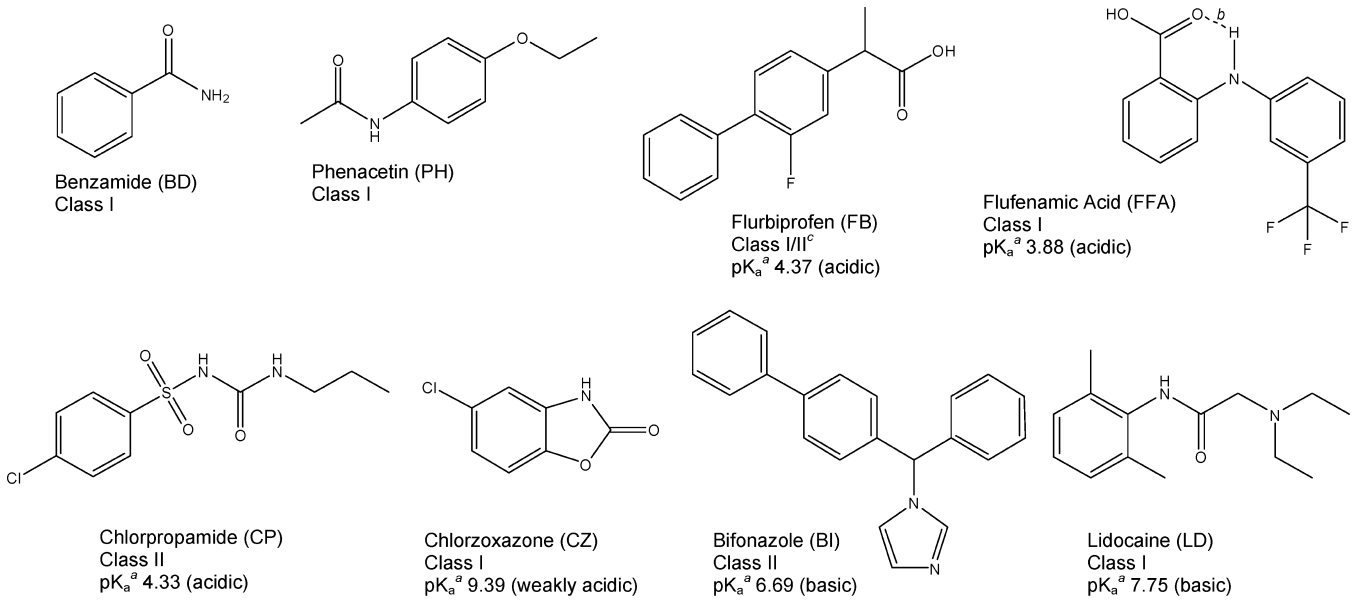

[a] pKa's were determined with ChemAxon calculator plugins using MarvinSketch 5.2.0 (ChemAxon Kft., Budapest, Hungary).

[b] intramolecular H-bond

[c] Class I from 1/1 EtOH/DCM (w/w), Class II from EtOH and DCM

Figure 2. Model drugs used in this study: structure, name, abbreviation, classification of crystallization behavior (class I = rapid, class II = intermediate[9]) and computed pK_a values for the acidic and basic drugs.

upon spin coating of solutions of the pure drug compound, as described earlier.[9] The selected compounds have diverse chemistries and include examples of acids, bases and amides. Although FFA contains both a carboxylic acid function and an aniline group, this compound can most likely be regarded as being able to interact intermolecularly only via the acid function for the following reason. The structure of FFA suggests a resonance-assisted hydrogen bond (RAHB) might be formed, resulting from a synergistic interplay between π-delocalization and hydrogen bond strengthening.[11] Upon analysis of the crystal structures of FFA with available coordinates, intramolecular hydrogen bonding motives can be observed with N···O distances of 2.682 (Cambridge Structural Database reference code: FPAMCA[12]) and 2.646 Å (Cambridge Structural Database reference code: FPAMCA11[13]) for forms III and I, respectively. These values are indicative of moderate to strong hydrogen bonds[14] and fall in the reported range of distances found for RAHB forming structures of this type (2.66−2.74 Å[11]). The occurrence of this type of six-membered ring as the result of the formation of an intramolecular hydrogen bond is common.[15] Consequently, the probability of intermolecular hydrogen bond formation with the aniline donor-H can be expected to be significantly reduced.[15] Therefore, it is reasonable to ignore the aniline function of FFA and regard the compound as being purely acidic. In addition to the structural variety seen for the compounds, differences in crystallization behavior (class I and class II) have been observed previously.[9] Class I describes a compound where rapid and nearly complete crystallization was observed immediately after spin coating. The crystallization behavior of a class II compound can be described as intermediate as little to no crystallization could be observed immediately after spin coating, but substantial crystallinity evolving during storage over a 7 day period. In contrast class III compounds did not show a large extent of crystallinity after 7 days of storage (for a more detailed description of the applied classification criteria, see previous work[9]). The latter compounds were not included in this study because, even without adding polymers, appreciable physical stability over the time frame of the experiment is expected. Figure 3 provides the structures of the polymers used in this work, together with the prevalence (mmol/g, calculated from the chemical structures of the polymers) of their respective functional groups. Again, a wide variety in chemistries can

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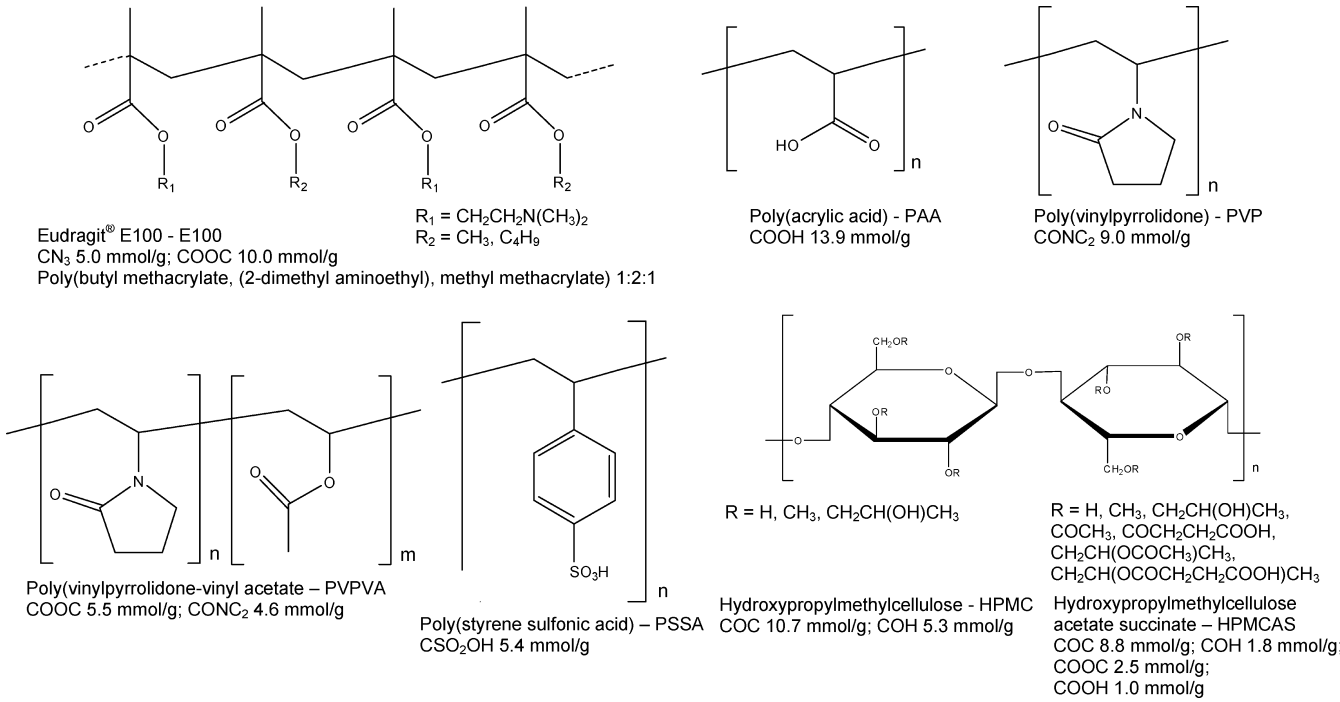

Figure 3. Model polymers used in this study: structure, name, abbreviation and prevalence (mmol/g) of their functional groups.

be noted among the different polymers. More specifically, amine (E100), carboxylic acid (PAA, HPMCAS), amide (PVP, PVPVA), ester (E100, PVPVA, HPMCAS), sulfonic acid (PSSA), alcohol (HPMC, HPMCAS) and ether (HPMC, HPMCAS) functional groups are present. While some of the functional groups are very prevalent in some polymers (e.g., PAA-COOH; 13.9 mmol/g), they are less dominant in others (e.g., HPMCAS-COOH; 1.0 mmol/g). Most of the polymers used in this work are commonly employed pharmaceutical excipients. One exception is PSSA, which was regarded as interesting based on the higher acidity of the sulfonic acid group, compared to that of the carboxylic acid. Although this type of polymer has, to the best of our knowledge, not previously been applied and/or approved as a pharmaceutical excipient, it is worth noting that ion exchange resins, which are cross-linked analogues thereof, have been used for the formulation of drugs.[16]

3.2. Crystallization Behavior of Spin Coated Films. Detailed data on the crystallization behavior of the spin coated films can be found in the Supporting Information. Based on these data, amorphicity indexes [AI (%)] were calculated for the different samples (see Supporting Information), from which average values were determined.

Comparison of the overall AI values for each compound, i.e. the general tendency to remain amorphous after 7 days of storage in the presence of all of the polymers for all of the different concentrations, is provided in Figure 4. The first trend that can be observed is that, even upon polymer addition, class I compounds still show a more pronounced crystallization tendency (lower AI) compared to class II compounds (higher AI). The AI values were as follows: PH = 47% (class I), CZ = 47% (class I), BD = 48% (class I), LI = 55% (class I), FFA = 59% (class I), FB = 68% (class II in EtOH and DCM, class II in 1/1 (w/w) EtOH/DCM), CP = 73% (class II), BI = 97% (class II). Based on the above, two important observations can be made: First, class I compounds can be considered much more challenging in terms of preventing crystallization both during formation and subsequent storage. They can therefore be considered as ideal model compounds to enable the crystallization inhibiting ability of different polymers to be discriminated. Interest-

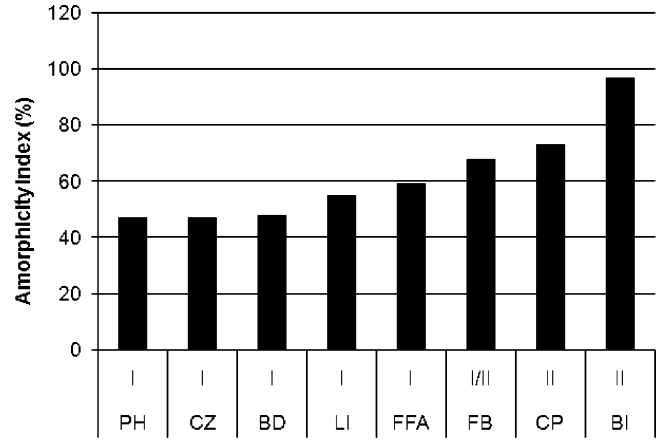

Figure 4. Average amorphicity indexes for the different compounds, ranked according to their crystallization tendency.

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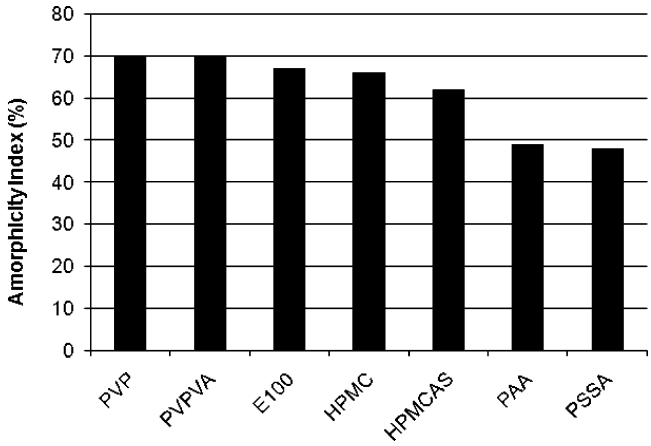

Figure 5. Average amorphicity indexes for the different polymers, ranked according to their crystallization inhibition efficiency.

Table 1. Average Amorphicity Indexes [AI (%)] of the Various Drug−Polymer Combinations

	class	E100	PAA	PVP	PVPVA	PSSA	HPMC	HPMCAS
BD	I	30	64	50	47	68	39	34
PH	I	13	67	49	47	78	38	37
FB	I/II	91	30	91	86	30	76	70
FFA	I	87	13	87	80	15	68	62
CP	II	96	31	94	95	12	95	88
CZ	I	63	25	68	63	8	55	46
BI	II	99	100	93	99	99	95	97
LI	I	58	61	29	42	71	62	61

ingly, compounds typically employed as models for research into solid dispersion properties are often class III compounds (based on our previously described classification system[9]), whereby the pure amorphous compound itself has a higher degree of physical stability. Second, these results suggest that knowledge of the crystallization tendency of the pure compound is extremely important during formulation development. Data similar to those generated in our study of drug crystallization from solution[9] could serve as an initial guidance to evaluate the feasibility of solid dispersion formulation for a given compound.

A comparison of the overall performance of the different polymers was made by comparing the AI values for a given polymer for all drugs; the average AI values show the following rank order (Figure 5): PVP = PVPVA (70%) > E100 (67%) > HPMC (66%) > HPMCAS (62%) > PAA (49%) > PSSA (48%). A question of interest to address is as follows: do higher average values indicate superior performance of the polymer, irrespective of the drug? In other words, do these results suggest that a particular polymer is universally superior to others in terms of its ability to inhibit crystallization during rapid solvent evaporation? The answer is clearly no, as can be seen upon closer evaluation of the data (Table 1). Here it is readily apparent that the ability of a given polymer to inhibit crystallization is highly dependent on the specific compound studied. This is best illustrated by considering the polymers having the lowest average performance, namely PAA and PSSA. Depending on the compound, they result in either the highest (BD, PH, BI, LI) or the lowest (FB, FFA, CP, CZ) AI values among all polymers. Furthermore, there appears to be an interesting relationship between the drug−polymer chemistry and the resultant crystallization tendency. For compounds having amide structures (BD, PH), the observed rank order for the AI is PSSA > PAA > PVP > PVPVA > HPMC > HPMCAS > E100. Thus the most acidic polymers are best at inhibiting crystallization for these compounds. For the basic compounds (BI, LI), the acidic polymers also yield the highest amorphous stability. Interestingly, the microscopic evaluation reveals that the precipitation sometimes seen for solutions of BI or LI with PAA and PSSA (section 2.2) does not indicate that crystalline material is formed. Rather, it appears that these drugs tend to complex with the polymers in solution forming amorphous precipitates. Precipitation with acidic polymers has been reported previously for mixtures of polymers.[17] E100, PVPVA, HPMC and HPMCAS were intermediate in their ability to inhibit crystallization of BI and LI, whereby the specific rank order varies between BI and LI. PVP yields the lowest AI values, indicating that it is not a very effective crystallization inhibitor for these compounds. The other drugs (FB, FFA, CP, and CZ) are all acidic (Figure 2). For these compounds, the acidic polymers PAA and PSSA are very poor crystallization inhibitors. HPMCAS, being substituted with only a limited number of COOH groups (1.0 mmol/g), is not quite such a poor crystallization inhibitor as the more acidic polymers, but is the next worse polymer. The inhibitory performance of HPMC is somewhat higher compared to HPMCAS but, except for CP, is lower than that of either E100, PVP or PVPVA. These three polymers tend to show the best performance at inhibiting crystallization of the acidic drugs.

The results described above suggest that both the drug and polymer properties are key in determining if it is possible or not to form and maintain and amorphous solid dispersion. However, it is less clear at this point what phenomena underlie this behavior. Nucleation and growth can occur during solvent evaporation and/or subsequent storage. During solvent evaporation, the solubility of the drug in the solvent system is exceeded at a certain point, potentially triggering nucleation and growth. By adding polymers to the solution, drug solubility might be potentially altered, thereby influencing supersaturation behavior. As the most pronounced effects could be seen for PAA and PSSA, we evaluated the effect of acidic additives on the solubility of the compounds in EtOH. Because separation of the saturated solution from the solids by centrifugation (or filtration) was difficult for polymeric solutions due to a high viscosity, low-molecular weight analogues of PAA and PSSA, acetic acid and benzylsulfonic acid respectively, were selected. These com-

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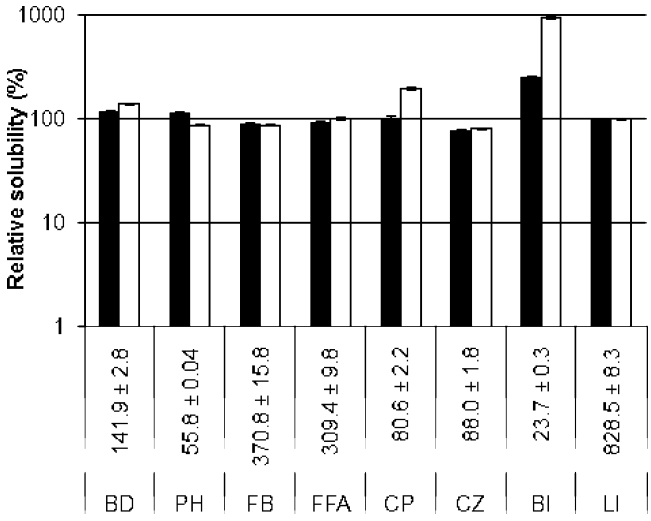

Figure 6. Solubilities of the different compounds in the presence of acetic acid (black bars) and benzenesulfonic acid (white bars), added in amounts corresponding to ethanolic solutions of 10% (w/w) of PAA and PSSA, respectively. Values are represented relative to those in pure EtOH, provided below the *X*-axis (mg/mL) ($n = 3$).

pounds were added at a concentration corresponding to that of a 10% (w/w) polymer solution, in terms of the number of acidic functions present. Solubility values in the presence of the acidic compounds, expressed relative to those in pure EtOH, and absolute values of the solubilities of the compounds in EtOH are provided in Figure 6. It is apparent that the influence of the acidic compounds on the solubility of the model drugs is in general minor. Significant solubility increases can be observed only in the case of BI. For LI, however, no significant increase in solubility could be seen. Although the high solubility of LI in EtOH might partially mask a solubility increase caused by acidic adjuvants, absolute increases similar to those seen for BI would still yield an appreciable effect on solubility; however, these cannot be observed for LI. For the other compounds, the acidic agents have little to no effect on solubility. Thus the large difference in the ability of the acidic polymers to inhibit crystallization of the basic and amide compounds versus the acid compounds cannot be explained by changes in solubility that would impact the supersaturation behavior of the solution during evaporation.

Therefore, the origins of the differences seen should be sought by considering the potential for drug−polymer interactions. Given the way in which polymers of similar chemistry group in their ability to inhibit crystallization, which in turn also appears to depend on the drug chemistry, it is reasonable to speculate that the formation of drug−polymer intermolecular interactions underlie the observed differences. Such interactions have been reported to influence important characteristics of solid dispersions, such as drug−polymer miscibility,[18] and have also been suggested to be important for inhibiting crystallization in solid dispersions.[19,20] The fact that patterns in polymer performance could be observed for different classes of drug chemistries strongly suggests that these interactions are extremely important in the prevention of crystallization. Although it is clear from this study that certain trends do occur, the number of compounds studied is still too small to enable a comprehensive rationalization of polymer performance in terms of the chemistry of the drug compound. A more elaborate study, aiming to arrive at a number of solid dispersion formulation rules based on the chemical structures of drug compounds and polymers is currently ongoing.

3.3. Crystallization Behavior in the Bulk. To further investigate whether the observed crystallization behavior can be considered as predictive for that seen in bulk powders, we selected two polymers showing clear differences in crystallization inhibition of the spin coated films. While PAA was successful for the amides (BD, PH) and the basic compounds (BI, LI), it showed poor performance for drugs containing acidic functions (FB, FFA, CP, CZ). PVP, on the other hand showed relatively good results with all compounds, except for the bases. Using these polymers, 50/50 (w/w) drug/polymer powders were prepared for the different compounds, using rotary evaporation. All drugs were evaluated, except BI, as based on the relatively high AI values seen for spin coated samples we expected differences in the bulk to be small for this compound. It should be noted that, in terms of evaporation kinetics, this process is much slower compared to spin coating, increasing the time frame over which nucleation and growth can occur in solution. Additionally, although minimized by using a relatively low water bath temperature (35 °C), the slightly elevated temperature employed can also potentially promote crystallization.

In a first pass attempt to assess the crystallinity of the samples, polarized light microscopy was used, as for the spin coated films. Some illustrative examples are provided in Figure 7. It was possible to differentiate between cases of crystallization and the absence thereof, as shown in Figures 7A (CP-PAA, 1 day) and 7B (CP-PVP, 1 day), respectively. However, this approach did not enable further evaluation of the extent of crystallization, as can be seen for BD-PAA and BD-PVP samples (Figures 7C and 7D, respectively) making a semiquantitative categorization, as performed for the spin coated films, impossible. Therefore, we approximated the extent of crystallinity for the different compounds as a function of time using DSC (Figure 8). These values cannot be taken as exact values, since a number of sources of error are inherent to the technique: apart from the fact that crystal

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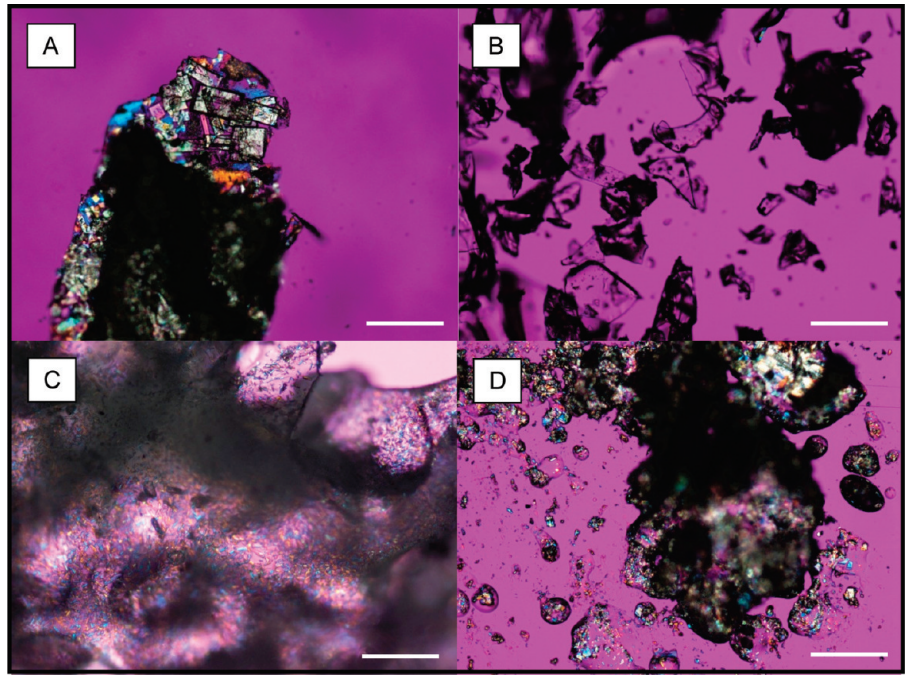

Figure 7. Representative polarized light microscopy images of different powders obtained by rotary evaporation [magnification 10×, day 1 time point]: (A) CP-PAA, (B) CP-PVP, (C) BD-PAA, and (D) BD-PVP. The bar represents 500 μm.

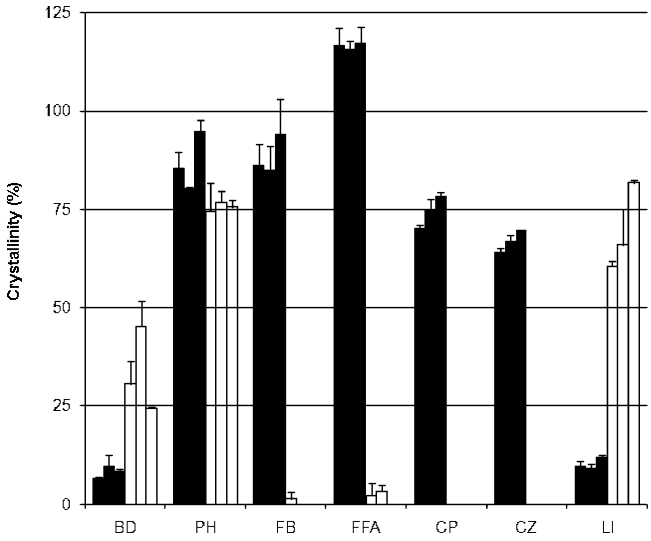

Figure 8. Crystallization behavior of the powders obtained by rotary evaporation [50/50 (w/w) drug/polymer], as a function of storage time under dry conditions, estimated from DSC measurements. Key: black bars = PAA, white bars = PVP; the three bars represent the day 1, day 3 and day 7 time points ($n = 2$).

disorder might lower melting enthalpies,[21,22] a number of compounds are known to show polymorphic behavior which might result in differences in melting enthalpies and/or melting−recrystallization−melting phenomena occurring upon heating. Furthermore, in cases where the drug and polymer are miscible, the apparent melting enthalpy might be reduced due to the heat released as a result of drug−polymer mixing in the melt state. However, trends can be derived from these results that enable comparison with the spin-coating samples (see Table 1 for overall results and the Supporting Information for more detailed results). It can be seen that good agreement is obtained for the acidic compounds (FB, FFA, CP and CZ) in terms of which polymers provide the best stabilization. For BD and LI, the rank order of both polymers is identical to that observed for spin coating, although some crystallization occurred upon rotary evaporation with PAA, whereas none could be observed in the spin coated samples. The only real deviation seen is for PH in combination with PAA; whereas spin coating yielded only a small extent of crystallization, rotary evaporation results in extensive crystallization. In summary, taking into consideration the differences in the two techniques, the agreement in crystallization behavior seen for spin coated films and that of bulk samples prepared by rotary evaporation is reasonable. Therefore, the spin coating technique can be potentially used as a screening tool to assess polymer performance, with minimal drug consumption. To further modify the technique to be predictive for unit operations such as spray drying, the screening approach can be further optimized, e.g. by conducting the spin coating process at temperatures relevant to those encountered during spray drying.

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4. Conclusions

A small scale screening method was developed to evaluate the crystallization tendency of drugs from solid dispersions prepared as thin films with a variety of polymers. The overall crystallization tendency of the model drug in the dispersions was found to be related to the crystallization tendency of the pure amorphous drug, prepared in a similar manner. Polymer performance in terms of crystallization inhibition was found to be highly compound dependent. This dependence was ascribed to the synergy or lack thereof between the drug and polymer chemistry. The crystallization behavior of the spin coated films and that of bulk powders prepared by rotary evaporation showed a good similarity, confirming the potential applicability of this approach as a small scale screening method.

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Supporting Information Available: Crystallization behavior of the spin coated samples upon storage under dry conditions and amorphicity indexes of the different drug−polymer combinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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