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Theoretical and Experimental Investigation on the Solid Solubility and Miscibility of Naproxen in Poly(vinylpyrrolidone)

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Abstract: The objective of the present study was to determine the solid state solubility and miscibility of naproxen in poly(vinylpyrrolidone) (PVP) and the mutual interaction using the standard thermodynamic models and thermal analysis. Solid dispersions were prepared by spray drying several compositions of naproxen and PVP with different molecular weights, viz., PVP K 12, PVP K 25 and PVP K 90, and analyzed using modulated differential scanning calorimetry (mDSC). The kinetic miscibility limit in terms of a single mixed phase glass transition temperature was found to be relatively similar for the dispersions containing PVP with different chain lengths ($\geq$50% w/w drug in PVP). But the systems with different PVP followed diverse patterns of composition dependent mixed phase glass transition temperature as well as the degree of plasticization by water. The crystalline solid solubility values of naproxen in PVP estimated by using its solubility data in *n*-methylpyrrolidone, a low molecular weight analogue of PVP, were 6.42, 5.85 and 5.81% w/w of drug in PVP K 12, PVP K 25 and PVP K 90 respectively. The values estimated for corresponding amorphous solubility showed no marked difference. The remarkable difference between thermodynamic solubility/miscibility and kinetic miscibility implied that naproxen was highly supersaturated in the PVP solid dispersions and only stabilized kinetically. The negative value of the drug−polymer interaction parameter (−0.36) signified the systems to be favorably mixing. The melting point depression data of naproxen in PVP pointed to the composition dependence and chain length effect on the interaction. The moisture sorption by the physical mixtures not only provided the composition dependent interaction parameter but also conferred an estimate of composition dependent miscibility of naproxen in PVP in the presence of water.

Keywords: Solid dispersion; solid solubility; amorphous miscibility; melting point depression; moisture sorption; drug−polymer interaction

1. Introduction

Amorphous forms of poorly water soluble drug substances are considered as one of the ultimate means to increase apparent solubilities and dissolution compared to their crystalline counterparts.[1−4] This results in higher systemic availability desired for the oral dosage form. However, due to higher tendency toward crystallization, these benefits are rarely sustained in formulating the purely amorphous active pharmaceutical ingredient. Therefore, the approach of formulating amorphous drugs in the form of amorphous solid dispersions with a polymeric carrier as a crystallization inhibitor has long been an active area of research.[5,6] Despite the extensive research, the development of a considerable number of stable and efficient formulations is yet to be achieved. The major challenge is to achieve molecule-level dispersions restraining favorable intermolecular interactions between the drug substance and the polymeric matrix. The maximum crystallization inhibition of a drug in a solid

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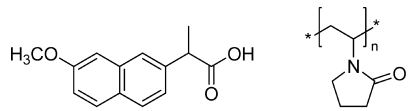

Figure 1. Chemical structure of naproxen (a) and PVP (b).

dispersion can only be achieved when the drug is dispersed homogeneously or best at the molecular level in the matrix. This suggests that the basis of the selection of the right polymeric excipient for the formulation of amorphous solid dispersions should be the limit of solid state solubility of the drug in the selected polymer.[7,8] Knowledge of correct phase behavior of the drug−polymer system helps to avoid potential phase separation driven by supersaturation of the drug substance beyond the solubility/miscibility limit in a particular polymer. Thus, drug−polymer miscibility and solid solubility of drug in the polymer provide the right estimates of the drug loading to manufacture stable solid dispersion formulations.

The present study is aimed at investigating the solid state solubility/miscibility and the strength of drug−polymer interactions of a water insoluble drug in a polymeric carrier using a multimethodological approach. Naproxen (Figure 1a) was selected as the model drug in the preparation of solid dispersions with three different molecular weight types of polyvinylpyrrolidone (PVP) (Figure 1b). The dissolution enhancement of naproxen by the preparation of naproxen−PVP solid dispersions has been extensively investigated, but little has been reported on the solid solubility behavior of these systems. Selection of the proper molecular weight PVP is important for the preparation of solid dispersions with improved performance. Velaz et al. reported the interaction between naproxen and *n*-vinylpyrrolidone (the monomer of PVP) by complexation.[9] Bettinetti et al. studied the dissolution behavior of the naproxen with PVP K 15, 30, and 90 at different compositions.[10] There are several studies on the solid state interaction between naproxen and PVP. The carboxylic acid group of both the monomer and dimer of naproxen are reported to interact with PVP.[11] However, Bogdanova et al. suggested that the catemer arrangement (instead of dimer arrangement as of ibuprofen) and the intermolecular interactions in the crystal of naproxen do not presume favorable hydrogen bonding interactions with the PVP.[12]

In the present study, we focused in finding out the kinetic as well as thermodynamic solubility/miscibility and interaction parameters of naproxen in PVP with different molecular weight. The apparent drug−polymer miscibility was determined by observing the glass transition behavior of solid dispersions prepared by spray drying. The commonly used thermodynamic relations derived from the Flory−Huggins (FH) lattice theory[13] and Hildebrand regular solution theory[14,15] were exploited together with the experimental solubility data in *n*-methylpyrrolidone, a low molecular weight analogue of PVP, to determine the equilibrium solid state solubility and interaction parameter of the drug in polymer. The composition dependent FH interaction parameters were estimated based on the extent of melting point depression of naproxen in the physical mixtures containing various compositions of PVP. The effect of water on the strength of composition dependent drug−polymer interaction was investigated based on the moisture sorption behavior of physical mixtures containing various compositions of naproxen and PVP.

2. Materials and Methods

2.1. Materials. Naproxen was obtained from CERTA Ltd. (Brain-l'Allend, Belgium). PVP K 12 (M_w = 2.4 kDa), PVP K 25 (M_w = 25 kDa) and PVP K 90 (M_w = 1,100 kDa)

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were kindly provided by BASF (Ludwigshafen, Germany). All other materials and solvents were of analytical or HPLC grade.

2.2. Methods. *2.1.1. Spray Drying.* Spray drying was used as the process to prepare the solid dispersions of naproxen in PVP at various compositions (5%, 10%, 15%, 20%, 30%, 40%, 50% and, 75% w/w drug in polymer) using a 5% w/v solution of powder blends in dichloromethane (Fisher Scientific UK Limited, Leicestershire, U.K.). A Buchi mini spray dryer B191 (Buchi, Flawil, Switzerland) was used for spray drying. The following process parameters were used: inlet temperature 50 °C, outlet temperature 30−40 °C, aspirator 100%, the pump 35%, and the air flow 800 L/h. All spray-dried powders were further dried in a vacuum oven (0.2 bar) at 25 °C in the presence of P_2O_5 for one week prior to analysis.

2.1.2. Thermal Analysis. DSC experiments were performed using the 2920 differential scanning calorimeter (TA Instruments, Leatherhead, U.K.) in a dry nitrogen purged chamber at a flow rate of 150 mL/min and helium purge at 40 mL/min. Samples were cooled using the refrigerated cooling system (RCS) accessory. The data analyses and processing were done using Universal Analysis 2000 software (TA Instruments, Leatherhead, U.K.). The enthalpy was calibrated with an indium standard, and the temperature scale was calibrated with octadecane, indium and tin. The heat capacity signal was calibrated by comparing the response of a sapphire disk with the tabulated value at 106.85 °C. The validated measurements of temperature, enthalpy and heat capacity of the same standard materials showed deviations of <0.5 °C, <1% and <1% for the temperature, the enthalpy and the heat capacity at 106.5 °C, respectively. All samples were analyzed in duplicate using aluminum pans (samples weighed and crimped with the aluminum lid) in modulated mode (mDSC) using the method containing three cycles of heating sequence. Cycle 1: From −20 °C, samples were heated at 2 °C/min up to 160 °C, with a modulation of ±0.212 °C every 40 s. Cycle 2: The sample was cooled back to −20 °C at the instrument's preset rate and held isothermally for 2 min. Cycle 3: Cycle 1 was repeated up to a final temperature of 180 °C. For the measurement of heat capacity of amorphous naproxen during its T_g, 5−10 mg of sample was melted during heating until 160 °C in a DSC pan (crimped with the lid), quench cooled by transferring the pan into liquid nitrogen and immediately analyzed using the same mDSC method with only cycle 1.

The water content in the samples was estimated by thermogravimetric analysis using a TGA Q500 (TA-instruments, Leatherhead, U.K.). The sample was heated at 10 °C/min from room temperature (30 °C) to 160 °C with a dry nitrogen purge at 100 mL/min. The data analysis was done using Universal Analysis 2000 software (TA Instruments, Leatherhead, U.K.).

2.1.3. Melting Point Depression. The melting point depression was evaluated by running physical mixtures of naproxen with PVP at different compositions (95%, 90%, 85%, 80% and 75% w/w naproxen in PVP) in DSC. For this, the desired composition of drug and polymer was grinded in the mortar for approximately 2 min and run in DSC using the method that comprised equilibration at 120 °C followed by heating at 2 °C/min up to 160 °C. The pure ground drug was analyzed as the control using the same method.

2.1.4. Density Determination by Helium Pycnometry. Density of the drug and PVPs was determined by helium pycnometry using a Beckman comparison pycnometer (model 930, Beckman Industries, Inc., Fullerton, CA). The drug and polymers used for the density measurements were dried in a vacuum oven at 40 °C for one week prior to the analysis. Measurements were performed in duplicate.

2.1.5. Determination of the Drug Content in the Solid Dispersions by HPLC. The drug content in the spray-dried binary solid dispersions was assayed using HPLC made up of a Merck Hitachi pump L7100, an ultraviolet (UV) detector (L7400), an autosampler (L7200), an interface (D7000) and a LiChrospher 60 RP Select-B C-18 (5 μm, 12.5 × 4) (all from Merck, Darmstadt, Germany) column. The method was isocratic with the mobile phase made up of 70% methanol (HiPerSolv Chromanorm, Belgium) and 30% 25 mM sodium acetate buffer (pH 3.5). The wavelength used for the detection was 270 nm. The samples were prepared by dissolving 5 mg of solid dispersion in 5 mL of diluents (mobile phase) to give 1 mg/mL concentration. The injection volume was 10 μL.

2.1.6. Moisture Sorption Studies. The physical mixtures of naproxen were made using dried PVP K 25 and PVP K 90 with drug content of 75%, 50% and 25%. The samples (pure drug, polymers and physical mixtures thereof) were weighed and kept in a desiccator with controlled relative humidity of 94% maintained by a saturated aqueous solution of potassium nitrate. All samples were reweighed after 48 h. The differences were considered as the equilibrium moisture gain by the samples.

2.1.7. Estimation of Equilibrium Solubility of Naproxen in n-Methylpyrrolidone (NMP). The equilibrium solubility studies of naproxen in NMP (Aldrich, Steinheim, Germany), a small molecular weight analogue of PVP, were done by shaking excess drug in NMP for 72 h using a mechanical rotor (Snijders Scientific, Tinburg, The Netherlands) in amber colored test tubes (to avoid possible photodegradation as reported for NMP[16]). The samples were withdrawn, filtered using a syringe filter of 0.2 μm (Henke Sass Wolf, Tuttlingen, Germany) and properly diluted. The diluted samples were injected in the HPLC and analyzed using the aforementioned method.

3. Results

3.1. Mixed Phase Glass Transition and Phase Behavior of Naproxen−PVP Dispersions. The most apparent experimental indication of the miscibility of two amorphous

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components is the presence of a single glass transition temperature, often referred to as mixed phase glass transition temperature (T_{gm}). For a binary mixture containing components with a considerable difference between individual T_g values, the position of T_{gm} will be intermediate between the two T_gs as a function of composition. The position of T_{gm} for a miscible but non interactive (athermal) system with merely equivalent cohesive and adhesive contributions between individual components can be estimated using various equations that follow a simple rule of mixing.[17] Of them, the Gordon−Taylor (GT) equation[18] with an implementation of the Simha−Boyler rule[19] is used extensively for pharmaceutical systems made up of drug and polymer. Equation 1 is the GT expression for the ternary system.

$$T_{gm} = \frac{W_1 T_{g1} + K_1 W_2 T_{g2} + K_2 W_3 T_{g3}}{W_1 + K_1 W_2 + K_2 W_3} \quad (1)$$

where $K_1 \approx (\rho_1 T_{g1}/\rho_2 T_{g2})$ and $K_2 \approx (\rho_2 T_{g2}/\rho_3 T_{g3})$; W, T_g and ρ are weight fraction, glass transition temperature and density of individual components, respectively. The smaller value of subscripts denotes the components with lower T_g. The terms containing W_3 are excluded from eq 1 in the case of binary systems.

In the case of pharmaceutical solid dispersions, phase separation is generally characterized by the presence of a melting endotherm or crystallization exotherm for the drug during heating.[5] Moreover, amorphous−amorphous separation or partial miscibility is indicated by the presence of multiple T_{gm}s corresponding to the heterogeneous drug−polymer dispersion systems with different compositions or physical structures such as interaction densities (for example hydrogen bonding density).[20]

Correlating with the heating program, the thermal history of the co-spray-dried naproxen and PVP samples in first heating and second heating (after cooling) would indeed be different. The features observed in the first heating cycle represent the native thermal behavior of the spray-dried products. The thermal histories of the samples are generally changed on completion of the first cycle, and the formation of more homogeneous mixtures can be assumed. The average T_g values (K) obtained of pure drug and polymers were 279.34 (±0.40), 370.10 (±0.21), 430.05 (±0.38) and 451.84 (±0.24) for naproxen, PVP K 12, PVP K 25 and PVP K 90 respectively. Likewise, the ΔC_p (J/g·K) values obtained for naproxen, PVP K 12, PVP K 25 and PVP K 90 were 0.79 (±0.02), 0.20 (±0.03), 0.21 (±0.01) and 0.22 (±0.01), respectively. The densities (g/cm^3) measured were 1.25 (±0.00), 1.11 (±0.10), 1.14 (±0.18) and 1.18 (±0.15) for naproxen, PVP K 12, PVP K 25 and PVP K 90, respectively (the numbers in parentheses are the ranges obtained by duplicate measurements). The ΔC_p value of naproxen was calculated by normalizing the values obtained for the percentage amorphous material formed during the quench cooling experiments (ca. 35%). The T_g (K) and ΔC_p (J/g·K) values for water were assigned as 136 and 1.38, respectively from literature.[21] The drug contents in the dispersions used for the calculations were determined by HPLC analyses. The experimental glass transition temperatures (T_{gm}) and the change in heat capacity during glass transition (ΔC_{pm}) of the spray-dried drug−polymer dispersions (first and second runs) are given in Table 1.

3.1.1. The First Heating Cycle and Glass Transition of the Spray-Dried Samples. The spray-dried products contained considerable amounts of water apparent from the TGA data and the broad endothermic peaks observed around the corresponding temperatures in the thermograms. The type and state of water a system contains prior to or at the time of glass transition, namely, bound/unbound, surface/bulk water, discerns the degree of plasticization of a system. Moreover the strength of plasticization of a system by water is also a function of the glass forming ability of the plasticizer, the difference between its T_g and the particle temperature and so forth.[17] It has been well documented for PVP that it does not contain freezable water even at water content >20%.[22] Therefore, the T_{gm} values were systematically calculated by including the water as the third component in the GT equation for composites exhibiting $T_{gm} < 100$ °C and by normalizing the binary weight fractions excluding the water for composites with observed $T_{gm} > 100$ °C. Distinctive and single T_{gm} without other noticeable events were observed in the reversing heat flow signals for all the compositions except 25% polymer composition. In the case of the latter composition, the melting endotherm of the phase separated drug appeared along with a T_{gm} corresponding to the remaining mixed phase. Also, second glass transitions due to the existence of a phase separated polymer rich amorphous fraction were quite noticeable. They were almost merged with the melting endotherms in the case of PVP K 12 and PVP K 25 containing dispersions while quite pronounced for the mixture of drug in PVP K 90. The enthalpy of fusion values of the melting endotherms observed

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Table 1. The Naproxen Content in Solid Dispersions Assayed by HPLC, T_{gm} and ΔC_p Obtained in First and Second mDSC Heating Cycle and Moisture Content Data by TGA of Naproxen−PVP Solid Dispersions

	second heating		first heating		
% naproxen in mixture	T_{gm} (K)	ΔC_p (J/g·K)	T_{gm} (K)	ΔC_p (J/g·K)	% water content
			Naproxen/PVP K 12[a]		
4.47 (±0.02)[b]	309.39 (±0.0)	0.18 (±0.03)	293.18 (±1.6)	0.43 (±0.02)	7.15
9.64 (±0.04)	338.09 (±3.6)	0.24 (±0.06)	291.60 (±0.8)	0.54 (±0.01)	5.74
14.32 (±0.03)	345.09 (±1.9)	0.35 (±0.02)	294.27 (±2.5)	0.50 (±0.03)	4.35
20.93 (±0.15)	339.22 (±1.7)	0.36 (±0.02)	290.96 (±0.5)	0.49 (±0.01)	4.28
29.42 (±0.09)	316.37 (±3.3)	0.38 (±0.03)	298.45 (±2.0)	0.38 (±0.02)	3.36
38.94 (±1.02)	305.91 (±3.5)	0.34 (±0.00)	299.25 (±0.4)	0.40 (±0.01)	2.08
50.46 (±0.43)	314.62 (±0.4)	0.33 (±0.00)	298.75 (±3.5)	0.45 (±0.00)	1.00
72.57[c] (±2.16)	294.25 (±0.3)	0.32 (±0.15)	297.68 (±0.5)	0.20 (±0.01)	1.42
			Naproxen/PVP K 25[a]		
5.78 (±0.73)	414.62 (±1.8)	0.25 (±0.00)	410.25 (±1.6)	0.38 (±0.00)	7.79
10.39 (±0.70)	404.81 (±0.3)	0.23 (±0.01)	399.85 (±1.1)	0.42 (±0.02)	7.26
15.13 (±0.47)	390.06 (±3.7)	0.28 (±0.00)	389.42 (±0.5)	0.41 (±0.00)	6.57
21.31 (±0.56)	380.15 (±0.2)	0.28 (±0.01)	378.31 (±2.0)	0.34 (±0.03)	5.83
28.78 (±1.27)	360.70 (±1.9)	0.28 (±0.01)	315.09 (±1.6)	0.37 (±0.00)	4.27
40.09 (±0.62)	341.51 (±1.1)	0.35 (±0.01)	311.15 (±0.5)	0.38 (±0.00)	4.31
49.98 (±1.49)	330.07 (±0.2)	0.36 (±0.04)	295.68 (±2.9)	0.42 (±0.01)	3.24
78.10[c] (±3.70)	298.28 (±0.4)	0.36 (±0.00)	291.52 (±0.7)	0.37 (±0.08)	2.34
			Naproxen/PVP K 90[a]		
4.28 (±0.07)	433.77 (±0.1)	0.23 (±0.03)	433.98 (±0.6)	0.20 (±0.01)	1.30
9.92 (±0.00)	415.80 (±0.4)	0.26 (±0.01)	414.25 (±1.4)	0.20 (±0.01)	7.62
12.28 (±0.12)	404.65 (±0.6)	0.20 (±0.01)	402.00 (±0.3)	0.30 (±0.01)	7.44
20.06 (±0.17)	391.92 (±0.6)	0.30 (±0.02)	389.87 (±1.6)	0.22 (±0.03)	6.18
30.90 (±0.04)	370.24 (±0.6)	0.29 (±0.02)	370.81 (±1.4)	0.17 (±0.01)	6.27
39.94 (±0.30)	351.54 (±1.0)	0.22 (±0.00)	328.01 (±0.0)	0.26 (±0.03)	6.31
51.59 (±0.23)	333.36 (±0.7)	0.32 (±0.00)	316.39 (±0.6)	0.32 (±0.01)	3.11
73.79[c] (±0.94)	295.38 (±0.2)	0.38 (±0.01)	289.94 (±2.3)	0.32 (±0.02)	2.33

[a] Spray-dried mixture. [b] Numbers in parentheses represent range of duplicate measurements. [c] Melting endotherm observed corresponding to the fraction of crystalline drug phase separated from the dispersion rendering back ca. 58, 55 and 52% w/w drug dispersed into PVP K 12, PVP K 25 and PVP K 90 respectively in first heating while 48%, 51% and 47% respectively in the second heating.

at 25% polymer containing composites were evaluated to measure the percentage of drug likely to be dispersed in PVP using the weight of drug alone in the dispersion. These values also ultimately indicate the kinetic miscibility of the drug with the polymer as given in Table 1.

The plots of the difference between T_{gm} observed in the first heating cycle and that by the GT equation for the corresponding compositions against PVP weight fraction are given in Figure 2a. The experimental T_{gm} showed negative deviations from the predicted values for all the naproxen−PVP dispersions. The observed T_{gm} of naproxen−PVP K 12 mixtures up to 80% polymer containing compositions showed higher deviation as compared to the subsequent mixture compositions. This suggested that the trace amount of water beyond this composition might have lesser plasticization effect. For naproxen dispersions with PVP K 25, a profound drop in T_{gm} values was observed below the 80% polymer content. By examining T_{gm} of an additionally spray-dried middle composition (75% polymer containing mixture) we could establish the consistent position in the trend (data not shown). Compositionally the dispersions can be divided into two regions above and below the 80% w/w polymer containing composite based on their T_{gm}. The predicted T_{gm} values of spray-dried naproxen−PVP K 90 mixtures showed a fairly similar trend as that of naproxen−PVP K 25 mixtures. The curve of experimental T_{gm} against PVP weight fraction showed a steep slope up to 85% polymer containing composites followed by a jump analogous to naproxen−PVP K 25 systems beyond 70% PVP content. This suggests that mixtures with the three regions of T_{gm} exist across the selected composition range for the naproxen−PVP K 90 system.

3.1.2. The Second Heating Cycle and Glass Transition of the Spray-Dried Samples. The first anticipation for the mixture generated after cooling the spray-dried drug−polymer mixtures is the loss of moisture and other volatiles rendering them more homogeneous. The presence of comparably shallow endotherms observed in the second heating cycle of some mixtures indicated the permanent loss or trace remains of the water from the system. Thus T_{gm} values calculated for the naproxen−PVP binary systems were compared with the T_{gm} observed in the second run over the entire composition range. But, the nature and the extent of the moisture loss are not straightforward to project. The incompleteness of moisture loss due to the location of the

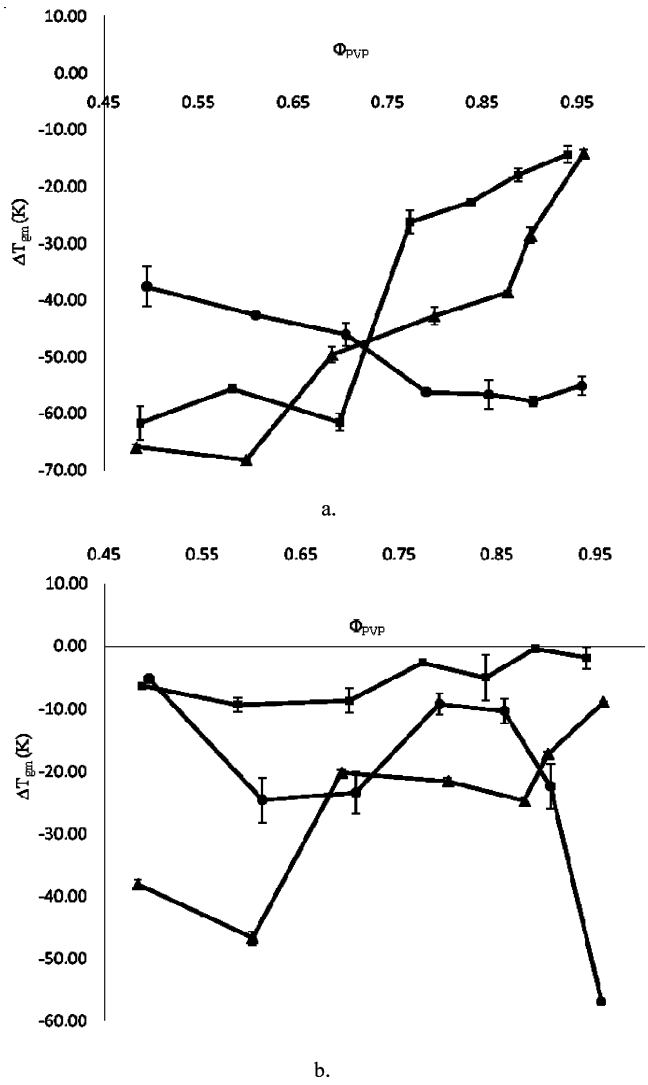


Figure 2. The difference between the observed and predicted mixed phase glass transition temperatures predicted by the Gordon−Taylor equation (ΔT_{gm}) versus composition (polymer volume fraction, Φ_{PVP}) in first heating (a) and second heating (b) for spray-dried naproxen−PVP K 12 (●), naproxen−PVP K 25 (■) and naproxen−PVP K 90 (▲) composites. The bars represent the difference between two measurements.

moisture (inclusion within the polymer matrices, bound, hydrated with the drug/polymer) in the mixture cannot be overlooked.

The experimental T_{gm} values obtained in the second heating showed the negative deviation from the corresponding predicted values too across almost an entire composition range. However, the extent of deviation was much reduced except for the composites with PVP K 12 toward higher polymer content end (Figure 2b). Surprisingly, the curve of observed T_{gm} of naproxen−PVP K 12 mixtures still showed a noncompositional pattern. More precisely, the values of T_{gm} observed for the 95% and 90% PVP K 12 containing composites were lowered markedly compared to the corresponding T_{gm} values predicted by the GT equation, even lower than the subsequent T_{gm} of the mixtures containing higher drug content. The extent of negative deviations of experimental T_{gm} from predicted T_{gm} notably decreased in the case of naproxen−PVP K 25 dispersions to nearly fit with the predicted line up to 20% polymer content. The sigmoid-like T_{gm} pattern of the naproxen−PVP K 25 system observed in the first heating was almost not distinct in the second heating cycle, although the negative deviations were more evident beyond the same composition (20% polymer content). The T_{gm} pattern observed in naproxen−PVP K 90 reveals a symmetrical decrease in deviations from the predicted values as compared to the first heating. Though the curve of experimental T_{gm} fell sharply up to the 85% polymer containing composite, the curve showed parallel deviation from the predicted values for the further compositions. The melting endotherms of the drug in the samples containing 25% polymer were observed around the same region as in the first heating cycle, but the areas under the endotherms were considerably higher, indicating that the amount of drug remaining dispersed in the polymer was lower (Table 1). However, the values of the melting endotherms were higher (by 20−25 J/g) than for the corresponding recrystallization exotherms. This implies that the fraction of supersaturated drug dispersed in the polymer at this composition forms a separate amorphous fraction in addition to the partial amorphization of the phase separated crystals while cooling the comelts. This is evident from the presence of endotherms related to the enthalpy recovery and recrystallization exotherms in the corresponding nonreversing heat flow signals. The recrystallization temperature observed was in the order PVP K 90 ≥ PVP K 25 > PVP K 12 (data not shown), indicating the effect of polymer chain length on kinetics of drug crystallization.

3.1.3. Entropy of Mixing the Drug into the Polymer and the Composition Dependence. Though enthalpy of mixing is the dominantly used indicator for the miscibility of drug in polymer and for describing miscibility behavior of drug in polymer and possible drug−polymer interactions in solid dispersions, some of the recent publications emphasize employing the quantitative entropy of mixing as a significant scale in looking to the miscibility of pharmaceutical glass mixtures.[17,23] The Cauchman−Karasz (CK) equation predicts the T_{gm} of the drug−polymer mixtures utilizing the ΔC_p of the individual components as a part of the entropy contribution in mixing.[24] The mixed phase glass transition (T_{gm}^{CK} is given by eq 2:

$$\ln T_{gm}^{CK} = \frac{x_1 \Delta C_{p1} \ln T_{g1} + x_2 \Delta C_{p2} \ln T_{g2}}{x_1 \Delta C_{p1} + x_2 \Delta C_{p2}} \qquad (2)$$

where T_{gm}^{CK}, x and ΔC_p are the mixed phase glass transition by the CK equation, the respective mole fraction of pure

(23) Schneider, H. A. Conformational Entropy Contributions to the Glass Temperature of Blends of Miscible Polymers. *J. Res. Natl. Inst. Stand. Technol.* **1997**, *102*, 229–248.

(24) Couchman, P. R.; Karasz, F. E. A Classical Thermodynamic Discussion of the effect of Composition on Glass Transition Temperatures. *Macromolecules* **1978**, *11*, 117–119.

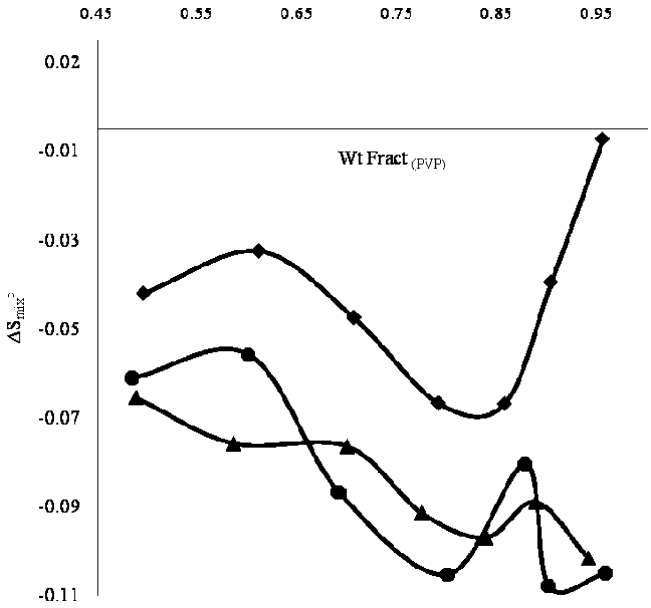


Figure 3. Plots of configurational entropy of mixing (ΔS^c_{mix}) versus PVP weight fraction calculated for spray-dried naproxen−PVP K 12 (◆), naproxen−PVP K 25 (▲) and naproxen−PVP K 90 (●) composites based on data from second heating cycles in mDSC.

components, and heat capacity difference between glassy and liquid state of the pure components (subscript 1 denotes the values for the component with lower T_g) respectively. Hence, it is interesting to investigate the entropic contribution during mixing by correlating the predicted T_{gm}, observed T_{gm} and ΔC_{pm}. The ΔC_{pm} is a summation of conformational, free volume and cohesive interaction contributions.[25] If the drug−polymer miscibility is through hydrogen bonding which substantially influences the composition dependence of both free volume and cohesive interaction energy, it will also affect the ΔC_{pm} associated with the T_{gm}, and will affect the configurational entropy (ΔS^c_{mix}) of mixing. Pinal[17] has derived an expression for ΔS^c_{mix} that correlates the deviation and observed T_{gm} with T^{CK}_{gm} taking ΔC_{pm} into consideration (eq 3).

$$T_{gm} = T^{CK}_{gm}[e^{-(\Delta S^c_{mix}/\Delta C_{pm})}] \quad (3)$$

In the present study, it was logical only to calculate ΔS^c_{mix} values with respect to the second heating cycle to omit the unpredictable entropic inputs of water content in miscibility.

As shown in Figure 3, the inspection of plots of ΔS^c_{mix} versus polymer content of the mixtures provided some further insight of the miscibility. The ΔS^c_{mix} pattern as a function of polymer weight fraction showed a defined entropy minimum of naproxen−PVP K 12 mixtures between 85% and 80% polymer containing composition. Two entropy minima were observed for naproxen dispersions with PVP K 25 and PVP K 90. In the case of naproxen mixtures with PVP K 25, the increasing entropy up to 90% polymer content followed by the fall toward 85% polymer content signifies the composition dependent abundance of energetic interaction. Similarly, the mixtures with entropy minima were those containing 90% and 80% polymer for naproxen−PVP K 90 system. These mixtures corresponded to the downward jumps displayed of the observed T_{gm} patterns below this polymer content (Figure 2b).

3.2. Relating Solubility Data of Naproxen in *n*-Methylpyrrolidone to That in PVP Solid Dispersions. As proposed by Marsac and co-workers,[7,8] it is reasonable to correlate the solubility of the drug in a polymer with that in the low molecular weight analogue or the monomer of the polymer which exists in the liquid state. Assuming the latter as the lattice of the polymer, its physical attributes like molecular weight and volume and the experimental solubility and activity coefficient of the drug can be introduced in the calculation of the solubility of the drug in the polymer. The expressions derived from Flory−Huggins (FH) lattice theory were used with assumptions of similar nature of interaction, and ideal combinatorial entropy of mixing in both drug−monomer and drug−polymer systems.[13] NMP (a low molecular weight analogue of PVP) was taken as the lattice in the FH lattice model, and its molecular volume was considered as lattice molecular volume ($MV_{lattice}$).

The equilibrium solubility of naproxen in NMP obtained from HPLC analysis was utilized to determine its activity coefficient (γ_{NMP}) in the same, which is the ratio of ideal mole fraction solubility (X_{id}) to the experimental mole fraction solubility (X_{exp}). X_{id} was calculated using eq 4.[26]

$$\ln X_{id} = -\frac{\Delta H_f(T_m - T)}{R(T_m T)} + \frac{\Delta C_p(T_m - T)}{RT} - \frac{\Delta C_p}{R}\ln\left(\frac{T_m}{T}\right) \quad (4)$$

where ΔH_f is the heat of fusion, T_m is the melting point of drug and ΔC_p is the heat capacity difference between liquid and crystal. R is the universal gas constant, and T is the absolute temperature for which the estimation is envisaged. The values of ΔH_f and T_m were obtained from the DSC analysis of pure crystalline drug powder while that of ΔC_p was taken from the literature.[27] The calculated value of γ_{NMP} was thus employed in the calculation of the activity coefficient in the polymer (γ_{PVP}) at the solubility limit using eq 5.

(25) Tanaka, N. Conformational effects on Glass Transition Temperature and Relaxation Phenomena of Polymers. *Polymer* **1978**, *19*, 770–772.

(26) Neau, S. H.; Flynn, G. L.; Yalkowsky, S. H. The influence of Heat Capacity Assumptions on the Estimation of Solubility Parameters from Solubility data. *Int. J. Pharm.* **1989**, *49*, 223–229.

(27) Neau, S. H.; Bhandarkar, S. V.; Hellmuth, E. W. Differential Molar Heat Capacities to test Ideal Solubility Estimations. *Pharm. Res.* **1997**, *14*, 601–605.

$$\ln \gamma_{PVP} = \ln(\Phi_{naproxen}/X_{exp}) + \left(1 - \frac{MV_{naproxen}}{MV_{PVP}}\right)\Phi_{PVP} + \left(\frac{MV_{naproxen}}{MV_{NMP}}\right)\ln \gamma_{NMP} \quad (5)$$

Here Φ and MV denote the particular volume fraction and molar volume respectively. Consequently, the mole fraction solubility of crystalline naproxen in PVP (X_{PVP}), which is the ratio of X_{id} to γ_{PVP}, was estimated and converted to % w/w solubility (S_c). As it is debatable to compare the crystalline solubility of naproxen in amorphous PVP with its kinetic miscibility in the glassy solution, the solubility of amorphous naproxen in amorphous PVP or "amorphous solubility" (S_a) was approximated from the crystalline solubility and entropy of fusion (ΔS_f) using eq 6.[28,29]

$$S_a = S_c\, e^{(\Delta S_f/R)[\ln(T_m/T)]} \quad (6)$$

ΔS_f is the ratio of ΔH_f to T_m.

Furthermore, these values were exploited to estimate the FH interaction parameter (χ) for the naproxen−PVP system (eq 7).

$$\ln \gamma_{PVP} = \ln\left(\frac{\Phi_{naproxen}}{X_{exp}}\right) + \left(1 - \frac{MV_{naproxen}}{MV_{PVP}}\right)\Phi_{PVP} + \ln \gamma_{NMP} + \left(\frac{MV_{naproxen}}{MV_{NMP}}\right)\chi\Phi_{PVP}^{\,2} \quad (7)$$

At last, the obtained χ value was implemented to profile the composition dependence of the Gibbs free energy of mixing (ΔG_{mix}) by applying eq 8 (Figure 4).

$$\frac{\Delta G_{mix}}{RT} = \frac{MV_{NMP}}{MV_{naproxen}}\Phi_{naproxen}\ln \Phi_{naproxen} + \frac{MV_{NMP}}{MV_{PVP}}\Phi_{PVP}\ln \Phi_{PVP} + \chi\Phi_{naproxen}\Phi_{PVP}^{\,2} \quad (8)$$

The first two terms on the right-hand side of eq 8 represent the entropy of mixing while the third represents the enthalpy of mixing. The ΔG_{mix} obtained would be composition dependent. The ΔG_{mix} for a system is reduced by the presence of a negative value of χ indicating exothermic (favorable) mixing. As entropy always favors mixing, for any drug−polymer system with enthalpy of mixing up to a certain unfavorable value, ΔG_{mix} will still remain negative. So, for athermal systems where there is no specific drug−polymer interaction ($\chi = 0$) also, ΔG_{mix} can still be negative. Beyond a positive value of interaction parameter, for an unfavorably (endothermic) interacting system, say $\chi_{critical}$, the value obtained for ΔG_{mix} will be positive at various compositions. Therefore the magnitude of is crucial in the predicted pattern of composition dependent drugpolymer miscibility.

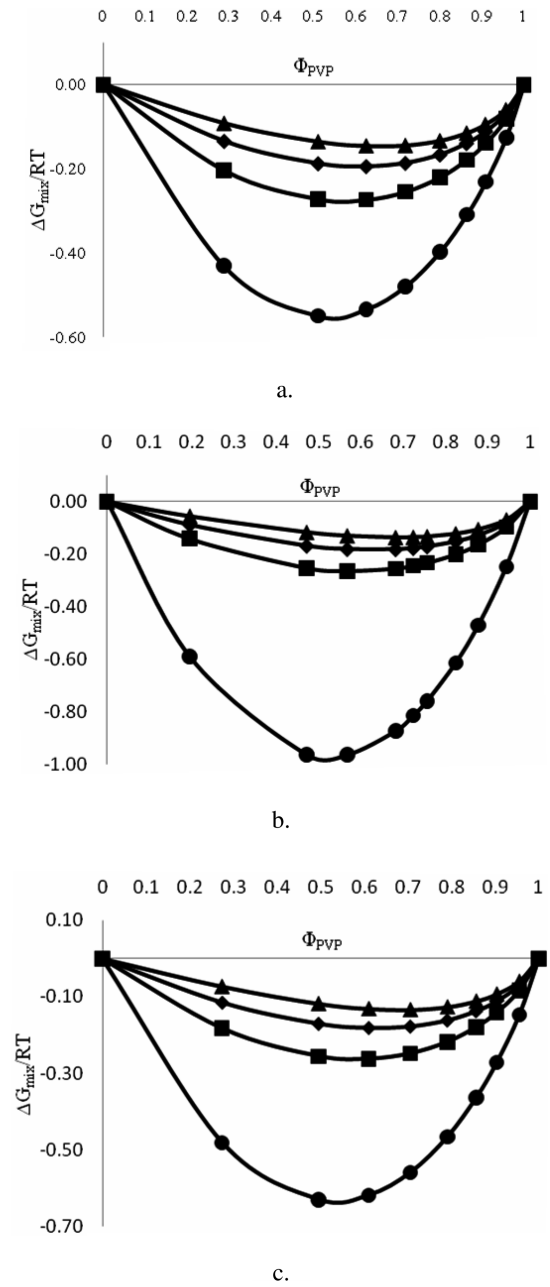


Figure 4. Gibbs free energy of mixing (ΔG_{mix})/*RT* versus polymer volume fraction (Φ_{PVP}) for naproxen−PVP K 12 (a), naproxen−PVP K 25 (b) and naproxen−PVP K 90 (c) systems with Flory−Huggins interaction parameter determined by the melting point depression (●), experimental solubility (■), solubility parameters (▲) methods and athermal systems ($\chi = 0$) (◆).

In addition, the theoretical approach derived from Hildebrand regular solution theory based on solubility parameters of the solute and solvent components[14] was used to have more insight on the solid solubility of drug in polymer by comparing with the experimental values. It assumes the repeating unit of polymer (monomer or an interacting unit) as the solvent and the drug molecule as the solute. The

(28) Hancock, B. C.; Parks, M. What is the true Solubility Advantage for Amorphous Pharmaceuticals. *Pharm. Res.* **2000**, *17*, 397–404.
(29) Lüder, K.; Lindfors, L.; Westergren, J.; Nordholm, S.; Kjellander, R. In Silico Prediction of Drug Solubility. 3. Free Energy of Solvation in pure Amorphous Matter. *J. Phys. Chem. B* **2007**, *111*, 7303–7311.

Table 2. Solid Solubility of Naproxen in PVP and the Related Values

components	values
molar volume of drug (MV_d)	195.14 cm^3/mol
molar volume of NMP (MV_{NMP})	96.43 cm^3/mol
mole fraction solubility in NMP (X_{exp})	0.11
heat of fusion (ΔH_f)	31578.51 J/mol
melting temp (T_m)	428.07 K
absolute temp (T)	298.00 K
universal gas constant (R)	8.31 J/mol·K
heat capacity change (ΔC_p)	108.60 J/mol·K[a]
entropy of fusion (ΔS_f)	73.77 J/mol·K
ideal mole fraction solubility (X_{id})	0.05
activity coefficient of drug in NMP (γ_{NMP})	0.49
solubility parameter of naproxen ($\delta_{naproxen}$)	23.37 $J^{1/2}/cm^{3/2}$
solubility parameter of PVP (δ_{PVP})	20.56 $J^{1/2}/cm^{3/2}$

	naproxen−PVP K 12	naproxen−PVP K 25	naproxen−PVP K 90
Values Estimated from Experimental Solubility			
molar volume of PVP (MV_{PVP})	2252.25 cm^3/mol	20000.00 cm^3/mol	932203.39 cm^3/mol
activity coefficient of drug in PVP (γ_{PVP})	2.01	2.14	2.15
mole fraction solubility in PVP (X_{PVP})	0.029	0.026	0.026
FH interaction parameter (χ)	−0.36	−0.36	−0.36
crystalline solubility of drug in PVP (S_c) (% w/w)	6.42	5.85	5.81
amorphous solubility of drug in PVP (S_a) (% w/w)	7.02	6.39	6.35
Values Calculated from Solubility Parameters			
mole fraction solubility in PVP (X_s)	0.04	0.04	0.04
solute solvent interaction parameter (χ_s)	0.21	0.21	0.21

[a] Taken from ref 27.

different degrees of interaction between the drug and the polymers might result in variable drug−polymer miscibility, expressed in terms of eq 9.

$$\ln X_S = -\ln X_{id} - \frac{(\delta_{PVP} - \delta_{naproxen})^2 MV_{naproxen} \Phi_{PVP}^{\ 2}}{RT} \quad (9)$$

X_s is molar fraction solubility of drug in PVP, and δ is the solubility parameter. The solubility parameters were calculated by the Fedors group contribution method.[30] The interaction parameter (χ_s) between drug and polymer was calculated using eq 10:

$$\chi_s = \frac{V_{site}(\delta_{PVP} - \delta_{naproxen})^2}{RT} \quad (10)$$

where V_{site} is the volume of the hypothetical lattice. The value of MV_{NMP} was taken as V_{site} for relevant comparison.

The values related to various components used for calculations and results obtained based on the aforementioned analysis are given in Table 2. The trend in solid solubility values of naproxen in PVP is in the order PVP K 12 > PVP K 25 > PVP K 90. The differences in the values of solid solubility, interaction parameter and activity coefficient of the drug in three PVPs are too small to account for the effect of chain length. The negative value obtained of χ from experimental solubility calculation agrees with the fact that naproxen is a favorably interacting drug with PVP in terms of mixing. Besides, this is even evident from the significant shifts reported of relevant peaks in infrared (IR) spectra of pure drug in the presence of PVP (in the form of colyophilized or physical mixtures) by Bettinetti et al.[11] Also, a less negative value of χ for the naproxen−PVP system compared to that reported for the indomethacin−PVP system obtained by the same methodology (−0.8)[8] reflects that it exhibits a comparatively weaker interaction with PVP. As mentioned in literature,[8] the values beyond unity of activity coefficients of the drug obtained in PVP signify them to be regular solution systems. So, it is safe to compare these data with those calculated using the Hildebrand regular solution model. To some extent, the solubility of naproxen predicted by the solubility parameters method also matched with the experimentally obtained values. The value of the interaction parameter obtained nearer to zero (0.21) supported the naproxen−PVP system being an interactive system. Unsurprisingly, the value of χ_s cannot account for the exothermic mixing system as none of the components in the right-hand side of eq 10 can be negative. As shown in Figure 4, the ΔG_{mix} line drawn from the values using interaction parameters obtained by both methods are negative. This indicates that χ values calculated by both the methods are below $\chi_{critical}$.

(30) Fedors, R. F. A Method for Estimating both the Solubility Parameters and Molecular Volumes of Liquids. *Polym. Eng. Sci.* **1974**, *14*, 147–154.

The comparison of kinetic miscibility with both the crystalline and amorphous solubility in PVP implies that naproxen is highly supersaturated in solid dispersions. As a result, the existence of drug−polymer miscibility at the macroscopic level was only attributable to kinetic stabilization that might subsequently lead to the phase separation.

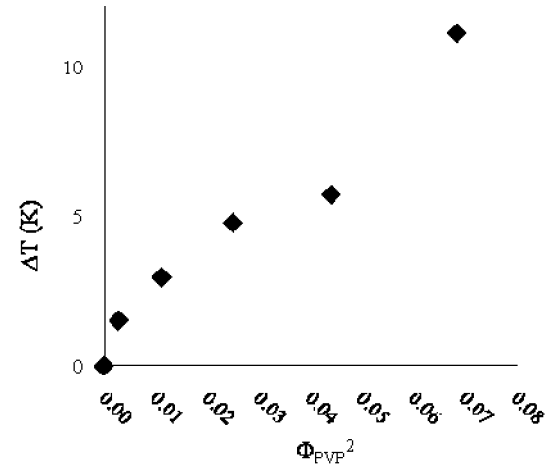
3.3. Melting Point Depression of the Drug in the Presence of the Polymer as an Indicator of Drug−Polymer Miscibility. The melting point depression of drugs in polymeric matrices has been explored in deriving the possible solid state interaction between drug and polymer.[7,8,31] The drop in chemical potential of drug molecules in the presence of the polymer makes the system cross the smaller temperature interval and has an equal chemical potential as that of the liquid phase leading to a reduced melting point (T_m^{mix}) compared to the melting point in the pure state (T_m^{pure}). The extent of depression is more in the case of strong exothermic mixing, less for weak exothermic or athermal or endothermic mixing and no depression in a totally immiscible system.[8] The extensively used procedure for accessing interactions between the components in the polymer blends described by Nishi and Wang[31] was used in the present studies. The interaction energy density, B, was estimated from the slopes of melting point depression (ΔT) plots (Figure 5) against the second power of the polymer volume fraction (Φ_{PVP}^2 by using the Nishi and Wang equation (eq 11). As evident from Figure 5, the trends corresponding to ΔT versus Φ_{PVP}^2 plots exhibit feasible linearity for the calculations with R^2 values of 0.956, 0.966, and 0.816 for the naproxen−PVP K 12, naproxen−PVP K 25 and naproxen−PVP K 90 systems, respectively.

$$\Delta T = T_{m^{pure}} - T_{m^{mix}} = T_{m^{pure}}\left(\frac{MV_{naproxen}}{\Delta H_f}\right)B\Phi_{PVP}^{\ 2} \tag{11}$$

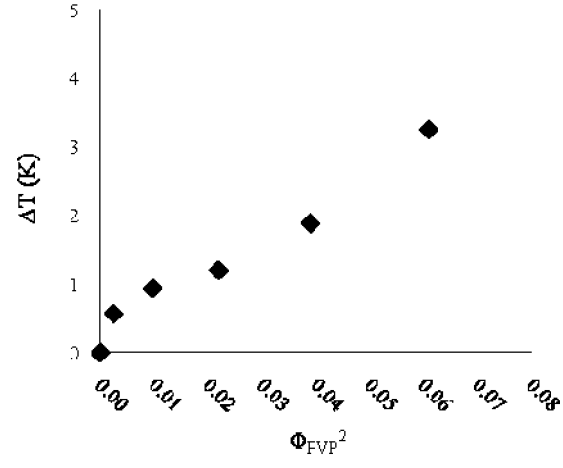
The value for the FH interaction parameter, χ, was further computed using eq 12:

$$B = RT_{m^{mix}}\left(\frac{\chi}{MV_{lattice}}\right) \tag{12}$$

Here also the value of MV_{NMP} was taken as the lattice volume, $MV_{lattice}$. The value of B is independent of composition. Rather, it represents the intensity of molecular interaction during mixing as a function of molecular weight of the mixing components. So, it should rely on the molecular weight of the mixing components. As the latter is constant for the drug, the value of B would be more negative with the increase in the molecular weight of polymer up to certain critical value. On the other hand, the FH interaction parameter (χ) is truly composition and temperature dependent. The values obtained for B and composition dependence of χ are listed in Table 3.



a.



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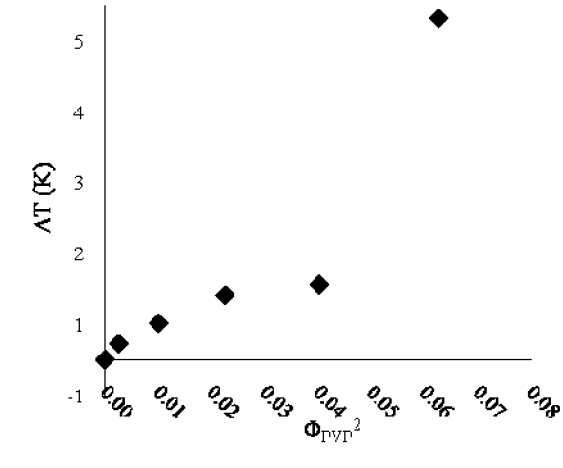

c.

Figure 5. The plot of melting point depression versus the second power of PVP volume fraction (Φ_{PVP}^2) for physical mixtures containing naproxen−PVP K 12 (a), naproxen−PVP K 25 (b) and naproxen−PVP K 90 (c).

The reduced melting point was calculated to consider the colligative melting point depression by the polymer in

(31) Nishi, T.; Wang, T. T. Melting-Point Depression and Kinetic Effects of Cooling on Crystallization in Poly (vinylidene fluoride)-Poly (methyl methacrylate) Mixtures. *Macromolecules* **1975**, *8*, 909–915.

Table 3. Composition Dependent Values of Drug−Polymer Interaction Parameter Obtained from Melting Point Depression Data by Solving the Nishi and Wang Equation

% naproxen	FH interaction parameter (χ)	interaction energy density (B)
	Naproxen−PVP K 12	
95	−1.44	−89.17
90	−1.44	
85	−1.45	
80	−1.45	
75	−1.47	
	Naproxen−PVP K 25	
95	−3.18	−118.03
90	−3.19	
85	−3.19	
80	−3.19	
75	−3.20	
	Naproxen−PVP K 90	
95	−1.83	−68.05
90	−1.83	
85	−1.84	
80	−1.84	
75	−1.85	

athermal mixtures by using a standard thermodynamic model excluding the interaction term (eq 13).

$$\left(\frac{1}{T_{m^{mix}}} - \frac{1}{T_{m^{pure}}}\right) = -\frac{R}{\Delta H_f}[\ln \Phi_{naproxen}] + \left(1 - \frac{MV_{naproxen}}{MV_{PVP}}\right)\Phi_{PVP} \quad (13)$$

The offset temperatures of the melting endotherms were taken for the calculations since an intimate mixing can occur by this point. The calculated (for athermal system) and observed melting point depressions were plotted against polymer volume fraction of the composites (Figure 6).

A remarkable compositional dependent depression in the melting point was observed. As observed in the plots, the melting point depressions calculated for the corresponding athermal systems using eq 13 were smaller. For naproxen−PVP K12 system the differences were found to be higher while lower for naproxen−PVP K 25 systems. As discussed for similar cases by Marsac et al.,[7] these results can be correlated with the difference between the melting region of mixtures and T_g values of PVPs. PVP K 12, having $T_g < T_{m^{mix}}$, exists in a liquid-like state bearing considerable molecular mobility leading to the better interaction and miscibility. Conversely, the glassy state of PVP K 90 with higher viscosity during melting of the drug in mixtures ($T_g > T_{m^{mix}}$) leads to less mixing and interaction.

The value of B was most negative for the systems made up of naproxen and PVP K 25. This signifies that the potential of interaction of drug is highest with PVP K 25. Also there should be some critical molecular weight or chain length of polymer wherefrom the strength of interaction would be reversed. As anticipated, the calculated χ values

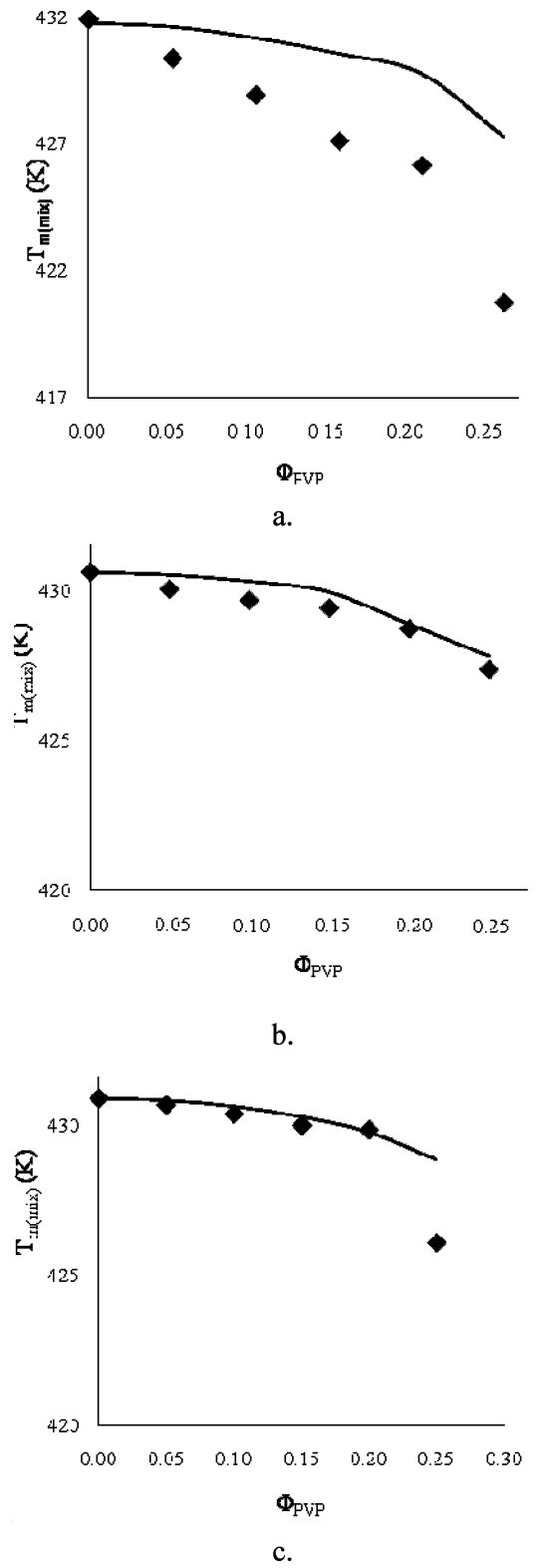

Figure 6. The plot of reduced melting point of naproxen in presence of PVP versus the PVP volume fraction (Φ_{PVP}) for physical mixtures containing naproxen−PVP K 12 (a), naproxen−PVP K 25 (b) and naproxen−PVP K 90 (c). The lines represent the melting points for the corresponding athermal mixtures.

were found appreciably negative for all the compositions. The negative value of χ increased consistently with an increase in polymer content in the mixtures. This can be taken as an indication of the compositional dependence of interaction. It would be logical to calculate the χ values of the system at the composition of solid solubility calculated by the experimental solubility method. But, for the mixtures from and beyond 50% PVP, there was no detectable melting endotherm present.

By virtue of comparing the value of χ with that obtained by the experimental solubility method, the lines were extrapolated to the drug content equivalent to the experimentally obtained solubility limits. The χ values obtained at the solubility limits for naproxen−PVP K 12, naproxen−PVP K 25 and naproxen−PVP K 90 systems are −2.02, −3.52, and −2.10 respectively. This reveals that the prediction of interaction between drug and polymer at ambient conditions needs to be corrected with respect to the temperature. This could be possible by reworking the values with the Wertheim thermodynamic perturbation theory which also correlated χ with the directional interaction apart from temperature.[32,33] The plots of ΔG_{mix} calculated by including the value of χ (the lowest of all the compositions for each polymer system) obtained by this method as function of polymer content were indeed deeper than that from the former ones (Figure 4).

3.4. Moisture Sorption Behavior of Physical Mixtures To Elucidate Drug−Polymer Interaction. The FH lattice model has been modified and extended to study the sorption behavior of the drug−polymer physical mixtures or solid dispersions.[34,35] This leads to the calculation of the composition dependent FH interaction parameter (χ) at a certain percentage relative humidity (% RH). This relationship can be expressed in terms of partial vapor pressures as given by eq 14:

$$\ln\left(\frac{P}{P_o}\right) = \ln V_1 + \left(1 - \frac{1}{X_{12}}\right)V_2 + \chi V_2^2 \qquad (14)$$

where V_1 and V_2 represent the volume fractions of solvent and solute respectively. P/P_o and X_{12} are the partial vapor pressure and the number of segments (monomer units) per solvent molecule. This relation was used first to calculate the drug water interaction parameter. A common expression derived from FH equation and Vrentas equation (eq 15) includes mutual interaction parameters between drug−polymer, drug−water and polymer−water pairs in the drug−polymer−water ternary system as follows:

$$\ln\left(\frac{P}{P_o}\right) = \ln V_1 + (V_2 + V_3) - \left(\frac{V_2}{X_{12}}\right) - \left(\frac{V_3}{X_{13}}\right) + [(\chi_{12}V_2 + \chi_{13}V_3)(V_2 + V_3)] - (\chi_{23}V_2V_3/X_{12}) \qquad (15)$$

where χ_{12}, χ_{13} and χ_{23} are FH interaction parameters for naproxen−water, PVP−water and naproxen−PVP respectively. X_{12} and X_{13} are the number of molecules of naproxen and the number of segments (monomer units) of PVP per unit water molecule respectively. V_1, V_2 and V_3 are the volume fractions of water, naproxen and PVP respectively. As eq 15 is reported to provide a better fit at the higher partial water vapor pressure, a 94% RH environment was used. The value of χ_{13} was taken as equal to 0.5 from literature.[35] X_{13} was taken as unity by assuming the interaction of one monomer unit of PVP with one molecule of water. The value of χ_{12} was calculated assuming $X_{12} = 2$ as reported for indomethacin,[35] a molecule bearing a similar interacting functionality (carboxylic acid) as that of naproxen. Physical mixtures containing PVP K 12 were excluded from the moisture sorption study due to its excessive hygroscopicity that posed trouble in accuracy of the moisture gain measurement. The values obtained by the moisture sorption based calculation are given in Table 4. The χ values obtained by this method showed pertinent composition dependence. The positive values of χ toward the higher drug content implied weaker or unfavorable drug−polymer interaction in them. However, at 25% w/w drug content the χ values are highly negative. Though these values from ternary systems are not precisely comparable with the drug−polymer binary system, an idea about the extent of interaction as a function of composition can be extracted in the presence of water.

Table 4. Composition Dependent Values Interaction Parameter Calculated from the Moisture Sorption Based Analysis

		interaction parameter		
mixture	% PVP in mixture	χ_{13} (polymer−water)	χ_{12} (drug−water)	χ_{23} (drug−polymer)
naproxen−PVP K 25	25	0.5	5.73	12.02
	50			4.53
	75			−1.70
naproxen−PVP K 90	25			11.05
	50			4.29
	75			−1.80

The deviation of the moisture gain behavior of the mixtures from the theoretically calculated values as a function of composition is shown in Figure 7. The negative deviations observed for all three compositions indicate the existence of favorable interaction between drug and polymer. The higher deviation seen at higher polymer content signifies the stronger interaction toward this composition.

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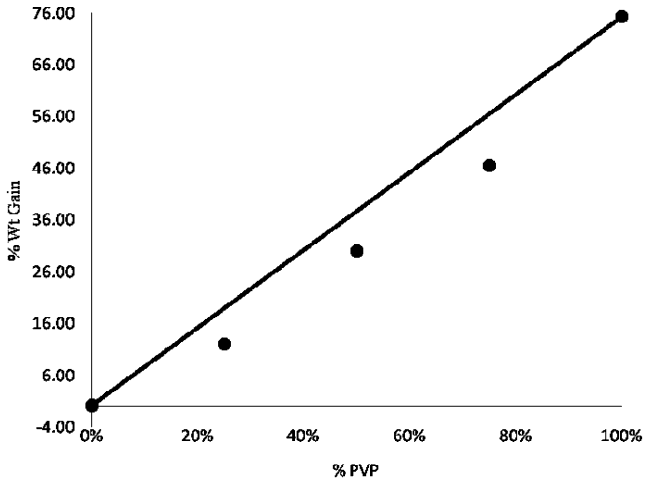
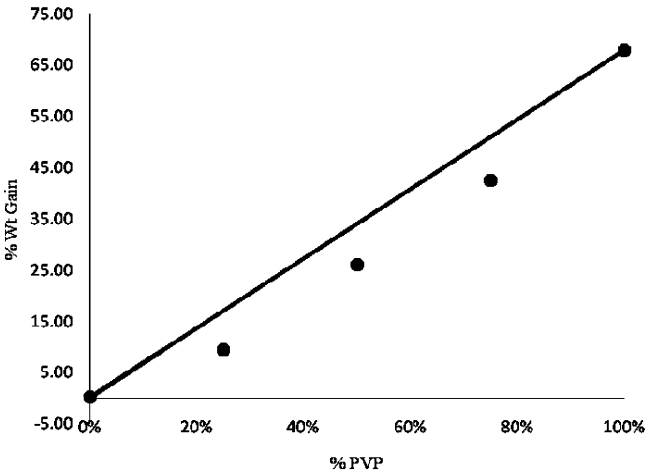


a.



b.

Figure 7. Moisture gains versus % w/w PVP in physical mixtures containing naproxen−PVP K 25 (a) and naproxen−PVP K 90 (b). The solid lines represent the theoretical moisture gains.

4. Discussion

The macroscopic examination of thermoanalytical data revealed that solid dispersions of naproxen and PVP prepared by spray drying are miscible up to 1:1 compositions. The effect of water in mixing is more pronounced for the system containing the hygroscopic polymer PVP K 12. The exceedingly lower T_{gm} values obtained in the second heating cycle of solid dispersion of naproxen containing 95% and 90% PVP K 12 could be due to the *in situ* moisture absorption by the hygroscopic PVP K 12 while cooling the drug−polymer mixture in the DSC cell. If we assume that the extent of absorption is up to the theoretical equilibrium moisture content (EMC) of the system, then it will gradually decrease with the increase of the drug content in the mixture so that the plasticization will be less. The EMC of a mixture decreases gradually with the decrease in the polymer content, and hence the decrease of T_{gm} values below 15% polymer content may be due to the plasticization effect of the drug only. The observation of deeper endotherms remaining in the nonreversing heat flow signals of the corresponding mixtures provided additional evidence of the presence of moisture.

Disregarding this observation, there are always two groups of drug−polymer composites in terms of T_{gm}, especially in the case of naproxen−PVP K 25 and naproxen−PVP K 90 systems. The solo role of plasticization by the water content in the mixtures with T_{gm} below 100 °C was overruled as the patterns were consistent during the second heating cycle as well. Nevertheless, this behavior can be correlated to the composition dependent strength of the drug−polymer interaction and hence the miscibility in this system. The possible interactions of PVP with the drug molecules are electrostatic (ion−ion, ion−dipole, dipole−dipole), van der Waals and hydrogen bonding interactions.[36] Such behavior can further be prevailed for the system with the prospect of potential saturable interaction between drug and polymer undergoing the mixing process. The term "saturable interaction" is implied to specific types of interaction such as hydrogen bonding which can get saturated with respect to mixture composition or mixing temperature. There is well documented evidence of the presence of saturable interactions between naproxen and PVP.[11,37] Here, the deviation of observed T_{gm} from that predicted using the GT equation reflects the strength of interaction which can render the integrity of miscibility. Also, it has been reported for naproxen that it can complex with *n*-vinylpyrrolidone (VP), a monomer unit of PVP, in 1:1 molar composition in solution.[9] However in solid state the scenario will not be the same as the molecular vicinity is different with comparable decrease in mobility. This is supported by the observation that the naproxen−PVP mixture with equimolar content of drug to VP molecules (67.47% w/w drug) already crosses the miscibility barrier. Thus, if the hydrogen bonding density (number of drug molecules hydrogen bonded with a monomer) is a function of composition for a system, the composition dependent deviation of T_{gm} from the predicted values can be due to the different types of structural mixtures. Interesting correlations have been drawn in a publication[22] for the composition dependent formation of single or double hydrogen bonds between the small units of PVP and PEG reflected by the deviation of T_{gm}. In a recent publication on interaction between PVP and aryl acetic acid nonsteroidal anti-inflammatory drugs (NSAIDS),[37] composition dependent miscibility behavior has been studied between naproxen and PVP K 30. As discussed by the authors, it is reasonable to assume an increase in the hydrogen bonding capacity as function of naproxen concentration with an increased diffusion of naproxen into the PVP chain due to its small molar

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volume. At a particular composition, the naproxen content in the mixture becomes excess apart from that interacts with PVP and immiscibility starts. However, it appears contradictory that naproxen is miscible through the whole composition range from 10% to 90% PVP K 30 containing mixtures. Besides these findings, more comprehensive spectroscopic investigations on the naproxen−PVP interaction and miscibility based on solid state ^{17}O-NMR[38] or pulsed field gradient (PFG) NMR[22] studies are necessary to ascertain the composition dependent hydrogen bonding behavior and its mechanistic explanation.

In comparison to ibuprofen, naproxen is considered as a weakly interacting molecule with PVP.[12,37] The weak interaction between naproxen and PVP due to the catemer arrangement of naproxen molecules in its crystal packing is reported.[12] However, the molecular geometry in the crystal structure rarely dictates the state of the drug after the treatment with the molecular chaos provided by the processing solvents and other process parameters during the manufacture of the solid dispersion. The information on the intra- versus intermolecular hydrogen bonding behavior of naproxen has been studied in diverse solvents (protic, aprotic, alcoholic and polar/nonpolar).[39] Rather, the persuasively supporting fact is that naproxen exhibits a higher number of self-assembling interactions (COOH···HOOC and COOH···−O−) as compared to ibuprofen (COOH···HOOC).[40] This poses an increased competition of naproxen against itself toward hydrogen bonding with the polymer. For such weaker interactions, there would be a certain influence of the molecular weight and chain length of PVP on the probability of hetero-contact formation.[23] Up to a certain increase in molecular weight the number of drug−polymer hydrogen bonding increases. Beyond this, the higher molecular weight of PVP with longer chain length provides opportunity for more coiling. This leads to a lesser accessibility of the interacting groups for a random hetero-contact formation.

The drug−polymer miscibility analyzed with the vision of entropy contribution gives a different picture. The conformational rearrangements play a vital role in the local ordering effect against hetero-contact formation for the weakly interacting systems.[23] Hence, for the systems like naproxen−PVP, the entropic contribution to the miscibility is remarkable. These effects will contribute to an increase of the free volume and a corresponding decrease of the T_{gm} from predicted values. Negative entropy of mixing can be expected for strongly interacting mixture components in structured mixtures.[17] However, the energetic interactions that are prevailing in the lower naproxen containing mixtures will cause the denser packing of the mixture components due to decreased mobility and free volume leading to an increase in hetero-contact formation and in turn an increase in the T_{gm} values. This is apparent from the obtained U shaped entropy plots as a function of mixture composition (Figure 3).

The equilibrium crystalline as well as the amorphous solubility obtained by the experimental solubility method over kinetic miscibility provided better insight about whether naproxen at certain composition is miscible with PVP on a molecular scale or is very close to being miscible in terms of supersaturation. The values obtained for amorphous miscibility ranged from 6.35 to 7.02% w/w while those obtained for crystalline solubility were 5.81−6.42% w/w. The values of the experimentally obtained amorphous solubility might be less than the calculated values at the given temperature due to simultaneous devitrification and plasticization effect on naproxen, a rapidly devitrifying molecule. The theoretical model is purely based upon the thermodynamics and, hence, does not take both phenomena into account.[41] Though the amorphous miscibility is related to the balance between cohesive and adhesive forces between the mixing components and crystalline solubility is contributed by the crystal packing and cavitation energy, the difference in drug solubility was marginal. However both values are far below the observed kinetic miscibility. This suggests that the drug−polymer systems are markedly supersaturated. The negative values of FH interaction parameters (−0.36) provided a mechanistic indication for the naproxen−PVP mixtures being an exothermically mixing system. Though the interaction parameter looks more realistic as calculated from data at ambient temperature and with the drug composition at its solubility limits, its composition dependence cannot be worked out by this methodology. Based on the chemical structure of the drug substance, the chain length of PVP is crucial in deciding the interaction based miscibility.[36,42] The effect of chain length on the dynamic structure of PVP and PEG mixtures in a polar solvent has been conferred in terms of its contribution to relaxation processes, its change in complexation density in a mixture and its segmental motion.[42] However, the influence of the PVP chain length on the estimated solubility and interaction parameter values could not be revealed by this methodology. This could be due to the inappropriate use of the FH model or the assumptions made in deriving the expressions as discussed earlier. Moreover, the main setback of the FH model is that it does not take into account the

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directional interactions or hydrogen bond related parameter in the expression. So, the influence of the latter is missed in the course of the calculations. Conversely, the solid solubility values obtained by this method are approximately equivalent to that by the solubility parameter method. The difference in solubility parameter values between drug and polymer has also been used for accessing the drug−polymer miscibility.[15,23] However, it is a bolder assumption to make all types of interactions (dispersive, dipolar and hydrogen bonding) that are included in the solubility parameter contribute similarly to the solid solubility. Thus, we assume that the Wertheim thermodynamic perturbation theory (WTPT)[33,34] can be a more appropriate model to describe the true phase behavior of the drug−polymer mixture exhibiting an existence of saturable interaction between the mixing components. This is the subject of our current investigation.

The other advanced mixing thermodynamics for modeling solute solubility in solvent and phase behavior are nonrandom hydrogen-bonding (NRHB) theory,[43,44] the universal functional activity coefficient (UNIFAC) model,[45] the nonrandom two liquid segment activity coefficient model (NRTL-SAC)[46] and the conductor-like screening model for real solvents (COSMO-RS).[47] NRHB has recently been used for modeling the phase behavior in mixtures of pharmaceuticals with liquid or supercritical solvents with promising results,[40] and even COSMO-RS has also been used for the pharmaceutical systems.[47] The challenges posed in modeling the phase behavior of the drug−polymer systems are their complex hydrogen bonding and interaction behavior, the presence of chirality in drug and unavailability of fluid state data for polymers.

The technique based on melting point depression provided a better compositional dependent interaction. The popular methodology in studying miscibility of polymer blends based on the Nishi and Wang expression has also been used for the physical mixture and solid dispersion system containing a steroidal hormone and EUDRAGIT.[48] The B values determined by curve fitting indicated the interaction between the mixing components. The melting point depression method demonstrated the propensity of predicting the composition dependence and PVP chain length effect on the interaction and miscibility of naproxen and PVP. The less negative value of B for naproxen−PVP K 12 systems (−89.17) compared to the value of the naproxen−PVP K 25 system (−118.03) revealed that the molecular interaction is denser in the latter case. However, the decrease in the absolute value of B for the naproxen−PVP K 90 system is logical when considering the effect of the molecular weight of PVP beyond a certain value. The extrapolations of the composition dependent interaction parameter up to the solubility limit estimated from the experimental solubility limits provided an interesting insight. As naproxen showed the temperature dependent decrease in the number of intermolecular hydrogen bonding per molecule with ethanol and acetone with an increase in temperature,[40] a similar scenario can be anticipated with PVP which in turn weakens the drug−polymer interaction. Hence, the value of the composition dependent interaction parameter would be less negative at ambient temperature as compared to that obtained from an extrapolation of the trend line to the desired composition by this method. The comparison of χ values from the experimental solubility method and melting point depression method can only be made after correction of this temperature term. However, the FH model does not offer preference for the same as it does not incorporate any hydrogen bonding related parameter in the calculation. Hence with this method, the temperature dependent interaction parameter cannot be obtained. So, WTPT will be capable of correlating the interaction parameter with the temperature.[49]

The methodology based upon the moisture sorption analysis also provided the composition dependent interaction parameter. The outcome from this method in some way projects the fate of drug−polymer miscibility in the presence of moisture. The influence of absorbed moisture in the miscibility of drug−polymer composites is well explored.[34,35] The solid solubility of drug in polymer at a particular composition decreases with an increase in supersaturation due to the sorbed moisture, a consequence commonly known as $\Delta\chi$ ($= \chi_{12} - \chi_{13}$) effect. The composition dependent immiscibility can be induced due to the extreme difference between interaction of water with hydrophobic naproxen (unfavorable interaction, $\chi_{13} = 5.73$) and hydrophilic PVP (favorable interaction, $\chi_{12} = 0.5$). There are some examples on the moisture induced phase separation of pharmaceutical amorphous solid dispersions.[50,51] This can be more pronounced toward higher drug containing mixtures as they are

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already supersaturated. The interaction parameters obtained by this method are perhaps more qualitative.

As noticed from Figure 4, the Gibbs free energy plots as a function of PVP molecular weight for the naproxen−PVP mixtures are highly comparable. All curves plotted from the values obtained with χ values except that from the solubility parameter method are lower than the corresponding athermal curves. The Gibbs free energy change minimum region that lies around the 50% w/w composition zone signifies the limit of kinetic miscibility.

5. Conclusions

The thermodynamic solid solubility estimated of naproxen in PVP was considerably lower than the observed kinetic miscibility. Solid state behavior of the solid dispersions prepared using PVP with varying molecular weight showed marked differences in terms of composition dependence of mixed phase glass transition temperatures. The crystallization temperature in the phase separated systems indicated an identical extent of crystallization inhibition. The information derived from the configurational entropy is important for weakly interacting systems like naproxen and PVP. The difference in the estimated solid solubility of naproxen in PVPs with different molecular weights using experimental solubility in *n*-methylpyrrolidone was negligible. This implies that the currently used FH thermodynamic lattice model for drug−polymer mixing lacks the intended parameters to account for chain length effect on interaction and miscibility such as hydrogen bonding. The treatments of data with the models that really tender the chain length effect of polymer in solid solubility of drug like Wertheim thermodynamic perturbation theory are preferred. The extent of solid−solid solubility and the strength of the drug−polymer interaction estimated by different methods varied extensively. The method that uses the experimental solubility of drug in the low molecular weight analogue of the polymer to estimate the solubility in the corresponding polymer offers more realistic values. This is due to the real time data generated for the downstream calculations at room temperature and toward lower drug content. It can be inferred from the melting point depression method that naproxen−PVP is a favorably interacting system with considerable negative values of the interaction parameter. Also, the composition dependent interaction parameters could be calculated by this method. However, it deals with mixing of the system around the melting point of the drug, which is practically very rare to reach, and the interaction parameter is truly composition/temperature dependent, especially for the systems exhibiting saturable interactions. The moisture sorption method provides an idea of the extent of weakening that water can cause to the drug−polymer interaction. It gives a qualitative estimate of the composition dependent interaction parameters.

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Supporting Information Available: DSC thermograms of crystalline and quenched cooled naproxen, PVP, spray-dried solid dispersions and melting point depression experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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