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Research Paper

Phase Behavior of Amorphous Molecular Dispersions II: Role of Hydrogen Bonding in Solid Solubility and Phase Separation Kinetics

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Purpose. To determine the factors influencing "solid solubility" and phase separation kinetics of drugs from amorphous solid dispersions.
Methods. Solid dispersions of griseofulvin-poly(vinyl pyrrolidone) (PVP) and indoprofen-PVP were prepared using solvent evaporation technique. Dispersions demonstrating single T_g were exposed to 40°C/69% RH for 90 days. Drug solid solubility in the polymer and phase separation rates were determined from changes in T_g of solid dispersions. FTIR spectroscopy and XRD were used to characterize drug-polymer interactions and drug crystallinity, respectively.
Results. Freshly prepared solid dispersion of up to 30% w/w griseofulvin and indoprofen were molecularly miscible with PVP. Hydrogen bonding was evident in indoprofen-PVP, but not in griseofulvin-PVP dispersions. When exposed to 40°C/69% RH, griseofulvin phase separated completely, whereas the solid solubility of indoprofen was determined as 13% w/w. The first-order rate constants of phase separation for 10%. 20%, and 30% w/w griseofulvin dispersions were estimated as 4.66, 5.19, and 12.50 ($\times 10^2$) [day^{-1}], and those of 20% and 30% w/w indoprofen dispersions were 0.62 and 1.25 ($\times 10^2$) [day^{-1}], respectively.
Conclusions. Solid solubility of griseofulvin and indoprofen in PVP is ~0% w/w and ~13% w/w, respectively. Drug-polymer hydrogen bonding in indoprofen-PVP dispersions favors solid solubility. Phase separation rate of drug from the solid dispersions depends on the initial drug content and the nature of drug-polymer interactions.

KEY WORDS: crystallization; hydrogen bonding; solid miscibility; solid solution; thermal analysis.

INTRODUCTION

Solid dispersion technology has been used for improving the dissolution rate and bioavailability of poorly water soluble drugs (1–3). Solid dispersions are generally prepared by incorporation of the poorly soluble drug into a water-soluble carrier via techniques like melt-extrusion or coprecipitation (4,5). Such processes generate amorphous drug dispersions (6). Although the amorphous drug dissolves faster compared to its crystalline alternatives, it is not physically stable and during the shelf-life may undergo unpredictable crystallization (7–9). Polymeric carriers have been shown to inhibit or delay drug crystallization from solid dispersions by forming a miscible phase, where the drug and the polymer are molecularly dispersed (10–12). The miscible phase is referred to as amorphous molecular dispersion.

A detailed evaluation of the factors influencing the physical stability of amorphous molecular dispersion reveals the presence of two opposing forces in such systems: On one hand, the polymer prevents drug crystallization by increasing the T_g of the mixture and (or) through drug-polymer interactions (11); on the other hand, it absorbs moisture and exhibits enhanced molecular mobility, which could increase the potential for drug-polymer phase separation leading to drug crystallization (13,14). The physical integrity of an amorphous molecular dispersion would depend on the extent of drug miscibility in the polymer in a specified moisture environment.

In an earlier study, we demonstrated that depending on the nature of drug-polymer interactions, a fraction of the drug can remain miscible with the polymer in the solid state even under extreme heat and humidity conditions (15). This fraction was defined as the solid solubility of drug in the polymer. Hydrogen bonding between the drug and the polymer was hypothesized as the force that is responsible for the solid solubility.

In view of the earlier findings, the primary objective of the study presented in this paper was to provide further evidence to determine the role of hydrogen bonding in the solid solubility and physical stability of solid dispersions by investigating the solid solubility of two hydrophobic drugs; namely, griseofulvin and indoprofen in poly(vinyl pyrrolidone) (PVP). Griseofulvin and indoprofen serve as good model compounds because, as inferred from their chemical structures (Fig. 1), griseofulvin does not have any proton donor groups, whereas indoprofen does. This difference makes it possible to assess

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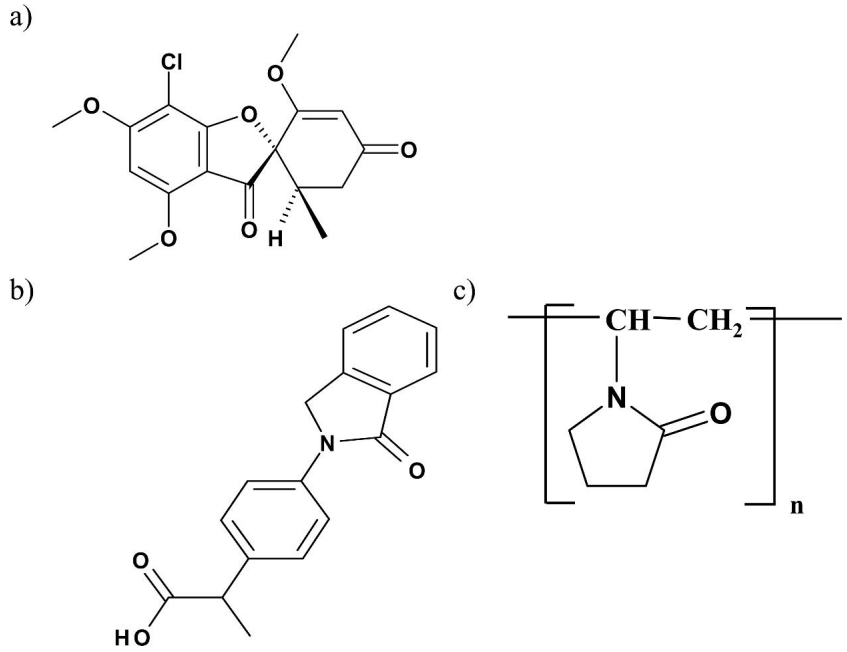

Fig. 1. Chemical structures of (a) griseofulvin, (b) indoprofen, and (c) repeat unit of PVP.

the effect of the hydrogen bonding ability of the drug and the polymer on solid solubility. Moreover, the drugs selected exist in highly crystalline forms. During the preliminary testing, amorphous griseofulvin crystallized rapidly, whereas indoprofen could never be converted to its amorphous form by using the techniques like melt-quenching and solvent evaporation.

The second objective of this study was to determine experimentally the kinetics of phase separation of the drugs from solid dispersions. Previously, it was demonstrated that the phase separation of a drug from solid dispersions is the first step toward its destabilization (15). Therefore, determining the phase separation rate of a drug would provide valuable information on the overall rate of physical instability. By understanding the phase separation and crystallization kinetics, an effective strategy for stabilizing solid dispersions can be developed. In this study, we have used a methodology that is typically used in crystallization kinetics to determine the phase separation rate of griseofulvin and indoprofen from their solid dispersions.

MATERIALS AND METHODS

Materials

Plasdone (poly(vinyl pyrrolidone)) PVP K29/32 with M_w 50 kDa was obtained from ISP Technologies Inc. (Wayne, NJ, USA). Prior to preparing solid dispersions, PVP was dried at 105°C under vacuum for at least 20 h until a constant weight was obtained. Griseofulvin ((2*S*)-*trans*-7-chloro-2′,4,6-trimethoxy-6′-methylspiro(benzofuran-2[3H], 1′-(2)cyclohexene)-3,4′-dione)) and indoprofen (α-methyl-*p*-(1-oxo-2-isoindolinyl) benzenacetic acid) were purchased from Sigma Chemical Company (St. Louis, MO, USA) and were used as obtained to prepare the solid dispersions. Copper chloride that was used to prepare saturated salt solution to obtain 69% RH at 40°C was purchased from Fisher Chemicals Co. (Fair Lawn, NJ, USA) (16).

Methods

Preparation of Solid Dispersions Using Solvent Evaporation Technique

Solid dispersions of drug (10–50% w/w at 10% w/w increments) in PVP were prepared by using solvent evaporation technique. Crystalline griseofulvin and crystalline indoprofen were dissolved (0.3–1.5 g) in dichloromethane and methanol, respectively, by sonicating the solution in a water bath at room temperature for about 15 min. PVP was added to the drug solution to make up the total weight of solids to 3 g. After all the PVP was dissolved, as determined visually, the solvent was evaporated with a rotary vacuum evaporator (Buchi Rotovapor R-200, Westbury, NY, USA) by keeping the solution heat at 37°C using a water bath. The solid dispersions thus obtained were further dried in a vacuum oven at room temperature for 24 h. They were ground with a mortar and pestle and were sifted through sieve no. 70 to reduce the particle size to less than or equal to 210 μm. The solid dispersions thus obtained were stored in vials over anhydrous calcium sulfate in a freezer when not being studied in order to minimize the drug crystallization during storage.

Isothermal Stability Studies

To determine the solid solubility of drugs in the polymer, solid dispersions containing 10, 20, and 30% w/w of griseofulvin and indoprofen in PVP were accurately weighed (8–12 mg) in standard differential scanning calorimetry (DSC) pans. The pans were placed in the desiccators containing saturated copper chloride solution that provides 69% RH in 40° ± 1°C ovens (Precision Scientific Inc., Chicago, IL, USA). By storing the samples in discrete DSC pans, the reproducibility could be assessed without disturbing the bulk properties of the aging samples. Samples were taken out from the desiccators for analysis at regular time intervals for up to 90 days.

They were crimped with aluminum lids having five pinholes to facilitate the removal of absorbed water during heating in modulated DSC.

Thermal Analysis

Thermal analysis was performed using modulated differential scanning calorimetry (MDSC; TA Instruments MDSC 2920, New Castle, DE, USA) with a liquid nitrogen cooling accessory. The analysis was performed under a purge of dry nitrogen gas (60 cc/min). High-purity indium and sapphire were used bimonthly (or after approximately 50 scans) to calibrate the heat flow and heat capacity of the instrument. Thermal history of the samples was not erased and the T_g was recorded during the first heating scan. Samples (8–12 mg) were initially cooled to –10°C for 10 min and were heated to 245°C at 1°C/min with modulations of 0.266° every 50 s. The specified amplitude and period were optimized to provide the best results for resolution. Each measurement was conducted with triplicate batches to ascertain the reproducibility of the experiments.

Determination of Solid Solubility

Glass transition temperatures (T_g) were measured with MDSC. The thermal scans from each storage time were evaluated for changes in T_g values with respect to the T_g of the freshly prepared solid dispersions. Phase separation of the drug, if any, would result in an increase in the polymer proportion in the drug-polymer miscible phase, which in turn demonstrate higher T_g value (i.e., when $T_{g\ drug} < T_{g\ polymer}$). The increase (or decrease) in T_g of the solid dispersion was monitored as a function of storage time until no further change in the T_g was observed [T_g equilibrium (T_g^{eq})]. The T_g^{eq} value was used to determine the solid solubility of the drug in the polymer at the specified moisture and temperature condition by comparing the T_g^{eq} with the T_g value of the freshly prepared solid dispersion of known composition. This approach was used earlier to determine the solid solubility of trehalose in dextran and PVP (15).

X-Ray Powder Diffraction (XRPD)

The X-ray powder diffractometer [Rigaku RINT (D/Max) 2200 equipped with an ultimagoniometer, Danvers, MA, USA] consisted of a 40 kV, 40 mA generator with a Cu K_α radiation anode tube. The ultimagoniometer alignment was verified using a corundum plate, NIST SRM 1976. XRD pattern was used to test the presence of crystallinity in the solid dispersions. The samples were sifted through sieve no. 70 and placed on a 0.5-mm quartz plate holder prior to exposure to X-ray. They were scanned over a 2θ range of 2° and 40° at a rate of 2° per minute in 0.02° step size.

Fourier Transform Infrared Spectroscopy (FTIR)

A Nicolet Nexus 470 FTIR spectrometer (Madison, WI, USA) equipped with a KBr beam splitter was used to obtain the infrared spectra. Calibration for wavenumber accuracy was performed by using polystyrene sample. Dry nitrogen gas was used to purge the beam splitter and the sample compartment. IR spectra were obtained using an attenuated total reflectance (ATR) accessory (single reflection bounce diamond crystal; Golden Gate accessory). For each spectrum, 32 scans were performed, and a resolution of 4 cm was chosen. The ATR accessory enables to obtain the spectra by pressing the solid material onto the diamond crystal without the use of potassium bromide (17). All the samples were dried under vacuum for 20 h prior to obtaining any spectra, to remove the influence of residual moisture.

RESULTS

Characterization of Drug Substance

The physical-chemical properties of griseofulvin and indoprofen are listed in Table I. Both compounds have similar melting temperatures (>200°C) and high heat of fusion representing their stable crystalline structure. Amorphous griseofulvin and indoprofen were prepared by rapidly cooling the molten crystalline drug in a DSC pan, and their T_gs were determined as 86°C and 50°C, respectively, by heating them at 1°C/min. Upon heating, amorphous griseofulvin and indoprofen recrystallized immediately above their T_g.

Characterization of Amorphous Solid Dispersions

Griseofulvin and indoprofen solid dispersions showed a composition-dependent single T_g for up to 30% w/w drug concentrations (Fig. 2). This behavior demonstrated the presence of the molecularly dispersed drug in the polymer at given concentrations. Above 30% w/w, multiple T_gs were observed in the griseofulvin solid dispersions, indicating partial phase-separation. Within the 30 and 40% w/w indoprofen-containing dispersions, a concentration-dependent T_g decrease was not observed, which suggested "immiscibility" in the dispersions containing 40% w/w and more indoprofen. The freshly prepared solid dispersions containing either drug in 30% w/w or lesser concentrations were free of crystalline peaks as monitored by X-ray diffraction. Although the X-ray pattern revealed slight crystallinity in freshly prepared 40% w/w solid dispersions of either drug, no significant melting endotherm of crystalline drug was noticed using MDSC (Fig. 2). Instead, a broad endotherm at 190–210°C (Fig. 2a), and at 170–180°C (Fig. 2b) was noticed. The absence of a sharper melting endotherm that was expected could be the result of dissolution of the crystalline drug in the polymer at temperatures above T_g. Similar behavior was also observed by Six *et al.* for itraconazole dispersions in hydroxypropyl methyl cellulose (HPMC) (18).

To confirm the presence of hydrogen bonding in the solid dispersions, the FTIR spectra of the carbonyl stretching region (1550–1750 cm^{-1}) of the freshly prepared solid disper-

Table I. Physical-Chemical Properties of the Drugs Used in Solid Dispersions

Drug substance	T_m	ΔH_f	T_g	T_c	ΔH_c	MW	H-bond acceptors and donors[a]
Griseofulvin	218	98	86	133	81	352	6 and 0
Indoprofen	214	127	50	75	58	281	4 and 1

T_m, melting temperature; ΔH_f, heat of fusion; T_g, glass transition temperature of amorphous drug; T_c, recrystallization temperature upon heating at 1°C/min; ΔH_c, heat of recrystallization; MW: molecular weight.

[a] From the chemical structure (Fig. 1).

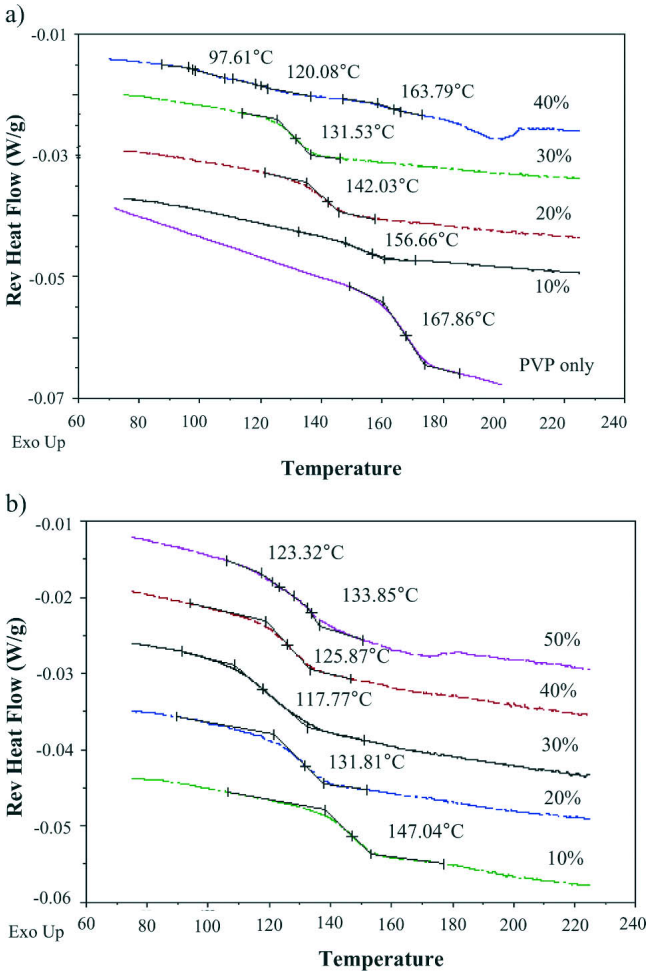

Fig. 2. MDSC reversing heat flow scans of solid dispersions of PVP with (a) griseofulvin and (b) indoprofen. Composition-dependent single T_g indicates molecular miscibility in solid dispersions of up to 30% w/w drug concentrations. The percentages refer to the drug concentrations.

sions were compared with their corresponding physical mixtures. FTIR spectroscopy is very sensitive to changes in the carbonyl stretching that can occur due to hydrogen bonding. In Fig. 3a, the carbonyl stretching of a 30% w/w griseofulvin solid dispersion is compared with its corresponding physical mixture containing amorphous griseofulvin. No significant differences were observed between the two spectra, indicating the absence of H-bond interactions between the drug and the polymer. Even an increase in griseofulvin concentration from 10 to 30% w/w caused no shift in the peak carbonyl position of PVP seen at 1667 cm^{-1}. The slight broadening of the peak and a shift in the wave numbers toward values of pure amorphous griseofulvin could be the result of the presence of the higher concentrations of griseofulvin.

Presence of 10–30% w/w indoprofen in the dispersions caused a significant lowering in the carbonyl stretching of PVP from 1667 cm^{-1} to 1654 cm^{-1} (Fig. 3b), suggesting hydrogen bonding possibility between the drug and the polymer. The spectrum of a 30% w/w solid dispersion, which demonstrated molecular miscibility as suggested by MDSC, was clearly different from the corresponding physical mixtures. Because of the strong tendency of amorphous indoprofen to crystallize during preparation and characterization of the physical mixtures, crystalline indoprofen was used. To ensure that the crystalline nature of indoprofen in the physical mixture did not contribute to the peak shift, the spectra of pure amorphous and pure crystalline indoprofen were compared. No significant differences were observed in the peak region of interest (i.e., 1667 cm^{-1} to 1654 cm^{-1}).

Stability Studies by Thermal Analysis

Griseofulvin and PVP Solid Dispersions

The MDSC reversing heat flow scans of 30% w/w griseofulvin solid dispersions stored at 40°C/69% RH for a period of 1–15 days are shown in Fig. 4a. A single T_g at 131°C was observed in the freshly prepared samples. Two T_gs referred to as T_{g1} and T_{g2} were observed in the samples during the 5-day storage period. Because T_{g1} was closer to the T_g of pure amorphous griseofulvin (i.e., 90°C), it is reasonable to assume that T_{g1} corresponds to the T_g of griseofulvin-rich phase and T_{g2} corresponded to the T_g of griseofulvin-poor (polymer-rich) phase. The formation of two T_gs indicated the phase separation of griseofulvin and PVP. Upon storage, the heat capacity change at T_{g1} decreased and that of T_{g2} increased in a time-dependent manner. The T_{g1} and T_{g2} values increased during storage, indicating a progressive phase separation, except for the 1- and 2-day-old samples, where a slight decrease in T_{g1} was noticed. While T_{g1} disappeared in the 9-day-old or older samples, T_{g2} values increased and seemed to reach a plateau at 166 ± 1.5°C (not shown in Fig. 4a). This value is termed T_g^{eq}.

The thermal events for 20% w/w griseofulvin solid dispersions followed the same pattern during stability testing (Fig. 4b). However, unlike 30% w/w griseofulvin dispersions, the T_{g1} decreased during the first 4 days and subsequently disappeared. This reduction in T_{g1} is most likely due to the increased plasticization of griseofulvin in the griseofulvin-rich, phase-separated fraction of the solid dispersion. When the griseofulvin-rich phase was saturated, and the drug crystallized out, the T_{g1} disappeared. In the multiple samples tested, the T_{g1} of 30% and 20% w/w solid dispersions reached the same value (~132°C) before disappearing, indicating the saturation of the griseofulvin-rich phase, prior to crystallization as seen from plasticization. Our failure to prepare a completely amorphous 40% w/w griseofulvin solid dispersion also supports the explanation given above.

Indoprofen and PVP Solid Dispersions

The MDSC reversing heat flow scans of 30% w/w indoprofen solid dispersions stored at 40°C/69% RH for a period of 1–90 days are shown in Fig. 4c. In contrast to the phase behavior of griseofulvin-PVP solid dispersions, a single T_g was detected in the indoprofen-PVP ones throughout the 90-day storage. The T_g values of the solid dispersions increased with storage time, although this was at a much slower rate when compared to the T_g changes in griseofulvin-PVP solid dispersions. The T_g values reached a plateau at T_g^{eq} of ~142°C in around 70 days of storage. The 20% w/w indoprofen solid dispersions also showed a similar increase in the T_g values until a plateau was reached at T_g^{eq} of ~142°C, suggesting similar changes in the phase composition when stored at

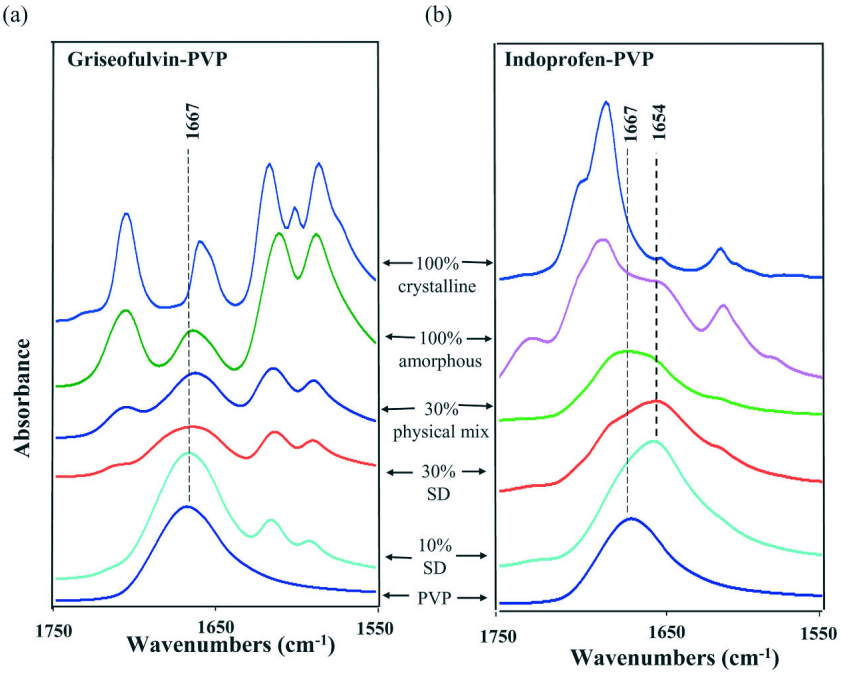

Fig. 3. Comparison of the infrared spectra of the carbonyl stretching region of solid dispersions and physical mixtures of PVP with (a) griseofulvin and (b) indoprofen. The percentages refer to the drug concentrations (SD = solid dispersion).

40°C/69% RH. The 10% w/w solid dispersions exhibited no measurable changes in the T_g values throughout the storage period, thus no phase separation.

Determination of Solid Solubility

The T_g values of 10, 20, and 30% w/w solid dispersions of griseofulvin and indoprofen solid dispersions that were subjected to 40°C/69% RH for 3 months is shown in Fig. 5. The T_{g2} values of all the griseofulvin solid dispersions reached a plateau (T_g^{eq}) at ~166°C during the 90-day storage, which is close to the T_g of pure PVP (167°C) (Fig. 5a). Because the T_{g2} values increased to the T_g of pure PVP, it is concluded that griseofulvin has no significant solid solubility in PVP at the storage conditions of 40°C/69% RH.

On the other hand, the solid dispersions of indoprofen and PVP behaved very differently as seen from Fig. 5b. During the 90-day storage, the T_g values reached a plateau at T_g^{eq} of ~142°C, which is significantly lower than the T_g of pure PVP (167°C). This difference can be due to the plasticizing effect of the molecularly dispersed indoprofen in the polymer (solid solubility). It is also seen from Fig. 5b that the T_g^{eq} for solid dispersions with different initial drug concentrations were the same. This behavior implies that indoprofen solid solubility in PVP is independent of the initial indoprofen concentration. In order to quantify the solid solubility, the T_g values of freshly prepared indoprofen solid dispersions were plotted against their drug concentrations, and the T_g^{eq} was used to identify the solid solubility, as shown in Fig. 6. From the graph, the solid solubility of indoprofen in PVP at 40°C/69% RH was quantified as 13% w/w.

X-Ray Diffraction Analysis

To determine whether the phase separation of the drugs from solid dispersions is followed by crystallization, X-ray diffraction was used. Melting endotherm of the phase-separated crystalline drug substance could not be detected with MDSC, which may be due to dissolution of the crystalline drug in the polymer at high temperatures during measurements (18). Figure 7a shows the X-ray patterns of 10% and 20% w/w griseofulvin solid dispersions that were kept at 40°C/69% RH for 10 days. The X-ray patterns of corresponding physical mixtures were used for comparison. As seen in Fig. 7a, crystallinity was developed in 10% w/w solid dispersions within 10 days of storage. Moreover, the peak intensities of the 10 and 20% w/w griseofulvin dispersions were slightly lower than the corresponding physical mixtures, which indicated a near complete drug crystallization and supported insignificant solid solubility data.

In Fig. 7b, the X-ray diffraction patterns of 10 and 20% w/w indoprofen solid dispersions that were exposed to 40°C/69% RH for 90 days are compared with their corresponding physical mixtures. No crystallinity in the 10% w/w solid dispersions was noticed even at the end of 90 days of storage. However, in the solid dispersions that contained 20% w/w indoprofen, the fractional crystallinity development, when compared to their corresponding physical mixtures, was attributed to the crystallization of a fraction of indoprofen that exceeded its solid solubility limit.

DISCUSSION

Hydrogen Bonding and Solid Solubility

Griseofulvin and indoprofen are drugs with high recrystallization potential, as indicated by their high melting temperatures and heats of fusion. Moreover, both drugs demonstrate relatively low glass transition temperatures in their amorphous states and recrystallize rapidly when exposed to relative humidity greater than 57%. Therefore, developing a

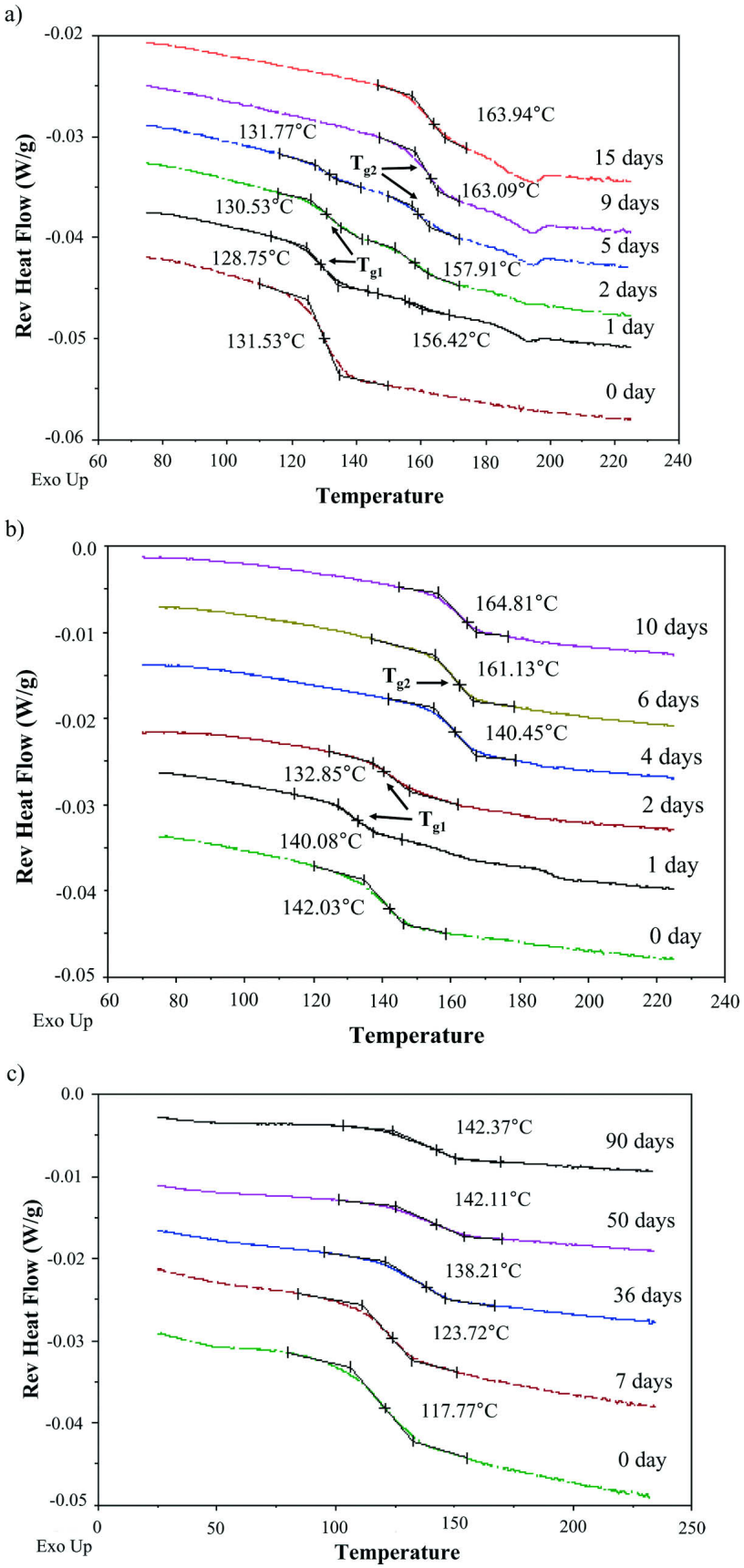

Fig. 4. MDSC reversing heat flow scans of solid dispersions exposed to 40°C/69% RH for different time intervals: (a) 30% w/w griseofulvin in PVP, (b) 20% w/w griseofulvin in PVP, and (c) 30% w/w indoprofen in PVP. [T_{g1}: T_g of griseofulvin-rich phase; T_{g2}: T_g of griseofulvin-poor (polymer-rich) phase].

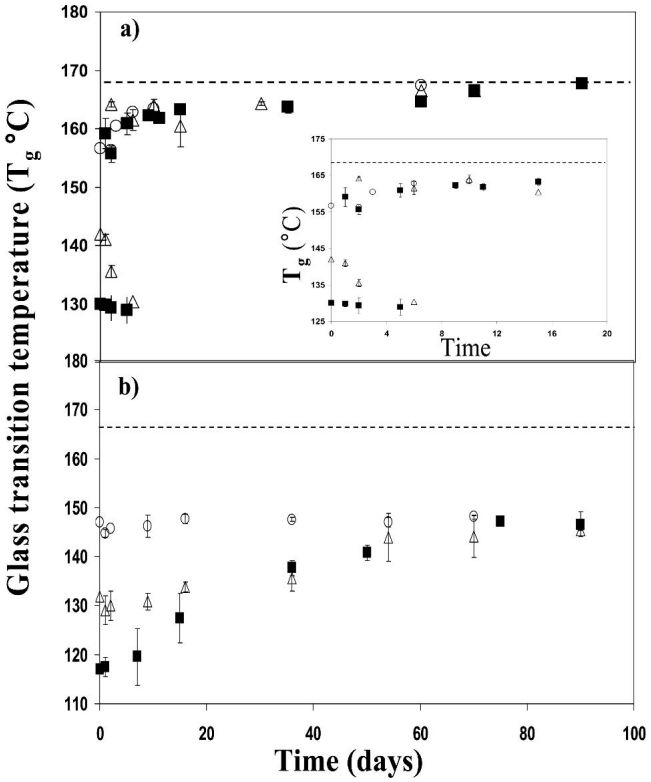

Fig. 5. Concentration-dependent variations in the glass transition temperatures of 30% w/w (■), 20% w/w (△), and 10% w/w (○) solid dispersions of PVP with (a) griseofulvin and (b) indoprofen. The dotted line represents the T_g of PVP (167°C). N = 3.

physically stable amorphous solid dispersion formulation of these candidates could be challenging.

When griseofulvin and PVP are molecularly mixed, no hydrogen bonding between the two components was noticed as inferred from the FTIR spectra. On the other hand, a hydrogen bond interaction between the hydroxyl group of –COOH of indoprofen and the carbonyl group of the pyrrolidone ring in PVP was evidenced by a decrease in the stretching of the carbonyl group of PVP from 1667 cm^{-1} to 1654 cm^{-1} in the 10–30% w/w solid dispersions.

In griseofulvin dispersions, despite the absence of hydrogen bonding, up to 30% w/w initial miscibility was achieved. The high initial miscibility of griseofulvin with PVP may be

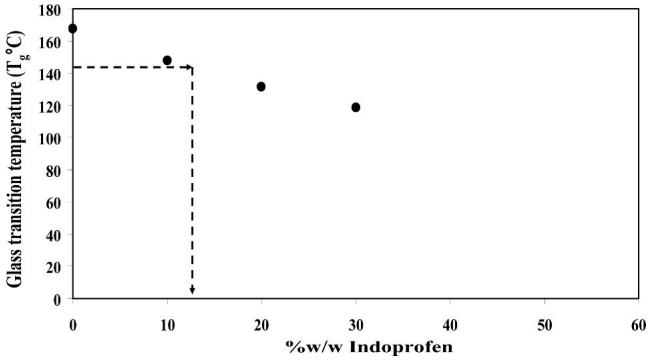

Fig. 6. Determination of solid solubility of indoprofen in PVP using the T_g^{eq} values and the plot of T_g of freshly prepared indoprofen solid dispersions.

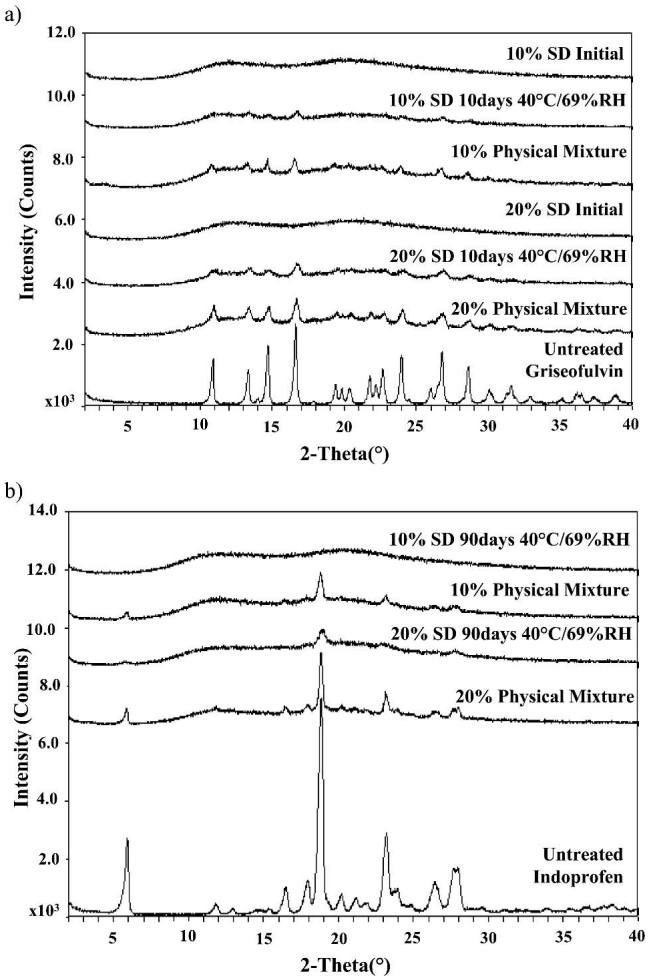

Fig. 7. X-ray diffraction patterns of solid dispersions and physical mixtures of PVP with (a) griseofulvin and (b) indoprofen.

favored through the gain in entropy of the griseofulvin system. Under a highly protective environment (i.e., low temperature and humidity), because of their high T_g values, griseofulvin solid dispersions may remain stable for extended periods due to lack of significant molecular mobility. However, under normal storage conditions, any uptake of moisture would cause lowering of T_g and consequently, an increase in the molecular mobility leading to potential phase separation and crystallization. Indeed, when griseofulvin solid dispersions were stored at 40°C/69% RH, complete separation and crystallization of griseofulvin was observed. Because one of the factors favoring miscibility is the drug-polymer affinity, in indoprofen solid dispersions a complete phase separation was not detected during stability testing. Although the moisture levels of griseofulvin and indoprofen solid dispersions were similar (Table II), the hydrogen bonding ability of indoprofen to PVP may explain the 13% w/w solid solubility of indoprofen solid dispersions. It is worth noting that the detection limit of DSC and XRD for crystalline fractions is around 3% and 5% w/w, respectively. Therefore, a complete phase separation implies that the solid solubility is below the detection limit of the instrument.

Kinetics of Phase Separation

The necessity of adding a drug to a given weight of a solid dispersion to obtain therapeutic doses may result in formula-

Table II. Kinetics of Drug Phase Separation at 40°C/69% RH

Drug	Concentration (% w/w)	Moisture (% w/w)	Rate constant of phase separation k (day^{-1}) ($\times 10^2$)	KJMA linear fit (R^2)
Griseofulvin	30	6.6 ± 1.5	12.50	0.868
	20	7.8 ± 0.6	5.19	0.958
	10	9.8 ± 0.7	4.66	0.970
Indoprofen	30	6.0 ± 0.5	1.25	0.988
	20	9.3 ± 0.5	0.62	0.968
	10	7.9 ± 3.0	NPS	NA

NPS, no phase separation; N/A, not applicable.
N = 3.

tions containing the drug well above their solid solubility limits. Because crystallization of the drug in such systems will take place during storage, understanding the kinetics of phase separation and crystallization is important to identify optimum storage conditions where the phase separation is minimum and the product is physically stable. A possible mechanism of drug crystallization from a solid solution is the segregation of drug molecules from that of polymers' prior to nucleation and subsequent crystal growth. Nucleation rate and crystallization are difficult to measure, characterize, and to reproduce. Therefore, measurement of the drug phase separation from the solid solution could provide a reliable estimate for the kinetics of physical instability.

Generally, X-ray diffraction technique is used to determine the crystallization rate of drugs from the solid dispersions (19). However, no method has been reported to determine the phase separation rate of a drug (either as amorphous or crystalline) from a solid dispersion. In this study, the kinetics of drug phase separation was determined by monitoring the changes in T_g of drug-polymer miscible phase. The time-dependent changes in T_g values (Fig. 5) were used in calculating the fraction of the drug phase separated ($1 - \alpha$) from the solid dispersions, where α is the fraction that remains miscible in the solid dispersion. The phase-separated fraction is assumed to be directly related to the shifts in the T_g values of the products. The fraction of the drug that was phase-separated at a specific storage time (t) was calculated by using the ratio shown below:

$$(1-\alpha)_t = 1 - \frac{T_{g(polymer)} - T_{g_{2(t)}}}{T_{g(polymer)} - T_{g(initial)}} \quad (1)$$

To estimate the rate constant of phase separation, the phase-separated fraction of the drug was plotted against the storage time and a linear fit obtained by using the Kolmogorov-Johnson-Mehl-Avrami (KJMA) first-order rate equation (Fig. 8). The slope of this linear fit provided the rate constant for phase separation. The KJMA equation has been used to obtain the rate constant for crystallization (20) and is described as:

$$[-\ln(1-\alpha)] = kt \quad (2)$$

where k is the rate constant for the solid-state transformation.

The calculated rate constants for phase separation [day^{-1}] are provided in Table II as a function of the drug concentration in the solid dispersions. As observed from the table, the phase separation rate is higher for the solid dispersions containing higher drug concentrations. A lower amount

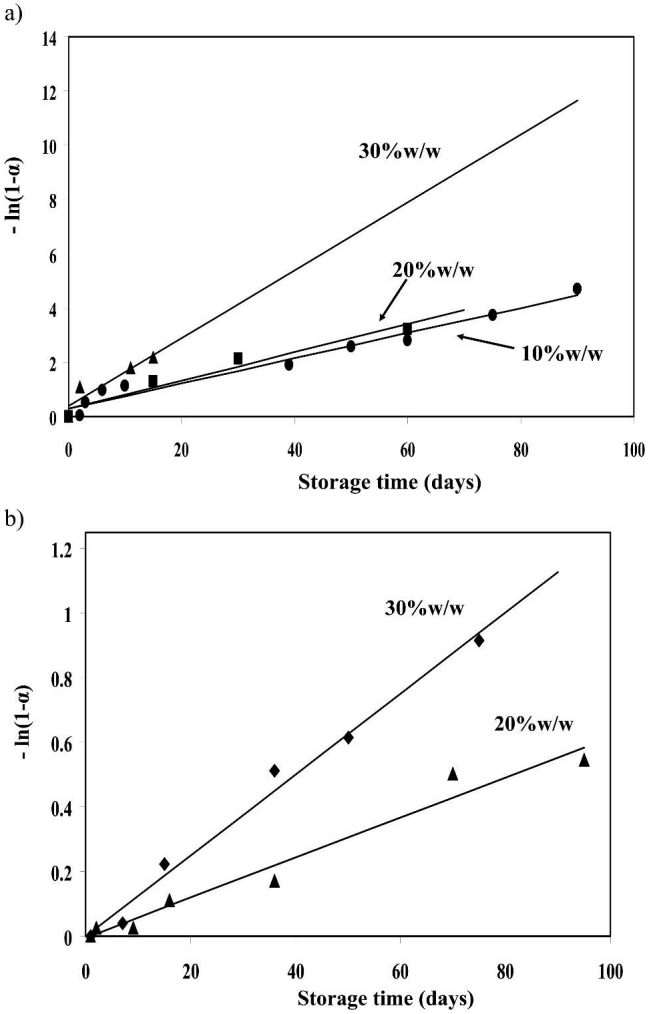

Fig. 8. KJMA fit of the extent of phase separation of (a) griseofulvin and (b) indoprofen from the PVP solid dispersions.

of drug dissolved in the polymer increases the differences in the chemical potentials between the supersaturated and the saturated states and the driving force for crystallization (21). For a given drug concentration, the phase separation rate was higher for griseofulvin solid dispersions than indoprofen systems. The higher rate constants for griseofulvin as compared to indoprofen at 40°C/69% RH can be attributed to the higher degree of drug supersaturation in griseofulvin dispersions, which is due to the inability of drug to interact with PVP.

The rate constants of phase separation that are obtained at accelerated storage conditions can potentially be used to predict the rate of phase separation at a desired storage condition. However, the effect of viscosity of the system and the moisture on the rate constants should be considered when developing the correlation.

CONCLUSIONS

The solid solubility of two crystallizable hydrophobic drugs, namely griseofulvin and indoprofen in PVP, was determined using MDSC. Griseofulvin did not exhibit any solid solubility in PVP, whereas a 13% w/w indoprofen remained molecularly miscible with the polymer under accelerated sta-

bility conditions of 40°C/69% RH. The higher solid solubility of indoprofen in PVP was attributed to the hydrogen bonding ability of the drug-polymer components of the solid dispersions. X-ray diffraction confirmed the MDSC obtained solid solubility values.

The phase separation kinetics of both griseofulvin and indoprofen from the solid dispersions were determined by using the fraction of drug phase separated. These values were obtained by using the shifts observed in T_g values of the solid dispersions in the KJMA rate equation. Accordingly, phase separation rates obtained were proportional to the drug content of the dispersion and related drug-polymer interactions.

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