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Research Paper

Evaluation of Drug-Polymer Miscibility in Amorphous Solid Dispersion Systems

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Purpose. To evaluate drug-polymer miscibility behavior in four different drug-polymer amorphous solid dispersion systems, namely felodipine-poly(vinyl pyrrolidone) (PVP), nifedipine-PVP, ketoconazole-PVP, and felodipine-poly(acrylic acid) (PAA).

Materials and Methods. Amorphous solid dispersion samples were prepared at different drug-to-polymer ratios and analyzed using differential scanning calorimetry (DSC), mid-infrared (IR) spectroscopy, and powder X-ray diffractometry (PXRD). To help with interpretation of the IR spectra, principal components (PC) analysis was performed. Pair Distribution Functions (PDFs) of the components in the dispersion were determined from the PXRD data, and the pure curves of the components were also extracted from PXRD data using the Pure Curve Resolution Method (PCRM) and compared against experimentally obtained results.

Results. Molecular-level mixing over the complete range of concentration was verified for nifedipine-PVP and felodipine-PVP. For felodipine-PAA, drug-polymer immiscibility was verified for samples containing 30 to 70% polymer, while IR results suggest at least some level of mixing for samples containing 10 and 90% polymer. For ketoconazole-PVP system, partial miscibility is suspected, whereby the presence of one-phase amorphous solid dispersion system could only be unambiguously verified at higher concentrations of polymer.

Conclusions. The three techniques mentioned complement each other in establishing drug-polymer miscibility in amorphous solid dispersion systems. In particular, IR spectroscopy and PXRD are sensitive to changes in local chemical environments and local structure, which makes them especially useful in elucidating the nature of miscibility in binary mixtures when DSC results are inconclusive or variable.

KEY WORDS: amorphous solid dispersions; calorimetry; differential scanning; infrared spectroscopy; miscibility; powder X-ray diffractometry.

INTRODUCTION

It is commonly accepted that the amorphous form of an active pharmaceutical ingredient (API) has higher apparent solubility when compared to its crystalline counterpart (1,2). For certain APIs, this difference in apparent solubility can be exploited as a strategy to increase its absorption, especially when dissolution is the rate-limiting step. However, appearance of the thermodynamically more stable crystalline phase during production or storage reduces the solubility benefit. Amorphous solid dispersions provide one approach to maintain the performance benefit of an amorphous form, allowing for the development of viable pharmaceutical products containing an amorphous acitve (3,4).

A solid dispersion is described as a mixture of the API in the amorphous form with a second component, such as a polymer. Studies have shown that the addition of a polymer can significantly delay the onset of crystallization (5–11). This physical stabilization of the amorphous form of the API has been attributed to several factors, such as reduction in molecular mobility, reduction in the thermodynamic driving force for crystallization, increase in the energy barrier for crystallization, disruption of molecular recognition necessary for drug crystallization, or a combination of these factors (12). Regardless of the specific mechanism, maximum stabilization of the amorphous form can only be realized if the drug and the polymer are intimately mixed at the molecular level. On the other hand, if only macroscopic mixing occurs between the drug and the polymer, inhibition of drug crystallization may not be observed, as is the case with indomethacin-PVP (13) and sucrose-PVP (14) physical mixtures. Thus, it is of interest to be able to determine whether or not the drug and the polymer in binary mixtures are intimately mixed.

One way to achieve this is by characterizing the number of amorphous phases present in the binary mixture. In a well-mixed binary system, where the components are intimately mixed at the molecular level, only one amorphous phase would be present. In contrast, a system with more than one amorphous phase present would have different amorphous regions with different API-to-polymer ratios. Such differences in composition would be reflected in physical

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properties measured. Implementation of different characterization techniques can thus be used to determine the number of amorphous phases present in amorphous solid dispersion samples, which in turn can be used to extract the limits to the formation of one-phase systems (e.g. composition or temperature).

In this study, three different experimental techniques were used to characterize binary mixtures comprised of a model API and a polymer. These techniques are differential scanning calorimetry (DSC), mid-infrared (IR) spectroscopy, and powder X-ray diffractometry (PXRD). DSC is a technique that is routinely employed to determine the number of amorphous phases present in multi-component mixtures. Originally used to determine the number of amorphous phases present in polymer mixtures (15–17), this technique has also been shown to be useful in determining the number of amorphous phases present in mixtures of small molecules or a small molecule and a polymer (17,18). Infrared spectroscopy is also commonly employed to study binary mixtures comprised of an API and a polymer. Since this technique is sensitive to changes in local chemical environments, it is well-suited to study the specific interactions in binary mixtures. The presence of changes in local chemical environments is usually indicative of miscibility between the drug and the polymer molecules. Among the three methods used, PXRD is the technique least commonly employed to probe miscibility in binary mixtures or the number of amorphous phases present. However, studies have shown that insight into nearest-neighbor interactions can be obtained through pair distribution function calculations (PDFs) (19). This technique is thus also amenable to the study of changes in local structure, presumably induced by changes in nearest-neighbor interactions due to API-polymer interactions, from which the number of phases present can be inferred. This was done, for example, by Newman *et al*. for mixtures of indomethacin and poly(vinyl pyrrolidone) (PVP) (20).

MATERIALS

Dichloromethane (ChromAR grade) and chloroform (AR grade) were obtained from Mallinckrodt Baker, Inc., Paris, KY, while ethanol (200 proof) was obtained from Pharmco-AAPER, Shelbyville, KY. Felodipine was a generous gift from AstraZeneca, Södartälje, Sweden. Poly(vinyl pyrrolidone) (PVP) K29-32 and poly (acrylic acid) (PAA, Average M_v ~450,000) were purchased from Sigma-Aldrich Co., St. Louis, MO. Ketoconazole and nifedipine were obtained from Hawkins, Inc, Minneapolis, MN. Prior to use, PVP and PAA were dried in a desiccator over powdered phosphorus pentoxide for at least 1 week.

METHODS

Bulk Sample Preparation

Binary mixtures of the model drug and polymer were prepared at different weight ratios, and then dissolved in a common solvent. For felodipine-PVP and nifedipine-PVP systems, the solvent was a 1:1 w/w mixture of dichloromethane and ethanol. For ketoconazole-PVP systems, chloroform was used, while for felodipine-PAA, the solvent was pure ethanol. All mixtures were visually inspected to confirm that the drug and polymer were completely dissolved, and the systems formed uniform one-phase solutions. The solvent was then removed using a rotary evaporator apparatus (Brinkman Instruments, Westbury, NY) over a period of about 10 min or less, and the samples were subsequently placed under vacuum for at least 12 h to remove any residual solvents.

Differential Scanning Calorimetry (DSC) Measurements

DSC measurements were carried out for felodipine-PAA and ketoconazole-PVP binary systems using a Q2000 DSC (TA Instruments, New Castle, DE) equipped with a refrigeration cooling system (RCS). Prior to sample analysis, the enthalpic response was calibrated using indium, and the temperature scale was calibrated using indium and tin.

For these measurements, bulk samples prepared as described were gently ground with a mortar and pestle yielding a fine powder. The resulting powder was placed in TZero™ aluminum pans with pinholes (TA Instruments, New Castle, DE). For felodipine-PAA, two sets of samples at different drug-to-polymer ratios were prepared and analyzed using different heating regimens. The first set of samples was equilibrated at 0°C, and then heated at 20°C/min to 180°C. The second set of samples was equilibrated at 0°C, heated at 20°C/min to 146°C, then held isothermally for 30 s. For ketoconazole-PVP, the bulk samples were equilibrated at 0°C, then heated at 20°C/min to 180°C. For all samples, the heating regimens described were cycled two additional times.

IR Spectroscopy Studies

Binary mixtures of the model drug and polymer were prepared at different weight ratios, and then dissolved in the same solvents used in the preparation of bulk samples. After the solids completely dissolved, one to two drops of the solution were placed on ZnS or KRS-5 substrates, which were immediately rotated on a KW-4A two-stage spin coater (Chemat Technology, Northridge, CA). The rotation speed was adjusted to produce a coating thickness that gave an absorbance intensity in the spectral region of interest between 0.4 and 1.0. Immediately after spin-coating, the substrates were transferred onto a hot plate set to 90°C for approximately a minute to remove any residual solvents. IR spectra of the resulting thin films were obtained in absorbance mode using a Bio-Rad FTS 6000 spectrophotometer (Bio-Rad Laboratories, Hercules, CA) equipped with globar infrared source, KBr beamsplitter, and DTGS detector. The scan range was set from 500 to 4000 cm^{-1} with 4 cm^{-1} resolution, and 128 scans were averaged together. During measurements, the spin-coated samples and the sample compartment of the spectrophotometer were flushed with dry air to minimize interference from absorbed and gas-phase moisture.

Powder X-ray Diffractometry (PXRD) Studies

Bulk solid dispersion sample powders prepared as described were gently ground to a powder using a mortar and a pestle in a glove-box flushed with dry air (RH<15%). The powder was then placed in a thin aluminum pan heated to approximately 10°C above the melting point of the drug

for at least 15 min, while simultaneously flushed with a dry nitrogen purge. The Al pan was then cooled by placing it in a mixture of ice and sodium chloride. The resulting glassy material was gently ground into a coarse powder.

PXRD patterns were collected from the powder using a PANalytical X'Pert Pro diffractometer (PANalytical Inc., Westborough, MA). The specimen was analyzed using Cu radiation produced using an Optix long fine-focus source. An elliptically graded multilayer mirror was used to focus the Cu Kα X-rays of the source through the specimen and onto the detector. The specimen was sandwiched between 3-μm thick films, analyzed in transmission geometry, and rotated to optimize orientation statistics. Beam-stop and helium purges were used to minimize the background generated by air scattering. Soller slits were used for the incident and diffracted beams to minimize axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen. Prior to the analysis, a silicon specimen (NIST standard reference material 640c) was analyzed to verify the position of the silicon 111 peak.

Data Analysis

SIMCA-P+(version 11.0, Umetrics AB, Umeå, Sweden) was used for principal component (PCA) data analyses of IR spectra. For this purpose, data from 700–4,000 cm^{-1} spectral wavenumber that had been unit normalized was used for the calculations.

PDF modeling was carried out using the procedure outlined in reference (20). Briefly, PDFs were calculated from PXRD patterns collected on amorphous dispersion samples as well as the reference amorphous API pattern and the excipient reference pattern. Resulting reference PDF patterns were inputted into a minimization algorithm (21) and minimized against the PDF pattern calculated from the dispersion PXRD data. The minimization varied the scale factors applied to each reference component (before they are summed) until a best fit was obtained. The quality of the fit was evaluated by calculating the difference between the sum-squared intensity at each point in the sum of reference PDFs and the PDF calculated from the dispersion data. Ratio of API to excipient in the best fit PDF pattern was recorded, as well as the best fit PDF pattern itself. Immiscibility was detected when the PDF profiles of each individual component taken in proportion to their compositions in the mixture agreed (in terms of peak positions) with the PDF of the mixture, indicating phase separation into independent amorphous phases. A lack of agreement of the PDF profiles indicated that the mixture with a unique PDF is miscible.

Pure Curve Resolution Method (PCRM) modeling was performed using the procedure outlined in reference (22). PCRM was used to extract the individual pure reference PXRD patterns for the API and excipient, directly from measured PXRD data of the amorphous dispersions prepared at different compositions of API and excipient. In this method, the variance between a series of powder patterns collected on binary dispersions is used to identify the number of variance components that characterize the set of mixed powder patterns. Each of these variance components can be projected back into a corresponding reference powder pattern or pure curve. Two of the reference powder patterns derived by PCRM should correspond to the excipient and API, as determined by direct comparison of amorphous halo positions and widths. In the case of a system with immiscible amorphous phases, the PCRM-derived curves should closely resemble the API and excipient reference PXRD patterns, and there should be no significant additional component(s) contributing to the variance. The presence of an additional component or shifting in the position of the amorphous halo(s) (on the order of 1 °2θ or greater) in the PCRM-derived curves that otherwise resemble the API and excipient reference patterns was taken as an indication of structurally-induced changes in the dispersion (relative to starting components' structures) and interpreted as indirect proof of miscibility.

RESULTS

DSC Results

DSC is commonly employed to determine the number of amorphous phases present in systems containing more than one component. The presence of a single amorphous phase, where molecules of the different components present are mixed "at the molecular level" is commonly inferred from the presence of a single T_g. In contrast, the presence of more than one T_g is indicative of the presence of more than one amorphous phase (15). While considered as the "golden standard" to determine miscibility in mixtures of amorphous components, DSC measurements have several inherent limitations. For example, it has been reported that formation of small domains (less than 15–30 nm) in binary amorphous mixtures containing more than one phase may result in failure to detect two distinct T_g events (15,20). Also, during DSC measurements, the temperature of the sample is constantly changing, which in turn could result in a shifting miscibility of the systems' components due to an increased or decreased miscibility with increasing temperature. Thus, the detection of a single T_g at temperatures higher than the T_g of the lowest individual component may not provide enough information to determine the number of amorphous phases present at room temperature.

For nifedipine-PVP and felodipine-PVP systems, studies reported that only one T_g was observed for the binary amorphous mixtures at different drug-polymer levels (10,23,24). The measured T_g values for the binary systems varied as a function of composition and were observed between the T_gs of the pure components. Such results are indicative of miscible amorphous systems, where the different components are mixed at the molecular level. Since no data could be found for felodipine-PAA and only select data was found for ketoconazole-PVP (6), DSC measurements were repeated for these systems at different drug-to-polymer weight ratios.

The DSC results for felodipine-PAA are summarized in Table I, as well as the glass transition temperature for the binary mixture $T_{g,mix}$, calculated using the Couchman-Karasz equation (25), where:

$$T_{g,mix} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2} \quad (1)$$

Table I. Glass transition temperatures (midpoint) for the felodipine-PAA system

% weight PAA in the mixtures	Measured T_g (°C) Experiment 1	Measured T_g (°C) Experiment 2	$T_{g,mix}$ predicted by Couchman-Karasz equation (°C)
0	48	48	48
10	48 / 133	46 / 130	59
30	48 / 132	48 / 133	79
50	48 / 121	102	96
70	121	86	112
90	114	84	126
100	132	132	132

[a] If two glass transition events were detected, both values are reported in the table as T_{g1} / T_{g2}.

Here, w_i and $T_{g,i}$ are the weight fraction and glass transition temperature of component *i*. In this equation, K is a constant, which can be calculated using the change in heat capacities ($\Delta C_p s$) at glass transition events for the pure components:

$$K = \frac{\Delta C_{p2}}{\Delta C_{p1}} \tag{2}$$

As mentioned in the Method section, two heating regimens were used to interrogate the samples. This was done to thoroughly characterize the miscibility of this system in case of heating-induced drug-polymer mixing. Using either heating regimens, two $T_g s$ were observed for samples containing 70 and 90% (by weight) felodipine. For these samples, the minimum ΔC_p value detected was 0.044 J/g°C. This value of ΔC_p is relatively small, but is reasonable considering the relatively small quantity of the polymer in the systems. For samples containing 10% and 30% felodipine, one T_g was observed using either heating regimen. However, variability in T_g values measured using the two different heating regimens was observed. In addition, deviation from values predicted by Couchman-Karasz equation was also seen. For samples containing 50% felodipine, the first heating regimen showed the presence of two $T_g s$ for the mixture, but the second heating regimen showed the presence of one T_g. The single T_g measured in the second heating regimen (102°C) again deviates from the value predicted by the Couchman-Karasz equation. These results suggest that felodipine and PAA are at least partially immiscible, as indicated by the presence of more than one glass transition events for samples containing 70 and 90% felodipine. In addition, variability in results obtained for the other samples could be an indication of temperature-dependent mixing and/or miscibility in the system.

DSC thermograms for the ketoconazole-PVP samples are shown in Fig. 1. Unlike results obtained for felodipine-PAA samples, a single T_g was observed for all ketoconazole-PVP samples. In addition, $T_{g,mix}$ values measured are in reasonable agreement with values predicted by Couchman-Karasz equation, as shown in Fig. 2. These results are consistent with results reported in literature, where it was reported that one T_g was observed for ketoconazole-PVP dispersions at 50% polymer content and above (6), and suggest molecular level mixing in ketoconazole-PVP samples investigated.

IR Spectroscopy Results

Nifedipine-PVP and Felodipine-PVP Systems

Studies have demonstrated that IR spectroscopy can be used to identify drug-polymer specific interactions in nifedipine-PVP and felodipine-PVP solid dispersion systems (9,23,26,27). Variations in the IR spectra of solid dispersions (absorbance peak shifts or development of shoulders) that could not be attributed to changes in sample composition were observed. These peaks or shoulders are attributed to drug-polymer specific interactions, or to disruptions in drug-drug or polymer-polymer specific interactions in the presence of the other component. The presence of drug-polymer specific interactions is evidence of molecular level mixing of the components, signaling the formation of one-phase amorphous solid dispersion systems. For example, shifts in the IR peaks assigned to the stretching frequency of the NH moiety of the drug molecules were observed, corresponding to the formation of drug-polymer hydrogen bonding (10,23,27). A concurrent increase in the relative intensity of the peak assigned to the free carbonyl moiety of drug molecules was also observed as the proportion of polymer in the mixture was increased. These results indicate disruption in drug-drug specific interactions in favor of drug-polymer specific interactions.

While examination of the IR spectra of solid dispersions can be used to identify changes caused by molecular level mixing between the drug and the polymer, the interpretation of such results are sometimes subjective and can be affected by operator experience. In this work, chemometric-based analysis methods were explored as a means to aid the interpretation of such results. This was accomplished by performing PCA analysis and using the following reasoning: It would be anticipated that two factors are potentially

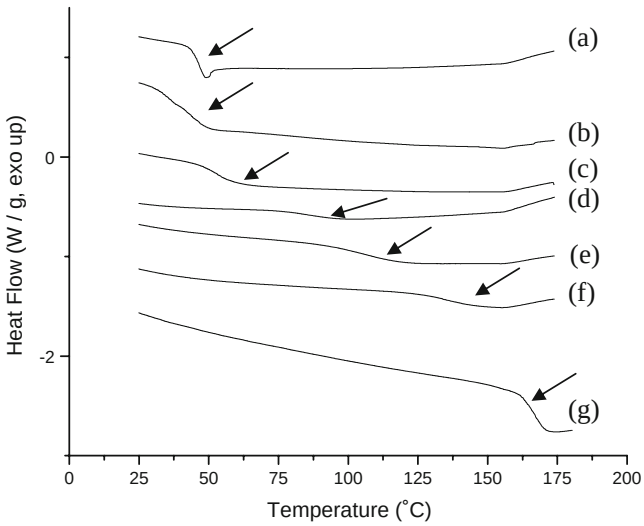

Fig. 1. DSC thermograms of ketoconazole-PVP amorphous solid dispersion systems containing (*a*) 0, (*b*) 10, (*c*) 30, (*d*) 50, (*e*) 70, (*f*) 90 and (*g*) 100% (dry weight basis) PVP. Arrows indicate glass transition events recorded.

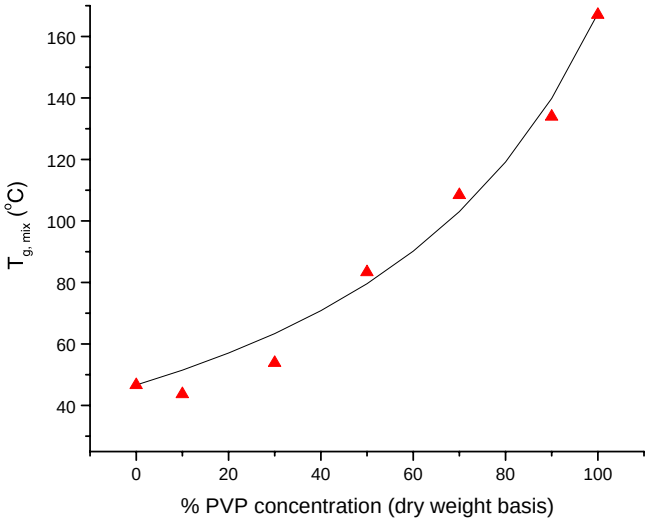

Fig. 2. Measured T_gs for ketoconazole-PVP solid dispersion samples containing different drug-to-polymer ratios. The line represents $T_{g,mix}$ values predicted from Couchman-Karasz equation.

responsible for changes in the IR spectral features of a set of solid dispersions samples of different drug-polymer ratios: changes due to the changing compositions, and changes due to the changing chemical environments of the drug and the polymer molecules when intimately mixed (e.g. caused by the presence of drug-polymer specific interactions). The former will always occur in binary mixtures of differing compositions. However, the latter will only occur if the components in the mixtures show a significant amount of molecular level mixing. Thus, in amorphous solid dispersions with no significant molecular level mixing (immiscible systems or physical mixtures comprised of pure amorphous drug and pure polymer), PCA analysis would show the presence of only one principal component (PC), whereby the loading plot resembles the spectrum of one of the pure components (e.g. pure amorphous drug) subtracted from the spectra of the second pure component (e.g. pure polymer) normalized by their respective absorptivity. This type of analysis has been conducted for physical mixtures of different powders (28). However, if drug-polymer specific interactions occur in the binary systems (indicative of molecular level mixing in the system), a second PC will be needed to explain all the variation in the data, and the loading plot of the second PC will represent the spectroscopic variations arising from the changed chemical environments of each component in the mixture, e.g. as a result of drug-polymer hydrogen bonding interactions.

The score plot from felodipine-PVP binary systems is shown in Fig. 3a and compares the scores obtained from solid dispersion spectra with those obtained from physical mixture spectra. The physical mixture spectra were calculated from experimentally obtained IR spectra of pure amorphous felodipine and pure PVP (see references (26,27) for calculation method). From the score plot, it is obvious that the first PC by itself is enough to explain trends observed for the calculated physical mixture spectra, i.e. they show little variation in the direction of the second PC. The scores for the solid dispersions are well-separated from the scores for the physical mixtures, indicating that they are spectroscopically different. Furthermore, a second PC was needed to explain trends observed with the solid dispersion samples. Loadings plots are shown in Fig. 3b. From this figure, it is apparent that the loading plot of the first PC is dominated by the compositional variations, since it is well-modeled by the weighted spectral difference of pure amorphous felodipine and PVP. The loading plot of the second PC is thought to arise from changes in the IR spectra arising from specific drug-polymer interactions. It can be seen that the regions of the loadings plot that show the largest variation correspond to changes in the NH and carbonyl regions, presumably reflecting changes in the spectrum arising from drug-polymer hydrogen bonding interactions. Similar results were also

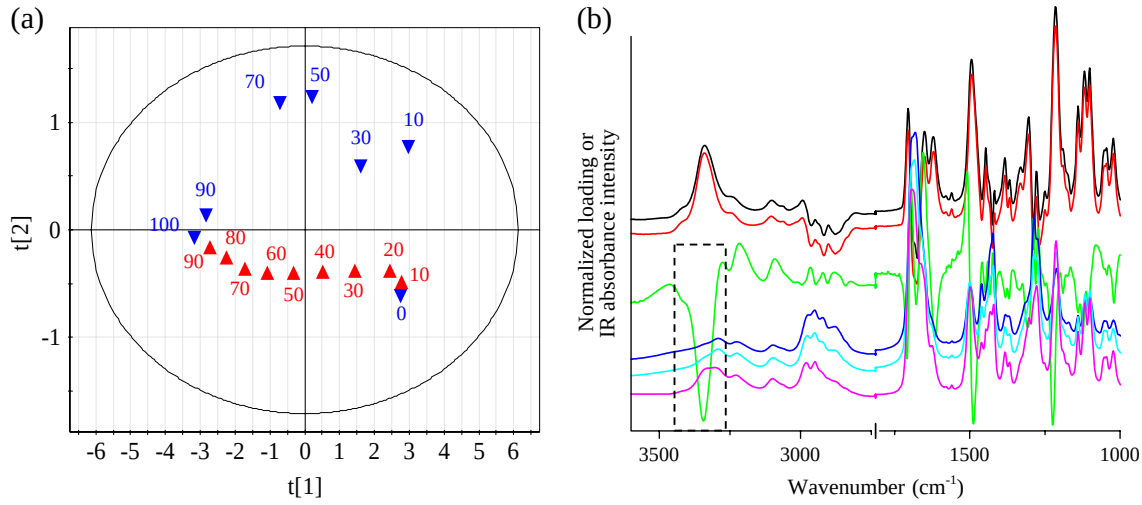

Fig. 3. **a** Score plot generated from PCA analysis of IR spectra of felodipine-PVP solid dispersions (blue) and physical mixtures (red). The numbers indicate the concentration of PVP (dry weight basis) in each sample. **b** The loading of the first PC (*red*) has identical features to the IR absorbance of PVP subtracted from the absorbance of amorphous felodipine (*black*), while the loading of the second PC (*green*) highlights spectral variations due to drug-polymer interactions, for example as shown in the NH region of solid dispersion samples containing 70 (*blue*), 50 (cyan), and 30% (*pink*) PVP, as highlighted by the rectangle.

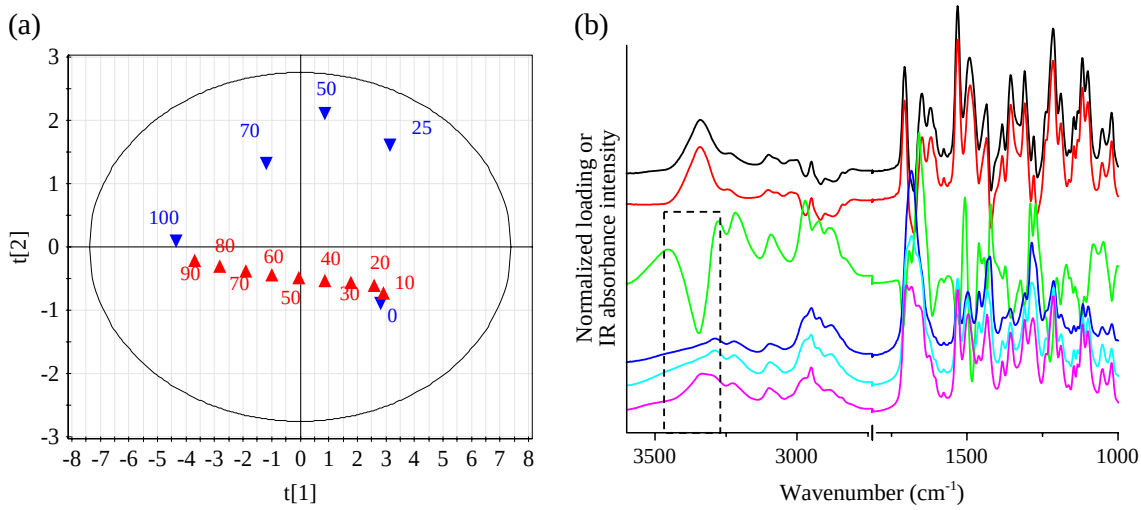

Fig. 4. **a** Score plot generated from PCA analysis of IR spectra of nifedipine-PVP solid dispersions (*blue*) and physical mixtures samples (*red*). The numbers indicate the concentration of PVP (dry weight basis) in each sample. **b** The loading of the first PC (*red*) has identical features to the IR absorbance of PVP subtracted from the absorbance of amorphous nifedipine (*black*), while the loading of the second PC (*green*) highlights spectral variations due to drug-polymer interactions, for example as shown in the NH region of solid dispersion samples containing 70 (*blue*), 50 (cyan), and 25% (*pink*) PVP, as highlighted by the rectangle.

obtained with nifedipine-PVP solid dispersions as shown in Fig. 4. Once again, it can be seen that the solid dispersions have different scores from the physical mixture spectra. Both visual observation of spectral changes and the PCA analysis suggest complete drug-polymer miscibility for both systems.

Ketoconazole-PVP

Unlike nifedipine-PVP and felodipine-PVP, interpretations of the IR spectra of ketoconazole-PVP solid dispersions were less straightforward, since no drug-polymer hydrogen bonds can be formed in this system, and, therefore, only minor changes in peaks were observed. Examination of the carbonyl region of the IR spectra for this system shows the presence of the peaks at the same wavenumbers as for the pure components. However, slight differences in peak relative intensities were observed when the experimentally obtained spectra of the solid dispersions were compared against calculated spectra of physical mixtures comprised of the amorphous drug and the polymer. These are illustrated in Fig. 5, where it can be observed that the carbonyl peak arising from ketoconazole in the solid dispersion is slightly lower than that predicted from the calculated physical mixture spectrum, a trend observed for all the dispersions. Changes in the relative height of the carbonyl peak of PVP have also been reported in literature (29), where the authors attributed this phenomenon to the ion-dipole interactions between PVP and their model compound. It is speculated that the differences in relative intensity for the ketoconazole-PVP system result from dipole-dipole type of interactions between ketoconazole and PVP molecules, since these species are incapable of forming hydrogen bond interactions. For ketoconazole-PVP system, the presence of these drug-polymer interactions again indicates that a different chemical environment is experienced by at least some of the drug and polymer molecules as a result of molecular level mixing. However, due to the very limited spectroscopic changes observed, further conclusions about the extent of miscibility are not possible. No other significant spectroscopic changes could be observed from visual examination of the spectra, and the solid dispersion spectra resembled the physical mixture spectra very closely.

Initial attempts to investigate drug-polymer miscibility using PCA analysis indicated that two PCs were needed to describe the calculated physical mixture spectra. Since the reason for the two PCs could not be elucidated, no further analysis was performed for this system.

Felodipine-PAA

For the felodipine PAA system, visual examination of the spectra indicated that the majority of the solid dispersion samples were very similar to the calculated physical mixture spectra as shown in Fig. 6. Following chemometric analysis, only one PC was needed to describe the physical mixture samples. The loadings plot for this PC was very similar to the

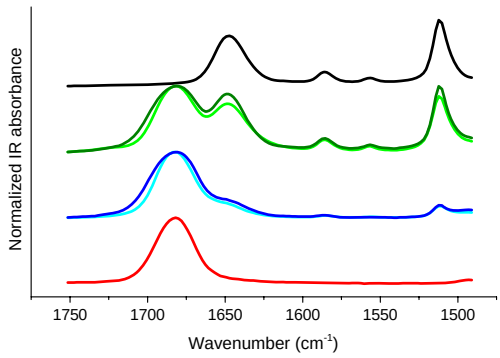

Fig. 5. IR spectra of the carbonyl region of amorphous solid dispersion systems comprised of ketoconazole and PVP containing 30 (light green) and 70% (cyan) (dry weight basis) polymer. Theoretically calculated spectra of physical mixtures comprised of amorphous drug and polymer at the same drug-to-polymer ratios (dark green and blue) are also included for comparison, as well as spectra of amorphous ketoconazole (*black*) and pure PVP (*red*).

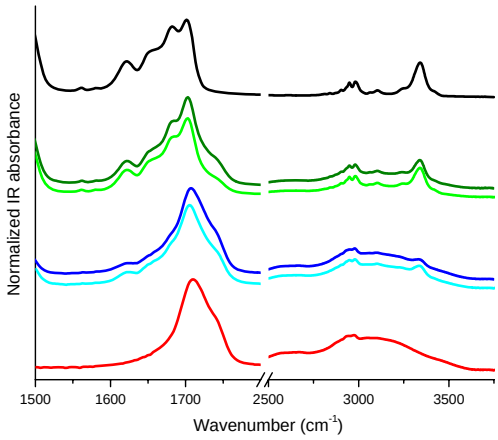

Fig. 6. IR spectra of the carbonyl and NH regions of amorphous solid dispersion systems comprised of felodipine and PAA containing 30 (*light green*) and 70% (cyan) (dry weight basis) polymer. Theoretically calculated spectra of physical mixtures comprised of amorphous drug and polymer at the same drug-to-polymer ratios (*dark green* and *blue*) are also included for comparison, as well as the spectra of amorphous felodipine (*black*) and pure PAA (*red*).

IR spectra of the pure drug subtracted from the IR spectra of pure PAA, normalized against their respective absorptivity, indicating that the spectral variation arose from compositional changes. However, for the solid dispersion samples, three PCs were found. The loading of the first PC was very similar to the loading generated from the physical mixture samples (Pearson's correlation coefficient $\rho > 0.99$, see Fig. 7b), and thus the first PC is describing variation arising from the different compositions of the samples. By comparing the scores of the physical mixtures and solid dispersions (Fig. 7a), it can be observed that solid dispersions samples containing 30, 50, and 70% PAA have scores that are similar to the corresponding physical mixtures, with little variation in the second PC. This suggests that the spectra of these samples are very similar to those of the physical mixtures and can be described simply by considering composition. This result suggests that these samples show a low extent of miscibility and resemble a physical mixture. However, samples containing 10 and 90% PAA were outliers in the composition trend. Further analysis shows that the IR spectrum of the sample containing 90% PAA can only be described by including the second PC, while the score for the IR spectrum of the sample containing 10% PAA shows variation in the third PC. These results suggest that while most of the trends in the IR spectra of the solid dispersions can still be explained by the first PC, there are features that cannot be explained for samples containing 10 and 90% PAA, suggesting that there may be some level of molecular level mixing for the last two samples.

PXRD Results

Miscibility Analysis Through Composition Determination Using Reconstructed PDFs

The PXRD results for the felodipine-PVP, ketoconazole-PVP, and felodipine-PAA solid dispersions are presented in Figs. 8a, 9a, and 10a, respectively. The absence of Bragg peaks in the PXRD profiles indicates that all the samples were X-ray amorphous. To estimate the number of amorphous phases present in the mixtures, further analyses were conducted using collected diffractograms. The results from the PDF analysis of the concentration of polymer in the amorphous solid dispersion samples are summarized in Table II. Poor agreement between actual sample compositions and the calculated compositions were observed for all

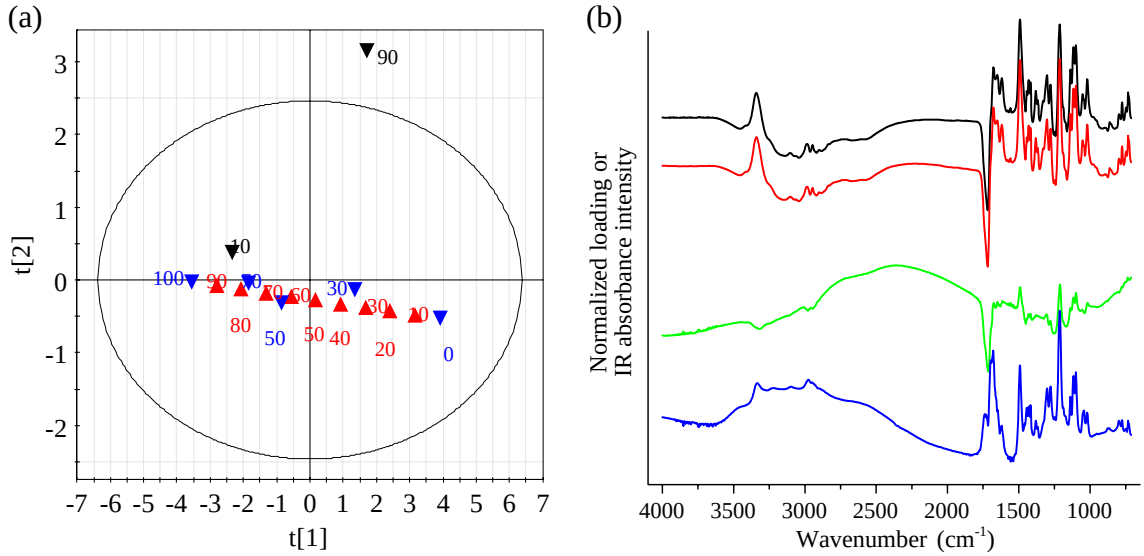

Fig. 7. **a** Score plot generated from PCA analysis of IR spectra of felodipine-PAA solid dispersions (*blue* and *black*) and physical mixtures (*red*). The numbers indicate the concentration of PAA (dry weight basis) in each sample. Solid dispersion samples containing 10 and 90% PAA are outliers in the polymer concentration trend observed along the first PC. **b** The loading of first PC (*red*) has identical features to the IR absorbance of PAA subtracted from the absorbance of amorphous felodipine (*black*), while the loadings of the second (*green*) and third (*blue*) PCs highlight spectral variations observed for samples containing 90% and 10% PAA, respectively.

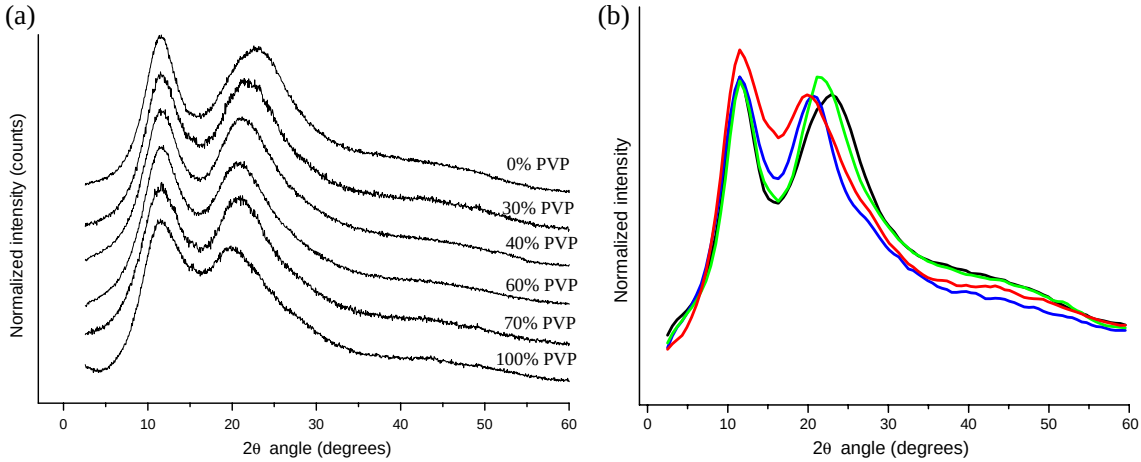

Fig. 8. a Measured PXRD diffractograms for felodipine-PVP system. **b** Measured (*black*) and predicted (*green*) diffractograms of pure amorphous drug, and measured (*red*) and predicted (*blue*) diffractograms of pure PVP. Smoothing and re-scaling were done to compare the different curves.

model systems analyzed except for felodipine-PAA samples containing 30 and 70% drug (dry weight basis) and the ketoconazole sample containing 70% drug. These results indicate at least partial miscibility between the drug and the polymer in felodipine-PVP, nifedipine-PVP, and ketoconazole-PVP, and limited miscibility for felodipine-PAA within the concentration limits investigated. Note that while good agreements between actual and predicted compositions may indicate limited miscibility, such results should also be supported by visual examinations of the resulting PDFs. Similarities between PDFs calculated directly from the measured diffractograms and those calculated from best-fit predictions (using diffractograms of the pure components) indicate similarities in the nature of the individual components in the solid dispersion as well as in their pure amorphous state. This was observed in the case of felodipine-PAA (see Fig. 11b), confirming limited miscibility in solid dispersion samples containing 30% and 70% polymer. In contrast, felodipine-PVP systems showed larger differences between PDFs derived from measured and calculated diffractograms as shown in Fig. 11a.

The results of the PCRM analysis of the felodipine-PVP, ketoconazole-PVP, and felodipine-PAA solid dispersion systems are presented in Fig. 8b, 9b, and 10b, respectively. In the felodipine-PVP system, the PCRM-calculated pure curve corresponding to felodipine shows a significant (> 1 °2θ) shift in the position of the second amorphous halo towards lower angles, as compared to measured PXRD data of amorphous felodipine. A similar, though lesser, shift is observed for the PVP curve. Such shifts are indicative of structural changes taking place as a result of mixing the API and the excipient, and are interpreted as an indirect sign of miscibility. The same results were also obtained for nifedipine-PVP system, indicating drug-polymer miscibility (results not shown). In contrast to these results, the shifts are not observed in the case of felodipine-PAA as shown in Fig. 10b. For the latter system, the PCRM-calculated pure curves accurately describe the measured PXRD data for the pure amorphous felodipine and

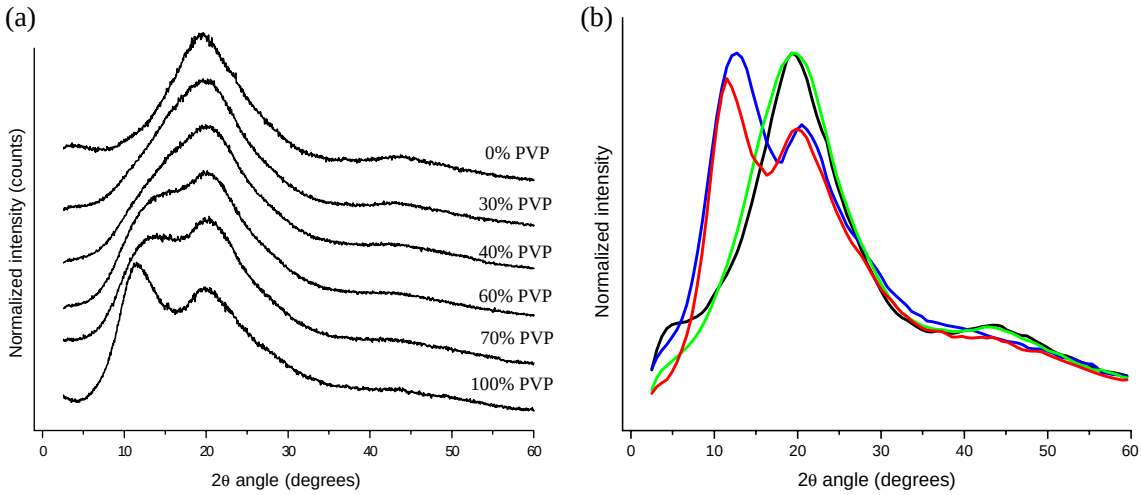

Fig. 9. a Measured PXRD diffractograms for ketoconazole-PVP system. **b** Measured (*black*) and predicted (*green*) diffractograms of pure amorphous drug, and measured (*red*) and predicted (*blue*) diffractograms of pure PVP. Smoothing and re-scaling were done to compare the different curves.

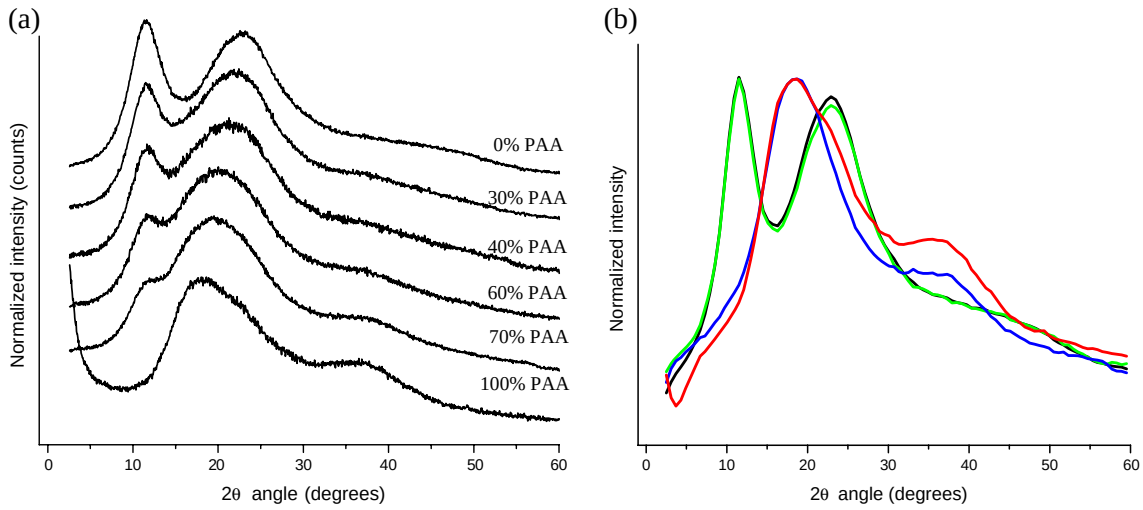

Fig. 10. a Measured PXRD diffractograms for felodipine-PAA system. **b** Measured (*black*) and predicted (*green*) diffractograms of pure amorphous drug, and measured (*red*) and predicted (*blue*) diffractograms of pure PAA. Smoothing and re-scaling were done to compare the different curves.

PAA. Therefore the system is thought to be immiscible over the range studied (30–70% drug concentrations).

The ketoconazole-PVP system was also studied using PCRM analysis, and the results are shown in Fig. 9b. A slight (< 1 °2θ) shift in the position of the halos was observed in the calculated pure curve of the PVP component, as compared to measured PXRD data. The ketoconazole pure curve did not exhibit an appreciable shift in the position of the amorphous halo. However, a noticeable halo broadening was observed in the pure curve, compared to measured PXRD data of pure amorphous ketoconazole. Such results could be indicative of minor structural changes taking place, confirming the hypothesis that this system is at least partially miscible over the range of drug-polymer weight ratios studied.

DISCUSSION

Different factors determine whether the formation of a one-phase binary amorphous system is thermodynamically favorable. Assuming ideality, the addition of a second component will increase the combinatorial entropy of the system, represented mathematically as (30)

$$\Delta S_{mix} = R(X_u \ln X_u + X_v \ln X_v) \tag{3}$$

Here, ΔS_{mix} represents the entropy of mixing, R is the gas constant, and X_is are the mol fractions of component *i*. Since the value of X_is are between 0 and 1, the value of ΔS_{mix} will always be positive, and entropy is always increased in mixtures (31).

The enthalpy of mixing (ΔH_{mix}) between two components is equal to the difference between the enthalpies of the pure components and the mixture, represented mathematically as

$$\Delta H_{mix} = (H_{ii} + H_{jj}) - H_{ij} \tag{4}$$

Unlike entropy, the value of ΔH_{mix} can be positive (exothermic mixing), negative (endothermic mixing), or zero (athermal mixing).

When the contributions from the enthalpic and entropic components of mixing are combined, the change in the Gibbs free energy upon mixing of two components can be calculated as

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} \tag{5}$$

When the value of ΔG_{mix} is positive, mixing between the two components is thermodynamically unfavorable, and when the value of ΔG_{mix} is negative, mixing is thermodynamically favorable.

For a binary mixture, $\boldsymbol{\Delta G_{mix}}$ values will vary as a function of composition and temperature, as shown schematically in Fig. 12. Based on their profiles, three different types of mixing behaviors can be determined. If $\boldsymbol{\Delta G_{mix}}$ values are negative and only one minimum is observed in the plot of $\boldsymbol{\Delta G_{mix}}$ *vs.* composition, then the two components are completely miscible, and they will form a uniform one-phase mixture over the complete range of compositions. On the other hand, if $\boldsymbol{\Delta G_{mix}}$ values are positive, the two components

Table II. Comparisons between Actual Polymer Concentration in the Binary Mixtures and Values Calculated from PXRD PDF reconstruction algorithm

	Actual values	Calculated from PDF reconstruction using pure components
Felodipine-PVP	30	37
	70	58
Nifedipine-PVP	30	53
	70	85
Ketoconazole-PVP	30	15
	70	69
Felodipine-PAA	30	29
	70	64

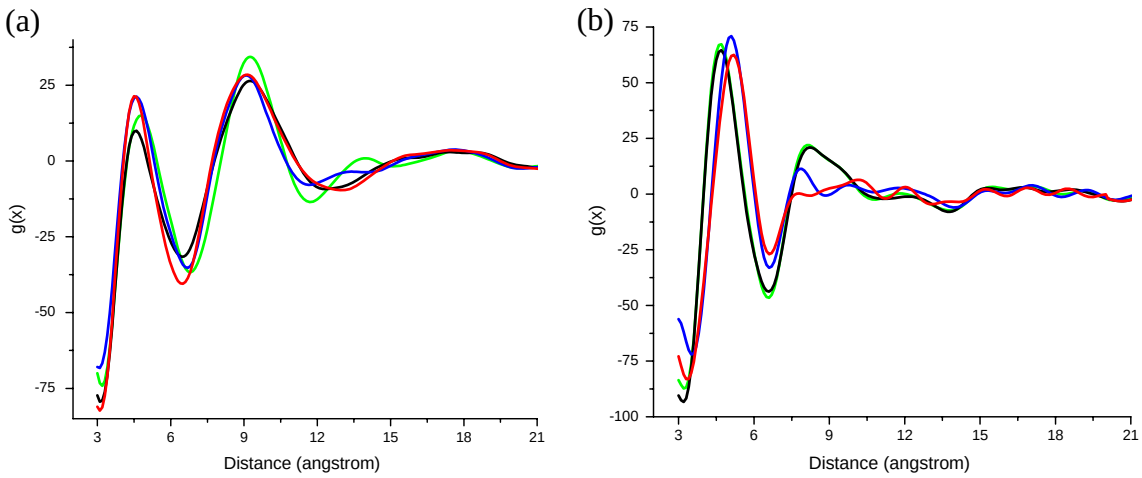

Fig. 11. PDFs of **a** felodipine-PVP and **b** felodipine-PAA solid dispersion samples. In both plots, the blue curves are PDFs for solid dispersion samples containing 30% polymer, and the black curves are the PDFs for solid dispersion samples containing 70% polymer. The red and the green curves are PDFs generated from the predicted diffractograms of physical mixtures with 30 and 70% polymer, respectively.

are not miscible and a completely phase-separated system will be formed. From a purely theoretical perspective, such systems are uncommon, since thermodynamics always favor the addition of one component into another system such that some amount of the first component will always be mixed with the second. However, if the amount mixed is extremely small, then the binary system can be considered immiscible from a practical point of view.

In many cases, binary systems exhibit partial miscibility, whereby a certain amount of one component can be mixed with the second to form a single phase at a certain temperature and pressure. If the proportion of the first component in the mixture exceeds this value, then the component in excess will not be uniformly dispersed throughout the system, and more than one phase will be formed. In such cases, the system achieves a lower free energy by forming regions with different compositions. When the ΔG_{mix} values for such systems are plotted as a function of composition, the values calculated are still negative, but two minima can be observed. These minima are the compositions where such systems are at their lowest free energy, and are called binodal points. These points envelope the metastable region, where phase separation is predicted to occur through nucleation and growth, and can be found by setting the first derivative of the curve describing ΔG_{mix} equal to zero. The inflection points between these binodal points and the point of maximum free energy are called spinodal points. These points envelope the unstable region, where phase separation is predicted to occur through spontaneous, explosive events, and can be found by setting the second derivative of the curve describing ΔG_{mix} equal to zero.

Although the theory highlighted above was originally developed for liquid mixtures, the same argument is extended to mixtures of amorphous solids in this work. Just as the case for binary mixtures of liquids, entropy favors mixing for binary mixtures of amorphous solids. Thus, if ΔH_{mix} value is negative, the two components will be completely miscible. On the other hand, if ΔH_{mix} value is positive, then the resulting binary amorphous mixture can still be completely miscible (if the entropic contribution to the overall free energy is larger than the enthalpic contribution, such that ΔG_{mix} is negative), partially miscible, or practically immiscible. ΔH_{mix} is determined from the difference of enthalpies between the pure components relative to the mixture, which in turn depends on the strength of inter-species interactions relative to intra-species interactions. Just as the case for binary liquids, if the interaction between the drug and the carrier (polymer) in amorphous solid dispersions is sufficiently favorable compared to intra-species interactions, only one minimum will be observed when ΔG_{mix} is plotted as a function of composition, and a one-phase binary amorphous system would be thermodynamically favored. On the other hand, if the interaction between the drug and the carrier is weak relative to intra-species interactions, more than one minimum will be observed, and the formation of more than one amorphous phase may be favored.

In general, the three experimental methods used in this study showed good agreement and clearly established that nifedipine-PVP, felodipine-PVP forms one-phase binary mixtures over the range of compositions studied. For these systems, drug-polymer specific interactions (in the form of hydrogen bonding) have been established (23,24,27,32). Thus,

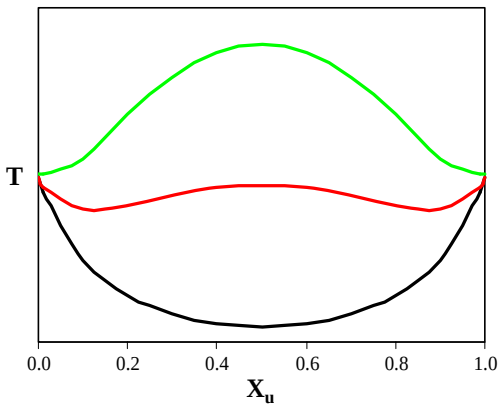

Fig. 12. Composition dependence of the free energy of mixing (ΔG_{mix}) for a binary hypothetical binary mixture, showing (*green*) complete immiscibility, (*red*) partial miscibility and (black) complete miscibility behaviors. Figure adapted from reference (34).

in addition to entropic effects, the presence of such interactions will be favorable to the mixing between the drug and the polymer, resulting in the formation of one-phase amorphous solid dispersions.

For ketoconazole-PVP system, no drug-polymer hydrogen bonding was possible. IR spectroscopy results show that some drug-polymer interactions were still observed, resulting in the minor changes in the relative intensity of certain peaks when compared to the spectra of physical mixtures at the same composition. However, results obtained from PXRD analysis show that significant molecular level changes were observed for samples containing 70% PVP, but not for samples containing 30% PVP. This seemed to suggest a partially miscible system, where significant drug-polymer mixing indicative of a single amorphous phase occurs only at higher levels of PVP. This system is challenging to fully characterize using IR spectroscopy, since partial mixing may still result in the enhancement of certain spectral features. The DSC results for this system indicate the presence of a single T_g over the complete range of composition; however, since DSC is subject to the aforementioned limitations, it is possible that the presence of a single amorphous phase is either driven by an increase in temperature, or that the presence of more than one amorphous phase for this system is not well-detected by this technique. This system clearly needs further investigation to fully understand its miscibility as a function of composition and temperature.

On the other hand, limited drug-polymer miscibility was detected for felodipine and PAA with all three experimental techniques. In particular, between 30 and 70% (by weight) polymer, no changes in drug-polymer chemical environments were detected by either IR or PDF/PCRM techniques, suggesting the presence of a drug-rich and a polymer-rich phase in the binary mixture that each contain only a small fraction of the second component. While the possibility of strong specific interactions between the drug and the polymer exists (in the form of hydrogen bonding), it is speculated that the lack of complete miscibility is caused by competition with intra-species interactions. It has been reported that PAA forms multiple intra-species hydrogen bonding (33), and their presence would decrease the value of ΔH_{mix} between felodipine and PAA.

PCA analysis of the IR spectra of samples containing 10 and 90% PAA suggest some miscibility between the drug and the polymer. However, the presence of more than one T_g for samples containing 90% PAA suggest the presence of more than one amorphous phase. It is speculated that at these drug-polymer ratios, some mixing occurred between the drug and the polymer. However, an excess amount of one of the pure components was also present, resulting in more than one amorphous phase.

CONCLUSIONS

Results obtained from this study show that the three experimental methods used to characterize drug-polymer miscibility in amorphous solid dispersion systems (DSC, IR spectroscopy, and PXRD) provide complementary results to each other. In particular, IR spectroscopy with principal component analysis can be utilized to verify drug-polymer mixing at the molecular level. PXRD with PDF and PCRM analysis, on the other hand, may be able to verify drug-polymer mixing for both completely and partially miscible systems. These techniques are especially useful to examine drug-polymer miscibility when DSC measurements are inconclusive or yield variable results.

Based on results obtained using these techniques, nifedipine-PVP and felodipine-PVP dispersions are miscible over the complete range of drug-polymer concentration, while felodipine-PAA dispersions are practically immiscible between 30 and 70% polymer concentration (dry weight basis). Ketoconazole-PVP, on the other hand, is suspected to be miscible at higher PVP loading, but not at lower PVP loading.

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