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Influence of various drugs on the glass transition temperature of poly(vinylpyrrolidone): a thermodynamic and spectroscopic investigation

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Abstract

Purpose: To determine the influence of hydrogen bonding and solubility parameter on the glass transition temperature (T_g) of various drug–poly(vinylpyrrolidone) blends. *Methods:* The T_g of PVP films containing either acetaminophen, naproxen, salicylamide, carbamazepine, griseofulvin or propranolol hydrochloride were measured using differential scanning calorimetry. Fourier transform infrared (FTIR) spectroscopy and X-ray diffraction was used to characterize the specific interactions between the drug–PVP blends and the physical state of the films, respectively. The total solubility parameter and its individual components were calculated using the method of Van Krevelen. *Results:* Salicylamide displayed the greatest plasticizing effect, depressing the T_g to the minimum. This was consistent with the FTIR data, which indicated the presence of hydrogen bonding with PVP. Griseofulvin showed the least plasticizing effect due to lack of interaction with PVP. All the drugs except griseofulvin were amorphous within the film up to 30% (w/w) drug composition. The correlation between the various components of the solubility parameters and the plasticizing effect of drugs was very poor. *Conclusions:* Spectroscopic investigation for the presence of interaction between the drugs and PVP proved to be extremely predictive of the plasticizing effect of various drugs. In contrast, solubility parameters appeared to be far less sensitive indicators of drug–PVP miscibility.

Keywords: Drug–polymer interactions; Solubility parameter; Glass transition; Spectroscopy; Poly(vinylpyrrolidone)

1. Introduction

The use of polymers for film coating of solid dosage forms has been rapidly increasing over the past few years. Most of the work on polymeric films has focussed on the importance of polymer–polymer blends. The influence of drugs in the

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polymeric films has received limited attention, despite their presence in film coatings. Several studies have shown that it is possible for a small amount of drug to either dissolve in the coating solution during film formation or migrate from the tablet core to the film surface (Aulton et al., 1983; Simpkin et al., 1983; Dansereau et al., 1993). Migration of the drug can occur either during the coating process or over a period of time, depending on the storage conditions. In addition, drugs can also be present as part of the coating formulation as in the case of drug loaded pellets.

The permeability and mechanical properties of a polymeric film are related to its glass transition temperature (T_g). At the T_g, an amorphous polymer softens, undergoing a transition from a glassy state to a rubbery state because of increased segmental mobility (Nyamweya and Hoag, 2000). Interactions between the drug and the polymer can influence the T_g of the polymer (Okhamafe and York, 1989; Wu and McGinity, 1999), and subsequently affect the end use properties of the film coating (such as permeability and mechanical strength). Coating defects such as cracking and edge splitting in film coated tablets, which have been associated with a high T_g of the polymer coating (Rowe, 1981) can also be altered by the presence of drugs.

Clearly, the drug–polymer interactions can significantly impact the quality of the film coating, and the bioavailability of a film coated dosage form. Despite their importance, very little work has been done on drug–polymer blends. The few studies reported so far in the literature have focussed on a single drug and polymer. To date, no study has attempted to relate the impact of drugs with different properties on the T_g of the corresponding drug–polymer blends. This makes it difficult to adequately assess the influence of drugs in polymeric films on the final film properties. Therefore, a knowledge of the nature of drug–polymer interactions and their influence on T_g would be extremely useful for effective formulation design of film coated dosage forms.

One approach to study the influence of drugs on the T_g of a polymer would be to compare the interactions of different drugs with a single polymer and the corresponding effect on the T_g of the drug–polymer blends. Fourier transform infrared spectroscopy (FTIR) is one technique that has been used both quantitatively and qualitatively to study the miscibility of polymer–polymer blends (Garton, 1992). The extension of this technique to study interactions in drug–polymer blends can provide valuable information regarding the interactions of drug–polymer blends at the molecular level.

Another approach for predicting the influence of drugs on the T_g of a polymer is to use the solubility parameter concept. The solubility parameter is defined as the square root of cohesive energy density and is a measure of the interatomic/molecular interactions. It has long been recognized that materials with similar solubility parameters will have similar intermolecular interactions, which will favor miscibility. A better understanding of the solubility parameter can be obtained by examining the equation for the free energy of mixing (Van Krevelen, 1990),

$$\Delta G_m = \Delta H_m - T\Delta S_m, \quad (1)$$

where G_m is the free energy of mixing, H_m, the enthalpy of mixing, T, the absolute temperature, and S_m, the entropy of mixing. Thermodynamically, miscibility will be achieved if there is a negative free energy of mixing. Since, the entropy of mixing is very low for polymer blends, the heat of mixing will determine the magnitude of change in the free energy of mixing. The heat of mixing can be obtained from the following expression (Van Krevelen, 1990),

$$\Delta H_m = \phi_1\phi_2(\delta_1 - \delta_2)^2 V_m, \quad (2)$$

where V_m is the total volume of the mixture, ϕ_1 and ϕ_2 refer to the volume fractions of components 1 and 2, and δ_1 and δ_2 refer to their solubility parameters, respectively. Similarity in the solubility parameters of the drug and polymer will therefore correspond to zero heat of mixing, which will lead to a negative free energy of mixing and miscibility of the components. The concept of solubility parameter has previously been applied to determine plasticizer efficiency (Lin et al., 1991). Solubility parameters have also been applied to predict polymer–polymer miscibility

(Rowe, 1986; David and Sincock, 1992), optimum solvent for polymer (Kent and Rowe, 1978), adhesion of tablet coat to tablets (Lin et al., 1991), and drug–excipient interactions (Rowe, 1989). Recently, Greenhalgh et al. used this approach to study the miscibility of solid dispersions (Greenhalgh et al., 1999).

The primary objective of this study was to determine the effect of drug–polymer interactions using FTIR on the T_g of various drug–poly(vinylpyrrolidone) films. The second objective was to examine the role of solubility parameters in predicting the plasticizing effect of drugs. Poly(vinylpyrrolidone) was chosen as the model polymer because of its extensive use in coating formulations. Six drugs were selected based on their solubility parameters. Naproxen, griseofulvin and propranolol hydrochloride had solubility parameters similar to PVP. Carbamazepine, acetaminophen and salicylamide had solubility parameters different from PVP.

2. Materials and methods

2.1. Materials

Acetaminophen, naproxen, carbamazepine, salicylamide, propranolol hydrochloride, and griseofulvin were purchased from Sigma Chemical Company, St. Louis, MO. Poly(vinylpyrrolidone), PVP K-90 with molecular weight average of 1300000 was obtained from International Specialty Products, Wayne, NJ.

2.2. Sample preparation

Films were prepared by the solvent casting method. Solutions containing 0.5 g of the appropriate ratios of the drug and PVP were dissolved in 8 ml of methanol. Due to its limited solubility in methanol, chloroform was chosen as the solvent for griseofulvin. The drug–polymer solution was poured into a Teflon petridish and dried at 40 °C to a constant weight. Amorphous forms of the drugs were prepared by initially melting the drug, followed by quench cooling over dry ice.

2.3. X-ray powder diffraction

X-ray powder diffraction patterns of the pure drug, physical mixtures and drug–polymer blends were obtained using a Bruker D8 diffractometer (Bruker Axs Inc. Madison, WI). Measurement conditions included target CuKα, voltage 30 kV, and current 40 mA. Patterns were obtained using a step width of 0.02° 2θ between 5 and 60° 2θ at ambient temperature.

2.4. Thermal analysis

Drug–polymer films and the amorphous forms of the drugs were subjected to thermal analysis, using a TA instruments DSC 2920 Module, New Castle, DE. High purity indium was used to calibrate the temperature and enthalpy values. All measurements were conducted in sealed non-hermetic aluminum pans. The samples were heated at a rate of 10 °C/min from -20 to 200 °C under a dry nitrogen gas purge. In the case of griseofulvin, the temperature was extended to 250 °C to encompass its melting point (220 °C). Typical sample weights ranged between 10 and 15 mg. All samples were initially heated to 200 °C at 10 °C/min to remove all the residual moisture/solvent and erase the effect of previous thermal history. All experiments were performed in triplicate.

2.5. Fourier transform infrared spectroscopy

Infrared spectra were obtained with a Perkin–Elmer 1600 FTIR spectrophotometer, (Perkin–Elmer, Norwalk, CT) using sodium chloride salt plates (Perkin–Elmer, Norwalk, CT). Sodium chloride was chosen due to its lack of absorbance within the infrared spectroscopy (IR) region of interest, 3800–1500 cm^{-1}. Thin films of the blends were obtained by placing 2–3 drops of the drug–polymer solution on to the plates. The plates were vacuum dried at 40 °C to completely remove any moisture and residual solvent. The spectra were obtained by averaging 64 scans at a resolution of 4 cm^{-1}.

2.6. Calculation of solubility parameter

The solubility parameter given in Eq. (2) provides information on the total cohesive energy density of the components. For a more detailed characterization of the drug–polymer blends, it is important to have knowledge of the relative strengths of the various types of forces present including dispersion forces, polar and hydrogen bonding. Therefore, in this study, we have used the Hansen's approach of partial solubility parameters (Van Krevelen, 1990),

$$\delta^2 = \delta_d^2 + \delta_h^2 + \delta_{pi}^2, \quad (3)$$

where δ is the total solubility parameter, δ_d, δ_h, δ_{pi} refer to the contributions from the dispersive forces, hydrogen bonding and polar components, respectively. The individual components were calculated using the group functional contributions for the drug molecule and PVP given by the following equations (Van Krevelen, 1990),

$$\delta_d = \frac{\sum F_{di}}{V}, \quad (4)$$

$$\delta_{pi} = \frac{\sqrt{\sum F_{pi}^2}}{V}, \quad (5)$$

$$\delta_h = \frac{\sqrt{\sum E_{hi}}}{V}, \quad (6)$$

where F_{di}, F_{pi} and E_{hi} refer to the functional group contributions to the dispersion, polar and hydrogen bonding components, respectively. The total molar volume (V) was determined from the true density and molecular weight. The true densities were determined by a helium pycnometer (Micromeritics Instrument Corporation, Norcross, GA). F_{di}, F_{pi} and E_{hi} for the various functional groups of the drug and PVP was obtained from the values compiled by Van Krevelen (Van Krevelen, 1990). Table 1 illustrates this technique for the calculation of solubility parameter of acetaminophen.

3. Results and discussion

3.1. X-ray analysis

The amorphous and crystalline nature of the drug within the PVP films was confirmed using powder X-ray diffraction (PXRD). Crystallinity was indicated by the presence of sharp peaks that were absent in the case of amorphous drugs (displayed a halo pattern). The diffractograms shown in Fig. 1 represent the compositions at which the physical state of the drugs changes from amorphous to crystalline. All the drugs (except griseofulvin) were amorphous in the PVP blends up to 30% (w/w) drug. Acetaminophen and propranolol hydrochloride were amorphous at all blend compositions. Salicylamide and carbamazepine were amorphous up to 40% (w/w) drug composition,

Table 1
Calculation of solubility parameters for acetaminophen

Group	F_{di} ($J^{1/2}$ $cm^{3/2}$ mol^{-1})	F_{pi}^2 (J cm^3 mol^{-2})	E_{hi} (J mol^{-1})
$-C_6H_5$	1270	12 100	0
–OH	210	250 000	20 000
–CO	290	592 900	2000
–NH	160	44 100	3100
$-CH_3$	420	0	0
Σ	2350	899 100	25 100
$\delta = 28.36$ $MPa^{1/2}$	$\delta_{di} = 22.11$ $MPa^{1/2}$	$\delta_{pi} = 8.92$ $MPa^{1/2}$	$\delta_{hi} = 15.37$ $MPa^{1/2}$

Molecular weight = 137.13 g mol^{-1}, true density = 1.29 g cm^{-3}, molar volume = 106.3 cm^3 mol^{-1}. Values for F_{di}, F_{pi}^2 and E_{hi} were obtained from Van Krevelen (1990).

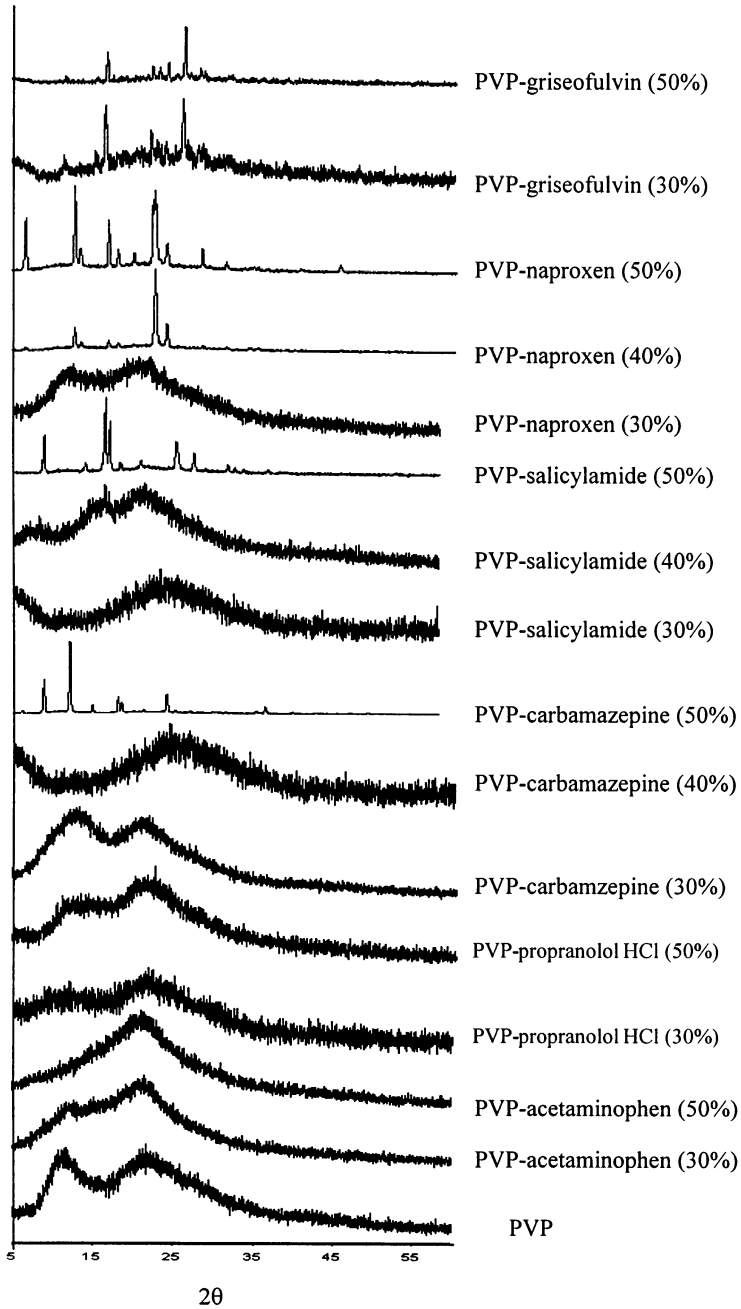

Fig. 1. PXRD patterns for the various drug–PVP films.

but showed distinct peaks at 50% (w/w) composition. The 30% (w/w) naproxen-PVP blend showed a halo pattern, but at higher naproxen concentrations (40 and 50% (w/w)) sharp peaks were evident. Griseofulvin, however, was crystalline at all blend compositions. The inhibitory effect of PVP on crystallization may be due to the interaction of the drug with PVP resulting in a change in the

molecular mobility of the drug, ultimately leading to an amorphous form of the drug (Yoshioka et al., 1995). PVP has also been shown to inhibit the crystallization of several other drugs (Sekikawa et al., 1978; Yoshioka et al., 1995).

3.2. Thermal analysis

There are several accepted ways of assigning T_g to the transition obtained by differential scanning calorimetry (DSC) (Kerč and Stčič, 1995). In this study, T_g was taken as the inflection point (the point on the curve with the steepest slope) in the heat capacity increment during the second heating cycle. Given the importance of the plasticizing effect of water on the films, all the films used in this study were initially heated to 200 °C at a rate of 10 °C/min. This was done to remove any residual moisture/solvent that would obscure the interpretation of T_g. The samples were then scanned twice under the same conditions. The T_gs from these two scans were reproducible indicating the absence of water or any residual solvent in the films.

With the exception of griseofulvin, the DSC scans for all the drug–polymer blends showed a single T_g intermediate to the drug and polymer. The presence of a single concentration dependent T_g lying between the T_gs of the individual components was used as a criteria for establishing drug–polymer miscibility. In contrast, the presence of two T_g corresponding to the T_gs of the individual components was an indication of immiscible blends. The presence of a single T_g for all the drug–PVP blends used in this study suggests complete miscibility between PVP and the drug within the concentration range studied. Fig. 2 illustrates the T_g versus blend composition for all the drug–

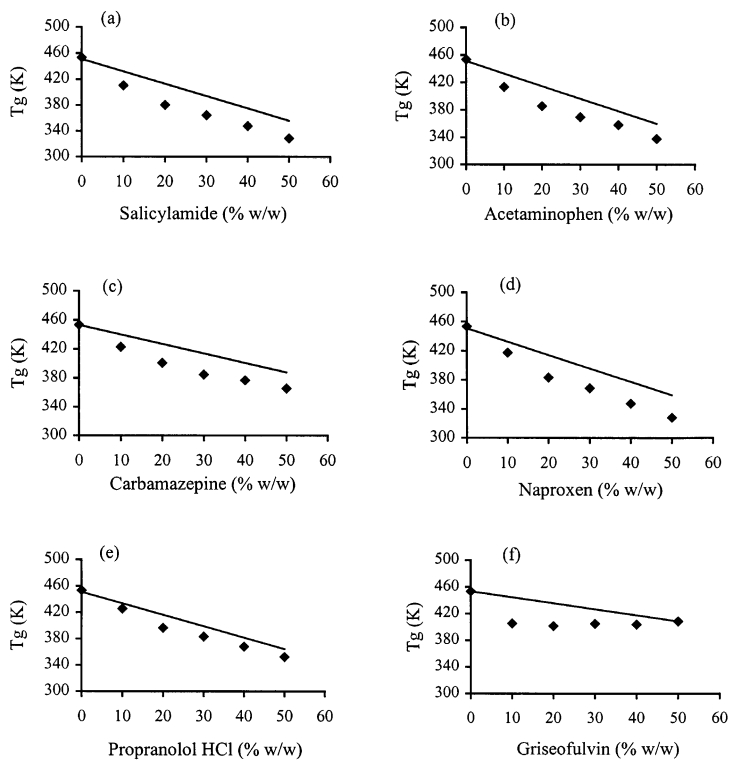

Fig. 2. Effect of drugs on the T_g of PVP. The solid line denotes the predicted values obtained from Gordon–Taylor equation. The symbols represent the measured T_g values. (a) salicylamide, (b) acetaminophen, (c) carbamazepine, (d) naproxen, (e) propranolol hydrochloride, and (f) griseofulvin.

PVP blends. Except for griseofulvin, the T_g of the blends was composition dependent, i.e., increasing the proportion of the drug in the PVP film resulted in a decrease in T_g. In contrast, griseofulvin lowered the T_g of pure PVP from 180 to $\approx$ 130 °C at all blend compositions.

Several empirical or semi-empirical equations have been used to predict the dependence of T_g on the composition of polymer blends. In this study we employed the commonly used Gordon Taylor equation to predict the T_g of the drug–polymer blends. This equation is based on the additivity of free volumes of the individual components characteristic of ideal mixing and is given by the expression (Gordon and Taylor, 1952),

$$T_{g12} = \frac{w_1 T_{g1} + K w_2 T_{g2}}{w_1 + K w_2}, \quad (7)$$

where T_{g12} is the glass transition temperature of the drug–polymer blend. w_1, w_2, T_{g1}, and T_{g2} are the weight fractions and glass transition temperatures (in Kelvin) of the drug and polymer, respectively. The constant K, which is a measure of interaction between the components, can be approximated using the equation (Simha and Boyer, 1962),

$$K \approx \frac{\rho_1 T_{g1}}{\rho_2 T_{g2}}, \quad (8)$$

where ρ_1 and ρ_2 refer to the true densities of the components. The use of the Gordon Taylor equation requires knowledge of the T_gs of the pure drugs. The T_gs of pure acetaminophen, carbamazepine, propranolol hydrochloride, and griseofulvin were found to be 23, 55, 34, and 89 °C, respectively. These values are in agreement with the T_gs obtained by other researchers (Kerč and Stčič, 1995). The T_g/T_m values for these drugs were in the range of 0.66–0.74. This is consistent with the ratios reported for similar low molecular weight compounds (Kerč and Stčič, 1995). The T_g of salicylamide and naproxen could not be detected in the DSC scan due to rapid recrystallization. Nevertheless, the T_g values were estimated to be 24 and 16 °C for naproxen and salicylamide respectively, based on the ratio $T_g/T_m = 0.70$.

The measured T_g values of salicylamide, acetaminophen, carbamazepine and naproxen blends (Fig. 2(a–d)), are lower than the T_g values predicted by Gordon Taylor equation, indicating a negative deviation from ideal behavior. Deviation from ideal behavior has often been explained in terms of the differences in strength of intermolecular interactions between the individual components and those of the blend. If the drug and the polymer bind more strongly to each other than to themselves, the T_g will be higher than expected, because the stronger binding lowers chain mobility. In contrast, if the drug and polymer bind less strongly with each other than with themselves, the T_gs of the blends are usually lower than expected. Moreover, negative deviation from the Gordon Taylor equation as in this study has been observed for blends where one of the components have a strong tendency to self-associate (e.g., form dimers) (Painter et al., 1991). The drugs that displayed negative deviations from ideal behavior in blends with PVP are capable of self-association, either through the carboxylic group as in the case of naproxen, or the amide group in the case of salicylamide, acetaminophen, and carbamazepine. Hence the difference between the experimental and predicted values is probably due to the stronger drug–drug interaction compared to the drug–PVP interaction.

In the case of propranolol hydrochloride, the theoretical and experimental T_g values are in closer agreement than the other drug–PVP blends. This indicates a similarity between propranolol hydrochloride–PVP interactions and propranolol hydrochloride–propranolol hydrochloride interactions. A constant T_g was seen at all PVP–griseofulvin compositions due to the lack of interaction between the components.

3.3. FTIR spectroscopy

IR has been the method of choice to probe the nature and extent of interactions in polymer blends. The premise of using an IR to study polymer blends is that the mixing of two components at the molecular level will cause changes in the oscillating dipole of the molecules. This will manifest itself as changes in the frequency and bandwidth of interacting groups in the spectrum. If the drug and PVP interact, then the functional

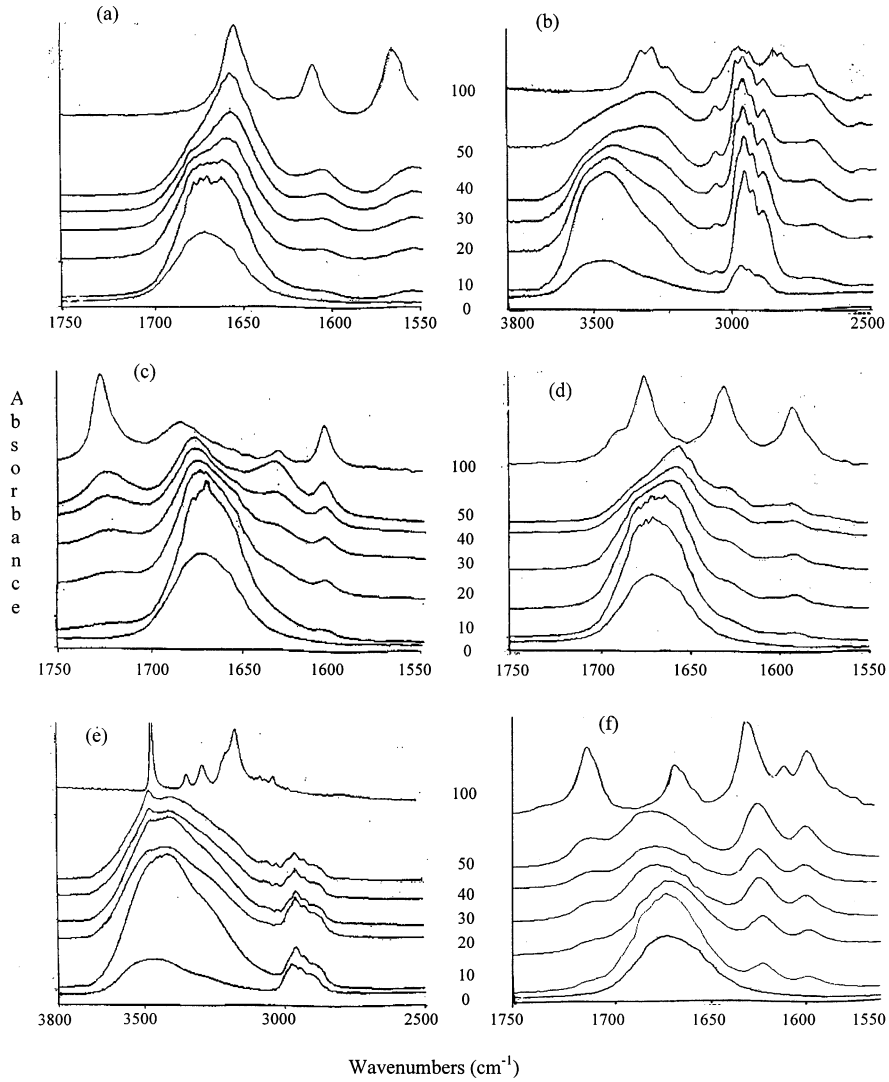

Fig. 3. FTIR spectra of films of PVP with (a) acetaminophen, (b) propranolol hydrochloride, (c) naproxen, (d) salicylamide, (e) carbamazepine, and (f) griseofulvin. The curves are arranged in the order of increasing drug composition (% w/w), 0 represents pure PVP and 100 represents pure drug.

groups in the FTIR spectra will show band shifts and broadening compared to the spectra of the pure drug and PVP (Silverstein et al., 1991). PVP is capable of forming a hydrogen bond either through the nitrogen or carbonyl group on the pyrrole ring. However, steric hindrance precludes the involvement of nitrogen atom in intermolecular interactions, thus making the carbonyl group more favorable for hydrogen bonding (Sekizaki et al., 1995).

The FTIR spectra in the absorbance mode for the various drug–polymer blends are shown in Fig. 3. Fig. 3(a) shows the carbonyl stretching from 1750 to 1550 cm^{-1} for the acetaminophen–PVP blends. Pure acetaminophen shows a peak at 1656 and 1565 cm^{-1} indicative of the C=O stretch

of the amide group and aromatic vibration, respectively (El-obdeid and Al-Badr, 1985). Pure PVP shows a band at 1670 cm^{-1} corresponding to its carbonyl group (Sekizaki et al., 1995). As the proportion of acetaminophen in the blend increases, the peak at 1670 cm^{-1} becomes broader and gradually shifts to lower wave numbers indicative of hydrogen bonding between the drug and PVP.

Fig. 3(b) shows the hydroxyl stretching region 3500–2800 cm^{-1} of the propranolol hydrochloride–PVP blends. Pure propranolol hydrochloride shows a broad band at around 3280 cm^{-1} due to an overtone of hydroxyl and N–H stretching vibrations. The band at 3448 cm^{-1} for pure PVP is probably due to the formation of hydrogen bond between PVP and water. The extremely hygroscopic nature of PVP makes it very difficult to obtain IR spectra without interference from water. A similar band between 3500 and 3300 cm^{-1} for PVP has also been reported in the Sigma and Aldrich FTIR spectral databases and by other researchers (Moskala et al., 1985). Nonetheless, using the position 3280 cm^{-1} of propranolol hydrochloride as a reference, the band corresponding to the hydroxyl group gradually shifted from 3441 cm^{-1} for 10% (w/w) blend to 3290 cm^{-1} for 50% (w/w) PVP–propranolol hydrochloride blend. If the change in this spectral region is due to an increase in water content, then the peak at 3448 cm^{-1} should move to lower wave numbers with an increase in PVP content (since more PVP is available for interaction with water), or one should see a random shift in the spectrum. However, in this case, we see a decrease in wave numbers with a decrease in PVP content (or with an increase in drug content) which indicates that the shifts are due to interaction between the drug and PVP and not due to PVP and water.

Fig. 3(c) shows the spectra for naproxen–PVP blends. The top spectrum of pure naproxen exhibits a infrared band at 1727 cm^{-1} attributed to the free or non hydrogen bonded carboxylic group (monomer) and a band centered at 1684 cm^{-1} corresponding to the hydrogen bonded carboxylic group (dimer), respectively (Hirasawa et al., 1998). As the proportion of PVP in the blend increases, the monomer and dimer peak decreases in intensity. The dimer peak is absent in the blends while the monomer peak reduces to a shoulder below 40% (w/w) naproxen. The reduction in intensity of monomer peak suggests the involvement of the unassociated naproxen in hydrogen bonding with PVP. In addition, a new peak with a frequency intermediate between the dimer peak of pure naproxen and the carbonyl peak of PVP is observed in the blends. Disappearance of the dimer peak and presence of a new peak suggests that PVP disrupts some of the dimers to itself form a hydrogen bond with naproxen. The peak in the blends is therefore assigned to the C=O stretch due to hydrogen bonding between the carbonyl group of PVP and the hydroxyl group of naproxen. It is important to note that though this peak occurs at a higher wave number than the C=O of PVP, hydrogen bonding will not always shift the C=O modes to lower frequencies. Although the shifts of the C=O stretching modes to lower frequencies are often considered to be an indication of hydrogen bonding, the shifts observed will depend upon the extent of self association in the pure components compared to their mixtures (Coleman and Painter, 1984). Similar shifts to a higher wave number for the PVP carbonyl group has also been observed for miscible indomethacin (capable of forming dimer)-PVP solid dispersions (Taylor and Zograffi, 1997). This shift is also consistent with the IR results obtained with other self-associated species (Moskala et al., 1985).

The results obtained for salicylamide–PVP blends (Fig. 3(d)) also reveal extensive hydrogen bonding between the drug and polymer. Pure salicylamide shows multiple bands around 1700–1550 cm^{-1} characteristic of the amide bending of primary amides (Silverstein et al., 1991). These bands are replaced by a single broad band in the blends, the frequency of the band decreasing with increasing drug composition relative to the carbonyl group (1670 cm^{-1}) of pure PVP.

In contrast to the acetaminophen–PVP, propranolol hydrochloride–PVP, naproxen–PVP and salicylamide–PVP blends, composition dependent interactions were not evident from the spectra of carbamazepine and griseofulvin blends. The spectrum of pure carbamazepine, Fig. 3(e), shows two bands of moderate intensity at 3463 and 3159 cm^{-1}

corresponding to the symmetrical and asymmetrical N–H stretching vibrations of primary amide groups (Silverstein et al., 1991). Below 20% (w/w) of carbamazepine, both these bands are replaced by a broader band indicating the involvement of $-NH_2$ group in hydrogen bonding with C=O of PVP. Above 20% (w/w) of carbamazepine in the blends, no further change in the peak width or wave number is seen. This may be due to saturation of the PVP binding sites, resulting in no further increase in the interaction between PVP and carbamazepine beyond 20% (w/w) concentration. The spectrum for pure griseofulvin (Fig. 3(f)) shows several bands between 1750 and 1550 cm^{-1} corresponding to the C=O stretch of the benzofuranone ring, cyclohexanone carbonyl and C=C stretch of the cyclic rings (Townley, 1979). Unlike naproxen, griseofulvin does not form any dimers. The small shifts observed in the blends towards higher frequency are therefore due to a lack of interaction between griseofulvin and PVP.

3.4. Correlation of the DSC, FTIR and X-ray results

The plasticizing effect of the drugs, expressed by the extent of lowering of the T_g (ΔT_g) is plotted in Fig. 4. A relationship was observed between the influence of the drugs on the glass transition temperature and presence of interaction from FTIR studies. The plasticizing effect in increasing order can be written as griseofulvin, carbamazepine, propranolol hydrochloride, acetaminophen, naproxen, and salicylamide. Griseofulvin showed the least effect on T_g and this is consistent with the FTIR data, which indicates little interaction between this drug and PVP. Despite its negligible interaction with PVP, the presence of a small drug molecule like griseofulvin (M.W., 325.77 g mol^{-1}) may be sufficient to increase the free volume of the polymer and thereby decrease its T_g (Okhamafe and York, 1989). This may be one of the reasons why the addition of griseofulvin resulted in a decrease of 50 °C in the T_g of PVP at all compositions.

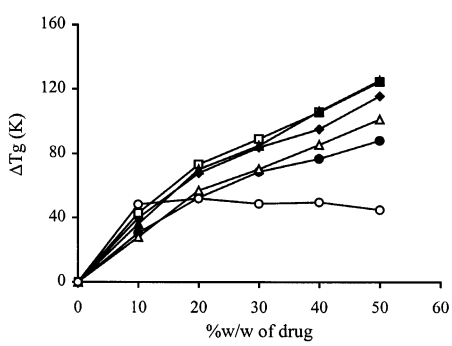

Fig. 4. Comparison of the plasticizing effect of various drugs on PVP. (□) Salicylamide, (▲) naproxen, (◆) acetaminophen, (△) propranolol hydrochloride, (●) carbamazepine, and (○) griseofulvin.

In the case of the drugs that displayed a composition dependent effect on the T_g of PVP, carbamazepine had the least effect on T_g which was in agreement with the FTIR results. The FTIR spectra of carbamazepine–PVP indicated that an increase in carbamazepine concentration beyond 20% (w/w) did not result in any further increase in interaction with PVP. This limited interaction between carbamazepine and PVP may be responsible for the relatively small depression of T_g observed for carbamazepine–PVP blends. Acetaminophen, naproxen, salicylamide and propranolol hydrochloride showed extensive hydrogen bonding with PVP, which is consistent with their greater plasticizing effect. The differences observed in the T_g of their blends may be related to the differences in the nature and strength of their hydrogen bonding with PVP and their molecular size. The small molar volume of salicylamide and acetaminophen facilitates their easy diffusion within the PVP chains. This might increase their accessibility to the PVP carbonyl group compared to the relatively larger propranolol hydrochloride molecule. Such similar influence of molecular size on T_g has been reported previously (Okhamafe and York, 1989; Gutièrrez-Roca and McGinity, 1994).

The observation of a single composition dependent T_g is only associated with the amorphous phase. Based on the results from the X-ray and DSC analysis, acetaminophen and propranolol hydrochloride blends exist as an amorphous phase (or glassy solution). Carbamazepine and salicylamide exists as a single amorphous phase up to 40% (w/w) drug composition. Above 40% (w/w)

Table 2
Total solubility parameter and its partial components for the various drugs and PVP

	δ_d	δ_{pi}	δ_h	δ ($MPa^{1/2}$) (literature)[a]	δ ($MPa^{1/2}$) (calculated)	$\Delta\delta$ ($MPa^{1/2}$)
PVP	16.06	12.13	8.75	21.2	21.95	0
Naproxen	23.25	3.17	8.28	22.1	24.88	2.93
Griseofulvin	27.44	6.69	8.66	21.3	29.54	7.59
Propranolol HCl	21.83	3.63	10.43	24.4	24.46	2.51
Carbamazepine	27.94	6.18	9.21	31.2	30.06	8.11
Acetaminophen	22.11	8.92	15.37	30.8	28.36	6.41
Salicylamide	19.82	8.94	17.15	31.3	27.69	5.74

[a] Hancock et al., (1997), Greenhalgh et al. (1999).

there is the possibility of two phases, a miscible amorphous phase containing both the drug and PVP and a second phase composed of only the crystalline drug. In the case of griseofulvin–PVP films, the presence of crystalline griseofulvin, a constant T_g and lack of interaction between PVP and griseofulvin confirms the immiscible behavior of this blend at all compositions. The decrease in T_g for naproxen films above 30% (w/w) despite the presence of crystalline naproxen in the blend is interesting. The presence of a crystalline component in the blend usually increases the rigidity of the polymer chain resulting in an increase in T_g. A detailed analysis of the composition dependent T_g and the physical state (amorphous/crystalline) of the drug reveals that changes in T_g is unaffected by crystallinity for naproxen–polymer blends. Similar composition dependent decrease in T_g despite the presence of crystalline poly (ε-caprolactone) (PCL) has also been reported for miscible (PCL)–poly(vinyl chloride) (PVC) system (Ong, 1973). Miscibility and hence the depression in T_g of the PCL–PVC blends were suggested to be due to the presence of PVC molecules within the PCL spherulites and interlamellar region. Similar reasoning may also be true for the naproxen–PVP blends. Another likely reason for the decrease in T_g, despite the crystallinity of naproxen, may be due to the small molecular size of naproxen relative to the high molecular weight PVP. This relatively small size facilitates easy diffusion of naproxen (regardless of its physical state) within the polymer chains. This reasoning is further substantiated if we consider the decrease in T_g of griseofulvin–PVP blends despite the presence of crystalline griseofulvin at all drug compositions.

3.5. Solubility parameter

Table 2 shows the values of δ, δ_d, δ_h, and δ_{pi} for PVP and the various drugs. The calculated values of δ appear to be in reasonable agreement with the literature values (Hancock et al., 1997; Greenhalgh et al., 1999), the only notable exception being griseofulvin. The difference in δ between PVP and the various drugs ranged between 2 and 8 $MPa^{1/2}$. Fig. 5 illustrates the relationship between ΔT_g and the total solubility parameter at all the drug–polymer compositions. A very poor correlation is observed between depression of T_g and differences in solubility parameter. A good correlation would show an inverse relationship

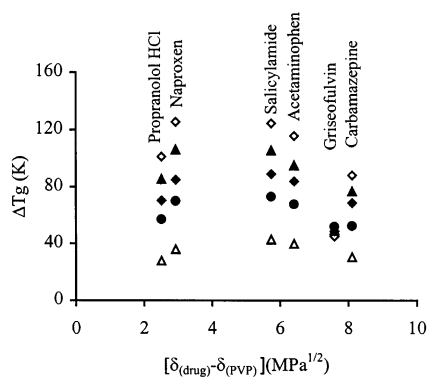

Fig. 5. Relationship between ΔT_g and the difference in total solubility parameter between the drugs and PVP at various % (w/w) drug composition (△) 10, (●) 20, (◆)30, (▲) 40, and (◇) 50.

between ΔT_g and $\Delta\delta$. Since, the total solubility parameter is an average value of the various contributions, its use to predict miscibility may be misleading. Given that the drug–polymer blends interact through their functional groups, we chose to examine the individual solubility parameter components separately and in combination to see if there exists any relationship between the solubility parameter and ΔT_g. Attempts were made to correlate ΔT_g with the differences in dispersion, polar and hydrogen bonding solubility parameters between the drug and PVP. All correlations again appeared to be equally poor. Slark suggested that the long-range forces (polar, hydrogen bonding) may be more important than short-range dispersion forces in the plasticizing influence of dyes (Slark, 1997). The use of polar and hydrogen bonding components of solubility parameters seems reasonable since all the interactions in this study involved the formation of hydrogen bond between the drugs and PVP. We therefore, attempted to correlate ΔT_g with the combined hydrogen bonding and polar component as a single parameter, $(\delta_{pi} + \delta_h)$. The data were scattered and a poor correlation was observed. Greenhalgh et al. also found that the total solubility parameter was not very useful for predicting the miscibility of solid dispersions (Greenhalgh et al., 1999). However, they suggested that the Hansen partial solubility parameters could be useful in predicting the miscibility of solid dispersions. Based on the results from our study it appears that neither the solubility parameter nor its individual components can be applied to determine the miscibility of drugs and polymers.

Several factors can account for the lack of any relationship between ΔT_g and solubility parameters. One of the reasons can be related to the accuracy of calculated δ values. The number and type of functional groups listed for calculation of solubility parameters are limited. Others have also observed similar errors in the calculated δ values (Coleman et al., 1990; Slark, 1997). Yet another main reason for the poor correlation between $\Delta\delta$ and ΔT_g may be due to the extensive hydrogen bonding observed in all the drug–PVP blends. Most of the drugs used in the study are capable of self-association. Under such situations the enthalpy of mixing can be positive due to the 'breaking' of hydrogen bonds in the self associated drug molecules as shown by Painter et al. (1991). Miscibility in these drug–PVP blends will then be driven by the entropy changes corresponding to the change in the number of self-associated interactions among the drug molecules. Such entropic changes may be significant enough to offset any positive ΔH_m value obtained due to difference in δ_{drug} and δ_{PVP}, (Eq. (2)). Therefore, despite any differences in the value of δ between the drug and polymer, miscibility and subsequent lowering of T_g can occur in the drug–PVP blends.

4. Conclusion

In conclusion, acetaminophen, naproxen, salicylamide, carbamazepine, griseofulvin, and propranolol hydrochloride depressed the T_g of PVP films to a varying extent. The FTIR results established a relationship between the plasticizing effect of these drugs and the presence of hydrogen bonding between these drugs and PVP. Spectroscopic study can thus be a very useful tool for predicting the miscibility of drug–polymer blends. A poor correlation was observed between the plasticizing effect and the difference in solubility parameter between these drugs and PVP. Solubility parameters, may therefore not be useful in predicting the miscibility of drug–polymer blends. The drugs in addition to being the active agent can also serve as a plasticizer, replacing the use of traditional plasticizers. Spraying of PVP–drug solutions onto inert tablet cores could be an alternative way of preparing an amorphous form of a poorly water soluble drug.

The results of this study may have major implications in the coating process, especially when it involves either the migration of the drug (from the core to the film) or the spraying of drugs in coating solutions. Time related changes in the release profile or bioavailability of film coated dosage forms may be related to changes in the T_g of the coating as a result of drug–polymer interactions due to changes in the distribution of drug.

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