# Spectroscopic Characterization of Interactions Between PVP and Indomethacin in Amorphous Molecular Dispersions

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**Purpose.** To study the molecular structure of indomethacin-PVP amorphous solid dispersions and identify any specific interactions between the components using vibrational spectroscopy.

**Methods.** Solid dispersions of PVP and indomethacin were prepared using a solvent evaporation technique and IR and FT-Raman spectra were obtained.

**Results.** A comparison of the carbonyl stretching region of γ indomethacin, known to form carboxylic acid dimers, with that of amorphous indomethacin indicated that the amorphous phase exists predominantly as dimers. The hydrogen bonding of α indomethacin is not as dimers. Addition of PVP to amorphous indomethacin increased the intensity of the infrared band assigned to non-hydrogen bonded carbonyl. Concomitantly, the PVP carbonyl stretch appeared at a lower wavenumber indicating hydrogen bonding. Model solvent systems aided spectral interpretation. The magnitude of the spectral changes were comparable for an indomethacin-PVP solid dispersion and a solution of indomethacin in methylpyrrolidone at the same weight percent.

**Conclusions.** Indomethacin interacts with PVP in solid dispersions through hydrogen bonds formed between the drug hydroxyl and polymer carbonyl resulting in disruption of indomethacin dimers. PVP may influence the crystallisation kinetics by preventing the self association of indomethacin molecules. The similarity of results for solid dispersions and solutions emphasises the "solution" nature of this binary amorphous state.

**KEY WORDS:** solid-state interaction; spectroscopy; amorphous; solid dispersion.

## INTRODUCTION

Amorphous materials can be formed by many routes including condensation from the vapour state, supercooling of the melt, mechanical activation of a crystalline mass and rapid precipitation from solution, whilst other materials such as many polymers are inherently amorphous (1). Binary amorphous mixtures of drug and excipient, sometimes termed glass solutions, are a type of solid dispersion and are considered to be homogenous systems in which a solute dissolves in a glassy solvent leading to enhancement of drug dissolution and bioavailability (2). Several factors are considered to contribute to the increase in dissolution rate of these systems including the greater solubility of the amorphous drug relative to the crystalline material, and increased wettability due to the incorporation of a hydrophilic excipient (3). Polymers (4) and other glass forming solids such as citric acid (5) have been used to form amorphous pharmaceutical dispersions with poorly water soluble drugs. However, since the amorphous phase is metastable relative to the crystalline state, phase transformations may occur during both storage and upon dissolution.

Poly(vinylpyrrolidone) (PVP) is commonly used to form solid dispersions, and it has been reported that over 60 drugs have been dispersed in this polymer (3). Previous studies have shown that PVP inhibits crystallisation in both solution (6) and amorphous solid dispersions (7). In solution, PVP has been found to interact with numerous organic molecules and it has been suggested that the mechanism of crystallisation inhibition is related to the extent of interaction between drug and polymer (6). Since crystallisation from the amorphous state is known to be related to molecular mobility (8), it has been suggested that a polymer such as PVP, with a high Tg (177°C (9)) will raise the Tg of the mixture and decrease the mobility of the phase at a particular temperature relative to drug alone, reducing the tendency to crystallise. Yoshioka et al. (7) studied the inhibition of indomethacin crystallisation by PVP and showed significant inhibition at relatively low levels of PVP. However, close analysis led to the conclusion that the inhibition could not be explained solely by the antiplasticising effect of the polymer.

In view of these earlier observations it is of interest to examine the structure of such binary amorphous mixtures of drug and polymer at the molecular level. Below the glass transition temperature they can be regarded as non-equilibrium supercooled liquids of high viscosity, but little is known about the nature of interactions between homo and hetero molecules in glasses. Several pharmaceutical studies have utilised vibrational spectroscopy to investigate interactions between two components in solid dispersions (10–12). However, these have compared the spectrum of the crystalline drug with spectra obtained from solid dispersions, where the drug is often present as the amorphous phase, and have postulated interactions based on these comparisons. Since changes in crystallinity result in variations in the vibrational spectra of a compound (13), there is a need for detailed studies on amorphous binary systems using spectra of the amorphous form as the reference state. Such studies should provide a better basis to consider the underlying role of PVP as an inhibitor of crystallisation in solid dispersions.

## MATERIALS

Indomethacin, 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid, as the γ crystal form, spectroscopic grade potassium bromide and 1-methyl-2-pyrrolidone were obtained from Sigma Chemical Co. Poly(vinylpyrrolidone), (PVP-K90) was obtained from GAF Corp. and was dried at 105°C for 12 hours under vacuum before use. All other materials used were reagent grade.

The α polymorph of indomethacin was prepared by dissolution in methanol and precipitation with water at room temperature as previously described (14). Amorphous indomethacin was prepared by melting indomethacin at 165°C for 5 minutes and quench cooling in liquid nitrogen. The amorphous material was warmed to room temperature under vacuum to prevent atmospheric moisture condensation on the sample and stored over phosphorous pentoxide at −20°C.

Solid dispersions of indomethacin and PVP were prepared using the solvent evaporation technique. 5g of the appropriate

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ratios of the two components were dissolved in 100 ml anhydrous methanol at 65°C. The solvent was removed under vacuum at 50°C using a rotary evaporator. Residual solvent was removed by drying under vacuum at room temperature for 24 hours. After preparation the solid dispersions were characterised as amorphous by X-ray powder diffraction using a PadV Scintag scanning x-ray powder diffractometer (Scintag Inc., Santa Clara, California) as previously described (15) and stored at −20°C over phosphorous pentoxide.

## METHODS

FT-Raman spectra were collected on a Bruker RFS 100 FT-Raman system with a near infrared Nd:YAG laser operating at 1064 nm. The laser power was typically 500 mW and a liquid nitrogen-cooled germanium detector was used. Back scattered radiation at an angle of 180° was collected and the Stokes scattering is reported. 200 scans over the wavenumber range 4000–50 $cm^{-1}$ at a resolution of 4 $cm^{-1}$ were averaged for each sample. Solids were analysed in aluminium holders and liquids in thin-walled glass vials.

IR absorbance spectra were obtained using a Mattson Galaxy 5020 FTIR spectrometer equipped with a DTGS detector. Liquids were sampled between NaCl windows. 0.8–1% of the test solid was mixed with dry KBr and the particle size of the powder reduced, in a Wig-L-Bug mixer, before forming into KBr pellets. 500 scans were collected for each sample at a resolution of 4 $cm^{-1}$ over the wavenumber region 4000–400 $cm^{-1}$.

## RESULTS

### Structure of Indomethacin Forms

Indomethacin has been shown to exist as two monotropic polymorphs, the stable γ form, the metastable α form, various solvates and in the amorphous state (16,17). The structure of the γ form is established with the single crystal structure determined and it is known that there are 2 molecules in the unit cell and that the carboxylic acid groups hydrogen bond to form cyclic dimers (18). However, the exact nature of the interactions between molecules in both the α and amorphous forms are unknown. Vibrational spectroscopy is a well established technique for characterising polymorphs and investigating crystallinity in general (13,19,20). Since the molecular species is identical, spectral differences represent differences in interactions within the different forms. Infrared and Raman spectra of the α and γ polymorphs and amorphous forms of indomethacin are shown in Figures 1 and 2 respectively. Several differences may be noted between the three forms.

The CH stretching region is most clearly seen in the Raman spectra (around 3000 $cm^{-1}$) where OH vibrations are weak. One peak can be observed at 3070 $cm^{-1}$ in both amorphous and α-indomethacin arising from aryl CH stretch whilst the γ form has an additional peak at 3022 $cm^{-1}$. The pattern of CH vibrations for the amorphous material generally resembles that of the α form more closely than that of the γ-form. The OH stretching region of the carboxylic acid group can be seen in the infrared spectrum as a very broad band between 3400 and 2500 $cm^{-1}$ superimposed on the CH stretching bands. Both the broad nature of this band and the position are characteristic

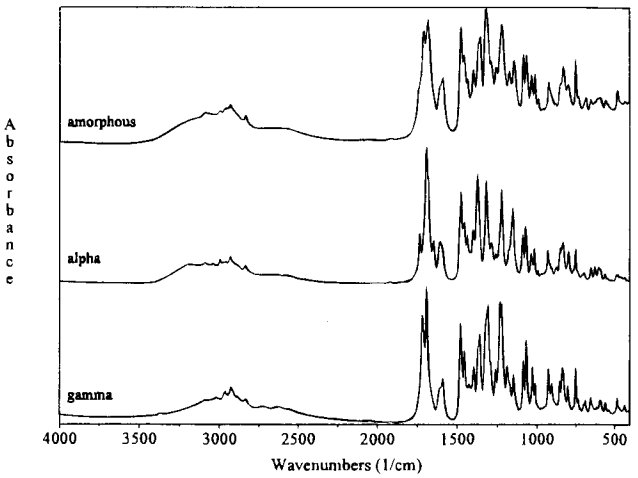



**Fig. 1.** IR spectra of γ-indomethacin, α-indomethacin and amorphous indomethacin over the spectral region 4000–400 $cm^{-1}$.

of a hydrogen bonded hydroxyl group (21). There are some differences in the shape of this band between the three forms suggesting that variations in hydrogen bonding may exist.

The pattern of vibrations between 1750 and 1600 $cm^{-1}$ is the region where the C=O stretch is typically observed. Indomethacin (Figure 3) contains two carbonyl groups; benzoyl and acid. Peaks seen at 1692 $cm^{-1}$ and 1698 $cm^{-1}$ in the infrared (Figure 4a) and Raman (Figure 4b) spectra respectively of γ indomethacin are assigned to the benzoyl vibration This vibration occurs at a high wavenumber for an amide group (usually 1695-1630 $cm^{-1}$(21)) in the γ form. In amides mesomerism can occur since the N atom can donate a lone pair of electrons. This reduces the force constant of the C=O bond and hence the frequency. However the contribution to the mesomeric form will be reduced in compounds in which the nitrogen atom forms part of a cyclic system which itself possesses resonance energy derived from the lone pair of electrons of the nitrogen. This has been observed in indole ketones (22). This would provide one explanation for the observed high frequency of the benzoyl C=O group in γ indomethacin. However, it has also been observed from single crystal data that the amide C=N bond in

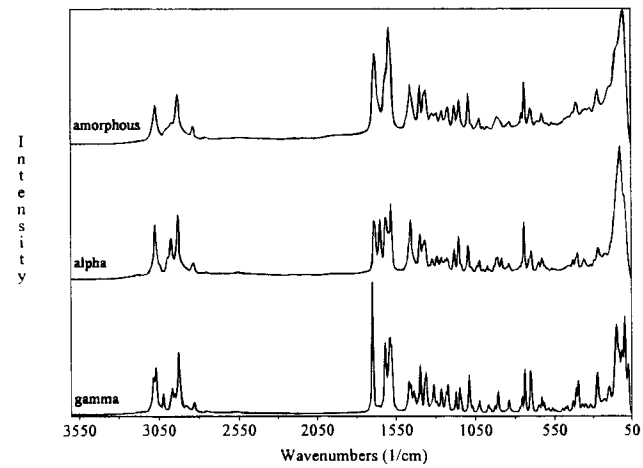
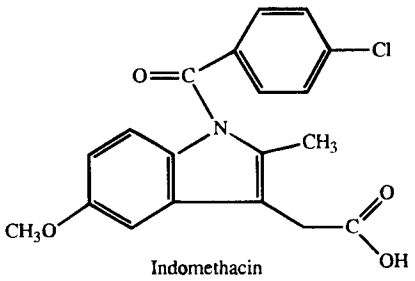
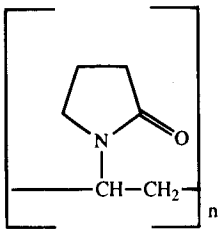


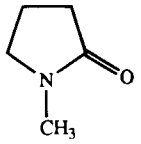

**Fig. 2.** FT-Raman spectra of γ-indomethacin, α-indomethacin and amorphous indomethacin over the spectral region 3600–50 $cm^{-1}$.




Indomethacin




PVP




N-methyl-2-pyrrolidone

**Fig. 3.** Structures of indomethacin, PVP and methylpyrrolidone.

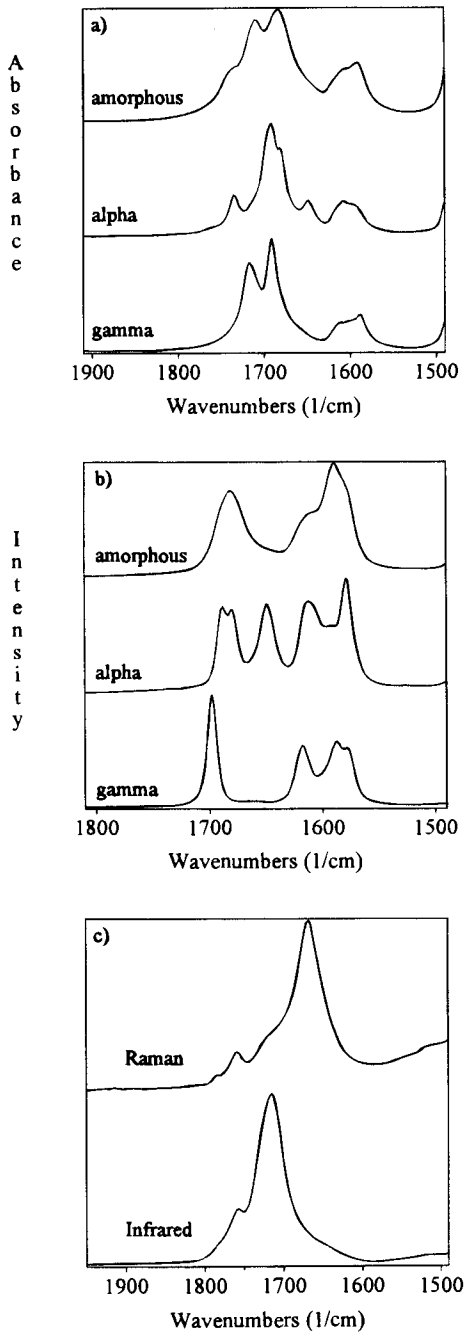



**Fig. 4.** a) IR and b) Raman spectra of γ-indomethacin, α-indomethacin and amorphous indomethacin showing the acid and benzoyl carbonyl vibrations, c) the carbonyl stretching region of acetic acid illustrating the asymmetric stretch observed in the IR spectrum and the symmetric stretch present in the FT-Raman spectrum.

indomethacin is longer than average (18) and this is attributed to the non-coplanarity of the carbonyl group with the indole ring which results from steric hindrance and strain in the molecule. This also prevents mesomerism. In the α and amorphous forms of indomethacin, the benzoyl vibration occurs at a lower wavenumber (see Table 1) suggesting that conformational restrictions may be reduced in these two forms and that the C=N bond has a greater double bond character. The vibrational changes observed on altering either the crystalline form or structural order of the material emphasise the need to characterise the structural form of the compound in the system of interest.

The acid carbonyl stretching vibration can provide important information about the hydrogen bonding between carboxylic acid groups. Carboxylic acids may hydrogen bond through (1) cyclic symmetric acid-acid dimers, (2) acid-acid catamers (chains) and (3) heterogenic associations involving other functional groups (23). The differences in these structures is reflected in their vibrational spectra. A cyclic dimer has a centre of symmetry and the mutual exclusion rule should be expected to hold (21). Thus the symmetric stretching motion produces no change in dipole moment and is Raman active, whilst the asymmetric stretching produces a change in dipole moment and is infrared active. There is a considerable energy difference between the two with the asymmetric vibration occurring at higher wavenumber than the symmetric vibration. A combination of infrared and Raman can thus be used to probe cyclic dimeric hydrogen bonding. If the infrared and Raman spectra of liquid acetic acid are compared (Figure 4c), the asymmetric carbonyl stretch can be seen at 1716 $cm^{-1}$ in the infrared spectrum and the symmetric stretch in the Raman spectrum at 1669 $cm^{-1}$.

The infrared spectrum (Figure 4a) of γ indomethacin shows a vibration at 1717 $cm^{-1}$ which has been previously assigned as acid carbonyl stretch (24). Since γ indomethacin is known, from single crystal data, to form cyclic dimers (18), this must correspond to the asymmetric stretch. However no

**Table 1.** Infrared and Raman Peak Positions and Assignments for the Carbonyl Stretching Region of Indomethacin, PVP and Acetic Acid

| Compound | Infrared ($cm^{-1}$) | Raman ($cm^{-1}$) | Assignment |
|---|---|---|---|
| γ-indomethacin | 1717 s | | asymmetric acid νC=O of a cyclic dimer |
| | 1692 s | 1698 s | benzoyl νC=O |
| α-indomethacin | 1735 w-m | | non-hydrogen bonded acid νC=O |
| | 1688 s | 1692 s | benzoyl νC=O |
| | 1681 sh | 1680 s | hydrogen bonded acid νC=O |
| | 1649 w | 1649 s | hydrogen bonded acid νC=O |
| amorphous indomethacin | 1735 sh | | non-hydrogen bonded acid νC=O |
| | 1710 s | | asymmetric acid νC=O of a cyclic dimer |
| | 1684 s | 1681 s | benzoyl νC=O |
| acetic acid | 1716 s | 1669 s | asymmetric νC=O (IR), symmetric νC=O (Raman) of a cyclic dimer |
| | 1759 sh | | non-hydrogen bonded νC=O |
| PVP | 1679 s | 1676 s | non-hydrogen bonded amide νC=O |

s = strong, m = medium, w = weak, sh = shoulder, ν = stretch

corresponding symmetric stretch is present in the Raman spectrum (Figure 4b). It is unlikely that this acid symmetric stretching vibration coincides with the benzoyl carbonyl vibration since the latter peak is highly symmetrical in shape. It appears that this peak is not active in the Raman spectrum and this has been observed previously for other carboxylic acids known to form cyclic dimers (25).

The spectra of α indomethacin is considerably more complex in this region. The infrared spectrum has a relatively weak vibration at 1735 $cm^{-1}$ previously assigned to C=O stretch (26). There are also two vibrations at 1680 and 1649 $cm^{-1}$ which coincide in the infrared and Raman spectra (Figures 4a and 4b) and are also assigned to C=O stretch. The coincidence of these vibrations in the Raman and infrared spectra indicate that hydrogen bonding patterns other than cyclic dimer formation are present. The most likely alternative pattern of hydrogen bonding would be the formation of chains of molecules interacting through the acid moiety (27). This type of structure would be consistent with the unit cell parameters for α indomethacin, calculated from the powder diffraction pattern obtained using synchrotron radiation, the dimensions of which would require a configuration of a trimeric repeat unit which is stackable in one crystallographic direction such that there are 6 molecules in the unit cell (28). Since these chains would be finite in length, the end molecule would have a non-hydrogen bonded carbonyl group which could account for the weak peak at 1735 $cm^{-1}$; free carbonyl is known to occur at higher wavenumbers (29). Further interpretation is hampered by the lack of single crystal data available for this polymorph but, hydrogen bond patterns in the α form appear to be more complex than in the γ form.

From Figures 4a and 4b it can be seen that the amorphous phase gives rise to infrared and Raman spectra similar to those observed for the γ form, with an asymmetric acid carbonyl peak in the infrared at 1710 $cm^{-1}$ and the corresponding symmetric stretch absent in the Raman spectrum. This suggests that the acid carbonyl is similarly hydrogen bonded as cyclic dimers in the amorphous phase as in the γ polymorph. However the amorphous vibrational peak also has a shoulder at 1735 $cm^{-1}$ which is absent in the γ form. Examination of the infrared spectrum of acetic acid reveals a similar band shape. The structure of liquid acetic acid has been extensively studied using vibrational spectroscopy and is considered to be composed mainly of cyclic dimers with other hydrogen bonded species and monomers also present. The shoulder present in the infrared spectrum at 1758 $cm^{-1}$ has been assigned to the non-hydrogen bonded carbonyl stretch of an end group of a chain of hydrogen bonded acetic acid molecules (30). It is reasonable, therefore, to suppose that amorphous indomethacin, which below Tg may be considered as a non-equilibrium supercooled liquid, likewise consists mainly of cyclic dimers with a small proportion of molecules hydrogen bonded to form a chain. The vibration at 1735 $cm^{-1}$ is therefore assigned to the non-hydrogen bonded

carbonyl stretch of an end molecule of such a chain. Further support is provided by the observation that this vibration occurs at the same wavenumber as the peak in the infrared spectrum of α indomethacin likewise assigned to the carbonyl stretch of a chain end group.

The 150–50 $cm^{-1}$ region of the Raman spectrum (Figure 2) contains peaks arising from lattice vibrations corresponding to librations and translations of the entire molecule in the lattice. The lattice vibrations are characteristic of the crystal structure and are sensitive to local order or disorder. Whilst γ indomethacin has sharp, well resolved peaks in this region indicating crystalline order, both amorphous and α indomethacin have broad peaks indicating more disordered structures (20). Since the γ form is the stable polymorph of the monotropic system, it should be more ordered than the α form (31), and the amorphous material by definition should show no long range order. It is interesting that spectral similarities are seen between the α and the amorphous forms in the aryl CH stretching and lattice vibration region, but that the hydrogen bonding of the carboxylic acid group is similar in the amorphous phase to that of the more ordered γ crystal.

## Influence of PVP on Indomethacin Structure in Solid Dispersions

Indomethacin and PVP solid dispersions show no x-ray diffraction peaks over the entire concentration range indicating that indomethacin is present as the amorphous form; PVP is an inherently amorphous polymer. Thus in probing interactions between PVP and indomethacin, spectra of amorphous indomethacin will be used as the reference state in conjunction with physical mixes prepared from amorphous indomethacin and PVP.

Consideration of the structures of PVP and indomethacin (Figure 3) illustrates that PVP can only act as a proton acceptor (through either the O or N atoms of the pyrrole ring) and indomethacin has only one proton donor site, the OH group of the carboxyl acid function. A change in the hydrogen bonding of indomethacin should thus be apparent in the acid carbonyl stretching vibration whilst hydrogen bonds formed between PVP and indomethacin should be reflected by shifts in either the PVP carbonyl or C–N vibrations, depending on the site of interaction. The carbonyl group of PVP is considered the most favourable site for interactions due to steric constraints on the nitrogen (32).

No changes in the PVP C–N stretch were observed in either the infrared or Raman spectra when dispersed with indomethacin, whilst changes were seen in the carbonyl stretching vibrations. Figure 5 shows infrared spectra of the carbonyl region for indomethacin, PVP and solid dispersions containing between 5 and 70% PVP. Physical mixes of amorphous indomethacin and PVP over the same composition range are also shown in Figure 5. Clearly, the spectra of the solid dispersions are different from those of physical mixes of the same composition. The PVP carbonyl occurs over the same wavenumber range as the indomethacin benzoyl group and changes are seen in this region. Additionally the acid carbonyl (which is also influenced, although to a lesser degree, by the PVP absorption) shows changes in the presence of PVP.

In order to aid in the interpretation of these spectral changes, model systems were studied. Acetic acid was chosen

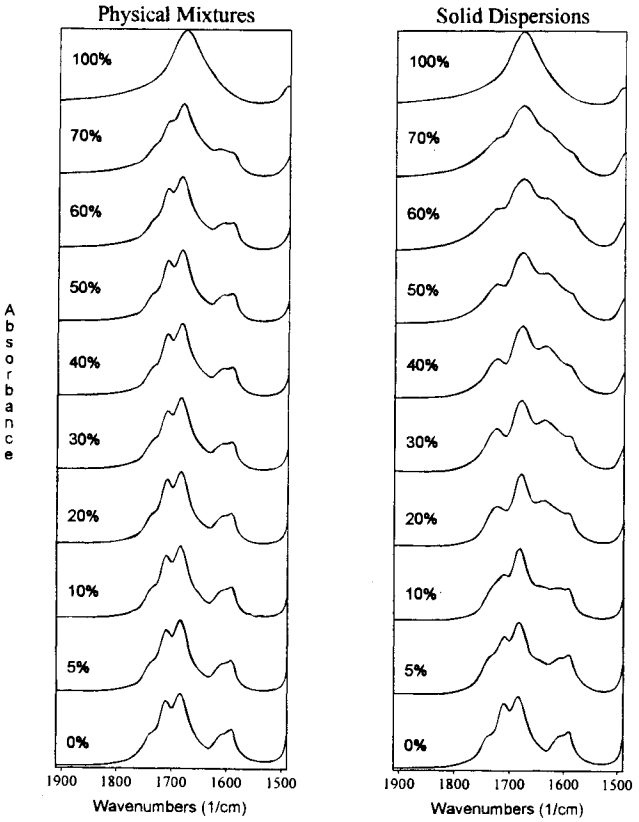



**Fig. 5.** IR spectra of the carbonyl stretching region comparing solid dispersions of indomethacin and PVP with physical mixes of corresponding composition. 0% corresponds to amorphous indomethacin whilst 100% represents pure PVP, intermediate percentages refer to the weight percentage of PVP present.

as a model of the indomethacin carboxylic acid group and methylpyrrolidone (Figure 3) as a model for PVP. Figure 6a shows infrared spectra of mixtures of acetic acid and methylpyrrolidone. For this system there are two intense carbonyl peaks, one arising from the carboxylic acid group of acetic acid at 1716 $cm^{-1}$ and the other from the amide of methylpyrrolidone at 1688 $cm^{-1}$. As the methylpyrrolidone concentration increases, the shoulder of the acetic acid carbonyl stretch at 1759 $cm^{-1}$, assigned to non-hydrogen bonded carbonyl, increases in intensity relative to the main cyclic dimer peak. The methylpyrrolidone carbonyl is intially seen in the mixture at 1652 $cm^{-1}$ which is 36 $cm^{-1}$ lower than that of the carbonyl stretch for pure methylpyrrolidone. This can be accounted for by the formation of hydrogen bonds between acetic acid and methylypyrrolidone which are not possible in pure methylpyrrolidone due to the absence of proton donors. As the concentration of methylpyrrolidone increases further, a second peak occurring at the same wavenumber as the pure material becomes evident at 1688 $cm^{-1}$. It appears that the addition of methylpyrrolidone disrupts the acetic acid carboxylic acid dimers by forming hydrogen bonds with the hydroxyl group of the acid. This results in an increase in non-hydrogen bonded acid carbonyl which has a higher frequency of vibration than the hydrogen bonded dimer carbonyl. Hydrogen bonding causes the methylpyrrolidone carbonyl to appear at a lower wavenumber. At some ratio of methylpyrrolidone to acetic acid (between 30 and 40%),

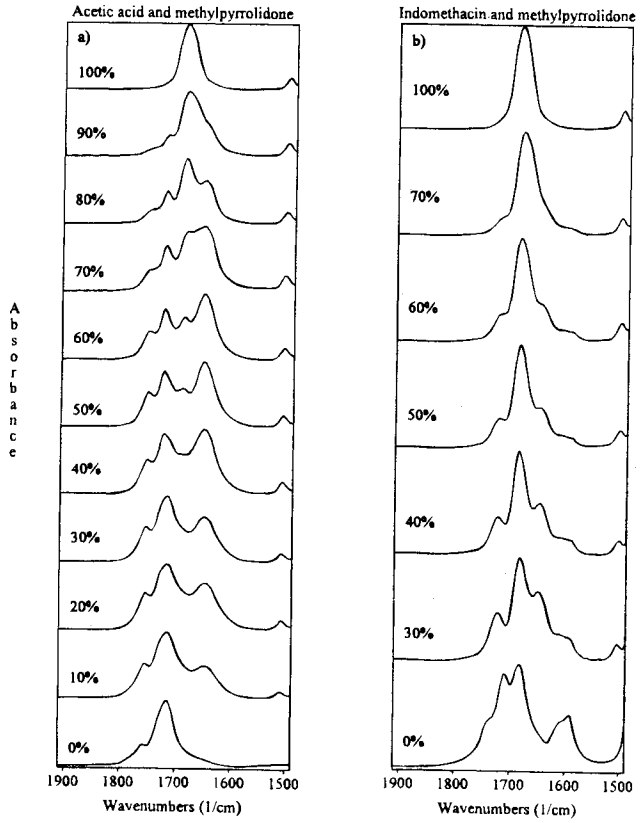



**Fig. 6.** a) IR spectra of the carbonyl stretching region of acetic acid (0%), methylpyrrolidone (100%) and various weight percentages of the two liquids. The percentages refer to the amount of methylpyrrolidone present, b) IR spectra of the carbonyl stretching region of solid amorphous indomethacin (0%), methylpyrrolidone (100%) and of various weight percentages of indomethacin dissolved in methylpyrrolidone. The percentages refer to the amount of methylpyrrolidone present.

the hydrogen bonding of methylpyrrolidone is saturated and non-hydrogen bonded carbonyl is also observed. Thus at certain acetic acid-methylpyrrolidone ratios, three species are present, hydrogen bonded methylpyrrolidone-acetic acid, dimeric acetic acid, and non-hydrogen bonded methylpyrrolidone.

Figure 6b shows infrared spectra of indomethacin dissolved in methylpyrrolidone. The indomethacin acid carbonyl is affected by the addition of the methylpyrrolidone with the peak at 1710 $cm^{-1}$ disappearing and the shoulder at 1735 $cm^{-1}$ developing into a single peak at 1723 $cm^{-1}$. At low methylpyrrolidone concentrations, a hydrogen-bonded methylpyrrolidone carbonyl peak is seen at 1649 $cm^{-1}$. The non-hydrogen bonded methylpyrrolidone carbonyl vibration coincides with that of the indomethacin benzoyl carbonyl making it difficult to study. However, the intensity of this peak increases with methylpyrrolidone concentration relative to the peak at 1649 $cm^{-1}$ even though the contribution from the indomethacin benzoyl carbonyl is decreased due to a dilution effect, suggesting that a population of non-hydrogen bonded methylpyrrolidone is also present at higher methylpyrrolidone concentration. The saturation of hydrogen bonding as the number of proton acceptors increases relative to the number of proton donors is comparable to that seen for the acetic acid-methylpyrrolidone system and the existence of analogous species can be postulated. Interestingly methylpyrrolidone has a similar magnitude of effect on the spectrum of indomethacin as does PVP.

The changes occurring in the indomethacin-PVP solid dispersion systems (Figure 5) are qualitatively similar to those observed in the two model liquid solvent systems and therefore observations made for the model liquid systems are used to interpret the results for the solid indomethacin-PVP dispersions. The cyclic dimer carbonyl peak decreases in intensity concomitant with an increase in non-hydrogen bonded carbonyl peak intensity between 5 and 20% PVP. At 20% PVP and above, a single broad peak at 1726 $cm^{-1}$ is present which develops into a shoulder as the concentration of indomethacin decreases further and the absorbance of the PVP carbonyl dominates the spectrum. This peak at 1726 $cm^{-1}$ is assigned to the non-hydrogen bonded carbonyl stretch of the acid group of an indomethacin molecule which is hydrogen bonded through the hydroxyl group to a PVP molecule. The peak at 1636 $cm^{-1}$, absent in the physical mixes, is present in solid dispersions containing 5–50% PVP and is assigned to hydrogen bonded PVP carbonyl. As the concentration of PVP increases further this peak merges with the non-hydrogen bonded carbonyl peak and is apparent only as shoulder (60–70%). The overall result is a considerably broader band relative to the physical mix.

In the FT-Raman spectra (data not shown), the acid carbonyl peak is not seen and the PVP carbonyl is again coincident with the benzoyl carbonyl. As the concentration of PVP is increased, spectra of the solid dispersions show a progressive decrease in the peak frequency and peak broadening relative to physical mixes. These results are consistent with the infrared data and the proposed hydrogen bonding of the PVP carbonyl.

## DISCUSSION

Spectral data support the fact that indomethacin forms hydrogen bonds with PVP at the expense of dimer formation. The more basic nature of the PVP amide group compared with the carboxylic acid group (33) would explain this ability of PVP to disrupt hydrogen bonding between dimers. Converting weight fractions to mole fractions, using a molecular weight of 111 to represent a PVP monomer unit, it is calculated that a 1:1 mole ratio of PVP monomer to indomethacin is present at 24% weight fraction PVP. Since the carbonyl group of PVP can potentially form 2 hydrogen bonds, in the absence of steric constraints, sufficient PVP is present at a weight fraction of 12% to hydrogen bond with all the indomethacin molecules. This is clearly not the case since spectral changes occur at PVP concentrations in excess of both this value and that calculated for a 1:1 ratio. This suggests that the equilibrium constant for the formation of PVP-indomethacin species is low and/or the stoichiometry is less than 1:1. Thus at low PVP concentrations, indomethacin is present as a combination of dimers and PVP-indomethacin species, whilst a fraction of non-hydrogen bonded PVP also exists (Figure 7). As the concentration is increased further and the PVP acceptor groups become far in excess of indomethacin donor groups, the quantity of non-hydrogen bonded PVP increases. At this point indomethacin dimers may still be present depending on the indomethacin-PVP equilibrium constant. The species present are shown in Figure 7 and the ratios will obviously vary with the concentration of PVP in the solid dispersion.

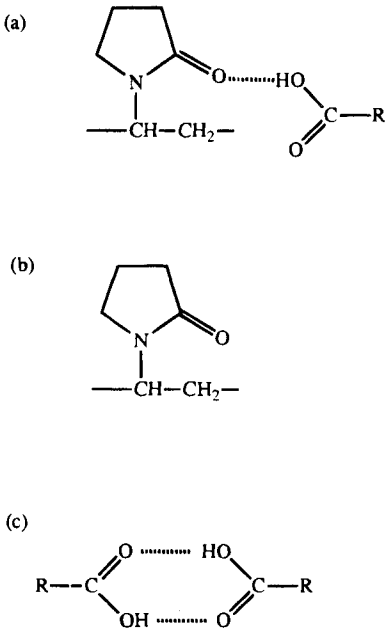



**Fig. 7.** Species proposed to be present in indomethacin-PVP solid dispersions. a) hydrogen bonded indomethacin-PVP species, b) non-hydrogen bonded PVP and c) indomethacin symmetric dimer.

Although several species are present, this in no way indicates that more than one phase is present. Rather it indicates that indomethacin and PVP are able to interact to some extent at a molecular level and that more than one species consequently exist. However, the distribution of these species is such that a single phase is formed. This picture is supported by two pieces of evidence. Previous studies have shown that PVP and indomethacin solid dispersions exhibit a single glass transition temperature over all composition ranges (7), which is generally considered indicative of a single phase (34). Secondly, the indomethacin-PVP solid dispersion system and the indomethacin-methylpyrrolidone liquid system are very similar, both in terms of the magnitude of interaction, the nature of the interactions and the species present. This does not preclude the possibility that the mixing of the components is non-ideal, or that in forming the glassy phase concentration fluctuations which occur in solution are frozen in. However the description of a glass as a non-equilibrium supercooled liquid seems to be reasonable for the system under investigation where two components mix and interact at the molecular level in a manner to be considered as consisting of "solvent" and "solute" molecules able to form both homo and hetero associations. This is consistent with the previously proposed idea that PVP is able to molecularly disperse a variety of compounds and that higher dispersibility is possible with those compounds capable of forming hydrogen bonds with PVP (35).

The formation of hydrogen bonds between indomethacin and PVP has two consequences; an indomethacin dimer is broken and the proton donating group, which is critical for dimer formation, is engaged in hydrogen bond formation with a different molecule. The implications of the interaction between PVP and indomethacin on crystallisation to the γ polymorph are immediately apparent since this crystal form consists of dimers. The formation of a critical nucleus of indomethacin would require the breaking of the PVP-indomethacin hydrogen bond to allow the indomethacin molecules to both form dimers and order with the other indomethacin molecules into the required spatial orientation. Although the single crystal structure of α indomethacin is unknown, the spectroscopic data gathered in this study indicates that hydrogen bonding also occurs between the carboxylic acid groups in some pattern other than dimers, probably chains. It would thus also be anticipated that hydrogen bonding with PVP would likewise inhibit crystallisation to the α form for the reasons discussed above.

## SUMMARY

The nature of the hydrogen bonding in α and amorphous indomethacin has been investigated using a combination of IR and FT-Raman spectroscopy and compared to that of the γ form, known from single crystal data. The α indomethacin form is postulated to exist as chains formed by hydrogen bonds between carboxylic acid groups. Amorphous indomethacin is considered to be composed mainly of carboxylic acid dimers as in the γ polymorph, with a small proportion of molecules hydrogen bonded to form chains.

The addition of PVP to amorphous indomethacin to form a miscible binary amorphous phase, results in the disruption of the indomethacin dimers. This is brought about by a hydrogen bond formed between the PVP amide carbonyl and the indomethacin carboxylic acid hydroxyl. No such interactions were observed in physical mixes of amorphous indomethacin with PVP. The magnitude and type of interactions formed between indomethacin and PVP in a solid dispersion were found to be similar to those formed in a solution of indomethacin and methylpyrrolidone, emphasizing the "solution" nature of this system, at least in terms of molecular interactions if not kinetics.

The formation of a hydrogen bond between indomethacin and PVP offers an explanation as to how PVP is able to inhibit crystallisation from the amorphous phase at levels where the antiplasticising effect is minimal.

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