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Spectroscopy of polymer/drug formulations processed with supercritical fluids: in situ ATR–IR and Raman study of impregnation of ibuprofen into PVP

S.G. Kazarian *, G.G. Martirosyan

Department of Chemical Engineering and Chemical Technology, Imperial College of Science, Technology and Medicine, Prince Consort Road, London SW 7 2BY, UK

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Abstract

In situ ATR (attenuated total reflectance)–IR spectroscopy has been used to study poly(vinylpyrrolidone) (PVP) films subjected to a solution of ibuprofen in supercritical CO_2. The process of impregnation of ibuprofen into PVP has been monitored in situ. It has been shown that the supercritical fluid impregnation process results in ibuprofen being molecularly dispersed in a polymer matrix with ibuprofen molecules interacting with the C=O group of PVP. Raman spectra of ibuprofen impregnated into PVP from supercritical fluid solution have also been measured and compared with the Raman spectra of crystalline ibuprofen. ATR–IR spectroscopy has also revealed specific interactions between the C=O groups of PVP and CO_2. Impregnation of ibuprofen into PVP makes the C=O groups of PVP less available for interactions with CO_2. It has also been demonstrated that the presence of ibuprofen in PVP also affects sorption of water into PVP.

Keywords: Infrared spectroscopy; Raman; Poly(vinylpyrrolidone); Carbon dioxide; Specific interactions; Hydrogen bonding

1. Introduction

Supercritical fluid technology has already proved its applicability to the area of preparation of pharmaceutical formulations. This includes particles formation via antisolvent precipitation, aerosolisation and rapid expansion of supercritical fluid solutions (Alessi et al., 1996; Benedetti et al., 1997; Kerc et al., 1999; Tom and Debenedetti, 1991; Yeo et al., 1993). Opportunities provided by supercritical fluid processes were explored for purification of proteins (Knutson et al., 1996; Yeo et al., 1993), preparation of liposomes encapsulating water-soluble compounds (Frederiksen et al., 1997), novel preparation of submicron particles of drugs (Young et al., 2000) and impregnation of biocompatible polymers with drug molecules (Kikic, 2000). The impact of the morphological properties of biodegradable polymer particles prepared with the aerosol solvent extraction system using supercritical (sc) CO_2 on drug content and release has been demonstrated re-

* Corresponding author. Tel.: +44-207-594-5574; fax: +44-207-594-5604.

E-mail address: s.kazarian@ic.ac.uk (S.G. Kazarian).

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cently (Charoenchaitrakool et al., 2000). $ScCO_2$ has also been applied to the foaming of biodegradable polymers in the preparation of scaffolds for tissue engineering (Sheridan et al., 2000).

A growing interest in these applications is due to the intrinsic advantages of supercritical fluids, primarily of $scCO_2$, compared with conventional methods of processing. Indeed, we have already demonstrated that the effect of $scCO_2$ on glassy polymers mimics the effect of heat inducing mobility of polymer chains and segments (Kazarian, 2000a; Kazarian et al., 1997). Conventional processes require heating of polymers to increase their mobility and to enhance mass transport properties. Due to the plasticising effect, $scCO_2$-assisted polymer processing of polymer/drug formulations becomes possible at lower temperatures. This is especially important for processing thermo-labile drug molecules. Such processing may include extraction and impregnation, extrusion and polymer modification. An additional advantage is that the process with $scCO_2$ does not leave residual solvent in the processed polymer/drug formulation since CO_2 is a gas under ambient conditions, and once the process is complete CO_2 leaves the sample. A preliminary report on impregnation of PVP with ketoprofen, nimesulide and piroxicam has discussed the effects of pressure and temperature on the preparation of polymer/drug formulations (Kikic, 2000). Unfortunately, the molecular state of drugs in a polymer matrix prepared by this method has not been studied. The molecular state of the drug within a polymer matrix determines its dissolution rate, and thus needs to be evaluated and compared with the molecular state of the drug in polymer formulations prepared using traditional methods.

Conventional methods for the preparation of solid dispersions of polymer/drug formulations include solvent evaporation, melt extrusion and mechanical treatment of the mixtures. One of the objectives of the preparation of solid dispersions is to enhance drug dissolution rates via dispersion of the drug within water-soluble polymer matrices. This is important because solid crystallised drugs often have a very low solubility in water. Thus, crystallisation of drugs embedded in a polymer matrix should be avoided due to its impact on the dissolution rate and consequently the therapeutic value of such products. Challenges and opportunities in the preparation of solid dispersions of poorly water-soluble drugs have recently been discussed in some detail (Serajuddin, 1999). Examples of preparation and spectroscopic studies of solid dispersions include ibuprofen–poly(ethyleneglycol) (Breienbach et al., 1999; Subramaniam et al., 1997), ibuprofen–PVP (Forster et al., 2001; Sekizaki et al., 1995), oxazepam–PEG (Forster et al., 2001), piroxicamin–PVP (Tantishaiyakul et al., 1999), hydrocortisone acetate–PVP (Raghavan et al., 2001), indomethacin–PVP (Taylor and Zografi, 1997), nifedipine–PVP (Forster et al., 2001).

Supercritical fluid impregnation offers a number of advantages in polymer/drug preparation routes by avoiding the use of organic solvents and heat (Berens et al., 1992). It is important to distinguish two different mechanisms in such impregnation processes. The first involves deposition of a substance soluble in supercritical fluid into the polymer matrix upon depressurising the cell containing supercritical fluid solution. In this case, even a solute that has low affinity to the polymer matrix can be trapped within a polymer matrix. However, this approach often results in the formation of re-crystallised substances within the polymer matrix without formation of the molecularly dispersed formulation. Another mechanism utilises the high affinity of the substance dissolved in supercritical fluid solution for certain polymer matrices. This could result in a high partition coefficient of solute between the polymer and fluid phases. In addition, specific interactions between solute and matrix prevent self-association of solutes and result in molecularly dispersed solute within a polymer matrix. The second mechanism, based on the affinity of a solute to the polymer matrix, has tremendous potential for supercritical fluid impregnation of drug molecules into polymers, and is explored in this work via in situ ATR (attenuated total reflectance)–IR spectroscopy.

Our related studies on supercritical fluid dyeing have demonstrated that the successful incorporation of dye molecules into polymeric matrices can

be effective even if the solubility of the dye in $scCO_2$ solution is low because of the high partition coefficient for a dye between the polymer and $scCO_2$ phases (Kazarian et al., 1999). The high partition coefficients are based on the affinity of dye molecules to the polymer matrix, e.g. due to H-bonding. Thus, FTIR spectroscopy of Disperse Red 1 dye impregnated into poly(methyl methacrylate) film has revealed H-bonding between the dye and the carbonyl groups of the polymer. It is believed that these interactions are responsible for the high partition coefficient of dye between polymer and a fluid (Kazarian et al., 1997). The principles of supercritical fluid dyeing and impregnation of drugs into polymers are, in fact, similar. The important difference in the products of supercritical dyeing and polymer/drug formulations prepared with $scCO_2$ is that the former needs to retain an impregnated substance while the latter is designed for drug release via dissolution.

The specific questions of interest for controlled drug release, which motivated our work on spectroscopy of polymer/drug formulations processed with supercritical CO_2, are:

- What is the molecular state of the drug within the polymer matrix?
- How does the drug interact with the polymer matrix?
- How does the presence of the drug affect interactions between CO_2 and polymer, and between water and polymer?

To answer these questions we applied ATR–IR spectroscopy in a novel manner that allowed us to study the process of impregnation of ibuprofen into PVP from $scCO_2$ solution. ATR–IR was used in a recent study (without supercritical fluids) to measure the interaction between the ester group of poly(L-lactic acid) and the hydroxyl group of starch in an attempt to elucidate the mechanism of conventional preparation of biodegradable polymer blends (Park et al., 1999). ATR–IR spectroscopy has also been applied to measure dissolution rates and drug release in polymer/drug formulations (Hanh et al., 2000). The ATR–IR method, utilising a 'Golden Gate' (Specac Ltd.) accessory with a heated diamond ATR element, has been used to study H-bonding interactions between drug and polymer that explain the anti-nucleating properties of the polymer. Formulations of indomethacin and nifedipine with PVP obtained by *melt extrusion* have been analysed via ATR–IR spectroscopy, and H-bonding between drug molecules and polymer has been proposed, and its implications on the stability of these glass solutions have been discussed (Forster et al., 2001). The IR spectroscopy has been used in transmission mode to study ibuprofen–PEG solid dispersions prepared via *mechanical mixing* (Shakhtshneider et al., 1996). It has been suggested that weak interactions between ibuprofen and PEG lead to the formation of the amorphous product. The formation of H-bonding between indomethacin and PVP prepared via *solvent evaporation* method has also been studied via IR transmission and FT–Raman spectroscopy, and it has been inferred that indomethacin forms hydrogen bonds with PVP at the expense of the formation of a dimer of the indomethacin in its crystalline form (Taylor and Zografi, 1997). An additional advantage of IR spectroscopy has been utilised in that work to analyse various polymorphs of the drug. In this work *supercritical fluid impregnation* of PVP with ibuprofen has been studied using in situ ATR–IR and Raman spectroscopy.

2. Experimental

2.1. Materials and methods

Ibuprofen has been supplied by Whitehall International. Polyvinylpyrrolidone (PVP k30) with an average molecular weight Mw = 40,000 and polydispersity of 2.9 has been purchased from Sigma. The molecular structures of ibuprofen and

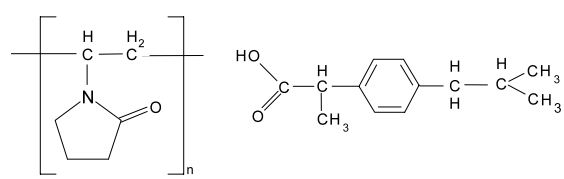


Fig. 1. Schematic presentation of the molecular structures of PVP (left) and Ibuprofen (right).

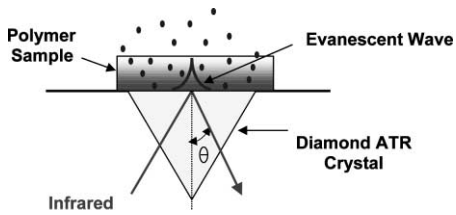


Fig. 2. Schematic presentation of the in situ ATR–IR experiment with the polymer sample (PVP) placed on the top of the diamond ATR crystal and subjected to supercritical CO_2. The evanescent wave does not probe the solution in $scCO_2$ but only the polymer film.

PVP are presented in Fig. 1. Carbon dioxide has been supplied by BOC (Guildford, UK) and has been carefully dried prior use.

An Equinox 55 spectrometer (Bruker, Germany) with an MCT detector was used to measure FTIR spectra; the resolution was 2 cm^{-1}. Raman spectra were collected using a Kaiser Holoprobe system using a fiber coupled, holographic filtered probehead. The laser power at the sample was ca. 27 mW at 785 nm from an attenuated Kaiser Invictus diode laser. A high-pressure, high temperature, low volume accessory has been developed to analyse ATR–IR spectra of supercritical fluids and polymers subjected to supercritical fluids. This accessory is based on the modified Golden Gate ATR accessory (Specac Ltd., Orpington, UK) that utilises a diamond as the ATR crystal. The optical configuration that focuses light on the crystal includes the use of KRS-5 lenses. The Golden Gate ATR accessory uses a single diamond crystal metal bonded at high-temperatures into a disk of tungsten carbide. The interface between diamond and tungsten carbide is leak-proof for liquids or gases at high pressures. A stainless steel high-pressure flow cell is placed on the top of the tungsten carbide disk and pressed to it using a clamp. This accessory has already been used to measure spectra of supercritical CO_2 and high-pressure ethane (Kazarian et al., 2001), to study ionic liquids under high-pressure CO_2 (Kazarian et al., 2000b) and to measure polymer sorption and swelling.

The film of PVP was cast from an ethanol solution on the surface of the diamond ATR crystal as shown in Fig. 2. The cast film of PVP was then heated in vacuum at temperatures of 100 °C for period of 1 h to remove the residual ethanol. Then the high-pressure cell is used to cover the diamond, and the polymer is subjected to high-pressure gas. The IR bands of the polymer provide information on the behaviour of the polymer matrix under high-pressure gas or fluid. At the same time, the absorbance of the IR bands of the gas sorbed into the polymer gives an estimate of gas sorption into the polymer. Most importantly, in the current context, monitoring of the impregnation of a solute dissolved in a fluid into polymer is possible following the observation of the IR absorbance bands of a solute being impregnated into polymer. Fortunately, this ATR–IR method eliminates absorbance due to fluid solution (as shown in Fig. 2) and consequently of the solutes dissolved in the fluid since the evanescent wave does not penetrate beyond the polymer film (with the thickness of the film ca. 10 μm). It would not be possible to eliminate the absorbance of the CO_2 fluid surrounding the polymer film and the corresponding absorbance due to the solute dissolved in CO_2 using transmission cells. Transmission IR spectroscopy has been used to study supercritical fluid impregnation of organometallic molecules into polyethylene films (Cooper et al., 1993; Poliakoff et al., 1995). The in situ ATR–IR spectroscopic approach used in the current work provides a way of measuring the spectrum of the polymer film subjected to a $scCO_2$ solution without interfering with the spectrum of the solution itself.

3. Results and discussion

The solubility of high-pressure CO_2 in polymer should be relatively high in order to make supercritical fluid impregnation possible. Therefore, first we studied the spectra of PVP film subjected to $scCO_2$ as it has not been previously reported. The PVP film was cast on the diamond from the solution of PVP in ethanol; ethanol was then removed by heating in vacuum at 70 °C. Fig. 3 shows spectrum of PVP subjected to $scCO_2$, the bands marked with asterisks show bands of CO_2 sorbed into PVP. The sorption of CO_2 into PVP

can be calculated based on the absorbance of the v_3 band of CO_2. Since the effective pathlength for the v_3 band is ca. 1.5 μm (with a diamond ATR crystal and the incident angle of 45°), the calculation of the CO_2 concentration becomes relatively straightforward using the data for the molar absorptivity of this band from the literature. Thus, we estimate that the solubility of CO_2 in PVP at a temperature of 40 °C and pressure of 100 bar is ca. 100 cc (at STP) g^{-1} polymer which is consistent with data on CO_2 sorption into other glassy polymers and gravimetric studies of CO_2 sorption into PVP (Kikic et al., 1999). Careful investigation of the IR spectrum in the bending mode region shows that the IR band of CO_2 at ca. 660 cm^{-1} corresponding to the bending mode of CO_2 is split into a doublet. Previously, we have shown that such splitting provides evidence for a weak interaction between CO_2 and basic sites in the polymers (Kazarian et al., 1996) which has also been supported by ab initio calculations. By analogy with our previous studies we suggest that the interaction between CO_2 and PVP occurs via Lewis acid–base interaction between CO_2 molecules and carbonyl groups in PVP. The study on interactions between PVP and ibuprofen provides additional, yet unusual, support for this assignment for interactions between CO_2 and the carbonyl groups of PVP, and will be discussed later in this paper.

Fig. 4 shows the IR spectral region of PVP film subjected to a solution of ibuprofen in $scCO_2$. The

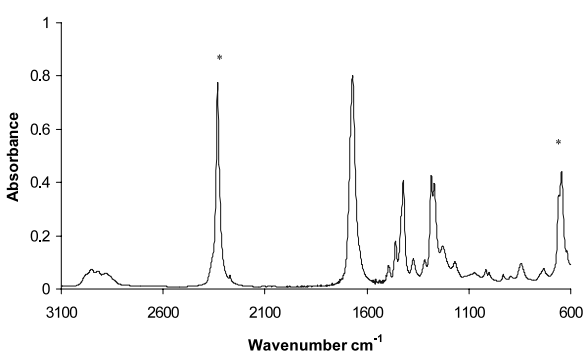


Fig. 3. ATR–IR spectrum of PVP subjected to $scCO_2$ (100 bar, 40 °C). Bands marked with an asterisk are bands of CO_2 in PVP.

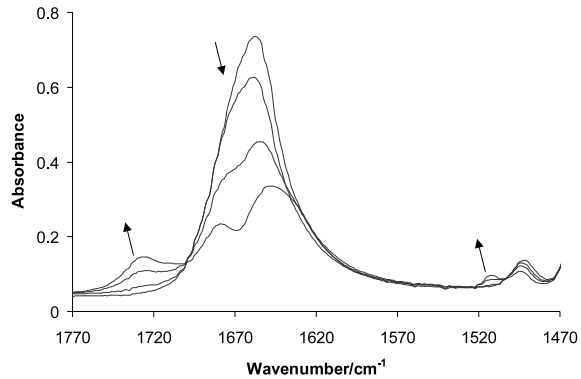


Fig. 4. In situ ATR–IR spectra of PVP subjected to a solution of ibuprofen in $scCO_2$ with time. The bands of ibuprofen increase in absorbance while the bands of PVP decrease in absorbance.

solubility of ibuprofen in $scCO_2$ was measured (Charoenchaitrakool, et al., 2000) and found to be in the range from 10^{-5} to 10^{-3} mole fraction (in the pressure range of CO_2 from 80 to 220 bar, and temperatures 35–45 °C). Concentration of ibuprofen in $scCO_2$ in our experiment was ca. 10^{-3} mole fraction. The spectra show an increase in the absorbance of the bands corresponding to the ibuprofen with time due to diffusion of ibuprofen into PVP. The concentration of ibuprofen in PVP was ca. 30 wt.% once the impregnation was complete. The spectra also show the decrease in the corresponding bands of PVP apparently due to swelling of the polymer matrix (since swelling would result in less amount of polymer probed by evanescent wave in this ATR–IR experiment). Another notable change in the spectra appears in the ν(C=O) region of PVP with the appearance and rise of a new band at 1636 cm^{-1} shifted to the lower wavenumbers compared to the ν(C=O) band of virgin PVP at 1652 cm^{-1} (Fig. 4). We assign this band to the ν(C=O) of the carbonyl group of PVP that are H-bonded with the O–H group of the ibuprofen, this will be discussed in more detail below.

The important implication of the in situ spectroscopic monitoring of supercritical fluid impregnation is that the amount of the impregnated drug can be controlled, and the process can be instantly stopped by depressurising the high-pressure cell

once the desired level of the impregnated drug is achieved. In addition, the process of impregnation that depends on the drug diffusion rate can be easily 'tuned' by the pressure of the supercritical fluid solution which influences the sorption and polymer swelling (Vincent et al., 1997).

The changes in the ν(C=O) spectral region are very important for the elucidation of the molecular state of the drug. Thus, Fig. 5 compares the spectrum of the virgin PVP film with the spectrum of PVP impregnated with ibuprofen, as well as the spectrum of solid crystalline ibuprofen in the ν(C=O) spectral region. The ν(C=O) of ibuprofen impregnated into PVP at 1727 cm^{-1} is shifted to the high-wavenumber region compared to the corresponding band of solid ibuprofen (at 1710 cm^{-1}). This indicates the breakage of the ibuprofen–ibuprofen interactions that are characteristic of the solid form of this drug once the ibuprofen molecules are impregnated into PVP from supercritical CO_2 solution. Similar observation of the ν(C=O) band of ibuprofen shifted to the high-wavenumber region compared to the band of the crystalline ibuprofen have been reported for solid dispersions prepared via conventional routes (Shakhtshneider et al., 1996). It is important to emphasise, however, that supercritical fluid impregnation results, as shown in Fig. 5, in the absence of the band characteristic of the solid crystalline form, unlike formulations prepared via conventional routes where some amount of the

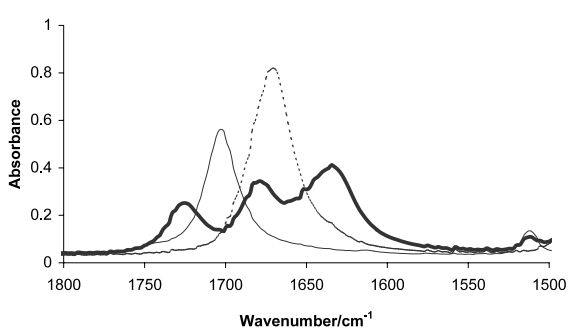
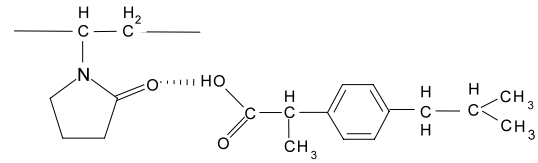


Fig. 5. ATR–IR spectra in the ν(C=O) spectral region. The thin line shows the spectrum of solid ibuprofen; the dashed line shows the spectrum of PVP film, the thick line shows the spectrum of PVP with impregnated ibuprofen from $scCO_2$ solution.



Scheme 1.

crystalline drug was still present. This observation indicates that the state of ibuprofen in PVP is molecularly dispersed without the presence of the crystalline formations of ibuprofen (which has the ν(C=O) band at 1710 cm^{-1}). Close inspection of the ν(C=O) band region of PVP provides further information on the molecular state of ibuprofen in PVP. Indeed, Fig. 5 shows that the ν(C=O) band of the molecularly dispersed ibuprofen is accompanied by the appearance of the ν(C=O) band of PVP at 1636 cm^{-1} shifted to the lower wavenumber compared to the ν(C=O) band of virgin PVP at 1682 cm^{-1}. We assign the band at 1636 cm^{-1} to the H-bonded carbonyl group of PVP with the O–H group of ibuprofen as presented in Scheme 1.

Interaction of the proton donors with the carbonyl oxygen via H-bonding is known to decrease the frequency of the ν(C=O) mode due to the weakening of the C=O bond. The fact that simultaneous growth of the ν(C=O) band of ibuprofen shifted to high-wavenumbers and the ν(C=O) band of PVP shifted to lower wavenumbers provides strong evidence that ibuprofen impregnated into PVP is H- bonded to PVP rather than being self-associated. The presence of H-bonding between PVP and ibuprofen has been suggested, based on the C^{13}-NMR spectra of this system that was obtained by conventional routes (Sekizaki et al., 1995). However, the IR spectra in that work did not provide evidence of the absence of the ν(C=O) band of ibuprofen at 1710 cm^{-1} corresponding to the ν(C=O) band of crystallites of ibuprofen. The supercritical fluid impregnation of ibuprofen into PVP results in a solid dispersion where essentially all drug molecules are H-bonded to the polymer as shown in Scheme 1. This interaction inhibits crystallisation of the drug within the polymer and results in a formulation that is suitable for drug delivery devices. Concentration

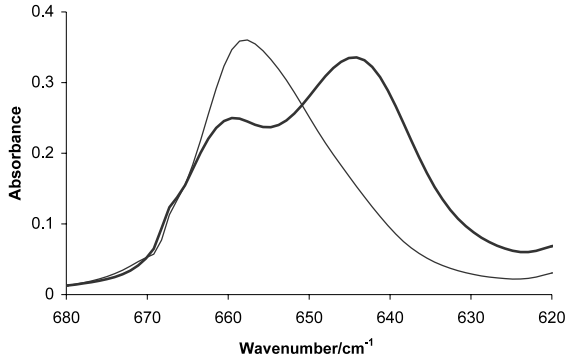
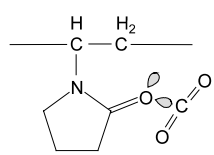


Fig. 6. ATR–IR spectra of CO_2 in the bending v_2 mode region at a pressure of 100 bar and a temperature of 40 °C. The thick line shows the v_2 band of CO_2 in PVP; the thin line shows the v_2 band of CO_2 in PVP that has been impregnated with ibuprofen. Note that the splitting of the v_2 band of CO_2 essentially disappears once the ibuprofen is impregnated.

of ibuprofen in PVP film after impregnation was in the range of 10–30 wt.% depending on the exposure time of PVP film to the solution of ibuprofen in $scCO_2$. This was estimated from the absorbance of the IR bands of ibuprofen in PVP after impregnation.

The H-bonding between ibuprofen and PVP has an effect on the interaction between PVP and CO_2. Fig. 6 shows the IR spectrum of PVP in the bending mode region of CO_2 before and after impregnation of ibuprofen. The molecules of CO_2 diffuse much faster into PVP than ibuprofen and are capable of interacting with the basic carbonyl groups of PVP via Lewis acid–base interaction with the lone pair of electrons on the carbonyl oxygen as presented in Scheme 2.

Evidence of this is shown by the split of the bending mode of CO_2 which is a strong indication of CO_2 interaction with a polymer (Kazarian et al., 1996). However, the splitting of the bending mode of CO_2 essentially disappears once ibuprofen is impregnated into PVP indicating that in such a case the CO_2 molecules do not interact with the C=O groups of PVP.



Scheme 2.

This can be rationalised as follows: competitive interaction of ibuprofen and CO_2 molecules with the carbonyl groups of PVP, favours the former rather than the latter. Ibuprofen is interacting more strongly with the C=O groups of PVP and thus expels CO_2 from the available for interactions basic carbonyl sites of PVP. The carbonyl group of ibuprofen itself is not as basic as that of PVP (this is reflected by the differences in their ν(C=O) frequencies) and the result of this is that most of the CO_2 molecules that are still present in PVP are not interacting with the C=O groups once ibuprofen is impregnated into the polymer. There are just some CO_2 molecules that are still interacting with the C=O group of PVP which may not be easily available for bulkier ibuprofen molecules. This is shown by the fact that some distortion of the bending mode of CO_2 still exists after ibuprofen has been impregnated. Nevertheless, Fig. 6 provides strong evidence that CO_2 molecules interact with C=O groups of PVP in the absence of the ibuprofen as the splitting of the bending mode of CO_2 disappears once ibuprofen (ca. 25 wt.%) is impregnated. This proposal is consistent with the previous report that the presence of the methanol in PMMA might have blocked the carbonyl groups of PMMA making them unavailable for the interaction with CO_2 (Kazarian et al., 1996). In the current work, explanation of a similar 'blocking' was provided by observation of the disappearance of the splitting of the bending band of CO_2 with the simultaneous low-frequency shift of the ν(C=O) band of PVP due to the H-bonding with ibuprofen. This observation supports our previous spectroscopic finding of the specific interactions between CO_2 and carbonyl groups in polymers, which had numerous implications ranging from the preparation of the scaffolds for tissue engineering via CO_2-assisted foaming of biodegradable polymers (Sheridan et al., 2000) to the synthesis of CO_2-soluble hydrocarbon polymers (Sarbu et al., 2000). The strength of interaction between CO_2 and the C=O groups in polymer was estimated to be of the order of 1 kcal mol^{-1}, and it is not surprising that H-bonding between PVP and ibuprofen (the

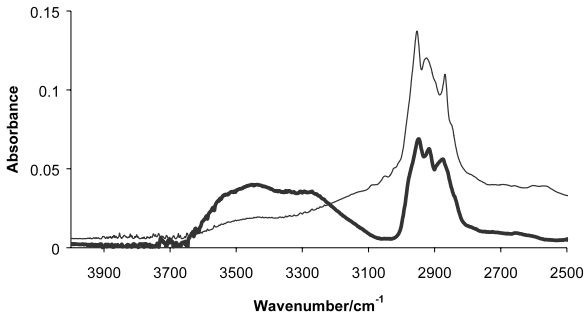


Fig. 7. ATR–IR spectra of PVP in the ν(O–H) stretching region before (thick line) and after (thin line) impregnation of ibuprofen. Note that the bands of water in PVP at ca. 3200–3600 cm^{-1} essentially disappear with the broad band at 2600–3300 cm^{-1} appearing due to the ν(O–H) band of ibuprofen.

energy of which should be on the order of 2–4 kcal mol^{-1}) 'wins' the competitive interaction over CO_2 with the carbonyl groups of polymer.

The analysis of the IR spectra of PVP impregnated with ibuprofen in the region of the ν(O–H) stretching vibrations has shown a decrease in the moisture uptake. Fig. 7 shows the ATR–IR spectrum of PVP film open to atmospheric air before and after impregnation of ibuprofen. The relatively strong absorption in the region between 3600 and 3200 cm^{-1} of the PVP film indicates the presence of water sorbed into PVP. The molecular state of water in PVP has been recently studied in some detail (Lebedeva et al., 2000). The solid line on Fig. 7 shows the same spectral region of PVP after the impregnation of ibuprofen. This PVP film was exposed to air at room temperature and at relative humidity of ca. 70% for period of 20–40 min. The absorption in the region between 3600 and 3200 cm^{-1} has essentially disappeared which indicates the relatively low presence of water in PVP. The broader absorption in the region between 3300 and 2700 cm^{-1} is characteristic of the ν(O–H) band of the impregnated ibuprofen. Thus, similar to the above case with the competitive interaction with CO_2 the impregnation of ibuprofen into PVP has the result that some of the C=O groups of PVP are not available for interaction with the water molecules. As a result, the moisture uptake from the atmosphere by such PVP film is significantly decreased which may have a positive effect on stability of such formulation.

Finally, Raman spectra of ibuprofen impregnated into PVP from $scCO_2$ solution have been measured and compared with the Raman spectra of crystalline ibuprofen (Fig. 8). Previous studies using confocal Raman spectroscopy (Breienbach et al., 1999) have demonstrated that the characteristic Raman band of crystalline ibuprofen absorbs at 1608 cm^{-1}. The presence of crystalline or amorphous drug has been confirmed by comparison with DSC and X-ray diffractometry. However, when ibuprofen is dissolved in solvent or processed as a hot melt extrudate with PVP it absorbs at 1613 cm^{-1}. In that work it has been shown that the position of the ibuprofen band at 1613 cm^{-1} is indicative of molecularly dispersed ibuprofen in the extrudate (Breienbach et al., 1999). As Fig. 8 shows, that characteristic Raman band of ibuprofen impregnated into PVP from $scCO_2$ solution also absorbs at 1613 cm^{-1}, with the absence of the band at 1608 cm^{-1} corresponding to the crystalline ibuprofen. Thus, these Raman measurements provide an additional support to our ATR–IR study that supercritical fluid impregnation of PVP results in molecularly dispersed drug within the polymer matrix. It is important to note that supercritical fluid impregnation was done at much lower temperatures than the melt extrusion.

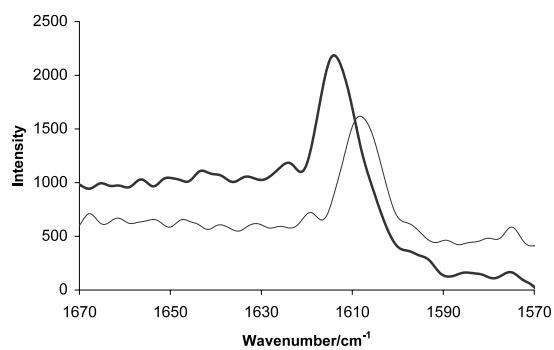


Fig. 8. Raman spectra of ibuprofen in the region of the band at 1608 cm^{-1}. The thin line shows spectrum of solid crystalline ibuprofen; the thick line shows spectrum of ibuprofen impregnated into PVP from $scCO_2$ solution. Note that in the latter spectrum the band is shifted to higher-wavenumber region.

4. Conclusions

We have studied supercritical fluid impregnation of PVP with ibuprofen using in situ high-pressure ATR–IR spectroscopy. It has been shown that this novel in situ spectroscopic approach is well suited for the analysis of polymer impregnation with drug molecules from supercritical fluid solution, and can be applied to a broad range of polymers. The experiment described in this paper has shown that supercritical fluid impregnation of drug into a polymer matrix results in molecularly dispersed drug molecules within the polymer matrix, and no formation of crystalline drug was detected by IR spectroscopy. The absence of crystalline drug within the polymer matrix has also been supported by measurements of Raman spectra of these formulations. Such polymer/drug formulations provide a good basis for the tailoring of controlled drug delivery devices since dissolution rates can be more easily controlled in the absence of crystallites of drug. The ν(C=O) spectral region provided strong evidence for formation of H-bonding between ibuprofen and PVP. Our spectroscopic results show that H-bonding between the hydroxyl group of ibuprofen and the carbonyl group of PVP is responsible for preventing self-association of ibuprofen. Interactions between CO_2 molecules and carbonyl groups of PVP have also been found, and it has been shown that a competitive interaction of impregnated ibuprofen molecules with the carbonyl groups of PVP prevents CO_2 molecules interacting with the carbonyl groups of PVP. In addition, IR spectroscopic evidence has been provided that similar interactions have an affect on water uptake into PVP. Thus, the PVP films impregnated with ibuprofen show much lower water uptake presumably due to the competitive interaction of ibuprofen with basic carbonyl groups of PVP.

In summary, in situ ATR–IR spectroscopy allows us to reveal the underlying principles of supercritical fluid impregnation of biocompatible polymers with drug molecules. The key to the successful preparation of amorphous polymer/drug formulations that are free of drug crystallites is to achieve dispersion of the drug molecules within a polymer matrix via binding each drug molecule to the basic sites of the polymer via H-bonding. This method is based on the affinity of drug molecules to the polymer matrix. The use of supercritical CO_2 as a carrier of drug molecules into the polymer matrix has advantages such as the plasticising ability of CO_2 that enhances diffusion rates of drug into the polymer and the ease of solvent removal. This provides an approach that rivals conventional methods of preparation of solid dispersions of drugs in polymers that have low solubility in water.

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