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Abstract: Stoichiometric ratios of poly(ethylene glycol) (PEG, Mw = 400) with poly(vinylpyrrolidone) (PVP, Mw = ±3.1 x 104 & Mw = 1.25 x 106 Mw) were prepared from ethanol cast solutions and in supercritical CO2. The complex formation was studied via glass transition (Tg) analysis obtained from differential scanning calorimetry (DSC) thermograms. PEG-PVP blends were also loaded with ibuprofen. The molecular dispersion of ibuprofen, mechanism of interaction, the effect of CO2 pressure and temperature and ageing of blends were also analysed with DSC, attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy and X-ray diffraction. Tg analysis indicated that supercritical CO2 can facilitate the formation of stoichiometric PEG-PVP complexes. Processing of PEG-PVP blends with ibuprofen results in the molecular dispersion of ibuprofen mainly bonded to PVP carbonyl groups, without significant disruption of the PEG-PVP complex. Increasing ibuprofen content leads to the disruption of PEG-PVP H-bond interactions and subsequently a breakdown of the PEG-PVP complex. Increasing process pressure results in extraction of some PEG fractions, while temperature increase only leads to increased foaming. Post-processing ATR-FTIR shifts in ibuprofen-PEG-PVP complexes is greater with supercritical CO2 processing. These shifts are mainly attributed to atmospheric moisture absorption, however some evidence of molecular rearrangement is also observed. Altogether, ibuprofen-loaded PEG-PVP complexes can be prepared from supercritical CO2 processing showing similar characteristics to such complexes prepared from solution casting.

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Professor Erdogan Kiran,
The Editor,
Journal of Supercritical Fluids

Dear Editor

I would like to submit a manuscript entitled **"Supercritical CO_2-assisted preparation of ibuprofen-loaded PEG-PVP complexes"** by Philip Labuschagne and Rotimi E. Sadiku for consideration in the Journal of Supercritical Fluids.

In this manuscript, the stoichiometric ratio for interpolymer complex formation between poly(ethylene glycol) (PEG) and poly(vinylpyrrolidone) (PVP) is prepared in supercritical carbon dioxide medium. In addition, supercritical CO_2 is used for the first time to prepare ibuprofen-loaded PEG-PVP complexes (used in the design of transdermal delivery devices). The use of supercritical CO_2 poses many advantages over the conventional solvent casting preparation method, however, there is a need to understand the effect of CO_2 in preparation of such systems.

In this manuscript we determine: 1) if supercritical CO_2 can facilitate the formation of stoichiometric PEG-PVP interpolymer complexes; 2) to what degree ibuprofen is molecularly dispersed within the PEG-PVP complex after CO_2 processing and how this compares with the conventional preparation method; 3) the structure of the ibuprofen-loaded PEG-PVP complex and how increased ibuprofen loading affects the complex; 4) how supercritical CO_2 process conditions (such as pressure and temperature) affects ibuprofen-loaded PEG-PVP complexes; 5) the effect of ageing on PEG-PVP complexes with increasing ibuprofen loadings and how preparation method (supercritical CO_2 processing and solvent casting) affects ageing..

Thank you for your consideration of this manuscript.

Yours Sincerely,

Philip Labuschagne

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***Graphical Abstract**

Supercritical CO_2-assisted preparation of ibuprofen-loaded PEG-PVP complexes

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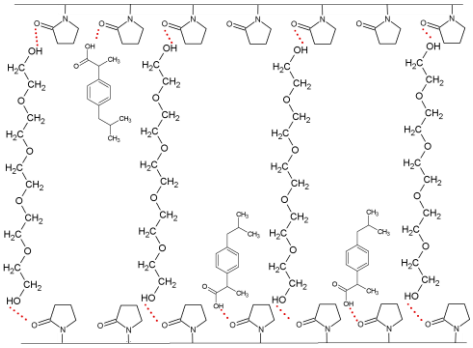

Research highlights

- Supercritical CO_2 facilitates the formation of stoichiometric PEG-PVP complexes
- CO_2 processing allows molecular dispersion of ibuprofen in PEG-PVP complexes
- CO_2 pressure & temperature has minimal effect on ibuprofen-PEG-complex
- Ibuprofen-PVP interaction occurs at the expense of PEG-PVP interaction

Supercritical CO_2-assisted preparation of ibuprofen-loaded PEG-PVP complexes

Abstract

Stoichiometric ratios of poly(ethylene glycol) (PEG, M_w = 400) with poly(vinylpyrrolidone) (PVP, M_w = ±3.1 x 10^4 & M_w = 1.25 x 10^6 M_w) were prepared from ethanol cast solutions and in supercritical CO_2. The complex formation was studied via glass transition (T_g) analysis obtained from differential scanning calorimetry (DSC) thermograms. PEG-PVP blends were also loaded with ibuprofen. The molecular dispersion of ibuprofen, mechanism of interaction, the effect of CO_2 pressure and temperature and ageing of blends were also analysed with DSC, attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy and X-ray diffraction. T_g analysis indicated that supercritical CO_2 can facilitate the formation of stoichiometric PEG-PVP complexes. Processing of PEG-PVP blends with ibuprofen results in the molecular dispersion of ibuprofen mainly bonded to PVP carbonyl groups, without significant disruption of the PEG-PVP complex. Increasing ibuprofen content leads to the disruption of PEG-PVP H-bond interactions and subsequently a breakdown of the PEG-PVP complex. Increasing process pressure results in extraction of some PEG fractions, while temperature increase only leads to increased foaming. Post-processing ATR-FTIR shifts in ibuprofen-PEG-PVP complexes is greater with supercritical CO_2 processing. These shifts are mainly attributed to atmospheric moisture absorption, however some evidence of molecular rearrangement is also observed. Altogether, ibuprofen-loaded PEG-PVP complexes can be prepared from supercritical CO_2 processing showing similar characteristics to such complexes prepared from solution casting.

Keywords: carbon dioxide, interpolymer complex, ibuprofen

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1. Introduction

Drug delivery systems generally consist of a drug dispersed within a biocompatible polymeric matrix which is designed to release the drug via diffusion or erosion mechanisms and to target a specific site in the body [1]. One of the requirements for controlled delivery is that the drug is molecularly dispersed within the polymer matrix, as crystalline drug in the polymer matrix would lead to uncontrolled dissolution or diffusion rates [2] This is usually achieved using solvent-based processing, after which the solvent is removed via air-, thermal-, vacuum- , spray- or freeze-drying techniques [3-9]. Apart from the risk of toxic solvent residues, many drugs are thermo-labile or solvent-labile. A “greener” alternative which has received much attention in the past decade is the use of supercritical carbon dioxide (CO_2) as processing medium. CO_2 is relatively inexpensive, non-toxic and is easily removed from the product. In addition, supercritical CO_2 can be reached at conditions above relatively mild pressure (71.8 bar) and temperature (31.8ºC). These properties have made supercritical CO_2 a suitable medium, for instance, for the impregnation of drugs into polymers [10-16].

Supercritical CO_2-assisted impregnation is based on the ability of polymers to be plasticised and drugs to be melted in supercritical CO_2. This allows transport of the drug into the swollen polymer matrix. Favourable partitioning of the drug into the polymer matrix, due to specific drug-polymer interactions, yields a molecularly dispersed drug inside a polymer matrix [10] Using this mechanism, the dissolution rates of poorly water soluble drugs have been enhanced by impregnation in a water-

soluble polymer. Examples of such systems that have been successfully produced with supercritical CO_2 as processing medium are: ibuprofen impregnated into β-cyclodextrin [17,18], PVP [10] and lipid composites [19]; ketoprofen impregnated into β-cyclodextrin [20] and PLGA [21]; indomethacin impregnated into HPBCD [22], PVP [13], chitosan [14], poly(sebacic anhydride) [23] and PLLA/PLGA [24], and budesonide impregnated into HPBCD [22]. Impregnation is achieved by using either of two methods: the drug is pre-dissolved in supercritical CO_2 and then the drug-$scCO_2$ solution is passed through a polymer matrix [10,17] or the drug is physically premixed into the polymer and then the drug/polymer mixture is exposed to supercritical CO_2 [13,14,22,23]. To optimize impregnated drug content, various conditions, such as the CO_2 pressure, operating temperature or exposure time should be optimised. Evidence of molecular dispersion of the drug is usually indicated by a lack of crystalline drug, either by the absence of a crystalline melting peak (DSC analysis), or the absence of crystalline diffraction peaks (XRD) and in certain cases, the visible absence of drug crystals in the polymer matrix (SEM). Further evidence of increased molecular dispersion of the drug was demonstrated through FTIR spectroscopic analysis [10], which showed that the molecular state of drug and its interactions (drug-drug or drug-polymer) can be assessed. Finally, dissolution studies are conducted to demonstrate the effect of increased molecular drug dispersion on dissolution rates [14,23].

The abovementioned studies were aimed at oral delivery systems in which bioavailability of drugs are determined by dissolution rates in aqueous media. Transdermal drug delivery is an alternative approach that aims to deliver a drug through the skin into the systemic circulation [25]. However, the excellent barrier properties of the skin, combined with both lipophilic and hydrophilic phases, impart great limitations on the range of drugs suitable for transdermal delivery [26]. Feldstein et al [27] addressed some of these issues by developing a matrix-type

transdermal delivery system, which combine favourable characteristics such as skin adhesion, controlled delivery and enhanced drug penetration. Their delivery system is a hydrogel formed by the interpolymer complexation between short chain polyethylene glycol (PEG) molecules, also a skin penetration enhancer, and high molecular weight polyvinylpyrrolidone (PVP), often used as a carrier to enhance the bioavailability of drugs. Both terminal hydroxyl groups of PEG form H-bonds with the carbonyl groups of PVP, resulting in a high free-volume network of PVP chains tied by comparatively long, flexible H-bond crosslinks [28]. The high free-volume imparts pressure-sensitive adhesive properties.

Behaviour of PEG-PVP blends were first studied by Fleming et al [29]. In a previous study, we compared homogeneity and H-bond interaction of PEG-PVP blends prepared in supercritical CO_2, cast from ethanol and physical mixtures [29,30]. It was shown that, in general, supercritical CO_2 processing does facilitate the formation of homogenous PEG-PVP blends, although, at higher PEG molecular weight, blends cast from ethanol showed greater homogeneity and degree of H- bond interaction than blends processed in supercritical CO_2. This was attributed to rapid vitrification upon CO_2 venting and the inability of the high molecular weight PEG molecules to self-diffuse in between PVP molecules. In a follow up study, the evolution of H-bond interactions between PVP and PEG *in-situ* under high-pressure CO_2 and during CO_2 venting was monitored [31]. It was shown that CO_2 sorption disrupts H-bond interaction between PEG and PVP, while upon CO_2 desorption, H-bond interaction recovers. The extent of H-bond disruption and recovery was dependent on many variables such as: polymer molecular weight, PEG-PVP ratio, operating pressure and temperature.

In this study, complexes of PEG-PVP with ibuprofen (a non-steroidal anti-inflammatory drug, often used in transdermal delivery for treatment of rheumatoid

arthritis and osteoarthritis) have been prepared [32]. Comparisons are made between mixtures prepared in supercritical CO_2 and mixtures cast from aqueous solution. Previous research has shown that ibuprofen interacts with both PEG and PVP via H-bonding: in the case of PEG, interaction occurs between the carbonyl group of ibuprofen and the terminal hydroxyl group of PEG [33], while with PVP, it occurs between the hydroxyl group of ibuprofen and carbonyl group of PVP [10]. Taking into consideration the fact that PEG-PVP complex formation requires interaction between the same functional groups of PEG and PVP, it can be expected that some degree of competitive interaction will occur with the addition of ibuprofen.

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Thus, the objectives of this study were to determine: 1) if supercritical CO_2 can facilitate the formation of stoichiometric PEG-PVP interpolymer complexes; 2) to what degree ibuprofen is molecularly dispersed within the PEG-PVP network complex after CO_2 processing and how this compares with the conventional casting method; 3) the structure of the ibuprofen-loaded PEG-PVP complex and how increased ibuprofen loading affects the complex; 4) how supercritical CO_2 process conditions can affect the interaction behaviour in ibuprofen-loaded PEG-PVP complexes; 5) the effect of ageing on PEG-PVP complexes with increasing ibuprofen loadings.

2. Experimental

2.1 Materials

PEG (M_w: 400) was purchased from Unilab, Germany. PVP Kollidon 17PF (±9 x 10^3 M_w), Kollidon 25PF (±3.1 x 10^4 M_w) and Kollidon F90 (±1.25 x 10^6 M_w) were purchased from BASF, South Africa. Carbon dioxide (99.995% purity) was purchased from Air Products, South Africa. Ibuprofen was purchased from Sigma-Aldrich, South Africa.

2.2 Preparation of PEG/PVP complexes

Mixtures cast from solution: PVP and PEG-400 were carefully weighed off, after which water was added to yield 50% aqueous solutions. The solutions were then stirred with a spatula until homogenous. The aqueous solutions were poured into a petri-dish and dried in an oven at 70ºC for 6hrs, resulting in samples with approximately 5% moisture content. The samples were then equilibrated in open atmosphere for 24hrs to equilibrium moisture content of approximately 12%.

Mixtures prepared in supercritical CO_2: PVP and PEG-400 were carefully weighed off and stirred with a spatula until homogenous. The mixtures were then placed in a supercritical CO_2 reactor as described in a previous paper [30], preheated to 40ºC and then pressurised to 120 bar. These conditions were maintained for 3 hours, after which CO_2 was vented and the sample removed. The mixture was then allowed to equilibrate in open atmosphere for 24hrs to equilibrium moisture content of approximately 12%.

For addition of ibuprofen in both cases, the same procedures were followed as above, except that PVP and ibuprofen were first ground in a mortar and pestle until homogenous. For samples cast from solution, ethanol was used as solvent due to the poor solubility of ibuprofen in water. FTIR analysis was used to monitor complete removal of ethanol prior to analysis.

2.3 Differential Scanning Calorimetry (DSC)

A DSC1/700 (Mettler Toledo Instruments) was used to perform the DSC analysis on the samples. A heating rate of 20°C/min was used in a nitrogen atmosphere, with flow rate 50 mL/min. The temperature range was -75 to 220 °C. Aluminium sample pans were used. The sample masses, which were accurately determined on an analytical balance, ranged between 5 - 7 mg.

2.4 Attenuated Total Reflection Fourier Transform Infrared (ATR-FTIR) Spectroscopy

ATR-FTIR spectra of the samples were obtained using a Perkin Elmer Spectrum 100 FTIR spectrometer, with wavenumbers ranging from 4000 cm^{-1} to 650 cm^{-1}.

2.5 X-Ray Diffraction (XRD)

Samples were analysed in a wide-angle X-ray diffractometer (X'Pert PRO from PANalytical) using Cu K_α radiation (λ = 0.1542nm) over 1-60º, with a step size of 0.0263º.

3. Results & Discussion

3.1 DSC analysis of PEG-PVP complexes without ibuprofen

The first aim was to determine whether supercritical CO_2 can facilitate the formation of stoichiometric PEG-PVP complexes. Complex formation between polymers are usually indicated by a large, usually positive, deviation from the normal rules of mixing such as the Fox and Gordon-Taylor equations [34,35]. In the case of PEG-PVP complexes, large negative deviations occur, due to the enhanced free volume resulting from the considerable length of PEG cross-links between PVP chains [36]. Figure 1 shows DSC heating thermograms of complexes of PEG with PVP (Kollidon 25PF & F90) measured after supercritical CO_2 processing.

The presence of absorbed moisture in all samples are characterised by a melting peak of free water at ca. 1ºC and a broad thermo-desorption endotherm in the temperature range ca. 40ºC to 170ºC. Of interest in this study, are the T_gs of the respective complexes. Both complexes show a T_g of -45ºC. According to the Fox equation (using T_g values shown in Table 1), the T_g of 36wt% of PEG-400 in Kollidon

25PF with 12% hydration should theoretically be -5.75ºC. Replacing with Kollidon 90F the Fox equation predicts a theoretical T_g of 0.54ºC.

(Table 1 references: [36], [37], [38]

A significant negative deviation from the simple rules of mixing is seen in all complexes. Thus, T_g values show that processing stoichiometric ratio's of PEG and PVP in supercritical CO_2 medium does result in the formation of high-free volume H-bonded PEG-PVP complexes.

An interesting observation was the possibility of CO_2-enhanced plasticization of high molecular weight PVP (M_w: 1.25 x 10^6) in the presence of PEG-400. In the neat state, PVP of such high molecular weight does not plasticize in supercritical CO_2 at 120 bar and 40ºC. The difficulty in plasticizing such high molecular weight PVP can be attributed to poor accessibility of CO_2 molecules to the PVP carbonyl groups due to low chain mobility, as reflected by a higher T_g value – which is also an indication of greater polarity, possibly due to stronger PVP-PVP dipole interactions. It is assumed that with the addition of PEG, the inter-chain distances between the PVP molecules are increased allowing greater access for CO_2 molecules to interact with the PVP carbonyl groups.

The next aim was to prepare ibuprofen-loaded PEG-PVP complexes using supercritical CO_2 as processing medium. It is expected that, since both PEG and ibuprofen interact with the carbonyl groups of PVP, competitive interaction could occur and that the species showing stronger interaction with PVP would limit or prevent interaction of the other species with PVP [10,39]. Interaction strength is strongly correlated with the position of spectral bands [40] and a previous study has shown that ibuprofen-PVP interaction leads to a PVP carbonyl wavenumber shift,

Δv(C=O), in the order of 46 cm^{-1} [10], while for PEG(400)-PVP interaction, Δv(C=O) is in the order of 24 cm^{-1} [41]. This would suggest that ibuprofen-PVP interaction is preferred and could occur at the expense of PEG-PVP H-bond interactions. However, it is important to consider the number of PVP carbonyl groups available for interaction. Feldstein et al [42] showed that in stoichiometric complexation between PEG and PVP (36 wt% PEG), only about 30% of PVP repeat units are occupied by H-bonding with PEG terminal hydroxyl groups. Thus, 70% of PVP repeat units remain free, if steric effects are excluded). Therefore, with a 30 wt% drug loading, a sufficient number of PVP carbonyl groups could be available for complex formation with PEG.

3.2 FT-IR spectroscopic analysis

Figure 2 shows the wavenumber region of the *v*(C=O) band in which the carboxylic C=O stretching band of ibuprofen and the cyclic amide *v*(C=O) band of PVP in PEG-PVP complexes are shown along with the spectra of an ibuprofen-loaded PEG-PVP complex in this spectral region. First to be noticed is the shift of ibuprofen v(C=O) from 1705 to 1725 cm^{-1} upon mixing in the PEG-PVP complex. This shift has been reported previously and is attributed to the breakup of ibuprofen dimers that occur in the solid state [10]. The “free” ibuprofen molecules then interact with the polymer via H-bonding as evidenced by the changes in the *v*(C=O) band of PVP in the ibuprofen-PEG-PVP complex. The band at ca. 1632 cm^{-1} was previously attributed to H-bonding between the carbonyl group of PVP and the hydroxyl group of ibuprofen [10].

No significant differences in spectra of samples prepared by casting from ethanol solution and those prepared in the supercritical CO_2 medium were evident, after

equilibrating to ca. 12% moisture content. This indicates similar drug-polymer interaction behaviour for both preparation methods.

3.3 X-ray Diffraction Analysis of ibuprofen-loaded PEG-PVP complexes

The X-ray diffractogram shows an absence of the ibuprofen diffraction pattern in all samples, which is further evidence of molecular dispersion of ibuprofen within PEG-PVP complex (Figure 3). In addition, the X-ray diffractograms give evidence in both complexes that the presence of H-bonded ibuprofen does not disrupt the high free-volume network structure of the PEG-PVP complex. This is inferred from the halo's shown in Figure 3. All the complexes show a halo at ca. 20 º, which corresponds closely with the halo in neat PEG-400 and represents the ordered arrangement of PEG chains bonded by its terminal hydroxyl groups to the oxyethylene units of neighbouring PEG chains [43]. The presence of the halo's indicate a similar ordered arrangement and would thus support the model of mutual chain orientation in PEG-PVP complexes, proposed by Feldstein et al [28].

3.4 DSC analysis of ibuprofen-loaded PEG-PVP complexes

Further evidence that the high free-volume network structure is maintained is found in the DSC thermograms. Figure 4 compares thermograms of neat ibuprofen with an ibuprofen-loaded PEG-PVP complex cast from ethanol solution and the same complex prepared in supercritical CO_2. In both cases, the complexes show a T_g significantly lower than expected from simple rules of mixing, indicating high free volume as expected from a PEG-PVP complex. Neat ibuprofen shows a sharp endothermic peak at 84.7ºC, corresponding to its crystalline melting point. However, in all the complexes this peak disappears completely, which is further evidence that

the ibuprofen is in an amorphous state [44]. Interestingly, a much reduced thermo-desorption endotherm is present when compared to the same complexes without ibuprofen (Figure 1). This suggests much reduced moisture absorption. Since PVP is the more hygroscopic of the two polymers, reduced moisture absorption can be attributed to ibuprofen molecules occupying the carbonyl groups of PVP via strong H-bonds, making them unavailable for interaction with water molecules [10].

The above results show that ibuprofen prefers interaction with PVP, and that the high free-volume PEG-PVP network is mainly intact. The proposed structure of the ibuprofen-PEG-PVP complex can thus be illustrated schematically as shown in Figure 5:

Thus, it is possible to produce ibuprofen-loaded stoichiometric PEG-PVP complexes using supercritical CO_2 as process medium, eliminating the need for long or energy intensive drying methods to remove excess solvent.

3.5 Effect of ibuprofen loading on PEG-PVP complex

Interestingly, PEG-PVP complexes loaded with 30 wt% ibuprofen showed a greater degree of foaming after CO_2 venting than complexes without ibuprofen (Figure 6).

The degree of CO_2-induced foaming can be influenced by a number of factors. Firstly, greater CO_2 sorption generally leads to a greater degree of polymer foaming [45]. However, previous research has shown that strong ibuprofen-PVP interaction leads to a reduction in CO_2 solubility, thus such foaming cannot be attributed to greater CO_2 sorption. Secondly, differences in the T_gs of the PEG-PVP complexes could also affect degree of foaming. Foaming only occurs above the T_g of the polymer-CO_2 mixture and at a certain stage during CO_2 venting, vitrification occurs

[46], terminating cell growth. It is therefore expected that a lower T_g would allow more time for CO_2-induced cell growth, resulting in a greater degree of foaming. DSC results (Figure 4) however, indicate a slightly higher T_g for complexes containing ibuprofen. A third possibility could be related to the viscosity of the PEG-PVP complex. A decrease in complex viscosity would pose less resistance to cell growth [47]. Such viscosity reduction would only be expected if the PEG-PVP "crosslink" density is reduced [28]. A decrease in "crosslink" density would also result in a T_g increase, as fewer PEG molecules bonded via both terminal hydroxyl groups to PVP chains would disrupt the high free-volume PEG-PVP network structure. This is supported by the T_g of the complexes containing 30% ibuprofen (Figure 4) showing an increase in T_g from ~-45ºC to ~-38ºC. Clearly then, ibuprofen-PVP interaction is preferred and does lead to some disruption of the PEG-PVP complex.

Following from the above, it would be expected that by increasing ibuprofen content further, degree of foaming will be enhanced. PEG-PVP complexes with 40 and 50 wt% ibuprofen were prepared and the degree of foaming shown in Figure 7.

As expected, greater foaming is found with 40 wt% ibuprofen, but at 50 wt% ibuprofen the degree of foaming is less. It is likely that the viscosity decreases to such an extent due to breakdown of the PEG-PVP complex, resulting in cell coalescence.

3.6 Effect of processing conditions

3.6.1 Pressure effect

Processing pressure was increased from 120 to 220 bar, after which ATR-FTIR spectroscopic analysis of processed samples was conducted to evaluate the molecular state of ibuprofen (30 wt% loading) and PEG-PVP interactions (Figure 8).

Figure 8 shows spectra overlays of 4 different samples taken from the same batch. The arrows indicate bands associated with PVP (C=O group) and PEG (C-O group). Variations in these band ratios are evident, indicating that the relative amount of PEG in PVP was different in the different samples taken. This can be explained as follows: increasing CO_2 pressure leads to increased sorption of CO_2 into the PEG-PVP complex and thus reduced PEG-PVP interactions. The relatively low M_w of the PEG molecules could result in some fractions being partitioned into the CO_2-rich phase, which is then extracted from the blend upon CO_2 venting. Most likely, only the PEG molecules located closer to the outer surface of the mixture were extracted since the high M_w of the PVP molecules would hinder PEG transport properties. Closer inspection of the PVP C=O and PEG C-O absorption bands show that in regions containing a lower fraction of PEG molecules the PVP C=O peak maxima is shifted to lower wavenumbers (1661 cm^{-1}) and the PEG C-O band is correspondingly shifted to higher wavenumbers (1115 cm^{-1}). This is evidence that the remaining PEG molecules are tightly bonded, via its terminal hydroxyl groups, to PVP molecules and that the PEG oxyethylene backbones are relatively “free” from association with other PEG molecules, resulting in a structure as illustrated in Figure 5. Increasing pressure has no effect on ibuprofen binding, as is expected since the ibuprofen-PVP interaction is very strong.

3.6.2 Temperature effect

Processing temperature was increased from 40 to 60ºC, for the same complex with 30wt% ibuprofen loading. Figure 9 shows spectra overlays of 4 different samples taken from the same batch. No difference in the PVP (C=O) and PEG (C-O) band ratios are shown. In addition, increasing process temperature had no effect on ibuprofen H-bonding to PVP.

The only visible difference with higher temperature processing was in the physical appearance of the end product, showing a “spider-nest” appearance (Figure 10).

With increased temperature, increased kinetic energy is expected to further reduce H-bond interactions between PEG and PVP, resulting in reduced viscosity. This leads to a very high degree of foaming. However, this structure was stable only for a short period after which it collapsed, most likely due to the liquid nature of the complex.

3.7 PEG-PVP complex stability at different ibuprofen loadings

Crystalline drug in the amorphous form is known to be unstable [48]. In addition, increased drug loading in a polymer could lead to supersaturation which would also result in recrystallisation of the drug [49]. The stability of ibuprofen with different weight% loadings in PEG and PVP (M_w: ±1.25 x 10^6) complexes were monitored over three weeks via ATR-FTIR analysis. Figure 11 compares spectra of complexes prepared in supercritical CO_2 (row A) and cast from ethanol (row B): immediately after preparation, after 1 week and after 3 weeks storage at 23ºC and 50% relative humidity.

A similar trend across all the spectra is that with increased ibuprofen loading, the intensity of the PVP *v*(C=O) band at ca. 1632 cm^{-1}, attributed to ibuprofen-PVP H-bonding, increases. This would indicate that even at high ibuprofen loadings, interaction with PVP is preferred. In addition, no evidence of ibuprofen recrystallisation is shown over the 3 week storage period, irrespective of processing method. Previous research has shown that the maximum ibuprofen loading which is expected to exist stably in the amorphous state in PVP is ca. 30 wt% [10]. However, in the PEG-PVP complex a 50 wt% ibuprofen loading relates to effectively a 61 wt% ibuprofen loading in PVP, if it is assumed that PEG hydroxyl groups are H-bonded to PVP and not available for interaction with ibuprofen. This could indicate towards some form of synergistic effect between PEG and PVP in stabilising ibuprofen. Nevertheless, stability tests need to be conducted over longer storage periods and under varying conditions to confirm such synergistic effects.

Small spectral differences between the two processing methods are noticeable. The supercritical CO_2-processed complexes show slightly greater post-processing ageing as reflected by greater variations in the shape of the PVP *v*(C=O) band over time. Due to the hygroscopic nature of the ibuprofen-PEG-PVP complex, these changes could be due to moisture absorption. For this reason, the hydroxyl stretching mode region between 3100 and 3700 cm^{-1} was studied. The general trend in all the samples, irrespective of processing method, was an initial increase in the intensity of the hydroxyl band after 1 week ageing. After 3 weeks ageing the intensity of the hydroxyl band decreased somewhat (Figure 12).

The slight decrease in moisture content after 3 weeks ageing could be due to molecular rearrangement in the ibuprofen-PEG-PVP complex (assisted by enhanced plasticisation due to present water molecules), thereby displacing a small amount of the absorbed water molecules. The slightly greater “ageing” noticed in the

supercritical CO_2-processed blends could simply be due to lower initial water content. This can be expected, since previous research has shown the ability of supercritical CO_2 to extract water from polymers [50].

Figure 13 illustrates changes in the shape of the band representing PEG oxyethylene repeat units. These bands show a new shoulder at 1117 cm^{-1} which we have found not be be present in neat PEG-400; PEG-400 exposed to high humidity (90% relative humidity for 6 hours); PEG-400 loaded with 50wt% ibuprofen; or in the neat PEG-PVP complexes. As is indicated in Figure 13, these shoulders become more pronounced with increasing ibuprofen content, and can be attributed to altered conformations of the PEG oxyethylene repeat units, possibly due to van der Waals interaction with the benzene ring of ibuprofen. The absence of such a shoulder in ibuprofen-PEG mixtures can be attributed to greater ibuprofen mobility, where close contact with the PEG oxyethylene units are limited. In the ibuprofen-PEG-PVP complex, molecular mobility is restricted resulting in increased interaction between the oxyethylene units and the ibuprofen benzene ring. The intensity of this band decreases over the three week storage period which, as indicated above, is also accompanied by increased moisture content. It is possible that some water molecules accumulate around the oxyethylene units, thereby shielding some of these van der Waals interactions.

4. Conclusions

Supercritical CO_2 is able to facilitate the preparation of stoichiometric PEG-PVP network complexes as confirmed by a large negative deviation of T_g from the simple rules of mixing. Processing of PEG-PVP blends even with very high M_w PVP ((±1.25 x 10^6) is possible due to PEG molecules increasing the inter-chain distances between the long PVP molecules, allowing greater access for CO_2 molecules to interact with PVP carbonyl groups.

Supercritical CO_2 processing of PEG-PVP blends loaded with ibuprofen results in complete molecular dispersion of ibuprofen molecules, H-bonded mainly to the carbonyl groups of PVP. Increasing the ibuprofen content disrupts PEG-PVP H-bond interaction which results in greater foaming due to reduced viscosity. Increasing CO_2 pressure from 40 bar to 60 bar does not affect ibuprofen-PVP interaction, but some of the low M_w PEG fractions are extracted upon CO_2 venting. Temperature increase only results in greater foaming of the ibuprofen-PEG-PVP complex.

In all the ibuprofen-PEG-PVP complexes, spectroscopical changes occur over a three week storage period, which is attributed primarily to moisture absorption. The effect is slightly greater in complexes prepared in supercritical CO_2, which is due to lower initial moisture content caused by the ability of supercritical CO_2 to extract moisture from polymers upon venting. ATR-FTIR analysis of the ibuprofen-PEG-PVP complex shows a new shoulder at 1117cm^{-1}. This shoulder is attributed to specific interactions between the oxyethylene repeat units of PEG and the benzene ring of ibuprofen.

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Tables

Table 1: The glass transition temperatures of PEG, PVP and water

Component	Tg (ºC)	Reference
PEG-400	-71	[36]
PVP Kollidon 25PF	155	[37]
PVP Kollidon 90F	185	Supplied by BASF
Water	-133	[38]

Figure(s)

Figures

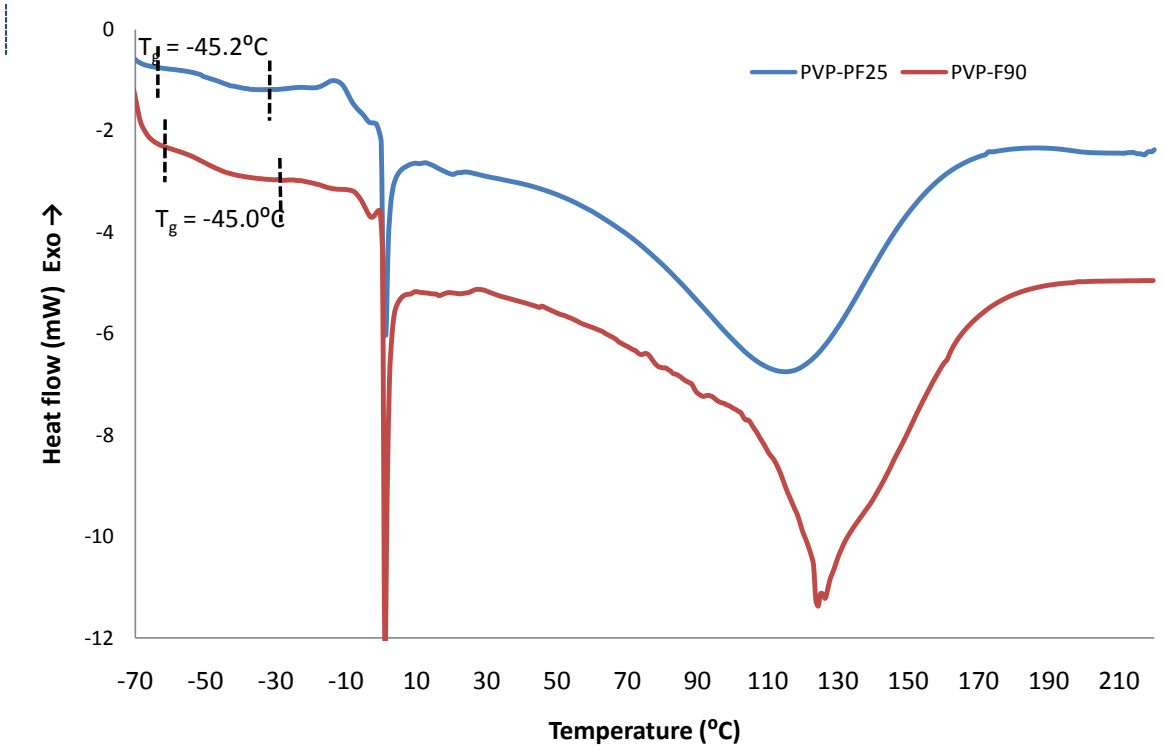

Figure 1: DSC thermograms of complexes of PEG with PVP (— 25PF; — 90F) processed in $scCO_2$.

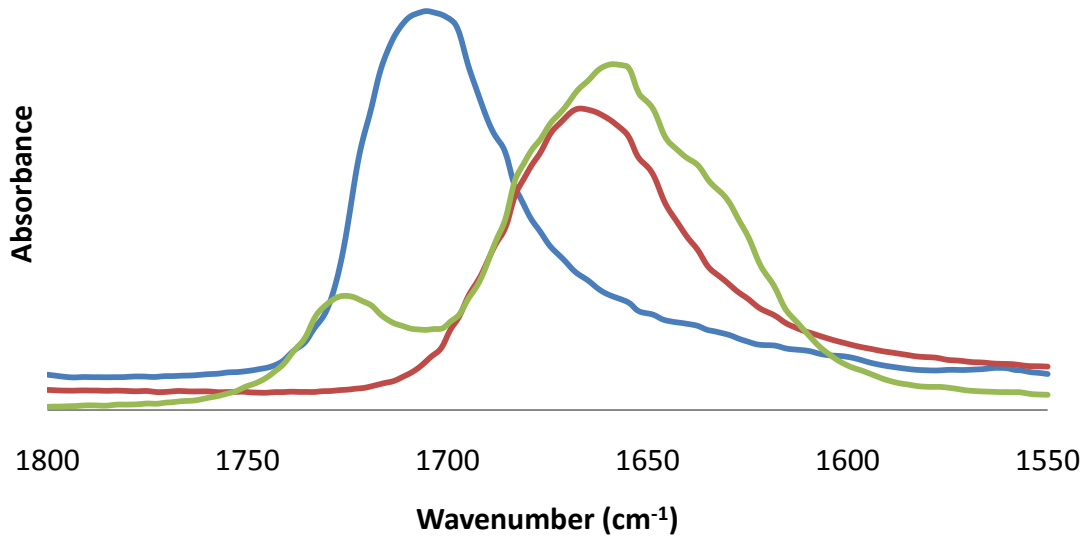

Figure 2: FT-IR spectra in the *v*(C=O) region for ibuprofen (—), PEG-PVP complex (—) and ibuprofen-loaded PEG-PVP complex (—)

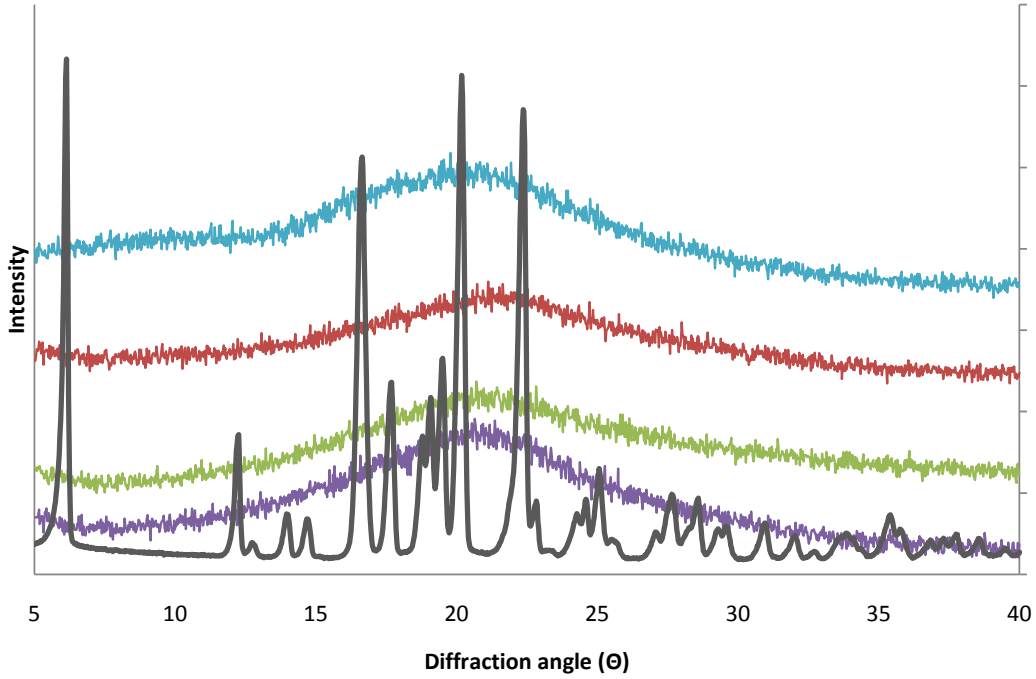

Figure 3: XRD diffractograms of solution cast PEG-PVP complex with PVP-PF25 (—) and PVP-90F (—**)**, supercritical CO_2 prepared PEG-PVP complex with PVP-PF25 (—) and PVP-90F (—), and pure ibuprofen (—).

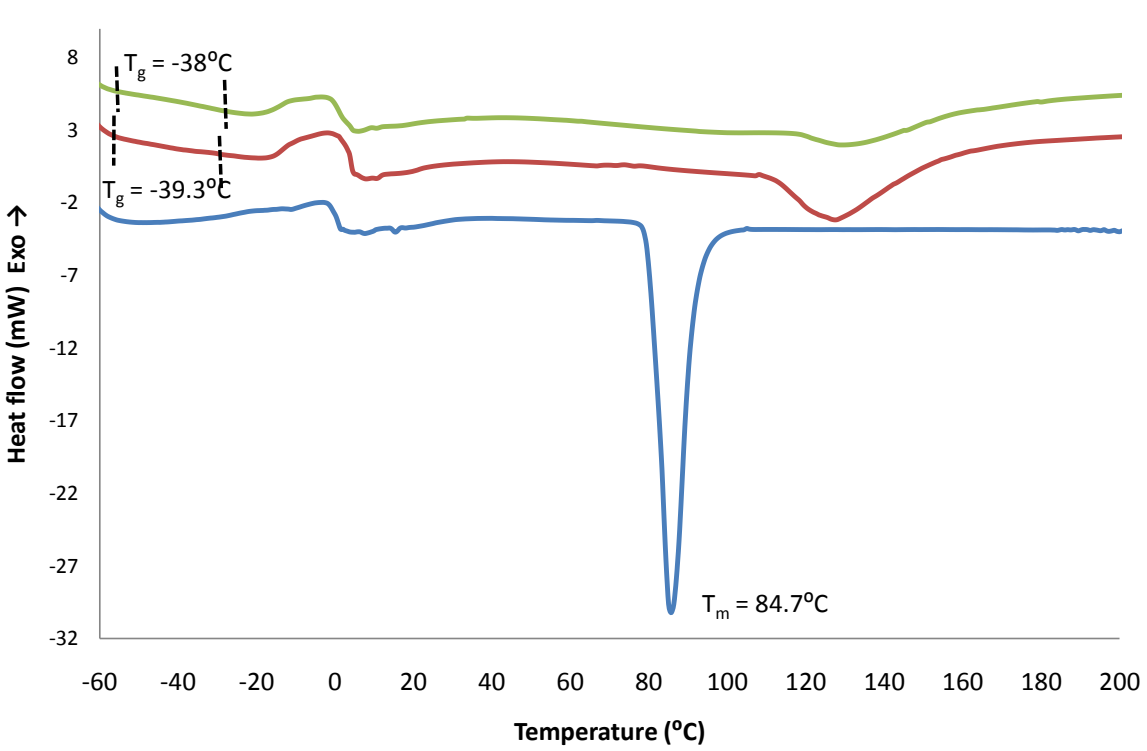

Figure 4: DSC thermograms of PEG-PVP complexes cast from ethanol solution (—), prepared from supercritical CO_2 (—) and pure ibuprofen (—)

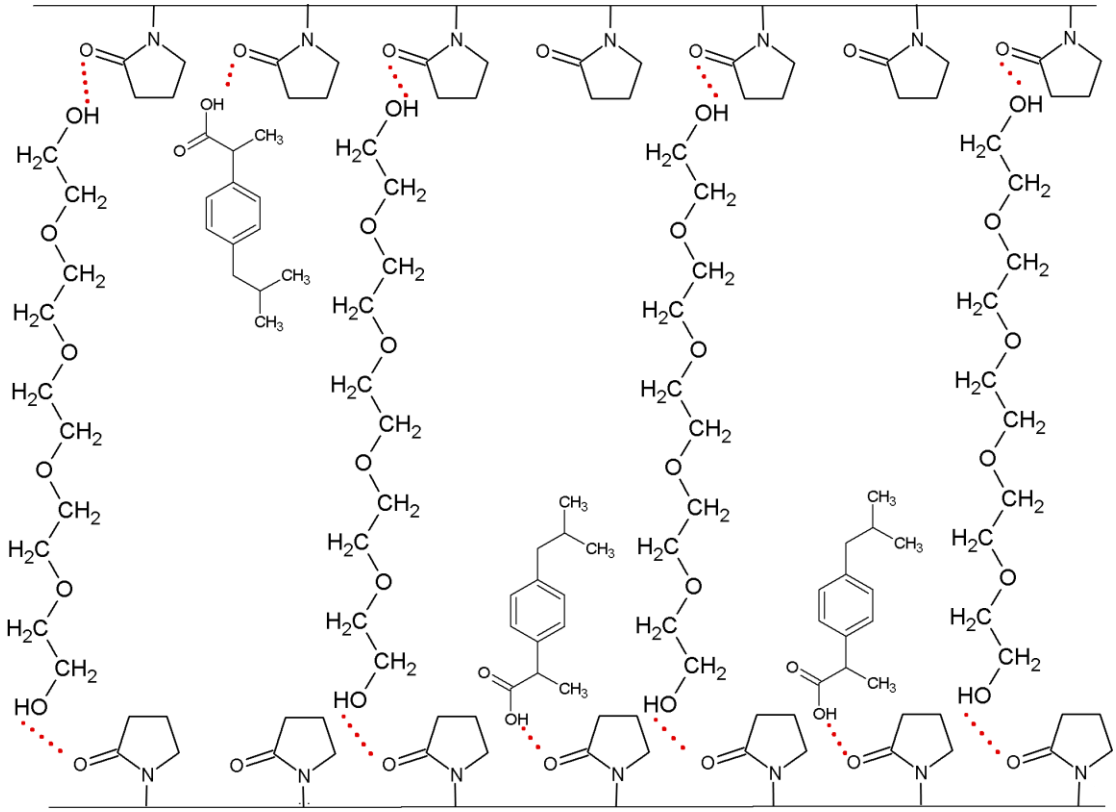

Figure 5: Schematic representation of the ibuprofen-loaded PEG-PVP complex

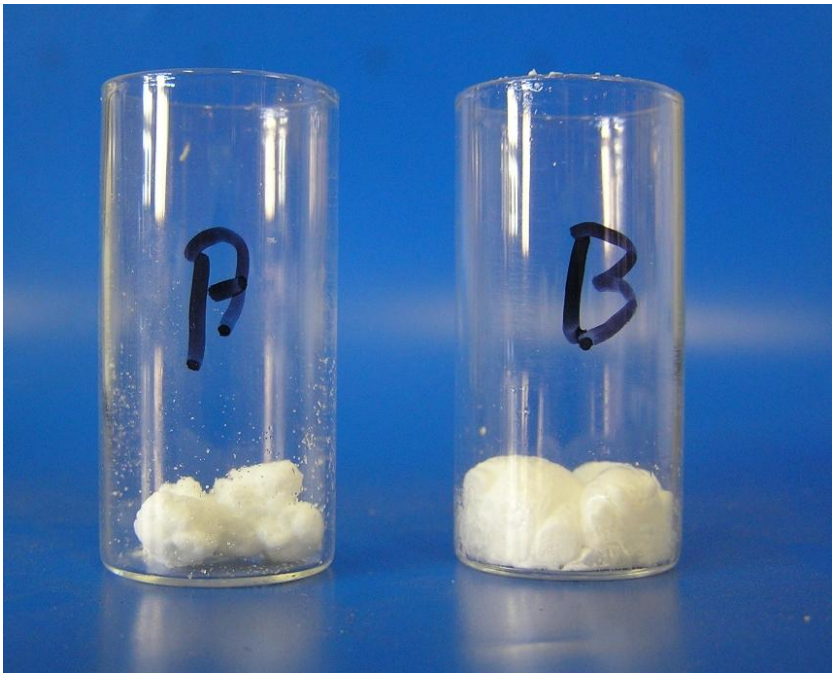

Figure 6: PEG-PVP complexes prepared in supercritical CO_2 without (A) and with (B) 30 wt% ibuprofen.

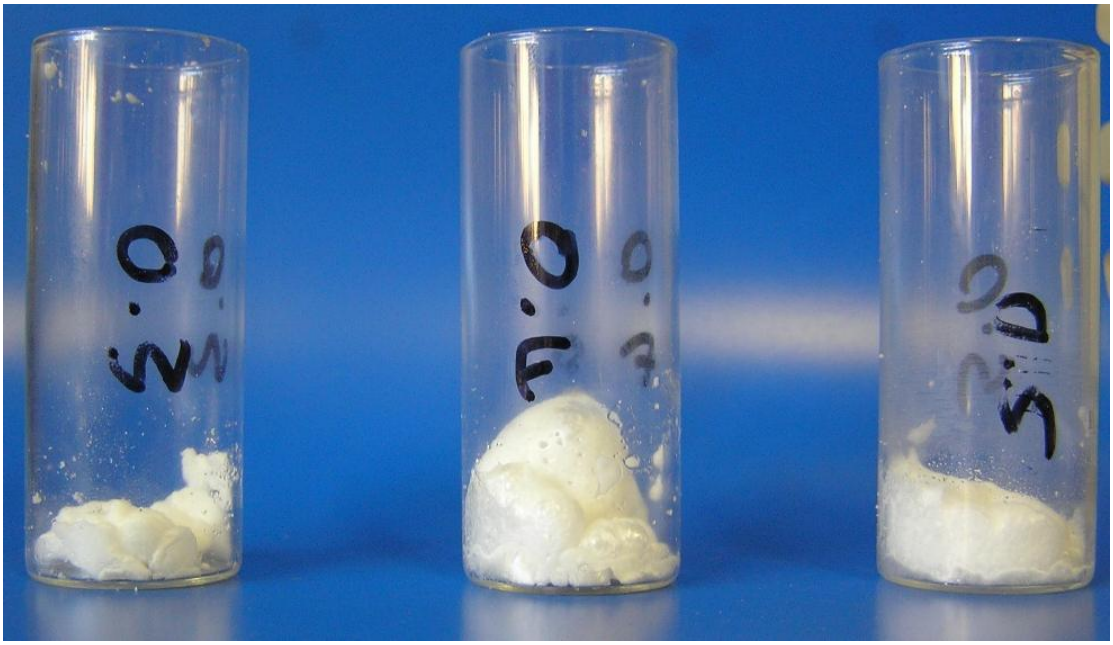

Figure 7: PEG-PVP complexes with 30, 40 and 50 wt% ibuprofen prepared in supercritical CO_2.

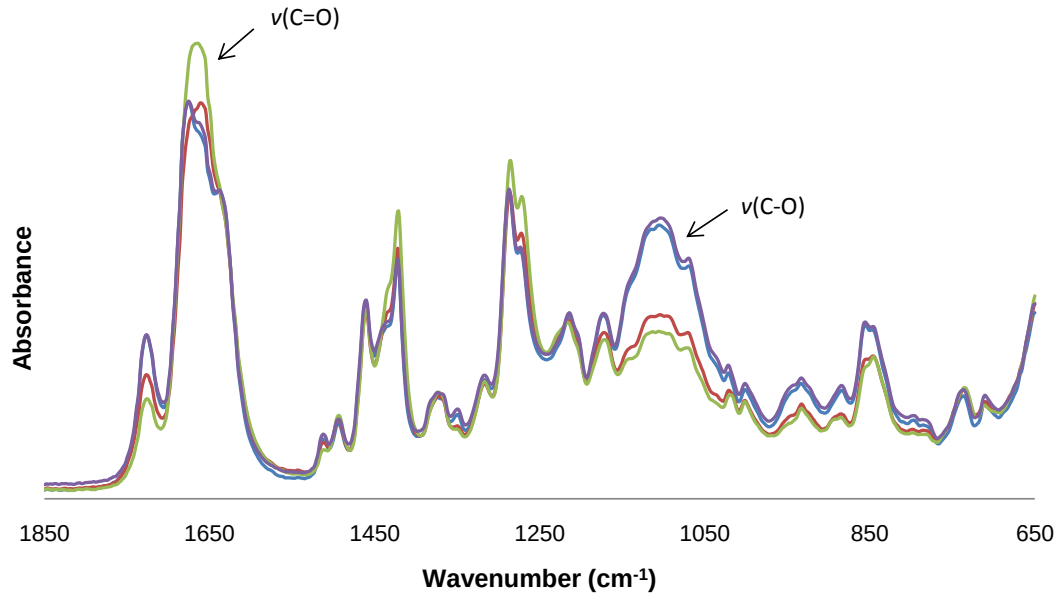

Figure 8: Overlay of ATR-FTIR spectra of 4 samples of 30wt% ibuprofen-loaded PEG-PVP complex processed at 220 bar.

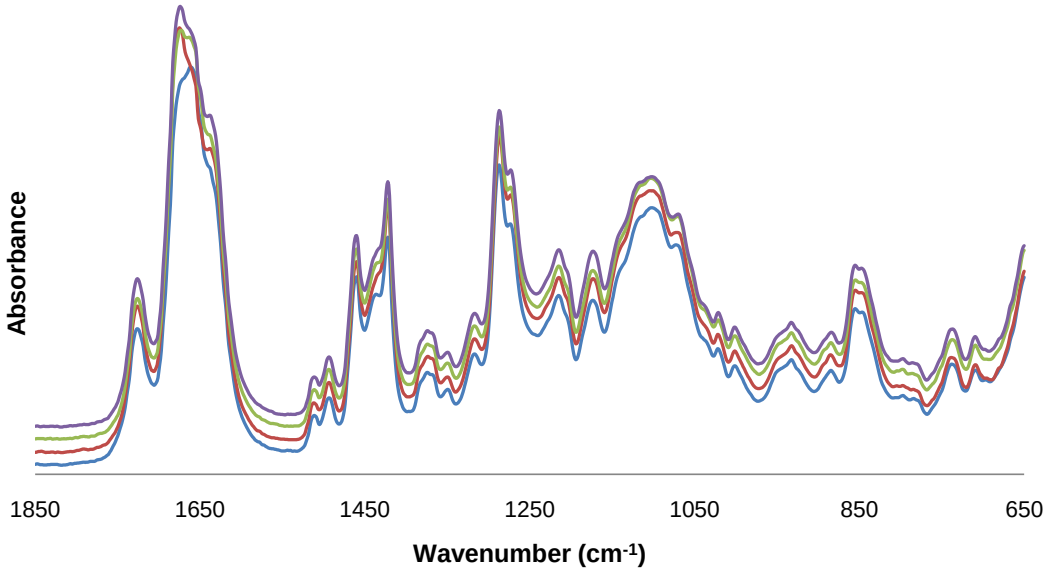

Figure 9: Overlay of ATR-FTIR spectra of 4 samples of 30 wt% ibuprofen-loaded PEG-PVP complex processed at 60ºC.

Figure 10: Physical appearance of 30wt% ibuprofen-loaded PEG-PVP complex processed at 60ºC

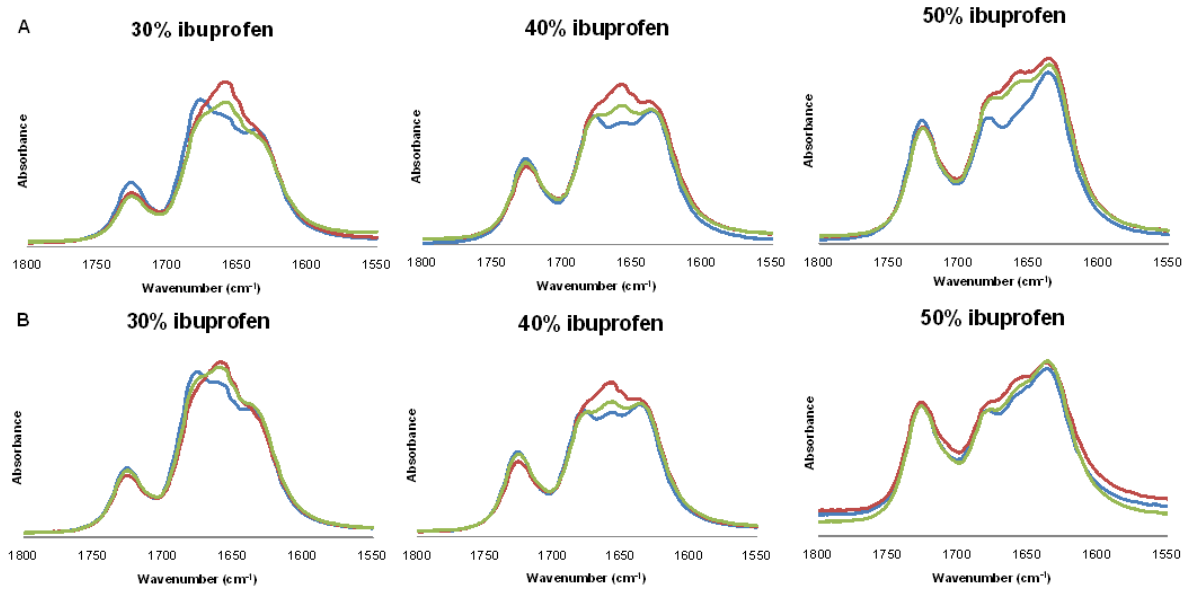

Figure 11: Comparison of spectra in the PVP *v*(C=O) region for ibuprofen-loaded PEG-PVP complexes prepared in supercritical CO_2 (row A) and cast from ethanol (row B): immediately after preparation (—), after 1 week (—) and after 3 weeks storage (—).

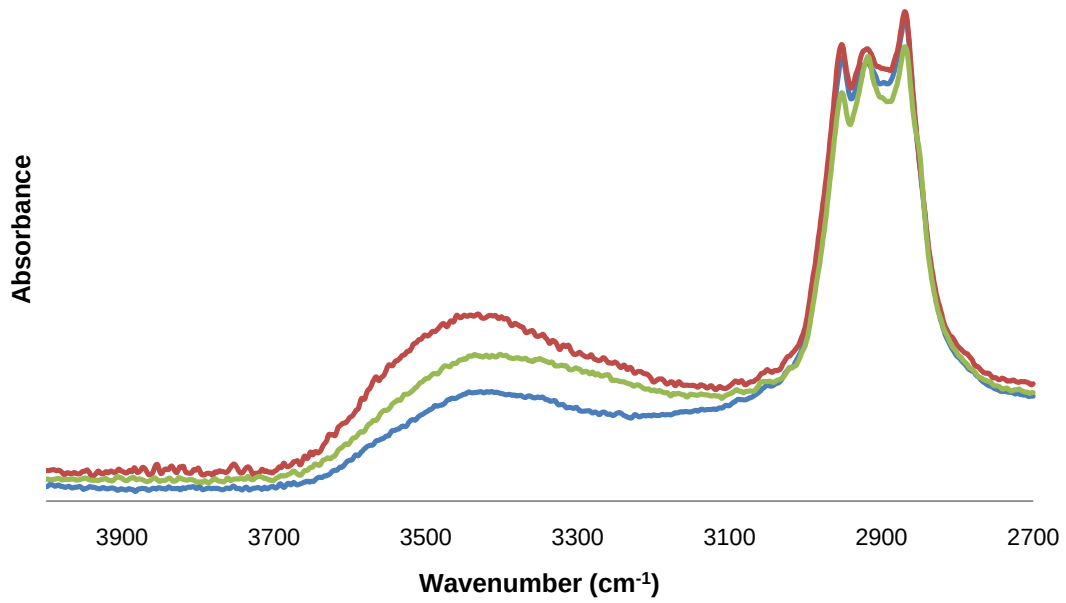

Figure 12: ATR-FTIR absorption spectra of an ibuprofen-PEG-PVP complex in the *v*(O-H) region showing intensity: immediately after preparation (—**)**; after 1 week storage(—); after 3 weeks storage (—)

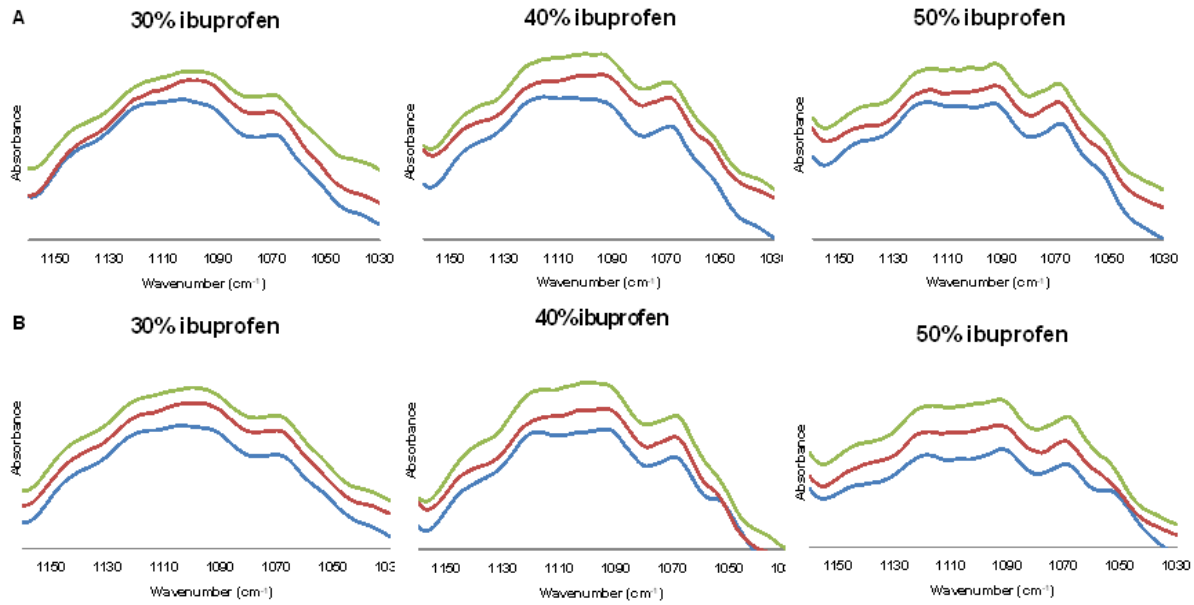

Figure 13: Comparison of spectra in the PEG oxyethylene absorption region for ibuprofen-loaded PEG-PVP complexes prepared in supercritical CO_2 (row A) and cast from ethanol (row B): immediately after preparation (—), after 1 week (—) and after 3 weeks storage (—).