Supercritical CO_2-assisted preparation of ibuprofen-loaded PEG-PVP complexes: Comparison with conventional processing methods

Philip W. Labuschagne[a], Sergei G. Kazarian[b], Rotimi E. Sadiku[c]

[a] Polymers and Ceramics, Materials Science and Manufacturing, CSIR, P.O. Box 395, Pretoria 0001, South Africa
[b]Department of Chemical Engineering, Imperial College London, South Kensington Campus, London SW7 2AZ, United Kingdom
[c]Tshwane University of Technology, Department of Polymer Technology, Private Bag X 025, Lynnwoodridge 0040, South Africa

Abstract

Transdermal drug-delivery systems based on the interpolymer complexation (IPC) between poly(ethylene glycol) (PEG) and poly(vinylpyrrolidone) (PVP) has so far only been prepared in aqueous or solvent medium. Supercritical CO_2 as alternative process medium is attractive since its "soft" process environment could allow a greater number of drugs to be incorporated in such IPC's for transdermal delivery. The aim of this study was to first determine if supercritical CO_2 can facilitate the formation of stoichiometric PEG-PVP interpolymer complexes. Then, comparisons between ibuprofen-loaded PEG-PVP complexes prepared via conventional solvent casting method and in supercritical CO_2 were made. Finally, the effects of supercritical CO_2 process conditions on the characteristics of ibuprofen-loaded PEG-PVP complexes were studied. Analytical techniques used were: differential scanning calorimetry (DSC), attenuated total reflection Fourier transform infrared (ATR-FTIR) spectroscopy and X-ray diffraction (XRD). Overall it was shown that ibuprofen-loaded PEG-PVP complexes can be prepared from supercritical CO_2 processing showing similar characteristics to such complexes prepared from solvent casting.

Keywords: carbon dioxide, interpolymer complex, ibuprofen
**Corresponding author: Tel.: +27 12 841 2149, Fax. +27 12 841 3553*
E-mail address: plabusch@csir.co.za

1. INTRODUCTION

Most studies on the preparation of drug delivery systems in supercritical CO_2 are 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. Feldstein *et. al.* [8] developed 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 (M_w) PVP, often used as a carrier to enhance the bioavailability of drugs.

In this study, stoichiometric 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 Comparisons are made between mixtures prepared in supercritical CO_2 and mixtures cast from aqueous solution. Also, the effects of supercritical CO_2 process conditions on the characteristics of ibuprofen-loaded PEG-PVP complexes were studied..

2. MATERIALS AND METHODS

2.1 Materials

PEG (M_w: 400) was purchased from Unilab, Germany. PVP Kollidon 25PF (±3.1 x 10^4 M_w) and Kollidon 90 F (±1.25 x 10^6 M_w) were purchased from BASF, South Africa. PVP samples were dried in an oven set to 100°C until no further weight loss was recorded. Carbon dioxide (99.995% purity) was purchased from Air Products, South Africa. Ibuprofen was purchased from Sigma-Aldrich, South Africa.

In all cases, gravimetric moisture content in the samples was measured using a Sartorius analytical balance with an accuracy of 0.01 mg.

2.2 Preparation of PEG/PVP complexes

Mixtures cast from solution: 1.28g of dried PVP and 0.72g of PEG-400 were carefully weighed off to yield a mixture with 36 wt% PEG-400, the stoichiometric ratio for PEG-PVP complexes. Afterwards water was added to yield a 50 wt% aqueous solution. 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 6 hours, resulting in samples with approximately 5 wt% moisture content. The samples were then equilibrated in open atmosphere for 24 hours to equilibrium moisture content of approximately 12 wt%.
Mixtures prepared in supercritical CO_2: 1.28g of PVP and 0.72g of PEG-400 were carefully weighed off and stirred with a spatula until visually homogenous. The mixtures were then placed in a supercritical CO_2 reactor as described in a previous paper[15], preheated to 40ºC and then pressurised to 120 bar. These conditions were maintained for 3 hours, after which CO_2 was vented at a rate of approximately 50 bar/minute and the sample removed. The mixture was then allowed to equilibrate in open atmosphere for 24 hours to equilibrium moisture content of approximately 12 wt%.

2.3 Differential Scanning Calorimetry (DSC)

A DSC1/700 (Mettler Toledo Instruments), calibrated with indium and zinc, was used to perform the DSC analysis on the samples. Samples were run in triplicate, with the reported T_gs the average of which varied by less than 5%. 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}, using 10 scans with a resolution of 4 cm^{-1}. Of each sample four spectra was obtained. Due to the gel-like nature of the product, it was possible to retrieve replicate samples from various depths inside the product. For in-situ ATR-FTIR tests a heated “Golden Gate” (diamond crystal with an

incident angle of 45°, ZnSe focusing lenses) was used. A specially designed “covering-cap” high-pressure cell, which was compatible with the single-reflection ATR accessories (Specac Ltd, UK), was used.

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

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 [9,11]. In the case of PEG-PVP complexes, large negative deviations occur, due to the enhanced free volume resulting from the considerable length of PEG physical cross-links between PVP chains [7]. Figure 1 shows DSC heating thermograms of complexes of PEG with PVP (Kollidon 25PF & 90 F) measured after supercritical CO_2 processing.

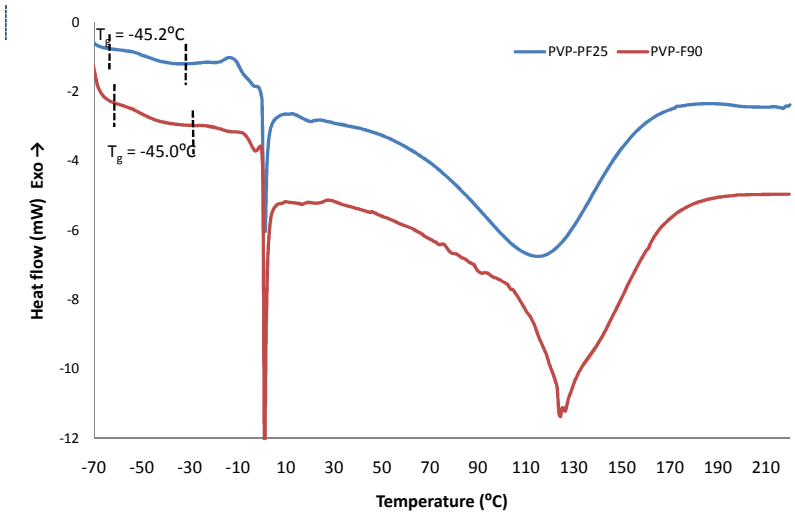

Figure 1: DSC thermograms of complexes of PEG with PVP (— 25PF; — 90F) processed in scCO_2 at 120 bar and 40°C.

The presence of absorbed moisture in all samples are characterised by a melting peak of free water at ca. 1ºC and a broad thermodesorption endotherm in the temperature range ca. 40ºC to 170ºC. While a previous study has shown that 12 wt% hydration in PEG-PVP complexes does not lead to a separate water phase (and thus no melting endotherm) [4], the presence of free water in these blends could indicate towards CO_2 processing affecting the phase state of hydrated PEG-PVP complexes. 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 36 wt% of PEG-400 in Kollidon 25PF with 12 wt% hydration should theoretically be -1.3ºC. Replacing with Kollidon 90 F the Fox equation predicts a theoretical T_g of 2.2ºC.

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

Component	Tg (ºC)
PEG-400	-66
PVP Kollidon 25PF	162
PVP Kollidon 90F	178
Water	-133[1]

A significant negative deviation from the simple rules of mixing is seen in all complexes, irrespective of preparation method. Thus, T_g values show that processing stoichiometric ratio's of PEG and PVP in supercritical CO_2 medium also 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 (Kollidon 90 F - 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[12].

3.2 ATR FT-IR spectroscopic analysis of ibuprofen-loaded PEG-PVP complexes

The next aim was to prepare ibuprofen-loaded (30 wt%) PEG-PVP(Kollidon 90 F) complexes using supercritical CO_2 as processing medium (120 bar & 40ºC). 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 [12,17]. Interaction strength is strongly correlated with the position of spectral bands [10] and a previous study has shown that ibuprofen-PVP interaction leads to a PVP carbonyl wavenumber shift, $\Delta\nu$(C=O), in the order of 46 cm^{-1} [12], while for PEG(400)-PVP interaction, $\Delta\nu$(C=O) is in the order of 24 cm^{-1} [14]. 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.* [4,6] showed that in stoichiometric complexation between PEG and PVP (36 wt% PEG), only about 20% of PVP repeat units are occupied by H-bonding with PEG terminal hydroxyl groups. Thus, 80% 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.

Figure 2 compares the ibuprofen ν(C=O) peak position with the ν(C=O) peak positions of the PEG-PVP(Kollidon 90 F) complex and ibuprofen-PEG-PVP(Kollidon 90 F) complex, both of which were prepared in supercritical CO_2. First to be noticed is the shift of ibuprofen ν(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

[3,12,13]. 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 [12].

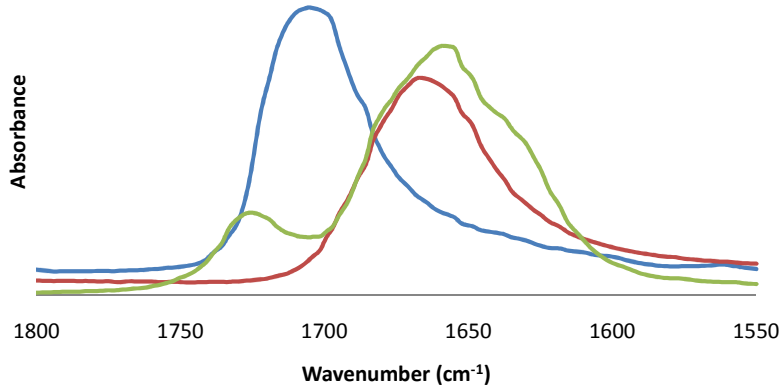

Figure 2: FT-IR spectra in the *v*(C=O) region for ibuprofen (—), PEG-PVP (Kollidon 90F) complex prepared in supercritical CO_2 (—) and ibuprofen-loaded (30 wt%) PEG-PVP (Kollidon 90F) complex prepared in supercritical CO_2 (—) (All prepared at 120 bar pressure and 40ºC)

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 wt% 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, irrespective of preparation method, 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 [16]. 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.* [5].

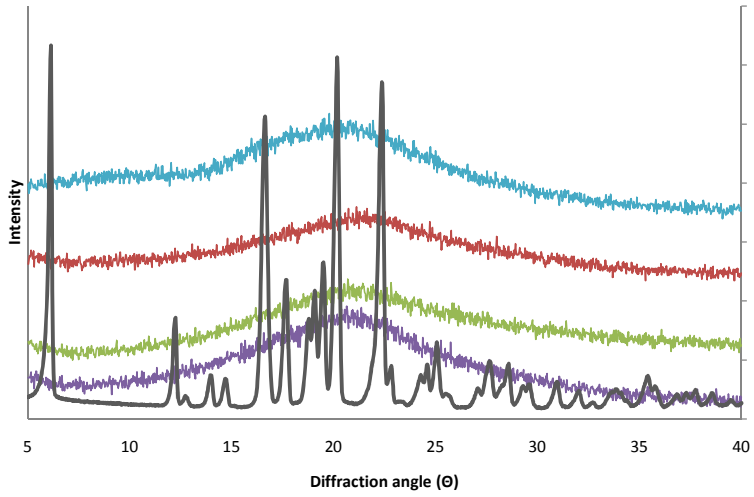

Figure 3: XRD diffractograms of solution cast ibuprofen(30 wt%)-PEG-PVP complex with PVP-PF25 (—) and PVP-90F (—) and supercritical CO_2 prepared (120 bar; 40°C) ibuprofen(30 wt%)-PEG-PVP complex with PVP-PF25 (—) and PVP-90F (—), and of pure ibuprofen (—).

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 (30 wt%) PEG-PVP(Kollidon 90 F) complex cast from ethanol solution and the same complex prepared in supercritical CO_2 at 120 bar and 40ºC. 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 [2]. Interestingly, comparisons of the area under the water thermodesorption endotherm (J/g) indicate that PEG-PVP complexes with 30 wt% ibuprofen (supercritical CO_2 processed: 98.6 J/g; cast from solvent: 60.9 J/g) has a lower water content than the same PEG-PVP complexes without ibuprofen (supercritical CO_2 processed: 140.9 J/g; cast from solvent: 140.6 J/g). The reason for reduced water content can be explained by competition between ibuprofen and water molecules for interaction with PVP carbonyl groups. Since ibuprofen molecules already occupy some of the PVP carbonyl groups via strong H-bonds, they are not available for interaction with water molecules [12]. However, some strongly bound water is always expected to be present in PVP, even after extensive drying. This is not expected to affect PEG interaction with PVP, since a previous study has shown that PEG molecules can interact with PVP carbonyl groups “through” water molecules already bonded to the PVP carbonyl groups [14]. In fact, such PEG-H_2O-PVP interactions have interaction strengths measuring 50.1 kJ/mol compared to 20.3 kJ/mol of PEG-PVP interactions.

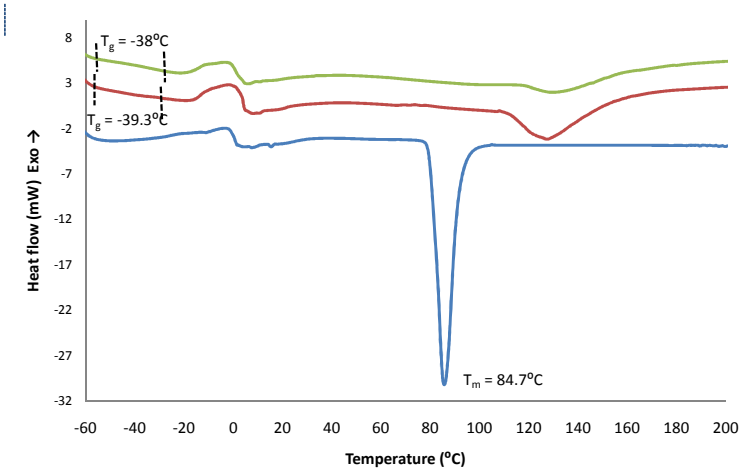

Figure 4: DSC thermograms of ibuprofen(30 wt%)-PEG-PVP(Kollidon 90F) complexes cast from ethanol solution (—), prepared from supercritical CO_2 (120 bar & 40ºC) (—) and pure ibuprofen (—)

The above results show that ibuprofen prefers interaction with PVP, and that the high free-volume PEG-PVP network is mainly intact.

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 In-situ ATR FTIR analysis

In-situ monitoring of spectral shifts of the PVP and ibuprofen ν(C=O) bands before and after CO_2 processing and under varying conditions of pressure, temperature and time were conducted (Figure 5):

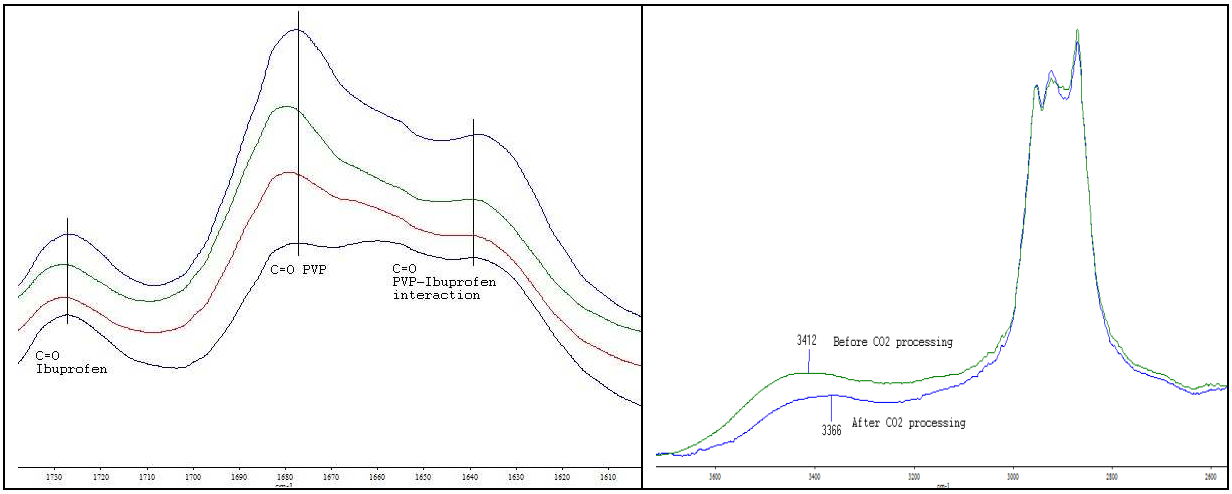

Figure 5: Spectral shifts of *ν*(C=O) bands of (from bottom to top): 0 bar/40°C; 100 bar/40°C - immediate; 100 bar/40°C – 3 hrs; after CO_2 venting. Image on the right shows spectral bands of the OH- absorption region before and after CO_2 processing.

Absorption of CO_2 into the drug-loaded PEG-PVP complex leads to an increase in intensity of the v(C=O) band that is associated with relatively weakly bound carbonyl groups versus the the v(C=O) band of more strongly bound carbonyl groups. This is expected as increased CO_2 concentration competes with PEG for interaction with the PVP carbonyl groups. The carbonyl group of ibuprofen is relatively unchanged. Interaction of PVP with ibuprofen is much stronger, thus it is unlikely that the CO_2 molecules can displace interacting ibuprofen molecules. Upon CO_2 venting, little change in the spectrum is noticed. Part of the reason can be seen in the image on the right showing the OH-absorption region before and after processing with CO_2. Here it can be seen that the OH-band intensity has decreased slightly and shifted to lower wavenumbers. The decrease in intensity could indicate towards extraction of loosely bound water molecules upon CO_2 venting.

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 ($\pm 1.25 \times 10^6$) 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 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.

CO_2 sorption into the PEG-PVP complex leads to disruption of PEG-PVP interaction, while ibuprofen-PVP interaction remains intact. Some fractions of loosely bound water molecules are extracted upon CO_2 venting.

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