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International Journal of Pharmaceutics 338 (2007) 191–197
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Synthesis of poly(sebacic anhydride)-indomethacin controlled release composites via supercritical carbon dioxide assisted impregnation

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Received 30 May 2006; received in revised form 26 January 2007; accepted 2 February 2007
Available online 11 February 2007

Abstract

Poly(sebacic anhydride), PSA and indomethacin drug composite (DC) formulations were prepared using supercritical CO_2 (sc-CO_2) aided mixing. The effect of the experimental temperature and sebacic acid purity on the physical properties of PSA–indomethacin DCs was investigated using a range of analytical techniques. The nature of the PSA–indomethacin interaction in composites after processing in sc-CO_2 under various conditions was investigated using differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, and powder X-ray diffraction (XRD) methods, respectively. The results indicate that processing at 130 °C of a 4:1 (w/w) ratio PSA–indomethacin mixture, renders the indomethacin amorphous and dispersed within the polymer matrix. The primary interaction between PSA and indomethacin appears to be hydrogen bonding between the carboxylic acid OH of indomethacin and the carbonyl group of PSA. In vitro dissolution studies revealed that the processed composites exhibit a substantially enhanced dissolution rate compared to the physical mixtures. Also, through the control of experimental conditions, the initial burst effect of the drug release was largely alleviated. Instead, the erosion of PSA (zero order degradation) became the dominant factor in controlling the drug release rate.

Keywords: Poly(sebacic anhydride); Indomethacin; Sc-CO_2; Supercritical fluid; Amorphous; Impregnation

1. Introduction

Controlled-release systems are widely used for treatment of diseases ranging from diabetes to cancer (Debenedetti et al., 1993). The administration route of the controlled-release systems can be through the form of oral tablet or implant devices according to the drug release rate from the system (Robinson, 1976). Furthermore, when degradable controlled-release system is used in implant device, it has an advantage over a non-degradable system as there is no need to surgically remove the drug depleted device (Vasheghani-Farahani and Khorram, 2002). The formulation of such a system requires a suitable matrix capable of releasing the active drug (Guney and Akgerman, 2002). Potentially, biodegradable matrix systems also enjoy a number of other advantages in terms of simplicity in design and predictability of release, if release is controlled largely through the degradation of the matrix (Heller et al., 1983; Langer, 2001).

Over the last two decades (Leong et al., 1985, 1986; Chasin et al., 1988; Mathiowitz et al., 1990), biodegradable polyanhydrides based on aromatic and aliphatic dicarboxylic acids, have extensively been used as delivery vehicles for therapeutic substances. Polyanhydrides are surface eroding polymers from which release of drugs is governed by surface erosion hydrolysis of the highly labile anhydride bonds. Thus, polyanhydride (PA) drug delivery devices differ from bulk eroding systems (e.g. based on PLA) in their mechanism of degradation. Since polyanhydrides are surface eroding polymers, they have a distinct advantage for stabilizing active agents (e.g. protein stabiliztion) in that they limit water penetration, thereby preventing proteins from denaturing in physiological conditions. Moreover, by synthesizing polyanhydride copolymers using aliphatic and aromatic monomers, precise control over the degradation rate can be achieved, from days to years (Quellec et al., 1999; Kissel et al., 1996; Cleland et al., 1997, 2001). Polyanhydrides can be easily prepared from low cost resources,

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doi:10.1016/j.ijpharm.2007.02.009

are biocompatible, and degrade in vivo into non-toxic diacid counterparts that are eliminated from the body as metabolites (Vogel and Mallapragada, 2005). Thus, they are of interest as biomaterials for the delivery of drugs to various organs such as the brain, bone, blood vessels, and the eyes (Brem et al., 1995; Brem and Lawson, 1999; Uhrich et al., 1999). For example, Li et al. (2002) a polyanhydride implant device for delivery of antibiotics in the treatment of osteomyelitis.

A range of synthetic methods has been investigated to load drugs into PA matrices. For example, Vasheghani-Farahani and Khorram (2002) successfully obtained polyanhydride microspheres loaded with theophylline and diltiazem hydrochloride (DHC) using a solvent removal method using an "oil-in-oil" (O/O) emulsion system. Poly(anhydride-*co*-imide) microspheres with entrapped bovine serum albumin (BSA), were also made using the double emulsion solvent evaporation process in a report by Hanes et al. (1998). As the use of large amounts of organic solvent can often leave cytotoxic residues or give imprecise control over drug or polymer particle properties (York, 1999), there is increasing interest in the use of more 'environmentally benign' solvents such as supercritical fluids (SCFs) in pharmaceutical processing (Yeo and Kiran, 2005).

Supercritical fluids are compressed gases that can display properties between those of liquids and gases (Darr and Poliakoff, 1999). The properties of supercritical fluids can be tuned by adjusting the fluid parameters such as pressure and temperature (Darr and Poliakoff, 1999; Yeo and Kiran, 2005). There is a huge amount of literature in the use of supercritical fluids as alternatives to organic solvents for preparing drug delivery formulations (Kompella and Koushik, 2001). In pharmaceutical processing, supercritical dioxide (sc-CO_2), offers a particular advantage in that the polymer plasticization processing can be carried out at low temperatures (Darr and Poliakoff, 1999). This can be important for thermally sensitive drug or biomaterials (e.g. enzyme) formulations where the incipient may degrade when exposed to high temperatures (Howdle et al., 2001). In particular, Howdle et al. (2001) and Ginty et al. (2005) have begun to look at supercritical fluid assisted mixing of drug particles and biological materials in degradable/non-degradable polymers. Our research group has identified several drug–polymer systems in which SCF can be used to yield an amorphous form of the drug via drug–polymer interactions (Gong et al., 2005, 2006, 2007). This has been observed for water soluble thermoplastic polymer (PVP) which displays rapid release profiles for indomethacin (Gong et al., 2005). We have also observed that for non-water soluble polymers (slowly degradable) impregnated with drugs, drug release can follow a 1/3 power law (Gong et al., 2007).

2. Materials and methods

2.1. Materials and equipment

Poly(sebacic anhydride), PSA ($M_n \approx 1900$) and indomethacin (99%) were purchased from Sigma–Aldrich Company Ltd. (Dorset, UK) and initially used as received. The PSA was later found to contain significant SA monomer, which was extracted to give pure PSA (see experimental Section 2.2). A liquid withdrawal CO_2 cylinder at 725 psi pressure was supplied by BOC gases. The CO_2 was chilled to −6 °C before being delivered via an Isco model 260D syringe pump with a chilled piston barrel. A custom made 220 ml stirred high pressure autoclave (approximate d = 340 mm, length = 45 mm) with a viewing window and paddle type stirrer.

2.2. Synthesis

The as received PSA from Sigma–Aldrich Company Ltd. contained significant sebacic acid monomer impurity (hereafter this is known as 'impure PSA'). An extraction procedure was devised to remove the monomer from the PSA matrix. Impure PSA was heated in warm toluene (50 °C) under stirring for 6.5 h and then filtered and dried in an oven at 37 °C overnight. This sample was known as 'pure PSA'.

For the polymer–drug composites, both pure and impure PSA, respectively, were used and compared. Typically, 4.00 g PSA and 1.00 g indomethacin were accurately weighed and gently mixed by hand with mortar and pestle for 10 min, before being transferred into the 220 ml magnetically stirred autoclave (with a window). The autoclave was sealed and filled with liquid CO_2 from the CO_2 cylinder at 725 psi (50 bar), and then pressurized slightly using the Isco pump. The autoclave was then held at 2500 psi (172 bar)/40 °C (or at 60, 80 and 130 °C, respectively) under stirring (180 rpm) for 2 h. At the end of the experiment, the stirrer was switched off and CO_2 was released over a period of 10 min. The color of final product was light yellow, strong yellow, grey and brown with processing temperatures of 40, 60, 80 and 130 °C, respectively.

2.3. Characterization

X-ray powder diffraction (XRD) data were collected for the powdered sample using a Siemens D5000 diffractometer, using Cu Kα radiation ($k\alpha_1$ = 1.5406 Å). Data were collected over the 2θ range 5–50° with a step size of 0.02° and step time of 1.0 s.

Differential scanning calorimetry (Perkin-Elmer DSC 7) was employed to study the thermal behaviour of PSA and indomethacin mixtures processed in sc-CO_2. The DSC was calibrated using pure samples of indium and zinc, respectively. From our experiments, samples containing indomethacin equivalent to 6.0 mg were carefully weighed in aluminium pans, and covered with an aluminium lid incorporating a pinhole. DSC curves of each sample were obtained from the first heating run at a rate of 10 °C/min under dry nitrogen atmosphere from 30 to 200 °C. Each sample was run in triplicate.

FTIR spectra were carried out using Nicolet 8700 FTIR spectrometer with a photoacoustic sampling cell (He purged). Spectra were obtained using 4 cm^{-1} resolution, averaging for 128 scans.

Scanning electron microscopy (SEM) was carried out on the products using a JEOL 6300^{TM} (accelerating voltage 10 kV). Prior to examination, samples were mounted onto 5 cm diameter circular aluminium stubs using double-sided adhesive tape and then coated with a thin layer of gold by using a sputter coater (Emitech K550) to render them electrically conductive.

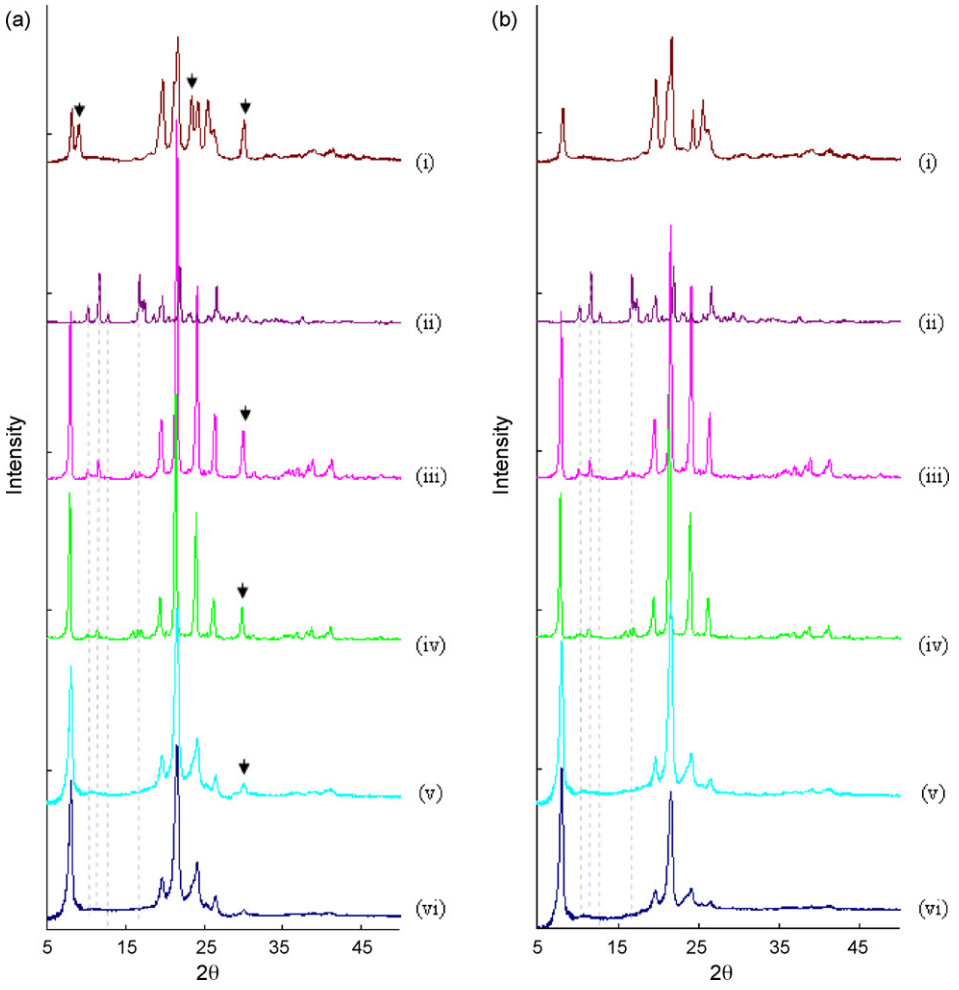

Fig. 1. X-ray diffraction pattern for (a) impure PSA mixture and (b) pure PSA mixture for the following: (i) PSA alone, (ii) pure indomethacin, (iii) PSA–indomethacin DC (40 °C), (iv) PSA–indomethacin DC (60 °C), (v) PSA–indomethacin DC (80 °C) and (vi) PSA–indomethacin DC (130 °C). All DCs were 4:1 (w/w) for PSA–indomethacin and processed at 2500 psi in sc-CO_2.

The dissolution rates of PSA–indomethacin physical mixture (PM), PSA–indomethacin (4:1 (w/w)) drug composites (DCs) prepared at different temperatures in sc-CO_2, were measured using UV–vis spectroscopy dissolution tests (Nicolet Evolution 500 UV–vis spectrophotometer). Each sample contained an amount equivalent to 50 mg indomethacin. The dissolution study was undertaken according to the USPXXI dissolution test method (Mi et al., 2001). The dissolution medium consisted of 1000 ml of phosphate buffer solution, PBS (pH 7.4), maintained at temperature of 37 ± 0.5 °C with a paddle rotation speed of 20 rpm. A 10.0 ml aliquot was collected at 1, 2, 4, 8, 12, 24, 48, 60, 72 and 80 h, respectively, with an equal volume of fresh deionised water supplemented into the dissolution flask immediately after sampling. The concentration of indomethacin released from DCs was calculated from the intensity of the UV–Vis data at 320 nm.

3. Result and discussion

X-ray powder diffraction was used to analyse the effect of the supercritical fluid processing parameters (i.e. temperature and pressure) on the crystallinity of indomethacin in the PSA matrix. Comparing to XRD patterns of pure indomethacin (Fig. 1a and b(ii)), the crystallinity of indomethacin gradually decreased with an increase in processing temperature in both the impure and pure PSA–drug composites (Fig. 1a and b(iii)–(vi)). PSA is a semi-crystalline polymer with the strong characteristic peaks observed in the XRD pattern. The peaks of interest for pure PSA are at 2θ values of 20°, 22°, 24° and 26°, respectively. The characteristic peaks at 2θ values of 10°, 23° and 30° (marked with arrows) for sebacic acid monomer (impurity) can be clearly observed in the XRD pattern of impure PSA (Fig. 1a(i)). The intensity of PSA peaks for both the pure and impure PSA DCs gradually decreased with an increase in temperature.

Differential scanning calorimetry (DSC) was conducted to confirm the molecular dispersion of indomethacin into pure PSA matrix. The single melting peak due to PSA was located at 87 °C (Fig. 2(i)). The melting point of final products appeared to be increase with an increase of processing temperature. This can be explained by an increasing cooperation of pure PSA with indomethacin. DSC data for pure PSA alone processed in sc-CO_2 at 80 and 130 °C, respectively, both showed a melting point of 76 °C (Fig. 2(ii) and (iii)). This could be due to a reduction in crystallinity of the treated matrix as a result of processing.

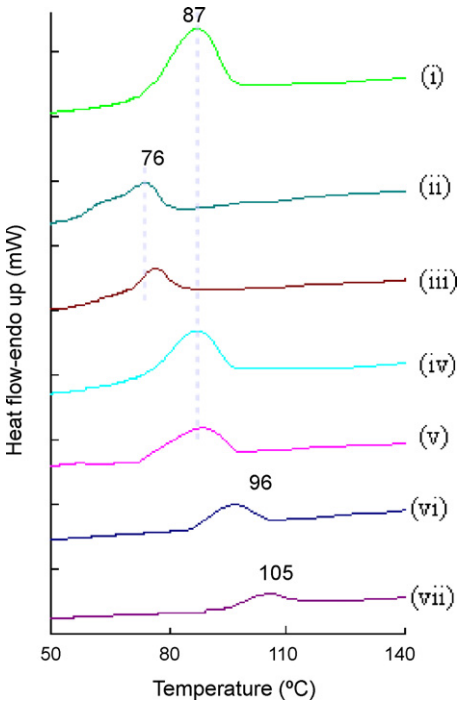

Fig. 2. DSC data for pure PSA mixture for the following: (i) PSA–indomethacin PM, (ii) PSA alone (80 °C), (iii) PSA alone (130 °C), (iv) PSA–indomethacin DC (40 °C), (v) PSA–indomethacin DC (60 °C), (vi) PSA–indomethacin DC (80 °C) and (vii) PSA–indomethacin DC (130 °C). All DCs possessed a ratio of PSA to indomethacin of 4:1 (w/w) and were processed at 2500 psi in sc-CO_2.

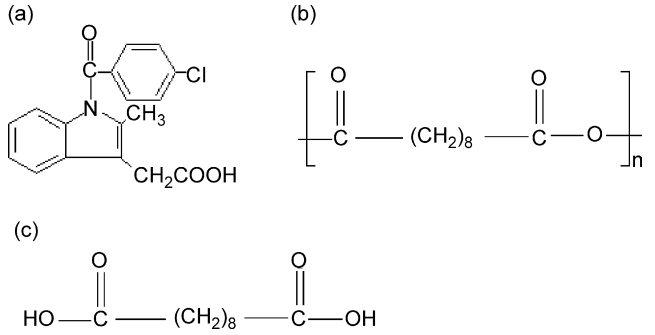

Fig. 4. Chemical structure: (a) indomethacin, (b) poly(sebacic anhydride) and (c) sebacic acid monomer.

FTIR spectroscopy was used to probe the interaction between PSA and indomethacin in the mixtures prepared in sc-CO_2. Characteristic peaks for pure PSA and indomethacin samples were easier to identify due to the simpler mixtures (Fig. 3b). Bands due to ν(C=O) bond stretches were studied to infer the physical state of the drug. In general, aliphatic anhydrides absorb at 1740 and 1810 cm^{-1} (Kumar et al., 2002), which can be observed in pure PSA (Fig. 3b(i)). In the pure PSA and indomethacin physical mixture, other than the characteristic bands for pure PSA, two additional carbonyl bands were located at 1729 and 1687 cm^{-1} due to the aliphatic and aromatic carbonyl stretching bands, respectively, of indomethacin (see Fig. 4 for the chemical structures of PSA and indomethacin). The changes in the FTIR spectra of the drug composites due to processing in sc-CO_2 can be observed in the fingerprint region (1800–1600 cm^{-1}) and are well defined. With increasing

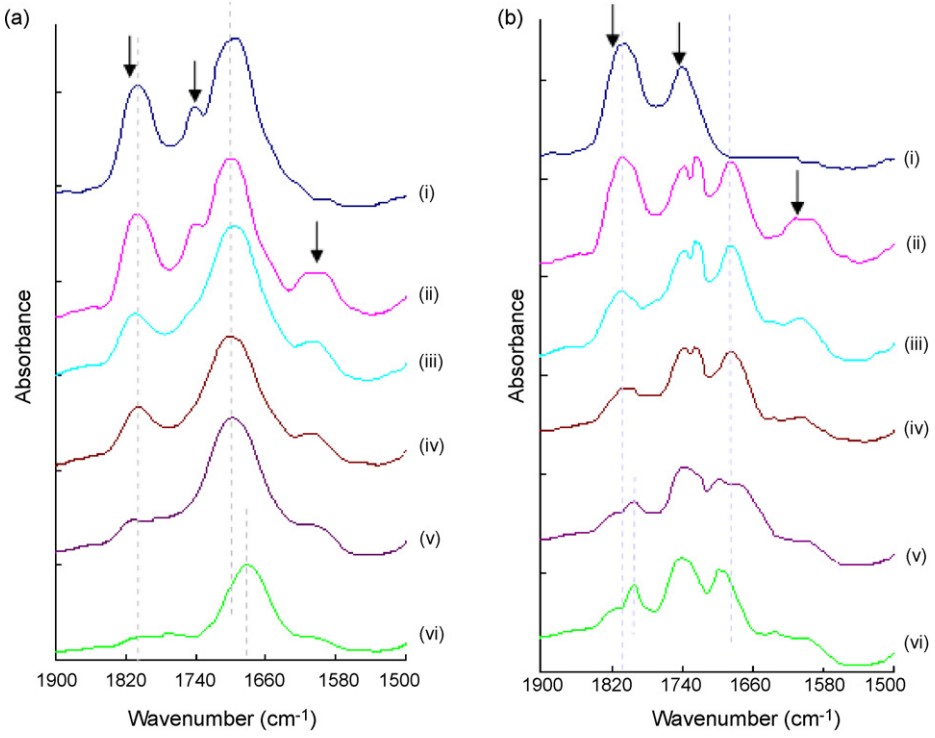

Fig. 3. FTIR spectra in the ν(C=O) spectral region (1900–1500 cm^{-1}) for (a) impure PSA mixtures and (b) pure PSA mixtures of the following: (i) PSA alone, (ii) PSA–indomethacin PM, (iii) PSA–indomethacin DC (40 °C), (iv) PSA–indomethacin DC (60 °C), (v) PSA–indomethacin DC (80 °C) and (vi) PSA–indomethacin DC (130 °C). All DCs were 4:1 (w/w) and processed at 2500 psi in sc-CO_2.

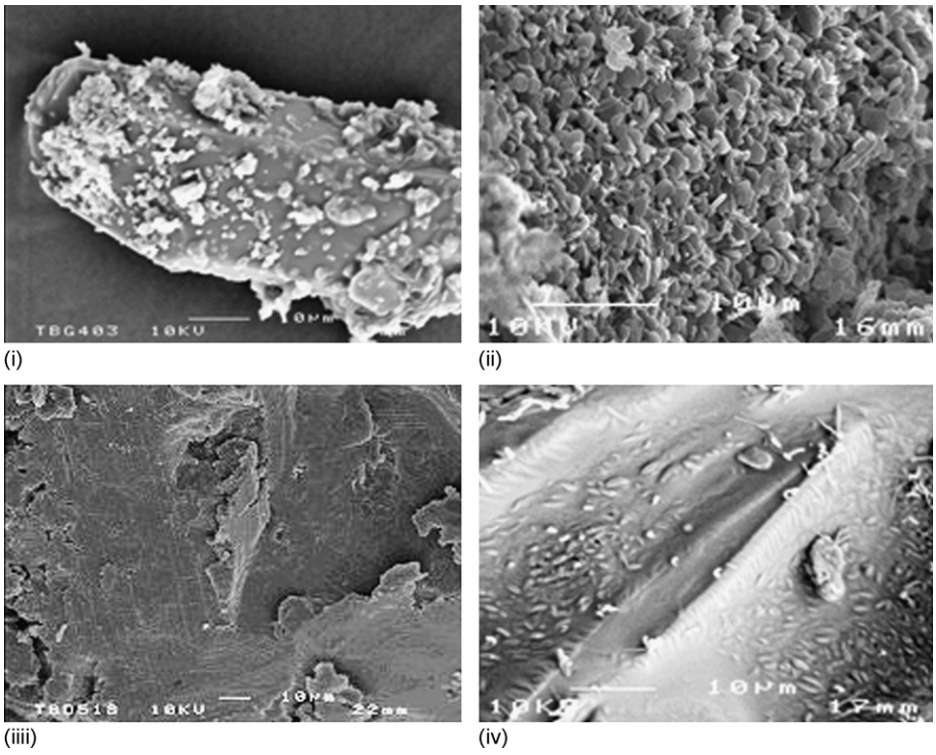

Fig. 5. Scanning electric microscope images for pure PSA mixture: (i) PSA–indomethacin physical mixture (PM), (ii) PSA–indomethacin drug composite (DC) at 40 °C, (iii) processed PSA–indomethacin DC (80 °C) and (iv) PSA–indomethacin DC (130 °C). All DCs were for a 4:1 (w/w) ratio and were processed at 2500 psi in sc-CO_2.

temperature, the carbonyl band at 1810 cm^{-1} (of pure PSA) decreased and shifted to a lower wavenumber, 1795 cm^{-1} (Fig. 3b (v) and (vi)). Also, the carboxylic acid carbonyl band of indomethacin at 1729 cm^{-1} was observed to change with the processing temperature, especially, for samples processed at 80 °C and 130 °C (Fig. 3b (v) and (vi), respectively). However, due to the overlap of carbonyl groups from both pure PSA and indomethacin in this spectral region (1780–1700 cm^{-1}), it is not clear whether the carboxylic carbonyl band of indomethacin decreased or shifted as a result of processing. However, the decrease of the intensity of aromatic ring C=C vibrational band of the indomethacin (1606 cm^{-1}) indicates a reduction in crystallinity of the indomethacin after processing. For the impure PSA–indomethacin mixtures, the strong carbonyl band at 1700 cm^{-1} due to the sebacic acid oligomer was observed. This band shifted to lower wavenumbers after high temperature (130 °C) sc-CO_2 processing (Fig. 3a (vi)), presumably due to the interaction between the carboxylic carbonyl group of sebacic acid oligomer with the carboxylic acid proton of indomethacin.

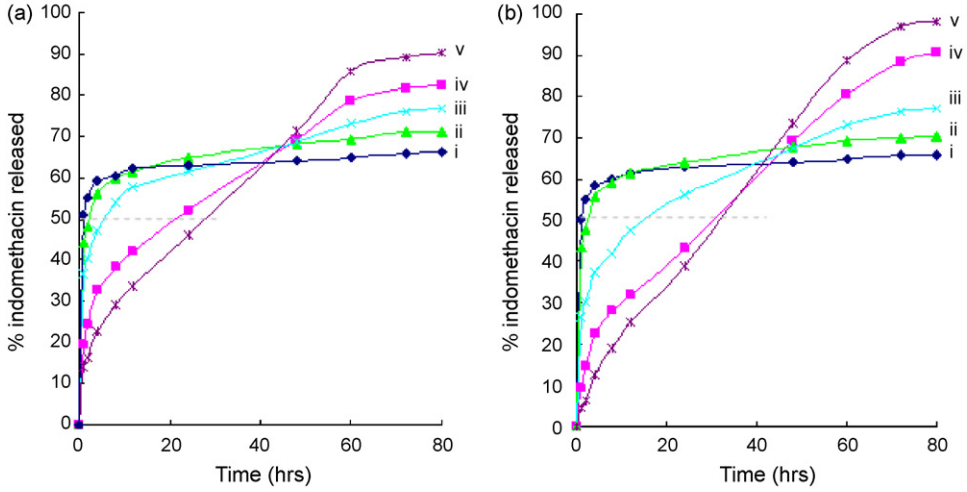

Fig. 6. Release profiles of indomethacin during 80 h for (a) impure PSA mixture and (b) pure PSA mixture for the following: (i) PSA–indomethacin PM, and for PSA–indomethacin DC processed at (ii) 40 °C, (iii) 60 °C, (iv) 80 °C and (v) 130 °C. All DCs were 4:1 (w/w) and processed at 2500 psi in sc-CO_2.

Scanning electron microscopy (SEM) was conducted on the pure PSA–indomethacin physical mixture and drug composites (DCs), to investigate any morphological changes after supercritical processing. Large drug crystals can clearly be seen in pure PSA–indomethacin physical mixture (Fig. 5(i)). Particle sizes for indomethacin crystals were reduced for the indomethacin in the DC processed in sc-CO_2 at 2500 psi and 60 °C (Fig. 5(ii)). When the processing temperature of 80 °C was used, the number of visible drug crystals was further reduced (Fig. 5(iii)), suggesting that the drug is largely amorphous and molecularly dispersed into the PSA matrix. As expected, when the temperature was increased to 130 °C, drug crystals essentially disappeared. It was also found that the surface of pure PSA matrix became rougher after processing at 130 °C (Fig. 5(iv)). SEM images for drug composites with impure PSA were essentially similar to the analogues pure PSA samples (see supplementary data).

Drug dissolution studies were carried out on the PMs and DCs (of pure PSA) (Fig. 6). The overall dissolution rate of indomethacin in DCs progressively increased with the processing temperatures used. Interestingly, the initial burst effect (observed for physical mixture) was significantly reduced for the DCs, particularly for the pure PSA DC. For pure or impure PSA–indomethacin DCs processed at low temperatures (40 and 60 °C), the drug release behavior was similar to that observed for the corresponding physical mixture in both case. The drug release behavior of the DCs was dramatically altered by processing at higher temperatures in both pure and impure DCs (Fig. 6a and 6b profiles (iv) and (v)). The burst effect of the indomethacin was significantly decreased compared with that from the low temperature DCs. Furthermore the release profile for the samples processed at 130 °C displayed a near zero-order release. This suggested that the most of the drug was amorphous and impregnated into the polymer matrix and that the drug release rate was controlled by erosion of PSA. The T_{50} values (shown as a dashed line) show indomethacin release is initially faster in impure PSA–indomethacin DCs, and that the accumulative drug release reaches the maximum value (∼65 h) significantly earlier than pure PSA–indomethcin DCs (∼75 h). This may be due to the faster dissolution of sebacic acid monomer compared to the PSA, which aids drug release. It has also been observed that the total amount of indomethacin release by (∼98%) in pure PSA DCs is higher than that (90%) for DCs containing impure PSA.

4. Conclusions

Amorphous drug composites of indomethacin in poly(sebacic anhydride) were successfully synthesized in supercritical CO_2 (up to 2500 psi and 130 °C). Analytical data suggest that, under certain conditions, the drug is dispersed into the polymer matrix as an amorphous dispersion. FTIR spectroscopy was used to study the nature of the drug–matrix interactions, and suggested the processed composites contain hydrogen-bonding interactions between the carboxylic acid protons (OH) of indomethacin and the carbonyl group (C=O) of pure poly(sebacic anhydride). Virtually zero order release profiles are observed for drug composites processed at 130 °C, with increased amount of drug being dissolved over the first 80 h compared to the physical mixture. In conclusion, the SCF processing method stabilized the amorphous form of indomethacin in poly(sebacic anhydride) which provides a very uniform release of the drug. The existence of the sebacic acid monomer/oligomer impurity shows a marked effect on the physical properties and drug dissolution rate of the final drug composites.

Acknowledgements

I would like to thank Vince Ford for dedicated work on building autoclave with view cell and EM unit of QMUL (Dr. Z. Lukinska and M. Willis) for their technical assistant on electronic microscopy.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2007.02.009.

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