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Characterization and drug release investigation of amorphous drug–hydroxypropyl methylcellulose composites made via supercritical carbon dioxide assisted impregnation

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ABSTRACT

Hydroxypropylmethyl cellulose (HPMC)–indomethacin (4:1, w/w) drug composites (DCs) were prepared via supercritical carbon dioxide (sc-CO_2) assisted impregnation. The effect of processing temperature (at fixed pressures) on the physical and other properties of the resulting HPMC–indomethacin DCs was investigated using a range of analytical techniques, including differential scanning calorimetry (DSC), Fourier transform infrared (FTIR) spectroscopy, Raman spectroscopy, and powder X-ray diffraction (XRD) methods. The data suggest that for a 4:1 (w/w) HPMC–indomethacin ratio prepared at 130 °C (17.2 MPa), the indomethacin exists entirely in an amorphous dispersion within the polymer matrix. The primary interaction between HPMC and indomethacin appears to be hydrogen bonding between the carboxylic acid carbonyl group of indomethacin and hydroxyl group of HPMC. The initial (first 15 min) and overall drug release behavior within a 5 h timeframe for the HPMC–indomethacin DCs, was analyzed. For the HPMC–indomethacin drug composite processed at 130 °C/17.2 MPa, drug release behavior obeyed a *n*-power law ($n = 0.54$).

1. Introduction

The use of hydrophilic matrices (HMs) for the preparation of controlled release dosage forms (for oral administration) has gained in interest in recent years [1]. Their convenience and ease of manufacture, coupled to significantly reduced manufacturing costs, makes these attractive ingredients in pharmaceutical formulations [2]. HMs can offer further advantages over carriers, *e.g.* when devices based on HMs are exposed to aqueous media, they become hydrated and develop into a viscous gelatinous surface barrier which subsequently modulates drug release according to the extent of water penetration into the centre of the HM carrier [3,4].

Until now, a large number of polymers (or their mixtures) have been tested as HM excipients, *e.g.* cellulose ethers, polyvinyl alcohol, hydroxyethyl methacrylate, ethylene–vinyl alcohol, poly(ethylene oxide), thermally modified starch, chitosan, schleroglucan, gelatine and carbopol [5–13]. Amongst these, hydroxypropylmethyl cellulose (HPMC), a cellulose ether, is the most popular excipient for a HM system due to its fast and viscous gel formation to control both initial and subsequent drug release [1]. HPMC's high swellability has a significant effect on the release kinetics of any incorporated drugs; upon contact with water (or biological fluid) water diffusion into the device results in polymer chain relaxation and volume expansion [14,15]. Thereafter, the incorporated drug diffuses steadily out of the system. Hence, at the present time, hydroxypropyl methylcellulose (HPMC) is one of the most important hydrophilic carrier materials used for the preparation of oral controlled drug delivery systems [2,16,17].

Over last decade, HPMCs have been co-formulated with a large number of active agents [12,14,18]. Ribeiro et al. [19] designed controlled release HPMC tablets incorporating the poorly soluble drug vinpocetine. Sodium dodecyl sulphate (SDS), a potent microbicide, was successfully loaded into a drug delivery system made of Carbopol and HPMC in Wang's report [20]. A wide range of methods has been used to formulate HPMC-based drug delivery devices. These include direct compressing [19] and solvent evaporation methods [21]. However, such methods largely produce inhomogeneous polymer–drug mixtures or can contain significant amounts of organic solvent residues which could be cytotoxic [22]. Also, such methods do not always result in improved bioavailability for certain highly crystalline pharmaceuticals [23].

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In this study, a supercritical fluid (*i.e.* sc-CO_2) assisted impregnation method was used to investigate formulation of novel HPMC–indomethacin drug composites. Indomethacin is a poorly water-soluble non-steroidal anti-inflammatory drug (NSAID) and, therefore, chosen as a model drug in such formulations. Supercritical fluids are compressed gases which can display properties between those of liquids and gases [24]. The properties of supercritical fluids can be tuned by adjusting the fluid parameters such as pressure and temperature [24,25]. For pharmaceuticals processing, supercritical carbon dioxide (sc-CO_2) offers a particular advantage due to its low critical temperature and pressure (T_c = 31.1 °C; P_c = 7.38 MPa), and its ability to plasticise or swell polymers at relatively low temperatures [24,26–29]. This can be important for thermally sensitive drugs, biomaterials or biomatter (*e.g.* enzyme) formulations where the incipient may degrade when exposed to high temperatures [30]. There has been a vast amount of literature in the use of supercritical fluids as alternative to organic solvents for preparing drug delivery formulations [23,25,31]. Compared to other supercritical fluids processing techniques such as rapid expansion of supercritical solution (RESS) and supercritical antisolvent precipitation (SAS), supercritical fluids assisted mixing and impregnation is simple and highly more attractive as it avoids the use of organic solvents [23,25]. According to the report of Kazarian et al. [32], there are two mechanisms of supercritical fluid impregnation of drugs into polymer matrices, *i.e.* simple deposition and preferential partitioning. In their later report, Kazarian and Martirosyan [33] proved that preferential partitioning occurred between PVP and ibuprofen during supercritical fluid assisted impregnation. However, due to the high glass transition temperature (T_g) [34] of HPMC, there is few successful examples of processing HPMC-based drug products via supercritical fluid techniques. Our group has identified drug–polymer formulations in which sc-CO_2 can be used to yield an amorphous form of the drug via what appears to be drug–polymer interactions [26–29]. To date, we have investigated drug release from water soluble (*e.g.* PVP), surface erodible (*e.g.* PSA), insoluble (*e.g.* chitosan) and porous (slowly water absorbing) polymer system (*e.g.* PEM/THFM) prepared in sc-CO_2 [26–29]. For example, in PVP–indomethacin drug composites (at polymer–drug weight ratio 4:1) prepared at 75 °C and 15.2 MPa in sc-CO_2, the drug was completely amorphous and overall drug release in 2 h timeframe was diffusion controlled and improved compared to that of pure crystalline indomethacin [26].

In this report, we describe the use of sc-CO_2 assisted impregnation and mixing to synthesize amorphous formulations of indomethacin with HPMC as carrier. In this case, of course we envisaged that the HPMC drug release would be via a swelled gel system upon contract with water.

2. Materials and methods

2.1. Materials and equipment

Hydroxypropylmethyl cellulose (HPMC; $M_n \approx 10{,}000$) and γ-indomethacin (99%; Mw = 358) were purchased from Sigma–Aldrich Company Ltd. (Dorset, UK) and used as received. A liquid withdrawal CO_2 cylinder at 5 MPa pressure (99% purity) was supplied by BOC gases. The CO_2 was chilled to −6 °C before being delivered to the autoclave via an Isco model 260D syringe pump with a copper cooling coil chilled piston barrel. A custom made 220 ml stirred 316 stainless steel high-pressure autoclave (approximate d = 340 mm, length = 45 mm) with a sapphire viewing window and paddle type stirrer was built in the mechanical workshop at QMUL.

2.2. Synthesis

4.00 g HPMC and 1.00 g γ-indomethacin (equivalent molar ratio 0.14:1) were accurately weighed and gently mixed by hand with mortar and pestle for 10 min, before being transferred into the 220 ml windowed autoclave. The autoclave was sealed and filled with liquid CO_2 from the CO_2 cylinder at 5 MPa, and then pressurized slightly using the Isco pump. The autoclave was then held at 17.2 MPa/50 °C (or 70, 110 and 130 °C, respectively) under stirring (180 rpm) for 3 h. At the end of the experiment, the controller was switched off and CO_2 was released over a period of 10 min. The colour of final product changed from a white starting material to a strong yellow coloured final product with increase in the operative temperature (50, 70, 110 and 130 °C, respectively).

2.3. Characterization

A range of characterization methods have been used to demonstrate the properties of HPMC and crystalline γ-indomethacin physical mixtures and sc-CO_2 processed HPMC–indomethacin drug composites. 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 5–35° with a step size of 0.02° and step time of 1.0 s for 55 min.

Differential scanning calorimetry (PerkinElmer DSC 7) was employed to study the thermal behavior of HPMC and indomethacin mixtures processed in sc-CO_2 at different processing temperatures. The DSC was calibrated using the melting points of pure samples of indium and zinc, respectively. From our experiments, samples containing indomethacin equivalent to 5.0 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^{-1} under dry nitrogen atmosphere from 30 to 200 °C. Each sample was run in triplicate.

FTIR spectra were obtained using Nicolet 8700 FTIR spectrometer with a photoacoustic detector using 4 cm^{-1} resolution, averaging for 128 scans. Raman spectra data were collected using a dispersive Raman spectrometer (Nicolet Almega XR with a 785 nm laser). Spectra were obtained for 32 scans at 8 s exposure time.

Scanning electron microscopy (SEM) was carried out using a JEOL 6300^{TM} (accelerating voltage 10 kV). Prior to examination, samples were first 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.

The dissolution rates of the HPMC–indomethacin physical mixture (PM) and all drug composites (DCs) were followed using UV–vis spectroscopy (Nicolet Evolution 500 UV-Vis spectrophotometer). Each sample contained an amount equivalent to 50.0 mg indomethacin. The dissolution study was undertaken according to the USPXXI dissolution test method [35]. The dissolution medium consisted of 1000 ml of phosphate buffer solution (PBS) (pH 7.4), maintained at temperature of 37 ± 0.5 °C. A paddle rotation speed of 50 rpm was employed. Samples of 5.0 ml were collected automatically at predetermined time intervals of 5 min for the first hour and thereafter at intervals of 15 min until the end of the measured time with an equal volume of fresh deionised water supplemented to the dissolution flask immediately after sampling. The concentration of released indomethacin was calculated using the intensity of the UV peak at 320 nm according to Beer–Lambert law [36].

The initial burst (within first 15 min) of HPMC–indomethacin formulations was analyzed using a one-way analysis of variance. A post hoc Tukey's HSD test was then performed to identify the nature

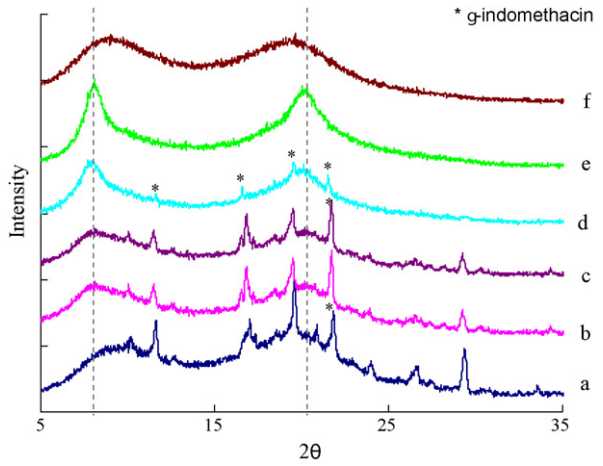

Fig. 1. Powder X-ray diffraction (XRD) pattern for (a) HPMC–indomethacin (4:1, w/w) physical mixture, and HPMC–indomethacin drug composites (DC) processed at (b) 50 °C, (c) 70 °C, (d) 110 °C, (e) 130 °C; XRD pattern of (f) virgin HPMC. All DCs were 4:1 (w/w) and processed at 17.2 MPa in sc-CO_2.

of the difference of drug dissolution between tested samples with the level of significance $\alpha = 0.05$.

3. Results and discussion

X-ray powder diffraction was primarily used to elucidate the presence of crystalline indomethacin in the HPMC matrix for a range of processing temperatures (Fig. 1). The XRD data for crystalline indomethacin showed peaks at 2θ values of 10.3°, 16.7°, 19.7°, 21.9° and 29.1°, respectively. The XRD data also clearly showed a decrease in the intensity of these peaks with ever increasing processing temperature in sc-CO_2. After processing of the mixture at 130 °C, the characteristic XRD peaks due to indomethacin were no longer visible (Fig. 1e), suggesting that the drug was completely amorphous in the composite. Interestingly, after processing in sc-CO_2 under all conditions (in the presence of drug), a shift was observed for the XRD peak positions of amorphous virgin HPMC located at $2\theta = 8.1°$ and 20.3° (by 1.2° and 0.6°, respectively). Similar observations were also reported by others [12,14].

Differential scanning calorimetry (DSC) was carried out to investigate the thermodynamic properties of the HPMC–indomethacin physical mixture and drug composites (DCs) processed in sc-CO_2. Since the amorphous state can be characterized by a loss of the melting peak, DSC was used to evaluate the amorphous content in our samples [37]. An estimation of indomethacin crystallinity was obtained using the difference between measured and theoretical (pure crystalline form) enthalpy of melting, calculated by

$$X_c = \frac{\Delta H_m}{\Delta H_m^{100\%}} \quad (1)$$

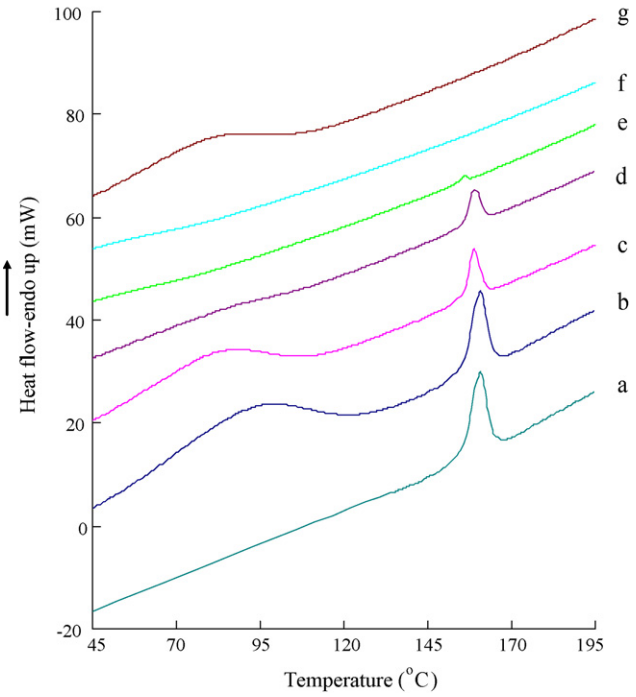

Fig. 2. DSC data for (a) pure crystalline indomethacin, (b) HPMC–indomethacin (4:1, w/w) physical mixture, HPMC–indomethacin drug composites (DC) processed at (c) 50 °C, (d) 70 °C, (e) 110 °C, (f) 130 °C; DSC data for (g) virgin HPMC. All DCs were 4:1 (w/w) and processed at 17.2 MPa in sc-CO_2.

where X_c is the crystallinity of indomethacin in the measured sample, ΔH_m is the enthalpy of melting of the sample studied, which can be calculated corresponding to the area under the DSC curve, and $\Delta H_m^{100\%}$ is the enthalpy of melting of 100% crystalline materials, in this case, the pure crystalline untreated indomethacin drug.

As shown in Fig. 2a and b, the melting peak of crystalline indomethacin for the pure drug or a physical mixture was located at 160 °C, which is consistent with that for the γ-indomethacin form of the drug (from 159 to 161 °C) [38]. The DSC data for the PM and the DCs processed at 50 °C, both show a broad endotherm at *ca.* 100 °C which is due to the absorbed water in the HPMC (Fig. 2b, c and g). This broad peak is not observed in the DSC plots for DCs processed at 70 °C and above (Fig. 2d, e and f), suggesting that the process was capable of removing the moisture absorbed in the composites, which was also observed in our previous analogous studies using PVP and chitosan [26,27] as indomethacin carriers. DSC plots for the DCs shows a gradual decrease in the intensity of the indomethacin-melting peak (endotherm) with increasing processing temperature, suggesting that more drug was converted to the amorphous form with an increasing operative temperature (Table 1), which is also in good agreement with XRD results (Fig. 1). Interestingly, when the processing temperature was increased to 110 °C, a new tiny peak (endotherm)

Table 1
The main thermodynamic parameters of HPMC–indomethacin formulations

Fraction of polymer (%)	Operative condition (MPa/°C)	Temperature of melting (°C)	Peak area (mJ)	Enthalpy of melting (ΔH_m/J g^{-1})	Degree of crystallinity (%)
0	NT	160.4 ± 0.3	547.03 ± 10.14	108.97 ± 2.02	100
80	PM	160.4 ± 0.5	507.31 ± 20.44	101.42 ± 4.09	93.5
80	17.2/50	160.3 ± 0.3	210.24 ± 14.19	42.15 ± 2.84	38.9
80	17.2/70	160.8 ± 0.4	134.98 ± 12.47	27.02 ± 2.50	25
80	17.2/110	157 ± 0.6	8.61 ± 1.48	1.72 ± 0.30	1.6
80	17.2/130	ND	0	0	0

Note: The weight equivalent of drug is ~5 mg; heating speed is 10 °C min^{-1}; NT means no treatment for pure drug; ND indicates not detected.

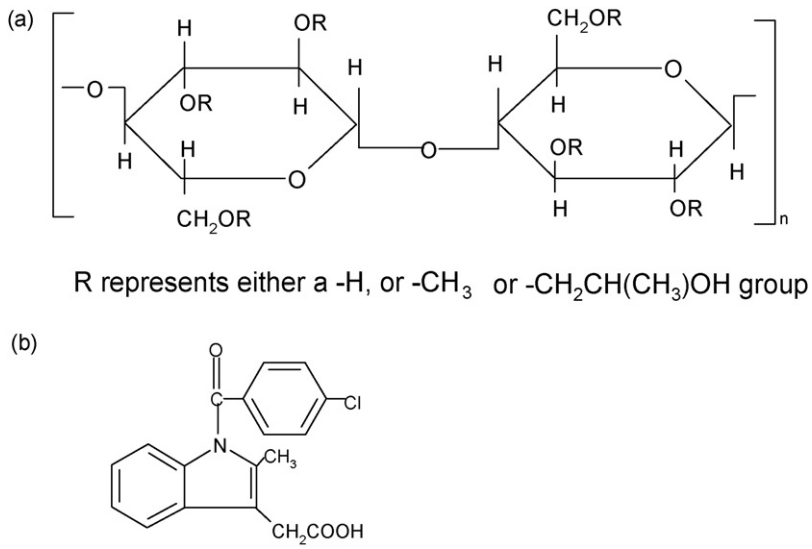

Fig. 3. Formula for (a) HPMC and (b) indomethacin molecules.

was observed at 157 °C (Fig. 2e), suggesting presence of a small amount (1.6%) known metastable crystal form of α-indomethacin [39]. The α-indomethacin was no longer observed at a processing temperature of 130 °C (Fig. 2f), suggesting a total amorphous drug form was present in this HPMC–indomethacin composite. Polymorphic transformation of indomethacin was also found in chitosan–indomethacin formulations made at 70 °C/20.7 MPa with 4:1 of polymer–drug weight ratio in sc-CO_2 [27] and other reports with certain polymer matrices such as hydroxypropyl-β-cyclodextrin (HPBCD), as reported in Bandi and coworkers' report [40]. In the latter paper, the supercritical fluid processing conditions used for preparing HPMCD–indomethacin (5:1, w/w) composites were 40 °C and 21.1 MPa with 20 h exposure time. However, due to the detection limits of the equipment, the T_g events were not observed. In this work, a glass transition was not observed in any of the DSC traces of the processed DCs reported herein; one possibility is that such weak transitions may also be beyond the detection limits of our DSC instrument. Indeed, we tried four different heating rates (not published herein) 5, 10, 20 and 30 °C min^{-1} without being able to identify a distinct T_g.

FTIR spectroscopy was used to study the bonding and any interactions between indomethacin and HPMC after processing in sc-CO_2. Bands due to υ(C=O) bond stretches were studied to infer the physical state of the drug. As expected, due to lack of carbonyl groups in the chemical structure of HPMC (Fig. 3a), its FTIR spectrum does not show any characteristic bands in investigated carbonyl region (Fig. 4a).

Three characteristic bands of indomethacin (Table 2) were observed for the physical mixture at 1729, 1691 and 1602 cm^{-1} (Fig. 4b), due to the aliphatic carbonyl, aromatic carbonyl (stretching bands), and aromatic ring C=C vibrational band, respectively [41]. With increasing processing temperature, the bands at 1602 cm^{-1} gradually decreased in intensity, disappearing completely for the sample processed at 130 °C, which could be due to the decrease of the drug crystallinity [42]. The carbonyl bands located at 1729 and 1691 cm^{-1} (Table 2) appeared to shift to lower wavenumbers of 1700 and 1650 cm^{-1} (by 130 °C), respectively, and became broader as the processing temperature increased, which could be due to formation of a hydrogen bond between an OH group of HPMC and the carbonyl group of indomethacin

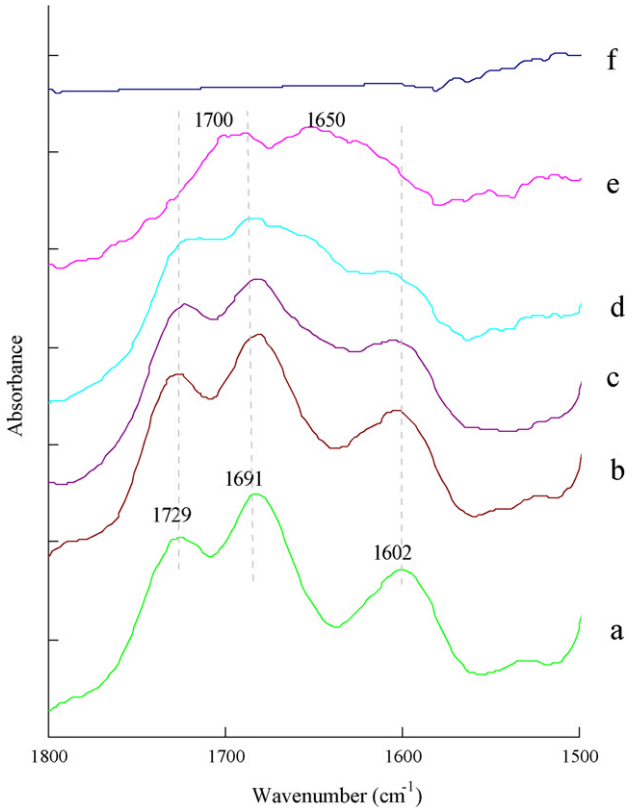

Fig. 4. FTIR spectra in the υ(C=O) spectral region (1800–1500 cm^{-1}) for (a) HPMC–indomethacin (4:1, w/w) physical mixture (PM) and HPMC–indomethacin drug composites (DCs) at (b) 50 °C, (c) 70 °C, (d) 110 °C, (e) 130 °C; FTIR spectrum of (f) virgin HPMC. All DCs were 4:1 (w/w) and processed at 17.2 MPa in sc-CO_2.

Table 2
HPMC–indomethacin mixture and drug composites FTIR peak assignments

Wavenumber (cm^{-1})	Assignment	Compound
1729	C=O (COOH) stretch	Indomethacin (pure)
1700	H bonded C=O (COOH)	Indomethacin (DCs)
1691	C=O (aromatic) stretch	Indomethacin (pure)
1650	H bonded C=O	Indomethacin (DCs)
1602	C=C (aromatic ring)	indomethacin

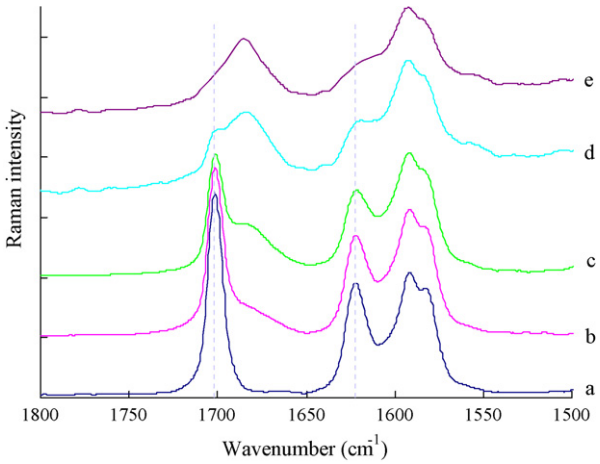

Fig. 5. Raman spectra in the region 1800–1500 cm^{-1} for (a) HPMC–indomethacin (4:1, w/w) physical mixture (PM) and HPMC–indomethacin drug composites (DCs) processed at (b) 50 °C, (c) 70 °C, (d) 110 °C, (e) 130 °C; all DCs were 4:1 (w/w) and processed at 17.2 MPa in sc-CO_2.

(Fig. 3b) as this would weaken the strength of carbonyl bond, causing the observed shifts in the C=O bond frequency. A similar carbonyl band shift of incorporated drug molecule with HPMC matrix was also reported by other researchers, such as for the drug nifedipine in the study of Cilurzo et al. [43]. However, their band shift (of *ca.* 17 cm^{-1}) was less than that reported in our study, which could be due to the difference of the nature of the drug molecules (between indomethacin and nifedipine) or the stronger and more complete interaction induced by supercritical processing compared to the spray drying method used in their study. A further study was undertaken in which a physical mixture containing amorphous indomethacin (obtained from quenching a γ-indomethacin melt in liquid N_2) and our HPMC. An FTIR spectrum of this material revealed a peak at 1738 cm^{-1} that was assigned to the stretching vibration of non-hydrogen bonded carboxylic acid (of indomethacin), which is in agreement with the finding in Zografi's work [45] (see supplementary Fig. S1). The disappearance of non-hydrogen bonded carboxylic acid band at 1738 cm^{-1} in our high temperature processed HPMC–indomethacin DCs (Fig. 4d and e) further supported our conclusion that H-bonding was formed between polymer and drug in sc-CO_2 treated formulations. H-bonding between functional groups of a polymer and

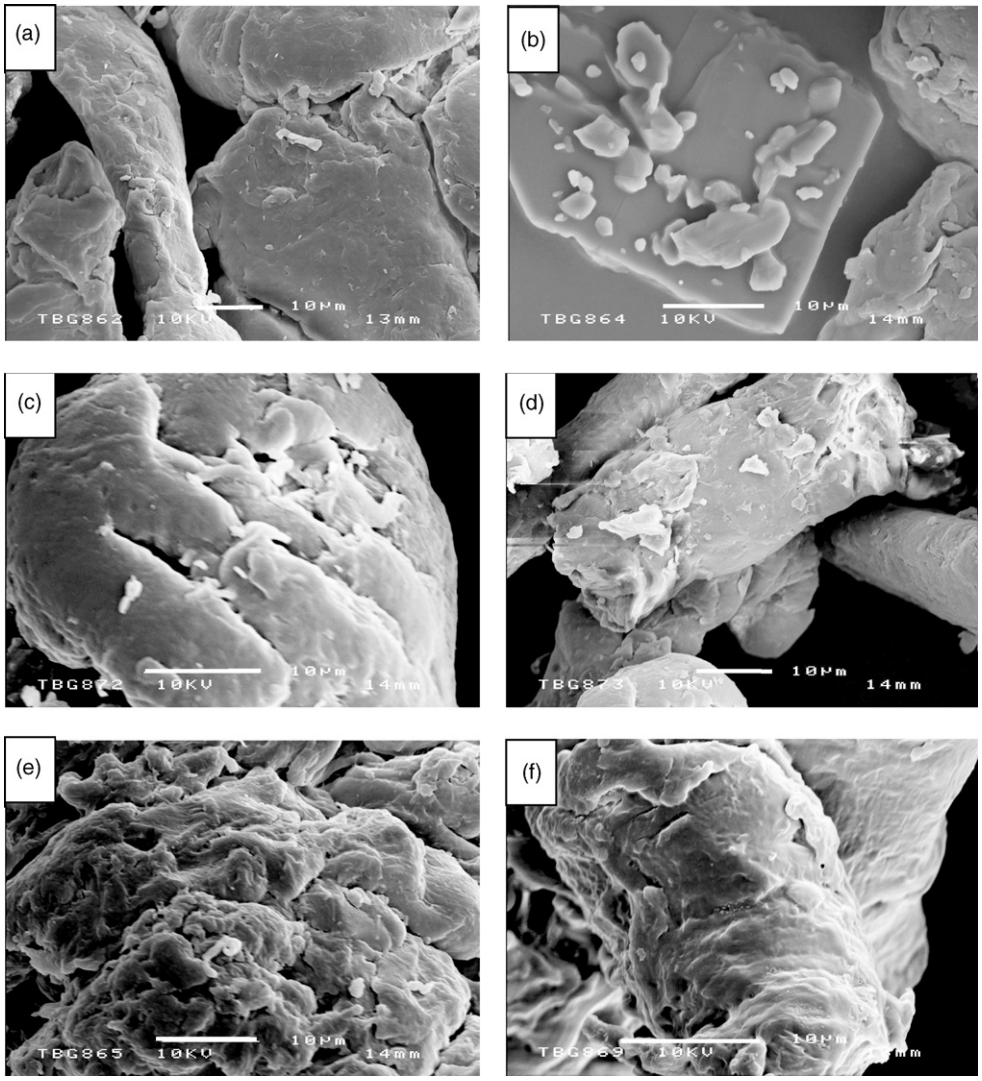

Fig. 6. SEM images: (a) virgin HPMC, (b) HPMC–indomethacin (4:1, w/w) physical mixture (PM), and HPMC–indomethacin drug composites (DCs) processed at (c) 50 °C, (d) 70 °C, (e) 110 °C and (f) 130 °C. All DCs were 4:1 (w/w) and processed at 17.2 MPa in sc-CO_2.

drug after SCF processing have also been observed in our previous work including chitosan–indomethacin DCs (processed at 20.7 MPa/70 °C) [27] and poly(sebacic anhydride)–indomethacin DCs (processed at 17.2 MPa/80 °C) [28]. The main FTIR assignments are summarized in Table 2.

Raman data for the physical mixture (Fig. 5a) revealed a carbonyl stretching vibration of crystalline indomethacin at 1700 cm^{-1} [44]. With the increasing processing temperature, the band became weaker, and a new Raman band at *ca.* 1680 cm^{-1} grew stronger (previously reported as amorphous indomethacin) [45]. For the sample processed at 130 °C, the carbonyl band of crystalline indomethacin at 1700 cm^{-1} was absent and the band at 1680 cm^{-1} reached maximum intensity. This suggests that the crystalline indomethacin has been fully dispersed into HPMC matrix in an amorphous form. Interestingly, the similar Raman shift was recently reported by Fini et al. [46]. They found that the indomethacin peak in the co-evaporated PVP–indomethacin system (prepared by ethanol evaporation at 14 mmHg/50 °C and at 1:1 (w/w) of polymer–drug ratio) is red-shifted to 1679 cm^{-1} compared to that of γ-indomethacin (at 1700 cm^{-1}). The same authors outlined that the two peaks at 1700 and 1679 cm^{-1} can be useful to distinguish the presence of the solid dispersion of crystalline or amorphous indomethacin inside the sample.

Scanning electron microscopy (SEM) was conducted to investigate the effect of SCF processing conditions on the morphology of the drug particles and the HPMC matrix. Comparing virgin HPMC (Fig. 6a) with the PM (Fig. 6b), crystalline drug particles can be clearly observed on the surface of HPMC matrix for the latter sample, which suggested no obvious change in the drug particle morphology by simple physical mixing. For HPMC–indomethacin DCs processed in sc-CO_2, the number of drug crystals were substantially reduced after processing at 50, 70 and 110 °C, respectively (Fig. 6c, d and e). After processing at 130 °C in sc-CO_2, the indomethacin drug particles were no longer visible on the surface of HPMC and the HPMC matrix appeared to be significantly rougher. This suggests that virtually all the drug was dispersed into the swollen HPMC matrix. This result is in agreement with Okimoto and co-workers' work [47], in which SEM images suggested that the investigated drug, nilvadipine, was adsorbed into swollen HPMC by ethanol evaporation processing at 40 °C in vacuum. Of course in our work, we avoided the use of such organic solvents, which is an advantage due to the difficulties of effectively removing the solvent. Interestingly, the increase in surface roughness of a thermoset biopolymer matrix caused by sc-CO_2 processing was observed in our previous report, when the polymer had high T_g (such as chitosan) or was semi-crystalline (such as poly(sebacic anhydride)) [28,29]. This is most likely due to the CO_2 diffusion during depressurization.

Drug dissolution tests were conducted to investigate the drug release behaviors from HPMC–indomethacin composites (DCs) processed at different temperatures, with the physical mixture as the control sample. The supercritical fluid processed DCs commonly showed enhanced drug dissolution (compared to the physical mixture) within the experimental time frame. In particular, the accumulated drug dissolution from DCs processed at the higher temperatures of 110 and 130 °C, was *ca.* 90% and 98%, respectively. However, according to Fig. 7I, these DCs showed slightly different drug release profiles. Close investigation of the drug release data for the first 15 min was carried out (see Fig. 7II). DCs processed at 110 and 130 °C showed very similar and the fastest drug release compared to other mixtures (these two were shown to be statistically identical by ANOVA and Tukey's Honestly Significant Difference (HSD) analysis with the absolute difference between the means of these two formulations less than HSD; see Tables 3a, 3b and 3c). On the contrary, DCs processed at 50 °C and the HPMC–indometahcin

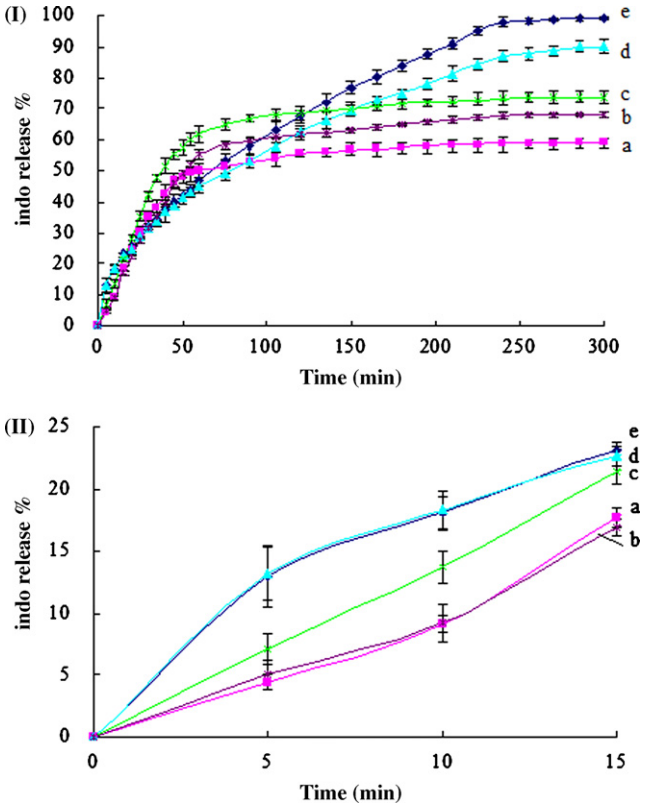

Fig. 7. Release profiles of indomethacin during 5 h (I) and initial burst over the first 15 min (II); (a) HPMC–indomethacin (4:1, w/w) physical mixture (PM), and HPMC–indomethacin drug composites (DCs) processed at (b) 50 °C, (c) 70 °C, (d) 110 °C and (e) 130 °C. All DCs were 4:1 (w/w) and processed at 17.2 MPa in sc-CO_2.

Table 3a
The main descriptive statistics that are used in the calculations associated with one-way ANOVA of the immediate drug release within 15 min of HPMC–indomethacin formulations

Groups	Count	Sum	Mean (%)	Variance
Group 1 (a)	6	106.2	17.7	0.60
Group 2 (b)	6	101.34	16.89	0.50
Group 3 (c)	6	128.04	21.34	0.79
Group 4 (d)	6	136.02	22.67	0.62
Group 5 (e)	6	138.78	23.13	0.46

Note: Group nos. 1–5 are corresponding to the tested formulations a–e in Fig. 7 II.

Table 3b
Summary of the output of the analysis of variance of drug dissolution within the first 15 min of HPMC–indomethacin formulations

Source of variation	SS	d.f.	MS	*F*	*F* critical
Between Groups	198.51	4	49.63	83.71	2.76
Within Groups	14.82	25	0.59		
Total	213.33	29			

Note: The result is derived based on Table 3a.

Table 3c
Tukey's HSD testing result of drug release within the first 15 mins of HPMC–indomethacin formulations

q	S^2	*N*
4.16	0.59	6
HSD = 1.30 (1)–(2) and (5)–(4) < HSD (*x*)–(*y*) > HSD		

Note: (1)–(2) and (5)–(4) means the absolute different between the means of the group (1) and (2), (5) and (4), respectively; (*x*)–(*y*) indicates the absolute different between any two groups other than (1)–(2) and (5)–(4).

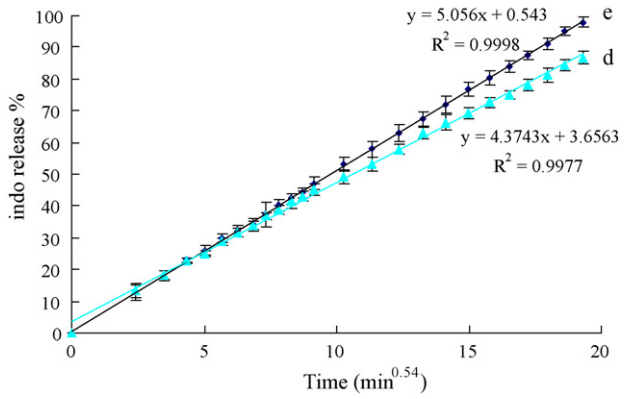

Fig. 8. Power law ($n = 0.54$) release profiles of indomethacin during first 4 h for HPMC–indomethacin (4:1, w/w) drug composites processed at 17.2 MPa and (a) 110 °C and (b) 130 °C, respectively.

physical mixture (PM) exhibited similar (and the slowest) initial dissolution rates, which were shown to be statistically identical by ANOVA and Tukey's HSD analyses (see Tables 3a, 3b and 3c, with the level of significance $\alpha = 0.05$). Initial drug release from these mixtures was generally observed to be the reverse of overall drug release behavior. This can be explained in terms of the different drug release mechanisms which occur. Immediate drug release in the first few minutes is mainly governed by dissolution of the unimpregnated drug particles and/or the amorphous drug bonded or dispersed on the HPMC matrix surface. This suggestion is consistent with other polymer–drug composites studied in the previous reports published by our group [26–29], where DCs with smaller particle size commonly showed faster immediate drug release. In agreement with the Noyes–Whitney equation [48], favorable properties of particle morphology were observed in DCs processed at higher temperatures (70, 110 and 130 °C), *i.e.* less crystalline material remains and smaller drug particle size (shown in the DSC analysis and SEM images, respectively). However, after the initial drug release stage, the swelling effect of the HPMC matrix became the dominant for determining drug release from the DCs processed at 110 and 130 °C (Fig. 7I, d and e). Interestingly, mathematical modeling (Eq. (2)) according to the power law was observed, as suggested by Peppas [49] from the Higuchi model [50]; overall drug release from the DCs processed at 110 and 130 °C showed a good fit ($R^2 > 0.99$ in both cases) with a n-power law ($n = 0.54$) model (Fig. 8) as given in the following equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where M_t and M_∞ are the absolute cumulative amount of drug released at time t and effectively infinite time, respectively; therefore, M_t/M_∞ in this work is equal to the indomethacin release percentage at time t. k is a constant incorporating structural and geometric characteristics of the device, and n is the release exponent, indicative of the mechanism of drug release. In contrast with our result (where $n = 0.54$), similar values of n can be found in reports of drug delivery systems based on hydrophilic polymer matrices, including HPMC. For example, caffeine release from a melt extruded HPMC ($n = 0.57$) drug delivery device was reported by Talukdar et al. [1]. Basak et al. [51] managed to achieve a range of n values (including $n = 0.50$, 0.54 and 0.57) by manipulating ambroxol release from HPMC matrix tablets. It is known from the literature that an n value between 0.5 and 1 is largely referred as anomalous drug release or non-Fickian diffusion release [49,52], and it has been suggested in this case that drug release behavior was a counterbalance between polymer swelling and drug diffusion release, however, this anomalous drug release was not observed in the low temperature treated DCs at 50 and 70 °C.

4. Conclusions

HPMC was used as a carrier polymer for indomethacin drug composites. In order to achieve a complete amorphous drug dispersion in HPMC, a range of processing temperatures were investigated, *i.e.* 50, 70, 110 and 130 °C. It was shown that the drug was impregnated into HPMC at a processing temperature of 110 °C or higher, according to XRD, DSC and SEM data. The H-bonding interaction between carboxylic acid group of indomethacin and OH groups of HPMC was observed from FTIR and Raman spectroscopic analysis. In our dissolution study, the DCs processed at 110 and 130 °C exhibited different drug release behavior compared to the DCs processed at lower temperatures of 50 and 70 °C, although an enhancement of overall drug dissolution was found for all DCs compared to the physical mixture. Due to the preparation of an almost complete amorphous dispersion of indomethacin into HPMC (at higher temperatures), drug release was mainly controlled by diffusion of amorphous drug out of the swollen HPMC system upon contact with the dissolution medium. The counterbalance between the polymer matrix swelling and drug diffusion led to an anomalous drug release profile which showed good fit to an $n = 0.54$ power law, despite the fact that the immediate drug release (within the first 15 min) was observed in these DCs. Our investigation into the immediate drug release revealed that dissolution of indomethacin drug particles presented on the surface of the HPMC matrix was the main driving force at this stage for all the DCs and physical mixtures.

Overall, this study showing matrix swelling as the drug release mechanism represents part of a larger body of work in which we have investigated supercritical fluid processed formulations exhibiting a range of drug release mechanisms; these include, controlled drug release due to biodegradation (surface erodible matrix) and diffusion controlled drug release [26–28].

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpba.2008.08.031.

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