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Drug release responses of zinc ion crosslinked poly(methyl vinyl ether-*co*-maleic acid) matrix towards microwave

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Abstract

The drug release characteristics of beads made of poly(methyl vinyl ether-*co*-maleic acid) using Zn^{2+} as the crosslinking agent were investigated with respect to the influence of microwave irradiation. The beads were prepared by an extrusion method with sodium diclofenac as a model water-soluble drug. They were subjected to microwave irradiation at 80 W for 5 and 20 min, and at 300 W for 1 min 20 s and 5 min 20 s. The profiles of drug dissolution, drug content, drug–polymer interaction and polymer–polymer interaction were determined by dissolution testing, drug content assay, differential scanning calorimetry and Fourier transform infrared spectroscopy. Treatment of beads by microwave at varying intensities of irradiation can aid to retard the drug release with a greater reduction extent through treating the beads for a longer duration of irradiation. The treatment of beads by microwave induced the formation of multiple polymeric domains of great strength and extent of polymer–polymer and drug–polymer interaction. The release of drug from beads was retarded via the interplay of O─H, N─H, C─H, $(CH_2)_n$ and C─O functional groups of these domains, and was mainly governed by the state of polymer relaxation of the matrix unlike that of the untreated beads of which the release of drug was effected via drug diffusion and polymer relaxation. In comparison to Ca^{2+} crosslinked matrix which exhibited inconsistent drug release retardation behavior under the influence of microwave, the extent and rate of drug released from the Zn^{2+} crosslinked beads were greatly reduced by microwave and the release of drug from these beads was consistently retarded in response to both high and low intensity microwaves.

Keywords: Drug–polymer interaction; Microwave; Polymer–polymer interaction; Poly(methyl vinyl ether-*co*-maleic acid)

1. Introduction

Poly(methyl vinyl ether-*co*-maleic acid) and analogs have been employed as encapsulating agent, thickener, denture adhesive as well as adjuvant for transdermal drug delivery system (Matsuya et al., 1996; Arbós et al., 2002, 2003; Luppi et al., 2003; Kockisch et al., 2004; Owens et al., 2005; Salman et al., 2005). The widespread use of these polymers is attributed to their biodegradability and low oral toxicity, typically ranges between 5 and 25.6 g/kg in animal models. Unlike carbohydrate polymers such as alginate and pectin, the poly(methyl vinyl ether-*co*-maleic acid) is a polymer made of bicarboxylic acid monomers (Fig. 1). Its potential in controlling the release of small molecule drugs from oral dosage forms has not been widely examined.

The small molecule drugs exhibit a fast rate of drug release via diffusion through the pores of the embedded matrix. Such rate of drug release is undesirable for colon targeting of drugs. Various formulation and processing approaches have been taken to negate the rate of release of small molecule drugs from matrix made of carbohydrate polymers (Wong, 2008). The latest processing approach lies in the application of microwave technology to modify the state of molecular interaction between the polymer chains (Wong et al., 2002, 2005; Nurjaya and Wong, 2005; Wong, in press; Wong and Nurjaya, 2008). However, the application of microwave technology in design of carbohydrate polymeric controlled-release matrix brought about varying degrees of success.

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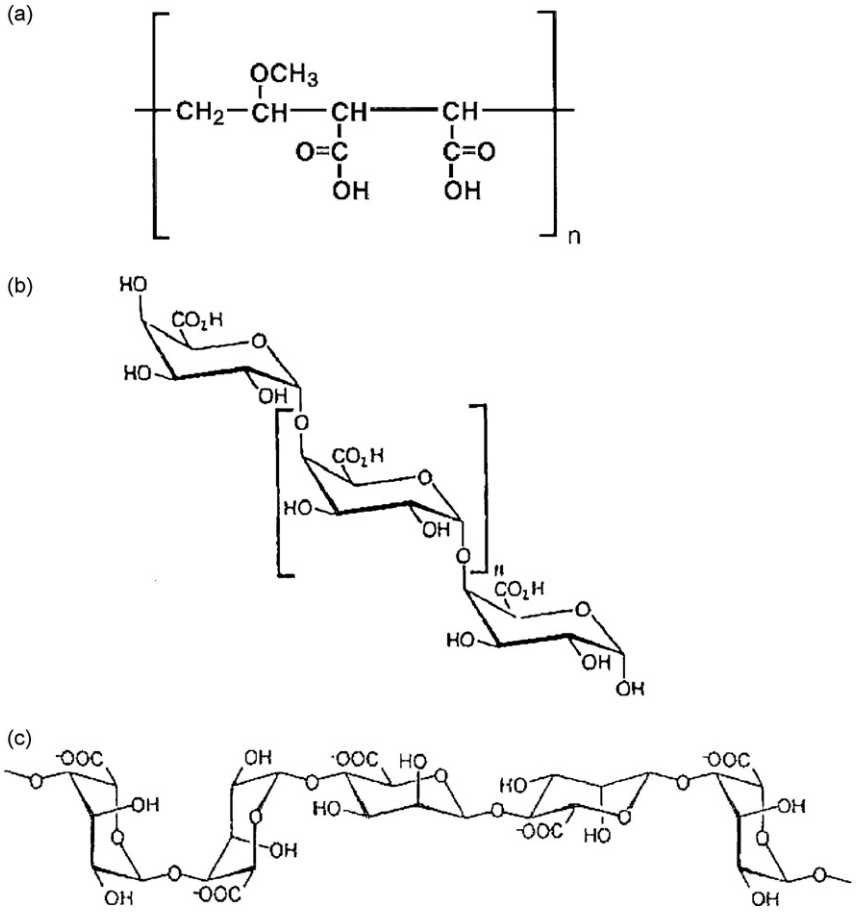

Fig. 1. Chemical structures of (a) poly(methyl vinyl ether-*co*-maleic acid), (b) pectin and (c) alginate.

The effects of microwave on the drug release property of poly(methyl vinyl ether-*co*-maleic acid) matrix prepared using calcium ions (Ca^{2+}) as the crosslinking agent have been investigated lately by Wong et al. (2007). It was found that processing of the formed matrix by microwave could lead to an increase or a decrease in the rate and extent of drug release, depending on the intensity of irradiation applied. In addition, a high concentration level of Ca^{2+} was needed in the preparation of such matrix. Thus, the present study aims to elucidate the drug release responses of zinc ion (Zn^{2+}) crosslinked poly(methyl vinyl ether-*co*-maleic acid) matrix in relation to the influences of microwave. Unlike the former, the preparation of poly(methyl vinyl ether-*co*-maleic acid) matrix by means of Zn^{2+} requires a lower concentration level of crosslinking agent. The Zn^{2+} are more reactive than Ca^{2+}. It is hypothesized that the polymeric matrix crosslinked by Zn^{2+} may be more responsive to the irradiation of microwave with respect to its capacity to retard the release of drug from the matrix, and its responsiveness can be less dependent on the irradiation intensity of microwave than Ca^{2+} crosslinked beads.

2. Materials and methods

2.1. Materials

Poly(methyl vinyl ether-*co*-maleic acid) (ISP, USA) was employed as a matrix polymer in the preparation of beads, with zinc chloride (Merck, Germany) as the crosslinking agent and sodium diclofenac (MP Biomedicals, Germany) as the model water-soluble drug. Other chemicals employed in this study included sodium hydroxide and potassium dihydrogen phosphate (Merck, Germany).

2.2. Equipment

A microwave oven (EM-G A, Sanyo, Japan) equipped with a single magnetron emitter operating at 2450 ± 50 MHz was used. The oven had power outputs of 80, 150, 300, 450, 700 and 850 W. The desired power setting and duration of irradiation were set using the electronic touch control panel. The oven consisted of a Pyrex® turntable on which the samples were placed and rotated to achieve a uniform irradiation.

2.3. Preparation of beads

An aqueous dispersion containing 4% (w/w) of poly(methyl vinyl ether-*co*-maleic acid) and 2% (w/w) of sodium diclofenac was prepared with its pH titrated to 5.5 using 0.5 M sodium hydroxide solution. It was then introduced dropwise into an aqueous solution containing 4% (w/v) of zinc chloride by extrusion through a 1.6-mm diameter orifice at a flow rate of 60 droplets/min aided by peristaltic pump (Watson-Marlow Bredel Pumps, UK). The bulk of the zinc chloride solution was

subjected to magnetic stirring throughout the preparation process and the stirring was continued for an additional period of 10 min after the last addition of the poly(methyl vinyl ether-*co*-maleic acid)–sodium diclofenac dispersion. The formed beads were removed from the zinc chloride solution by filtration and washed with deionized water. Blank beads were prepared in the same manner, except that no drug was incorporated. All beads were oven-dried at $40 \pm 0.5\,^{\circ}C$ for 3 days and subsequently equilibrated to a constant weight by storing in a desiccator at $25 \pm 1\,^{\circ}C$.

2.4. Bead morphology

The size and shape of the beads were determined using a digimatic vernier caliper system (Mitutoyo, Japan). The length and breadth were measured from each bead and its size calculated from the average of these two dimensions. The shape of the bead was represented by the elongation ratio which is the quotient of its length to breadth. An elongation ratio of value unity represents a perfect sphere while higher values represent greater elongation. 10 beads were randomly selected for measurement and the results averaged.

2.5. Microwave treatment of beads

An accurately weighed amount of beads was subjected to microwave treatment at 80 W for 5 and 20 min, as well as, 300 W for 1 min 20 s and 5 min 20 s, respectively. The irradiation time was varied between the treatments at 80 and 300 W in order to provide similar levels of energy, but at varying intensities of irradiation. The color and weight variation of beads were noted before and after the beads were treated with microwave.

2.6. Drug release and drug content

The drug release profiles of the beads were determined using phosphate buffer USP (pH 6.0) in simulation of the intestinal medium. Acidic dissolution medium was omitted in test as an insignificant level of drug was expected to release from the matrices owing to drug precipitation via the acid–base reaction (Nurjaya and Wong, 2005; Wong et al., 2007). An accurately weighed amount of sample was placed in 500 ml of dissolution medium and was agitated in a shaker bath (Memmert GmbH+Co. KG, Germany) at 50 strokes/min at $37 \pm 0.2\,^{\circ}C$. Aliquots were withdrawn at various time intervals and assayed spectrophotometrically for sodium diclofenac at the UV wavelength maxima of 275 nm (Cary 50 Conc, Varian Australia Pty Ltd., Australia). The percentage of drug released was calculated with respect to the drug content of the beads. The drug content was expressed as the percentage of drug encapsulated in a unit weight of beads. The drug content was determined by subjecting the same sample of beads from the drug release study for an additional 15 h of magnetic stirring followed by ultrasonication for at least six consecutive periods of 10 min before assaying for drug. Each experiment was carried out in triplicate with blank beads as the control sample and the results averaged.

2.7. Kinetics of drug release

The drug content and percentage of drug released from the beads treated by microwave irradiation were compared to those of the untreated beads. The statistical significance of the effects of microwave irradiation on the drug release property and drug content of the beads was assessed using Student's *t*-test, unless otherwise stated. The mechanism of drug release was investigated by fitting the drug release data into Korsmeyer–Peppas dissolution model as expressed by

$$F = kt^n \tag{1}$$

where F is the percentage of drug released at time t (min), k is the drug release rate constant incorporating the properties of the polymeric system and drug, and n is the release exponent indicative of the drug release mechanism. The n and k values were obtained from the plots of $\log F$ against $\log t$ and the goodness of fit of the drug release data was evaluated by linear regression. The value of $n = 0.5$ represents Fickian diffusional (Case I) release, $0.5 < n < 1.0$ represents non-Fickian (Anomalous) release, $n = 1.0$ indicates Case II (zero order) release and $n > 1.0$ indicates Super Case II release. Case II release refers to transport of drug solute via the dissolution of polymeric matrix due to relaxation of polymer chains, whereas anomalous release refers to the summation of both drug diffusion and polymer dissolution controlled drug release. Super Case II release denotes drug dissolution which is controlled by polymer relaxation and is characterized by a sigmoidal release pattern (Wei et al., 2006).

2.8. Fourier transform infrared spectroscopy (FTIR)

1.5% (w/w) of sample, with respect to the potassium bromide (KBr) disc, was mixed with dry KBr (FTIR grade, Aldrich, Germany). The mixture was ground into a fine powder using an agate mortar before compressing into a disc. Each disc was scanned at a resolution of $4\,cm^{-1}$ over a wavenumber region of $400–4000\,cm^{-1}$ using a FTIR spectrometer (Spectrum RX1 FTIR system, PerkinElmer, USA). The characteristic peaks of IR transmission spectra were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

2.9. Differential scanning calorimetry (DSC)

DSC thermograms were obtained using a differential scanning calorimeter (Pyris 6 DSC, PerkinElmer, USA). 2 mg of sample was crimped in a standard aluminium pan and heated from 30 to 380 °C at a heating rate of 10 °C/min under constant purging of nitrogen at 40 ml/min. The characteristic peak temperature and enthalpy of the melting endotherm and exotherm were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

3. Results and discussion

The formed polymeric beads had a size of 2.13 ± 0.11 mm and an elongation ratio of 1.08 ± 0.06. Irradiation of beads by

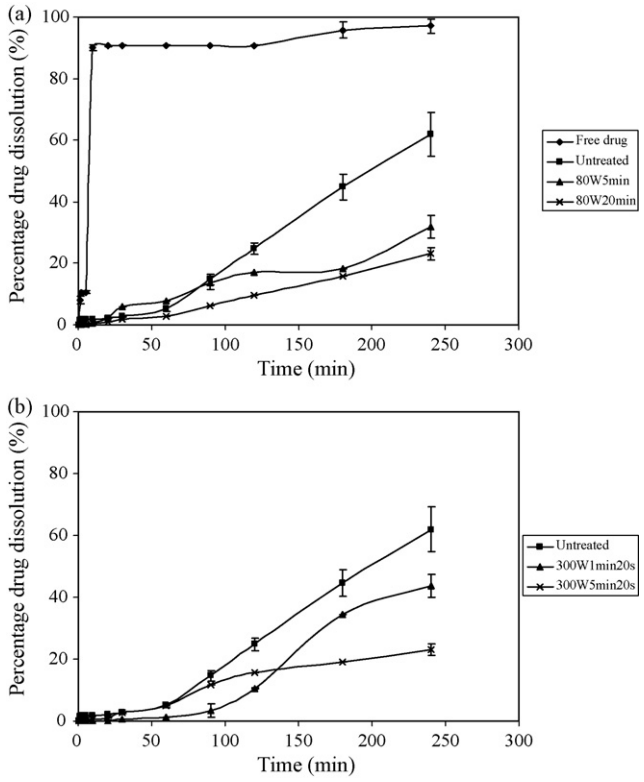

Fig. 2. Drug release profiles of untreated beads and beads treated by microwave at (a) 80 W and (b) 300 W, with dissolution profile of untreated free sodium diclofenac shown in (a).

microwave did not result in significant color and weight variations of beads under all the given experimental conditions. The observation of insignificant weight change in beads (≤0.02%, (w/w)) indicated that all the beads used were appropriately dried and there was minimal loss of substances through volatilization. The drug content of beads was amounting to 6.19 ± 0.03% (w/w). The drug contents of both treated and untreated beads were not significantly different from each other (Student's *t*-test, $P > 0.05$).

3.1. Drug dissolution

Encapsulation of sodium diclofenac in the polymeric beads reduced the extent of drug release after 4 h of dissolution from 97.08 ± 2.41 to 62.01 ± 7.11% (Fig. 2). The decrease in the release extent of drug following encapsulation was ascribed to the availability of polymeric barrier and probable conversion of sodium diclofenac to zinc salt. Nonetheless, preliminary study indicated that the latter factor was expected to have a low level of influence on the release property of drug from beads as the formation of zinc diclofenac required long hours of reaction (Bucci et al., 2000) and its formation could probably be hindered by short reaction time and heterogeneous drug phase in the present investigation. Irradiation of polymeric beads by microwave at 80 W decreased the extent of drug dissolution from 62.01 ± 7.11% to 31.87 ± 3.66 and 23.11 ± 1.98% in samples treated for 5 and 20 min, respectively (Table 1; Student's *t*-test, $P < 0.05$). Similarly, the extent of drug released from beads after 4 h of dissolution decreased from 62.01 ± 7.11% to 43.82 ± 1.09 and 23.06 ± 0.40% in samples treated at 300 W for 1 min 20 s and 5 min 20 s, respectively (Table 1; Student's *t*-test, $P < 0.05$). Unlike the polymeric beads prepared using Ca^{2+} as the crosslinking agent of which an increase in the extent of drug release was effected in beads subjected to microwave treatment at 80 W whereas a decrease in the extent of drug release was noted in beads treated at 300 W (Wong et al., 2007), the treatment of Zn^{2+} crosslinked beads by microwave promoted the retardation of drug release regardless of the intensity of irradiation employed (Fig. 2).

3.2. Beads untreated by microwave

DSC analysis showed that the sodium diclofenac melted at 295.2 ± 0.5 °C with a melting enthalpy of 116.1 ± 2.8 J/g, as well as, onset and end temperatures of 291.1 ± 1.1 and 297.5 ± 0.6 °C, respectively (Fig. 3a). The thermogram of unprocessed poly(methyl vinyl ether-*co*-maleic acid) was characterized by three endothermic peaks (Fig. 3b). These endotherms had melting enthalpies of 22.9 ± 3.3, 185.5 ± 26.4 and 30.8 ± 7.7 J/g, respectively, and corresponding onset temperatures of 154.0 ± 0.1, 172.8 ± 5.0 and 228.9 ± 0.9 °C, as well as, end temperatures of 157.4 ± 0.1, 184.7 ± 2.7 and 254.6 ± 1.1 °C. Crosslinking of poly(methyl vinyl ether-*co*-maleic acid) with Zn^{2+} resulted in the formation of blank polymeric beads which exhibited multiple endothermic domains under the DSC scan, different from those of unprocessed polymer and Ca^{2+} crosslinked matrix (Fig. 3c; Wong et al., 2007). It was reported that the endotherm of unprocessed polymer at the peak temperature of 241.4 ± 0.0 °C was an attribute of COOH and/or COO^- functional moiety of the polymer chains (Wong et al., 2007). The formation of multiple endothermic peaks between 217 and 303 °C with dissimilar enthalpy val-

Table 1
Drug release kinetics of poly(methyl vinyl ether-*co*-maleic acid) beads treated under various microwave irradiation conditions

Condition of microwave irradiation			Drug release kinetics (Korsmeyer–Peppas model)			Extent of drug released after 4 h (%)
Power (W)	Time	Energy (kJ)	k (%/min^n)	n	r^2	
0	0 min	0	0.7056	0.67	0.76	62.01 ± 7.11
80	5 min	24	0.0493	1.23	0.96	31.87 ± 3.66
80	20 min	96	0.0089	1.46	0.96	23.11 ± 1.98
300	1 min 20 s	24	0.0001	2.31	0.98	43.82 ± 1.09
300	5 min 20 s	96	0.0425	1.19	0.99	23.06 ± 0.40

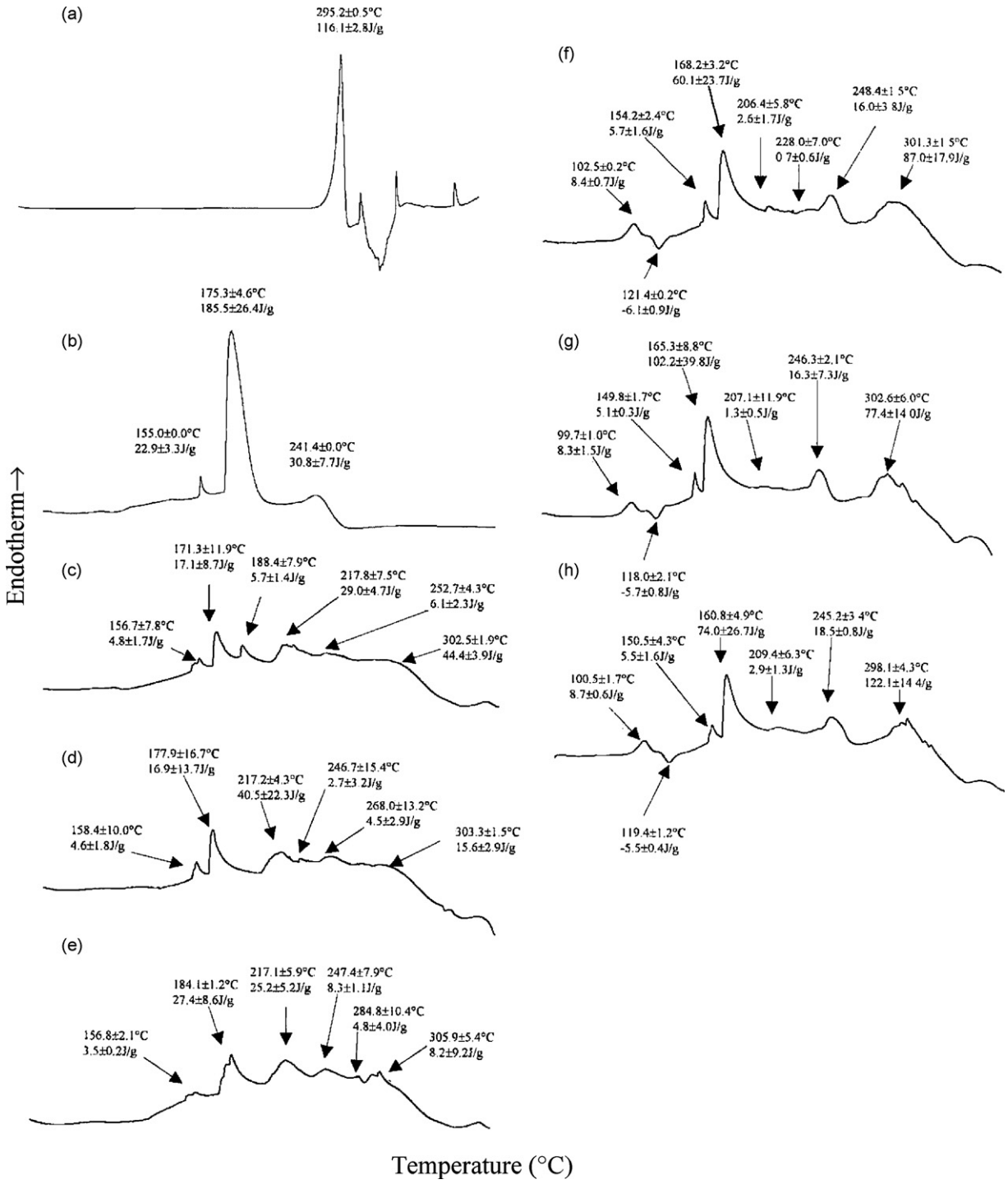

Fig. 3. DSC thermograms of (a) sodium diclofenac, (b) polymer powder, (c) blank beads and beads treated at 80 W for (d) 5 min and (e) 20 min, (f) drug loaded beads and beads treated at 80 W for (g) 5 min and (h) 20 min.

ues in the thermogram of blank beads suggested that polymeric crosslinkages with Zn^{2+} via the COOH and/or COO^- functional moiety were effected and polymeric domains of different conformations were formed in the matrix. The strength and extent of polymer–polymer interaction varied across these domains of beads. The formation of polymeric domains with varying strength and extent of polymer–polymer interaction did not confine to the regions of COOH and/or COO^- moiety. This was characterized by the transformation of the single endotherm of unprocessed polymer at $175.3 \pm 4.6\,^{\circ}C$ to dual endotherms of blank beads at 171.3 ± 11.9 and $188.4 \pm 7.9\,^{\circ}C$ (Fig. 3b and c). Similar to Ca^{2+} crosslinked matrix, the endothermic enthalpy of Zn^{2+} crosslinked beads at $156.7 \pm 7.8\,^{\circ}C$ was lower than that of the unprocessed polymer. This was indicative of the loss of water molecules from beads through oven and desiccator drying, apart from the possibility of water molecules being replaced by

polymer–polymer interaction (Nurjaya and Wong, 2005; Wong et al., 2007).

Examination of the FTIR spectra indicated that the spectrum of crosslinked matrix had a sharper transmission peak attributing to O–H moiety of polymer at the wavenumber region between 3000 and 4000 cm^{-1}, unlike the unprocessed polymer (Fig. 4b and c). Crosslinking of polymer by Zn^{2+}, and processes of hot air and desiccator drying could have reduced the propensity of direct interaction between the COOH moieties, COOH and COO^- moieties, as well as, COOH moiety with the sorbed water molecules via the O–H functional group. The transmission band ascribed to COOH moiety of the polymer chains at $1726.2 \pm 0.1\ cm^{-1}$ was receded upon the transformation of polymer into matrix (Fig. 4b and c). During the process of bead preparation, the polymer solution was alkalinized using the sodium hydroxide solution. A part of the COOH moieties of polymer would have converted to COO^- prior to polymer–polymer crosslinking by Zn^{2+}. The formation of COO^- moiety and crosslinking of COO^- and/or COOH moiety of the polymer chains with Zn^{2+} led to the formation of new FTIR peaks at the lower wavenumbers of 1408.8 ± 1.7 and $1593.5 \pm 1.3\ cm^{-1}$ representing the symmetric and asymmetric stretching transmission bands, respectively (Fig. 4c). The poly(methyl vinyl ether-*co*-maleic acid) is a polymer made of bicarboxylic acid monomers. Inter-polymeric and intra-monomeric interactions between the adjacent COO^-, COOH or COO^- and COOH moieties were represented by two FTIR peaks at the respective wavenumbers of 1092.3 ± 1.6 and $1183.4 \pm 4.3\ cm^{-1}$ of which denoted as acyclic and cyclic C–O stretching transmission bands (Fig. 4b). The FTIR wavenumber of polymer at $1092.3 \pm 1.6\ cm^{-1}$ was markedly reduced to $1071.9 \pm 1.2\ cm^{-1}$ in the case of blank beads following the formation of acyclic crosslinkages between the adjacent polymer chains via Zn^{2+}, whereas the FTIR wavenumber of polymer at $1183.4 \pm 4.3\ cm^{-1}$ was markedly increased to $1289.8 \pm 4.2\ cm^{-1}$ following the replacement of cyclic complex in polymer chains by the newly formed acyclic Zn^{2+} crosslinkages in blank beads (Fig. 4c). The crosslinking of polymer chains by Zn^{2+} could involve the $(CH_2)_n$ moiety of polymer through changes in polymer conformation to accommodate the formation of crosslinkages. It was found that the FTIR band of unprocessed polymer ascribing to $(CH_2)_n$ moiety at $649.5 \pm 1.8\ cm^{-1}$ displayed dual peaks at 558.8 ± 2.4 and $704.9 \pm 3.3\ cm^{-1}$ in the case of blank beads (Fig. 4b and c). This can be aptly explained by the formation of polymeric domains of different conformations in the matrix.

The incorporation of sodium diclofenac in beads was marked by an increase in endothermic enthalpy value of blank samples at the melting peaks of 171.3 ± 11.9, 252.7 ± 4.3 and $302.5 \pm 1.9\ °C$ to 60.1 ± 23.7, 16.0 ± 3.8 and 87.0 ± 17.9 J/g, respectively in the drug loaded matrix, as well as, an increase in melting peak temperature of blank samples at 188.4 ± 7.9 to $206.4 \pm 5.8\ °C$ in drug loaded beads (Fig. 3c and f). This was due to an increase in the extent and strength of drug–polymer and/or polymer–polymer interaction in beads. In addition, an endotherm followed by an exotherm was found in the thermogram of drug loaded beads at 102.5 ± 0.2 and $121.4 \pm 0.2\ °C$, respectively (Fig. 3f). The endotherm represented a new polymeric domain, whereas the exotherm could denote the incidence of crystallization of this domain with heat. Unlike Ca^{2+} crosslinked beads (Wong et al., 2007), the FTIR spectra of drug loaded Zn^{2+} crosslinked matrix exhibited marked characteristics of drug (Figs. 4 and 6). It was envisaged that the propensity of drug–polymer interaction was lower in drug loaded Zn^{2+} crosslinked beads than that of Ca^{2+} counterparts. Zn^{2+}, being more reactive than Ca^{2+}, had interacted with the polymer chains at various domains thereby reducing the probability of drug–polymer interaction in the formed matrix. This in turn accounted for a higher extent of drug released from the Zn^{2+} crosslinked beads ($62.01 \pm 7.11\%$) than that of Ca^{2+} crosslinked samples ($25.87 \pm 0.64\%$; Wong et al., 2007) at 4 h of dissolution.

3.3. Beads treated by microwave

Treatment of blank polymeric beads by microwave at 80 W brought about polymer–polymer interaction which was translated to the subsidence of endothermic peaks at 171.3 ± 11.9 and $188.4 \pm 7.9\ °C$ of the untreated blank samples, but the formation of new polymeric domains at higher melting peak temperatures of 284.8 ± 10.4 and $268.0 \pm 13.2\ °C$ in samples treated for 20 and 5 min, respectively (Fig. 3c–e). In addition, an increase in endothermic enthalpy value at $184.1 \pm 1.2\ °C$ was noted with blank beads treated by microwave for 20 min, possibly following the coalescence of polymeric domains as characterized by the melting peak temperatures of 171.3 ± 11.9 and $188.4 \pm 7.9\ °C$ of the untreated blank samples. In the case of drug loaded matrix, there was an increase in endothermic enthalpy values of untreated samples at 168.2 ± 3.2 and $301.3 \pm 1.5\ °C$ to 102.2 ± 39.8 and 122.1 ± 14.4 J/g in beads treated for 5 and 20 min at 165.3 ± 8.8 and $298.1 \pm 4.3\ °C$, respectively (Fig. 3f–h). The increase in endothermic enthalpy values as well as formation of melting peaks at higher endothermic temperatures of the treated beads were apparently attributed to a rise in the extent and strength of polymer–polymer and/or drug–polymer interaction. This in turn reduced the propensity of drug released from beads treated by microwave at 80 W for 5 and 20 min after 4 h of dissolution (Fig. 2).

Analysis of FTIR spectra indicated that the treatment of blank polymeric beads by microwave at 80 W promoted the interaction between polymer chains via the $(CH_2)_n$ moiety. This was supported by an increase in FTIR transmission intensity and a decrease in FTIR wavenumber at 546.4 ± 15.8 and $550.3 \pm 3.1\ cm^{-1}$ of spectra ascribing to samples treated for 5 and 20 min, respectively (Fig. 4c–e). In addition, the strength of polymer–polymer interaction via the O–H moiety was increased in blank beads treated by microwave for 20 min as indicated by a reduction in the FTIR wavenumber of untreated samples at $3476.0 \pm 12.1\ cm^{-1}$ (Fig. 4c and e). The summation effect was that the treated beads exhibited a lower extent of drug released than that of the untreated samples and matrix treated for 20 min demonstrated the highest degree of drug release retardation in spite of a reduction in the propensity of interaction between the polymer chains via C–H, acyclic and cyclic C–O moieties (Fig. 2). The loss of

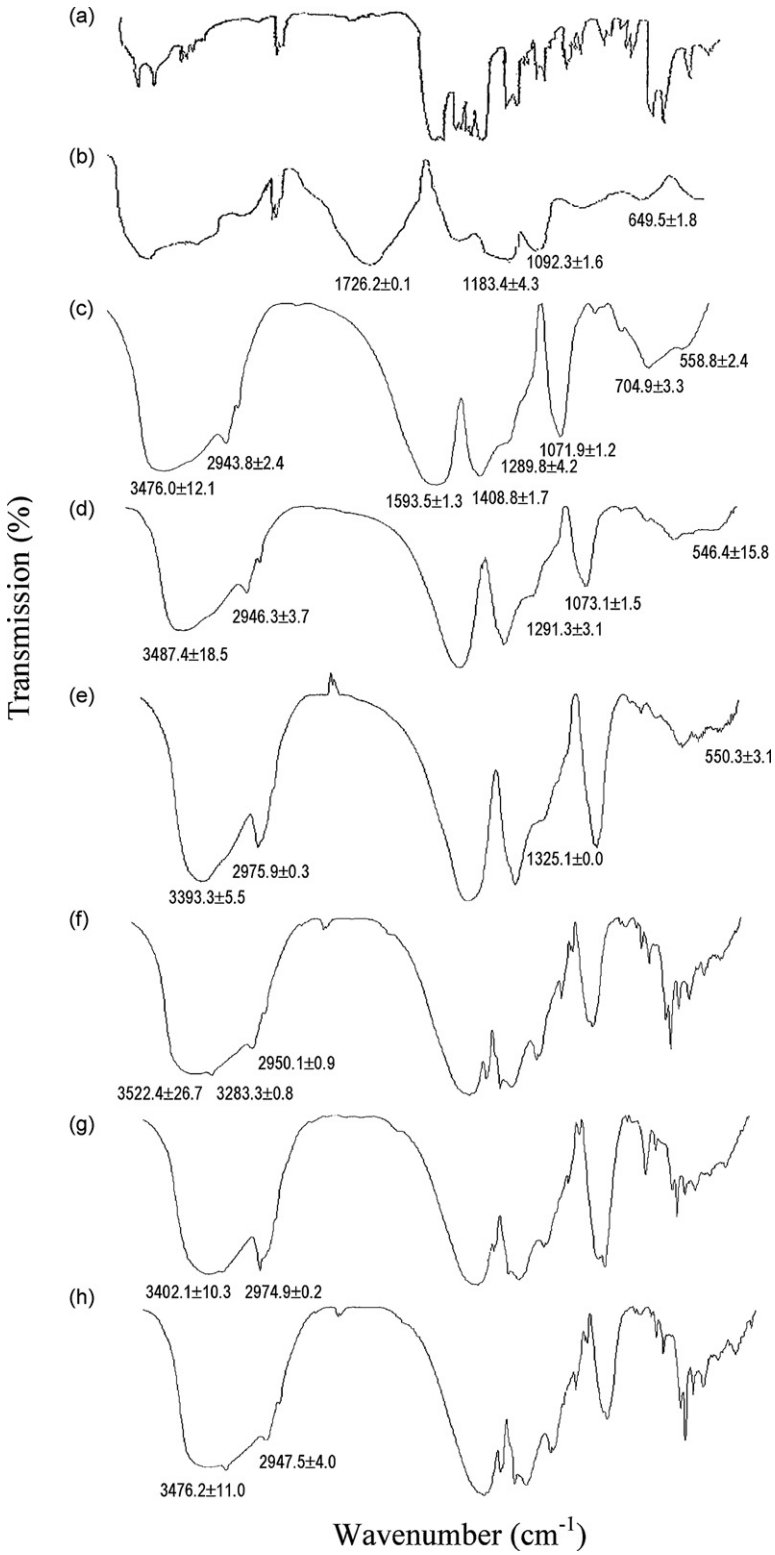

Fig. 4. FTIR spectra of (a) sodium diclofenac, (b) polymer powder, (c) blank beads and beads treated at 80 W for (d) 5 min and (e) 20 min, (f) drug loaded beads and beads treated at 80 W for (g) 5 min and (h) 20 min.

polymer–polymer interaction via the C–H and C–O moieties of matrix was marked by a reduction in the FTIR transmission intensity at 2943.8 ± 2.4 and $1071.9 \pm 1.2\,cm^{-1}$, as well as, an increase in the FTIR wavenumber at 1289.8 ± 4.2 and $2943.8 \pm 2.4\,cm^{-1}$ of the untreated blank beads when they were treated by microwave for 20 min (Fig. 4c and e). Similar to that of blank samples, the treatment of drug loaded polymeric beads by microwave induced polymer–polymer and/or drug–polymer interaction via the O–H and/or N–H moiety. The FTIR wavenumber ascribing O–H and/or N–H moiety of

untreated drug loaded beads at $3522.4 \pm 26.7\,cm^{-1}$ was reduced to 3402.1 ± 10.3 and $3476.2 \pm 11.0\,cm^{-1}$ in samples treated by microwave for 5 and 20 min, respectively (Fig. 4f–h). The drug loaded beads treated by microwave for 5 min underwent a greater strength of matrix interaction via the O–H and/or N–H moiety of polymer and drug. Nonetheless, the propensity of drug–polymer and/or polymer–polymer interaction at the domains of C–H and C–O moieties in beads incorporating drug and treated by microwave for 5 min became lower when compared to that of treated for 20 min. In the latter, a greater fraction of free C–H and C–O moieties was available following a reduction in the extent of polymer–polymer interaction via these functional groups under the influence of microwave. This was translated to a higher propensity of drug–polymer interaction via C–H and C–O functional groups in addition to O–H and/or N–H moiety, thereby leading to a greater extent of reduction in the degree of drug released from these beads at 4 h of dissolution than that of treated by microwave for 5 min (Figs. 2 and 4).

The treatment of blank polymeric beads by microwave at 300 W led to a reduction in the endothermic enthalpy values of untreated samples at 171.3 ± 11.9 and $302.5 \pm 1.9\,°C$, as well as, the subsidence of endotherm of untreated matrix at $188.4 \pm 7.9\,°C$ and that of at $217.8 \pm 7.5\,°C$ in the case of blank beads treated for 1 min 20 s (Fig. 5a–c). These were accompanied by the formation of new endothermic peaks at 195.4 ± 4.2 and $204.0 \pm 1.5\,°C$ of blank beads treated by microwave for 1 min 20 s and 5 min 20 s, respectively (Fig. 5a–c). In addition, an increase in the endothermic enthalpy value of blank beads treated for 5 min 20 s at the melting peak of $217.1 \pm 0.8\,°C$ was noted (Fig. 5a and c). In the case of drug loaded matrix, endotherms with high enthalpy values were found in the thermograms of samples treated for 1 min 20 s and 5 min 20 s at 156.4 ± 3.3 and $157.5 \pm 8.4\,°C$, respectively following the coalescence of endotherms of untreated drug loaded beads at 154.2 ± 2.4 and $168.2 \pm 3.2\,°C$, and at $297.2 \pm 2.9\,°C$ in samples treated for 5 min 20 s (Fig. 5d–f). The increase in endothermic enthalpy values as well as formation of melting peaks at higher endothermic temperatures of the treated beads were apparently attributed to a rise in the extent and strength of polymer–polymer and/or drug–polymer interaction.

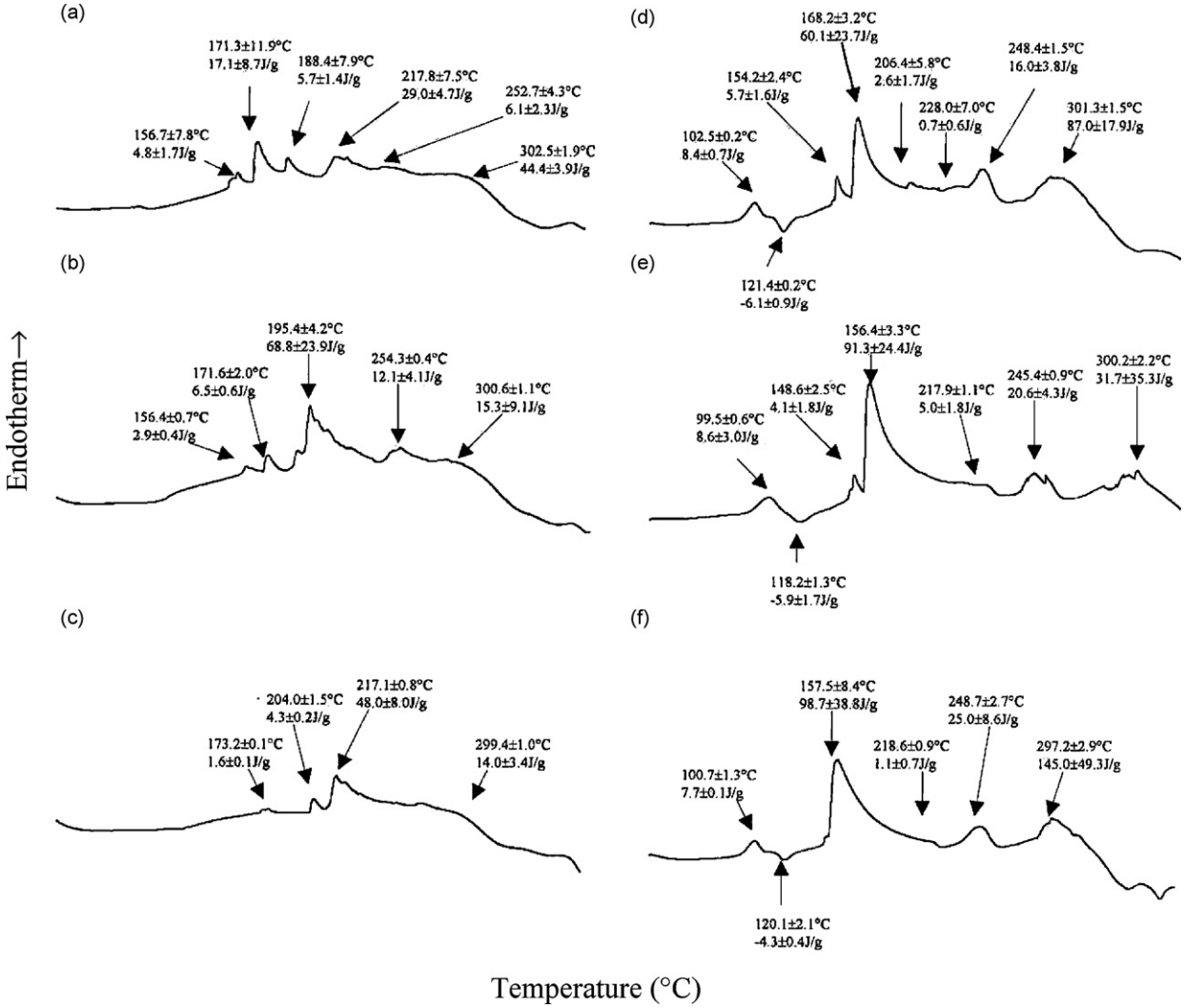

Fig. 5. DSC thermograms of (a) blank beads and beads treated at 300 W for (b) 1 min 20 s and (c) 5 min 20 s, (d) drug loaded beads and beads treated at 300 W for (e) 1 min 20 s and (f) 5 min 20 s.

The findings suggested that the propensity of polymer–polymer and/or drug–polymer interaction in these beads was greatly enhanced by the microwave via the involvement of various matrix domains. This in turn reduced the propensity of drug released from beads treated by microwave at 300 W for 1 min 20 s and 5 min 20 s at 4 h of dissolution (Fig. 2).

Similar to that of polymeric beads treated by microwave at 80 W, the treatment of beads at 300 W led to polymer–polymer and/or drug–polymer interaction via the O–H and/or N–H moiety, as well as, $(CH_2)_n$ functional group of the matrix, thereby leading to a reduction in the extent of drug release. This was shown by a decrease in the FTIR wavenumber of untreated blank and drug loaded beads ascribing OH and/or N–H moiety at 3476.0 ± 12.1 and $3522.4 \pm 26.7\,cm^{-1}$, respectively in the corresponding batches of microwave-treated samples (Fig. 6). In addition, a marked increase in transmission intensity and a decrease in wavenumber of FTIR peaks ascribing $(CH_2)_n$ moiety of microwave-treated blank samples for 1 min 20 s and 5 min 20 s at 551.8 ± 5.7 and $554.2 \pm 0.0\,cm^{-1}$, respectively were noted (Fig. 6a–c). In contrast to drug loaded beads treated by microwave at 300 W for 5 min 20 s, the treatment of the same beads for 1 min 20 s led to an increase in the FTIR wavenum-

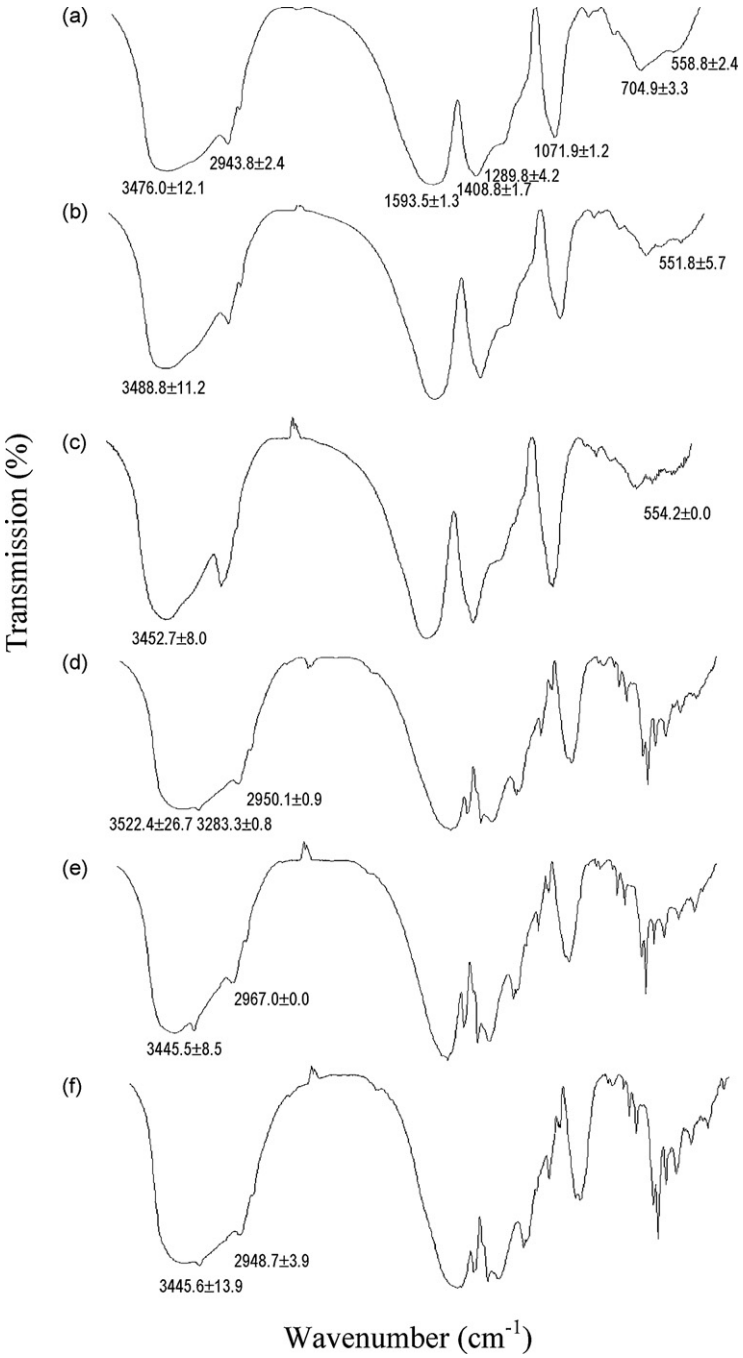

Fig. 6. FTIR spectra of (a) blank beads and beads treated at 300 W for (b) 1 min 20 s and (c) 5 min 20 s, (d) drug loaded beads and beads treated at 300 W for (e) 1 min 20 s and (f) 5 min 20 s.

ber ascribing to C–H moiety of the matrix at $2967.0 \pm 0.0\,cm^{-1}$ when compared to that of the untreated counterparts (Fig. 6d–f). It was envisaged that the strength of matrix interaction via the C–H moiety was lower in samples treated by microwave for a shorter duration of time. Similar to that of beads treated by microwave at 80 W, beads treated by microwave at 300 W for 5 min 20 s had a greater fraction of free C–H and C–O moieties following a reduction in the extent of polymer–polymer interaction via these functional groups under the influence of microwave (Figs. 4c and e and 6a and c). This was evidenced from the reduction in the transmission intensity of FTIR peaks of untreated blank matrix at 2943.8 ± 2.4 and $1071.9 \pm 1.2\,cm^{-1}$ of which denoted C–H and C–O moieties of polymer, respectively, following the irradiation of these beads by microwave (Fig. 6a and c). Incidentally, a higher propensity of drug–polymer interaction was promoted via C–H and C–O moieties in addition to O–H and/or N–H functional group in beads treated by microwave at 300 W for 5 min 20 s, and this led to a greater extent of reduction in the degree of drug released from these beads at 4 h of dissolution than that of treated by microwave for 1 min 20 s (Figs. 2 and 6).

3.4. Kinetics of drug release

Practically, the treatment of polymeric beads by microwave led to a reduction in the rate of drug released from the matrix. Inferring from the n values, the kinetics of drug released from the untreated beads tend to mediate by means of drug diffusion through the pores of the matrix as well as polymer relaxation (Table 1). On the other hand, the microwave-treated beads had marked Super Case II release characteristics particularly that of treated at 300 W for 1 min 20 s (Table 1). The good fit of drug dissolution data of the microwave-treated beads into the dissolution model suggested that drug release characteristics of beads was mainly governed by the state of polymer relaxation of the matrix of which in turn could be affected by the state of polymer–polymer and/or drug–polymer interaction in beads. The interaction between polymers and/or drug in beads could have affected the pore characteristics and drug diffusion process thereby resulting in polymeric chain mobility being crucial for drug dissolution kinetics.

4. Conclusions

Unlike the Ca^{2+} processed beads, crosslinking of poly(methyl vinyl ether-*co*-maleic acid) with Zn^{2+} brought about the formation of matrix with various conformational domains. The treatment of Zn^{2+} crosslinked matrix by microwave brought about polymer–polymer and drug–polymer interaction at different polymeric domains in beads, thereby retarding the extent and rate of drug release. The drug released from Zn^{2+} crosslinked polymeric beads was able to retard by microwave of both low and high intensities of irradiation. At the same intensity of microwave irradiation, the degree of drug released from beads was reduced to a greater extent through treating the beads for a longer duration of irradiation. The release of drug from beads was retarded via the interplay of O–H, N–H, C–H, $(CH_2)_n$ and C–O functional groups of polymer and drug. Using Korsmeyer–Peppas equation, it was found that the release of drug from the untreated beads tend to be effected via drug diffusion and polymer relaxation. In response to the influence of microwave, the drug release profile of beads became markedly governed by the state of polymer relaxation of the matrix of which in turn could be affected by the state of polymer–polymer and/or drug–polymer interaction in beads. Through modifying the drug release property of polymeric beads by microwave, it is envisaged that the poly(methyl vinyl ether-*co*-maleic acid) can be employed as matrix polymer of drug carrier for colonic delivery.

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