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Effects of Microwave on Drug Release Property of Poly(Methyl Vinyl Ether-co-Maleic Acid) Matrix

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ABSTRACT The drug release behavior of beads made of poly(methyl vinyl ether-co-maleic acid) was 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. The beads 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 using dissolution testing, drug content assay, differential scanning calorimetry, and Fourier transform infra-red spectroscopy. Keeping the level of supplied irradiation energy identical, treatment of beads by microwave at varying intensities of irradiation did not bring about similar drug release profiles. The extent and rate of drug released from beads were markedly enhanced through treating the samples by microwave at 80 W as a result of loss of polymer-polymer interaction via the $(CH_2)_n$ moiety, but decreased upon treating the beads by microwave at 300 W following polymer-polymer interaction via the O–H, COOH, and COO^- moieties as well as drug-polymer interaction via the N–H, O–H, COO^-, and C–O moieties. The beads treated by microwave at 300 W exhibited a higher level of drug release retardation capacity than those that were treated by microwave at 80 W in spite of polymer-polymer interaction via the $(CH_2)_n$ moiety was similarly reduced in the matrix. The mechanism of drug release of both microwave-treated and untreated beads tended to follow zero order kinetics. The drug release was markedly governed by the state of polymer relaxation of the matrix and was in turn affected by the state of polymer-polymer and/or drug-polymer interaction in beads.

KEYWORDS Drug-polymer interaction, Microwave, Polymer-polymer interaction, Poly(methyl vinyl ether-co-maleic acid)

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INTRODUCTION

Carbohydrate polymers, such as alginate and pectin, are widely used in the design of drug delivery systems for small molecule drugs (Acarturk & Takka 1999; Adkin et al., 1997; Ashford et al., 1994; Chan & Heng 2002; Chan et al.,

1997; El-Gibaly 2002; Fu Lu et al., 1991; Fundueanu et al., 1998; Gupta et al., 2001; Liu & Krishnan 1999; Macleod et al., 1997; Munjeri et al., 1997; Murata et al., 2004; Nurjaya & Wong 2005; Pillay & Fassihi 1999; Pillay et al., 1998a, b; Sriamornsak et al., 1997; Sriamornsak & Nunthanid 1998; Takka & Acarturk 1999; Wan et al., 1993; Wan et al., 1994; Wong et al., 2002a, b, c; Wong et al., 2005; Wong In Press). Nonetheless, the embedded drug molecules exhibit a fast rate of drug release via diffusion through the pores of the matrix. Such rate of drug release is undesirable in the case of the need to target the drugs to the lower part of gastrointestinal tract, particularly, the colon. As such, various formulation and processing approaches have been taken to negate the rate of drug release from these polymeric matrices. The latest processing approach lies in the application of microwave technology to modify the state of molecular interaction between the polymer chains (Nurjaya and Wong 2005; Wong et al., 2002c, 2005). Under the influence of microwave irradiation, it is found that the drug release could be further retarded in the matrix made of alginate through changing the profiles of polymer cross-linkage and complexation. Nevertheless, the treatment of pectinate matrix by microwave brings about the higher extent and rate of drug release.

Poly(methyl vinyl ether-co-maleic acid) and analogs are used as thickening agent, encapsulating agent, denture adhesive as well as adjuvant for transdermal drug delivery system (Arbós et al., 2002, 2003; Kockisch et al., 2004; Luppi et al., 2003; Matsuya et al., 1996; Owens et al., 2005, Salman et al., 2005). The wide application of these polymers is attributed to their biodegradability and low oral toxicity, typically ranges between 5 to 25.6 g/kg in animal models. Unlike 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 examined. As the application of microwave technology in design of alginate and pectinate controlled-release matrices brought about varying degrees of success, the present study proposes to investigate the drug release kinetics of matrix made of poly(methyl vinyl ether-co-maleic acid) and the effects of microwave on the drug release property of the matrix.

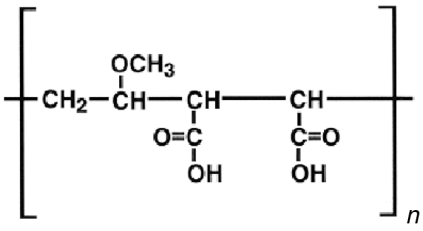

FIGURE 1 Chemical structure of poly(methyl vinyl ether-co-maleic acid).

EXPERIMENTAL

Materials

Poly(methyl vinyl ether-co-maleic acid) (ISP, USA) was employed as a matrix polymer in the preparation of beads, with calcium chloride dihydrate (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).

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.

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 10% w/v of calcium chloride dihydrate 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, Bredel Pumps, UK). The bulk of the calcium 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 calcium 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 ± 0.5°C for 3 days and subsequently equilibrated to a constant weight by storing in a desiccator at 25 ± 1°C.

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. Ten beads were randomly selected for measurement and the results averaged.

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.

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 & Wong, 2005). An accurately weighed amount of sample was placed in 500 mL of dissolution medium (sink condition with an amount of drug load placed in 500 mL of dissolution medium < 10 % of sodium diclofenac solubility in phosphate buffer pH 6) and was agitated in a shaker bath (Memmert GmbH + Co. KG, Germany) at 50 strokes/min at 37 ± 0.2°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 hr of magnetic stirring followed by ultrasonication for at least six consecutive periods of 10 min before assaying for sodium diclofenac. Each experiment was carried out in triplicate with blank beads as the control sample and the results averaged.

Kinetics of Drug Release

The drug content and percentage of sodium diclofenac 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). The mean dissolution time (MDT) was also computed from the drug dissolution data using the following equation:

$$\mathrm{MDT} = (n/n+1)(k/100)^{-(1/n)} \qquad (2)$$

The MDT value denotes the release rate of drug from polymeric beads. A higher value of MDT indicates a higher drug release retardation capacity of polymeric beads.

Fourier Transform Infra-Red 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, Perkin Elmer). The characteristic peaks of IR transmission spectra were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

Differential Scanning Calorimetry (DSC)

DSC thermograms were obtained using a differential scanning calorimeter (Pyris 6 DSC, Perkin Elmer). 2 mg of sample were 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 peaks and specific heat of the melting endotherm were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

RESULTS AND DISCUSSION

The formed polymeric beads had a size of 2.40 ± 0.24 mm and an elongation ratio of 1.07 ± 0.06. Irradiation of beads by 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 6.37 ± 0.21% w/w. The drug contents of both treated and untreated beads were not significantly different from each other (Student's *t*-test, $p > 0.05$).

Drug Dissolution

Encapsulation of sodium diclofenac in the polymeric beads reduced the extent of drug release after 4 hr of dissolution from 97.08 ± 2.41% to 25.87 ± 0.64% (Fig. 2). Irradiation of these beads by microwave at 80 W increased the extent of drug dissolution from 25.87 ± 0.64% to 34.26 ± 2.83 and 34.94 ± 2.22 % in samples treated for 5 and 20 min respectively (Table 1; Student's *t*-test, $p < 0.05$). Interestingly, the extent of drug released from beads after 4 h of dissolution decreased from 25.87 ± 0.64% to 21.82 ± 0.10 and 18.54 ± 0.17% in samples treated at 300 W for 1 min 20 s and 5 min 20 s, respectively (Table 1; Student's *t*-test, $p < 0.05$). At the similar levels of supplied microwave energy, the treatment of beads at 300 W

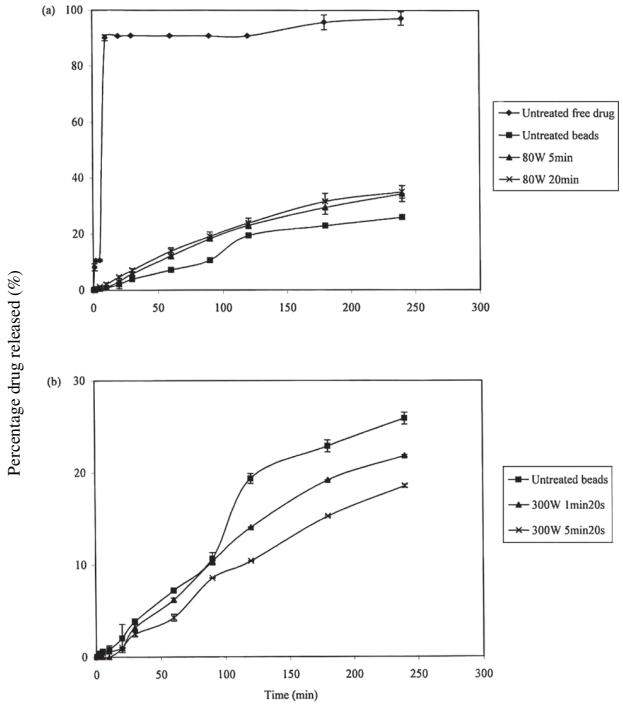

FIGURE 2 **Drug release profiles of untreated beads and beads treated by microwave at (a) 80 W and (b) 300 W, with dissolution profile of untreated free sodium diclofenac shown in (a).**

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 hr (%)
Power(W)	Time	Energy (kJ)	k(%/min^n)	n	r^2	MDT(min)	
0	0 min	0	0.10	1.07	0.96	373.4	25.87 ± 0.64
80	5 min	24	0.13	1.05	0.97	279.2	34.26 ± 2.83
80	20 min	96	0.28	0.92	0.99	290.6	34.94 ± 2.22
300	1 min 20 s	24	0.04	1.19	0.95	377.1	21.82 ± 0.10
300	5 min 20 s	96	0.08	1.03	0.97	631.2	18.54 ± 0.17

promoted the retardation of drug release, whilst the treatment of beads at 80 W enhanced the extent of drug dissolution (Fig. 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). Further heating of sodium diclofenac beyond 300°C resulted in drug decomposition, which led to the generation of irreproducible peak pattern, at temperatures ranging from 300 to 380°C. 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 Ca^{2+} resulted in a decrease in melting peak temperatures (Fig. 3c). The melting enthalpy of the unprocessed polymer at the peak temperature of 155.0 ± 0.0°C was reduced from 22.9 ± 3.3 J/g to 8.02 ± 0.7 J/g in untreated blank beads. Nonetheless, the melting enthalpy of the unprocessed polymer at the peak temperature of 175.3 ± 4.6°C was markedly increased from 185.5 ± 26.4 J/g to 414.9 ± 17.6 J/g in untreated blank beads. The latter observation was accompanied by the formation of an endotherm with a broader melting range, between 158.9 ± 3.5 and 200.0 ± 2.4°C. Unlike the thermogram of unprocessed polymer, a similar endotherm characterized by the peak temperature of 241.4 ± 0.0°C in the former was not found in the case of untreated blank beads. The DSC results

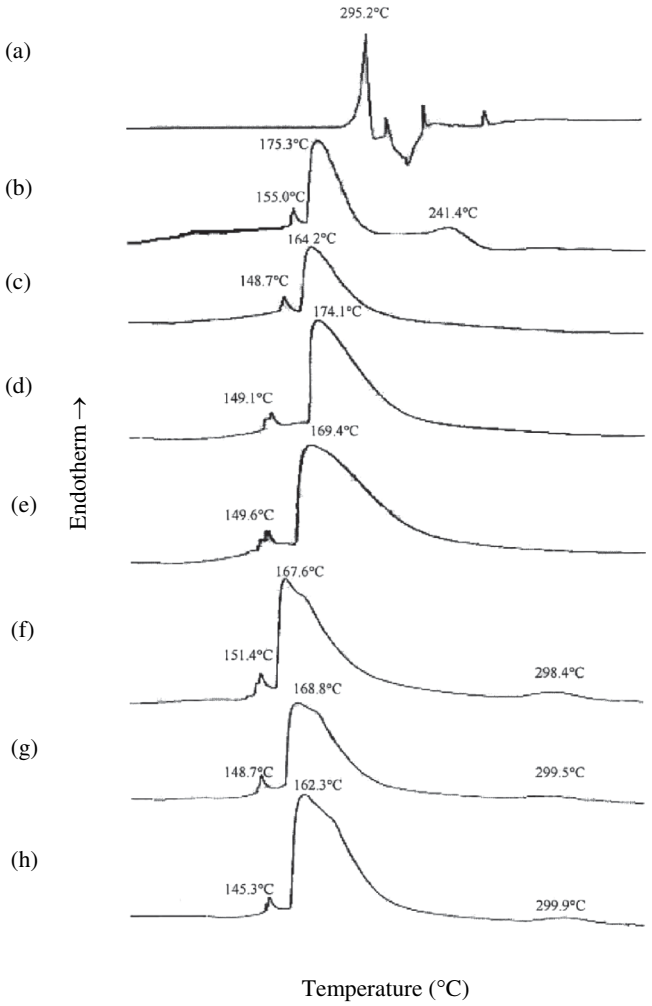

FIGURE 3 **DSC thermograms of (a) sodium diclofenac, (b) polymer powder, (c) blank beads and beads treated at 80 W for (d) 5 min and (e) 20 min, (f) drug loaded beads and beads treated at 80 W for (g) 5 min and (h) 20 min.**

indicated that a crosslinked polymeric matrix was formed. The reduction in the melting enthalpy of endotherm at 148.7 ± 2.6°C 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 Ca^{2+} in polymer-polymer cross-linkage and/or direct polymer-polymer interaction (Nurjaya & Wong, 2005). The endotherm of the unprocessed polymer at the peak temperature of 241.4 ± 0.0°C was possibly an attribute of COOH and/or COO^- functional moiety of the polymer chains and such melting characteristic was lost in beads as a result of polymer crosslinking with Ca^{2+} via these functional groups. The cross-linkages of matrix had a lower strength than that of the unprocessed polymer and this led to a reduction in melting peak temperatures. Nonetheless, the extent of polymer-polymer interaction was markedly enhanced at specific domains of beads thus giving rise to an endotherm with a larger melting enthalpy at the peak temperature of 164.2 ± 1.9°C, but with varying strength across the domains as reflected by the wide melting temperature distribution of endotherm.

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 Ca^{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 groups. The transmission band ascribed to COOH moiety of the polymer chains at 1726.2 ± 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 Ca^{2+}. The formation of COO^- moiety and crosslinking of COO^- and/or COOH moiety of the polymer chains with Ca^{2+} led to the formation of new FTIR peaks at the lower wavenumbers of 1423.4 ± 1.2 and 1574.0 ± 4.7 cm^{-1} representing the symmetric and asymmetric stretching transmission bands, respectively. The poly(methyl vinyl ether-co-maleic acid) is a polymer made of bicarboxylic acid monomers. Interpolymeric 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 ± 4.3 cm^{-1} of which denoted as acyclic and cyclic C–O

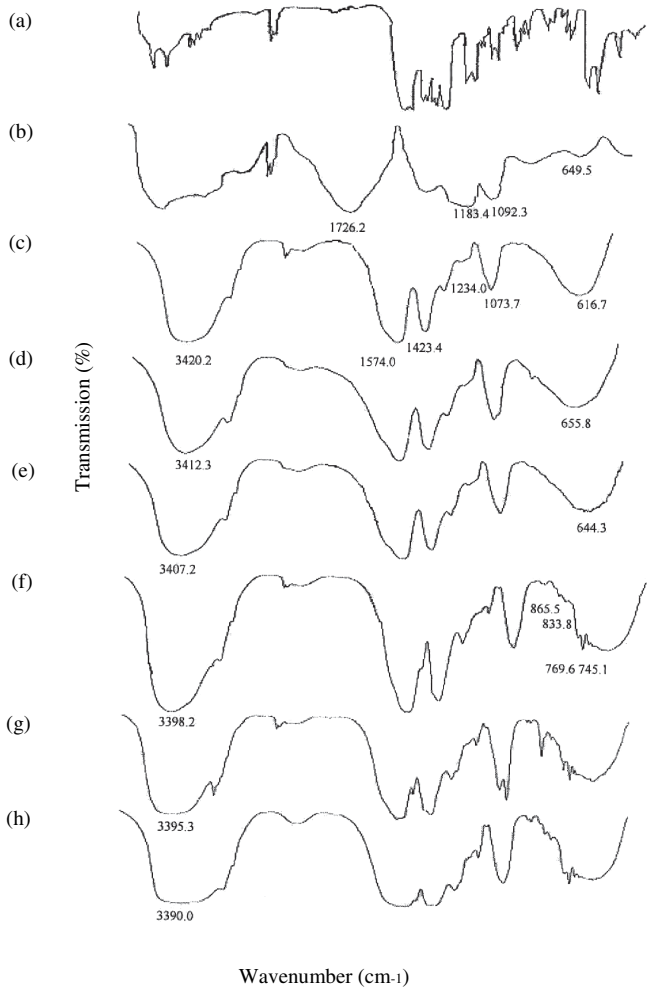

FIGURE 4 **FTIR spectra of (a) sodium diclofenac, (b) polymer powder, (c) blank beads and beads treated at 80 W for (d) 5 min and (e) 20 min, (f) drug loaded beads and beads treated at 80 W for (g) 5 min and (h) 20 min.**

stretching transmission bands (Fig. 4b). The FTIR wavenumber of polymer at 1092.3 ± 1.6 cm^{-1} was markedly reduced to 1073.7 ± 0.5 cm^{-1} in the case of untreated blank beads following the formation of acyclic cross-linkages between the adjacent polymer chains via Ca^{2+}, whereas the FTIR wavenumber of polymer at 1183.4 ± 4.3 cm^{-1} was markedly increased to 1234.0 ± 0.0 cm^{-1} following the replacement of cyclic complex in polymer chains by the newly formed acyclic Ca^{2+} crosslinkages in untreated blank beads (Fig. 4c). The cross-linking of polymer chains by Ca^{2+} could involve the $(CH_2)_n$ moiety of polymer through changes in polymer conformation to accommodate the formation of cross-linkages. It was found that the FTIR wavenumber of unprocessed polymer ascribing to $(CH_2)_n$ moiety at 649.5 ± 1.8 cm^{-1} was markedly reduced in the case of untreated blank beads.

The incorporation of sodium diclofenac in beads was marked by the appearance of a new endothermic peak at 298.4 ± 1.9°C with onset and end temperatures of 283.2 ± 0.7 and 313.8 ± 2.6°C, respectively (Fig. 3f), as well as various distinct FTIR peaks chiefly, 745.1 ± 0.6 cm^{-1} for C–H, 769.6 ± 1.9 cm^{-1} for C–Cl and/or benzene rings, and 833.8 ± 1.6 and 865.5 ± 0.0 cm^{-1} for C–H of benzene rings (Fig. 4f). In addition, a reduction in the melting enthalpy of blank sample at the peak temperature of 164.2 ± 1.9°C to 257.7 ± 22.2 J/g was noted (Fig. 3c and f). Apparently, the endothermic enthalpy was greatly reduced by 37.9%; beyond that could be accounted by the inaccuracy derived from the enthalpy computation owing to the introduction of drug mass in matrix. The observation suggested that the drug-polymer interaction had taken place in the formed matrix. The interaction of drug with polymer was accompanied by a loss in polymer-polymer interaction. The strength of drug-polymer interaction was greater than that of the drug molecules or polymer chains alone, and had a higher degree of variability in its magnitude of interaction. This could be aptly explained by the rise in melting peak temperature and temperature distribution of the endotherm ascribing to drug at 298.4 ± 1.9°C when compared to that of the pure sodium diclofenac.

Beads Treated by Microwave

Treatment of blank polymeric beads by microwave at 80 W for 5 and 20 min brought about a reduction in the melting enthalpy of the untreated sample at 164.2 ± 1.9°C from 414.9 ± 17.6 J/g to 308.6 ± 12.7 and 292.1 ± 93.0 J/g respectively (Fig. 3c, d, and e). In the case of drug loaded polymeric beads, treatment of beads by microwave at 80 W for 5 and 20 min brought about a reduction in the peak temperature at 151.4 ± 0.6°C (Fig. 3f, g, and h). Correspondingly, the onset and end temperatures of the same endotherm were reduced from 150.5 ± 0.7°C to 147.6 ± 0.1 and 144.0 ± 1.1°C, and from 154.8 ± 0.8°C to 152.0 ± 0.3 and 148.1 ± 1.2°C, respectively. The decrease in peak, onset, and end temperatures, as well as the reduction in melting enthalpy of the treated beads, was apparently attributed to the reduced strength and extent of polymer-polymer and/or drug-polymer interaction. This in turn promoted the propensity of drug released from beads treated by microwave for 5 and 20 min after 4 hr of dissolution.

Analysis of FTIR spectra indicated that the treatment of blank polymeric beads by microwave demoted the interaction between polymer chains via the $(CH_2)_n$ moiety. It was noted that there was an increase in the FTIR wavenumber of the untreated blank beads at 616.7 ± 8.9 cm^{-1} in samples treated by microwave at 80 W for 5 and 20 min (Fig. 4c, d, and e). The release of drug from the matrices treated by microwave for 5 and 20 min was enhanced, albeit it was observed that there was an increase in molecular interaction between the polymer chains via the O–H moiety following the same conditions of microwave irradiation. The FTIR wavenumber of O-H moiety at 3420.2 ± 0.2 cm^{-1} of the untreated blank beads was reduced in samples treated by microwave for 5 and 20 min (Fig. 4c, d, and e). Treatment of drug-loaded beads by microwave at 80 W brought about variable interaction between the polymer and drug as marked by spectra changes in the wavenumber region between 600 and 1000 cm^{-1} (Fig. 4f, g, and h). The extent of drug released from these beads was a net balance of the state of interaction between the drug and polymer as well as polymer chains via the $(CH_2)_n$ and O–H moieties.

Different from polymeric beads treated by microwave at 80 W, the DSC analysis indicated that the endothermic peak temperature of the untreated blank polymeric beads at 164.2 ± 1.9°C was increased in the case of sample treated by microwave at 300 W for 1 min 20 s (Fig. 5a and b). On the other hand, the treatment of blank beads by microwave at 300 W for 5 min 20 s brought about a rise in the melting peak temperature of the untreated sample at 148.7 ± 2.6 to 152.0 ± 0.7°C, as well as the onset and end temperatures of the same endotherm from 146.3 ± 2.3 to 150.5 ± 0.7°C and 151.9 ± 2.2 to 155.6 ± 0.7°C, respectively (Fig. 5a and c). The findings suggested that the strength of polymer-polymer interaction in these beads was greatly enhanced via the modification of different matrix domains by microwave irradiation at 300 W. This led to a reduction in the extent of drug released from beads when compared to that of the untreated sample, albeit it was found that the endothermic enthalpy of the untreated blank beads at 164.2 ± 1.9°C was reduced from 414.9 ± 17.6 to 317.4 ± 20.3 J/g in the case of sample treated by microwave at 300 W for 5 min 20 s implying that a reduction in the extent of polymer-polymer interaction was taken place in matrix following the irradiation of beads by microwave.

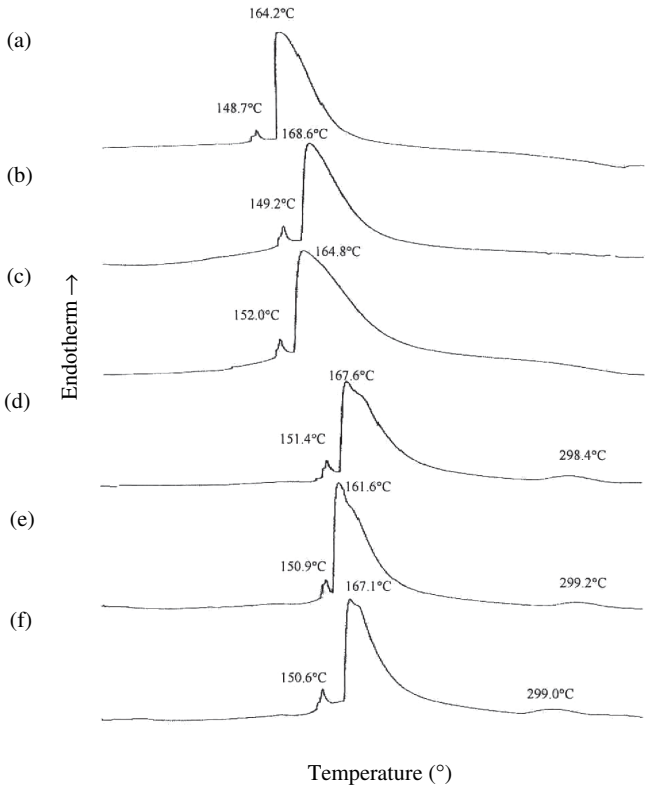

FIGURE 5 DSC thermograms of (a) blank beads and beads treated at 300 W for (b) 1 min 20 s and (c) 5 min 20 s, (d) drug loaded beads and beads treated at 300 W for (e) 1 min 20 s and (f) 5 min 20 s.

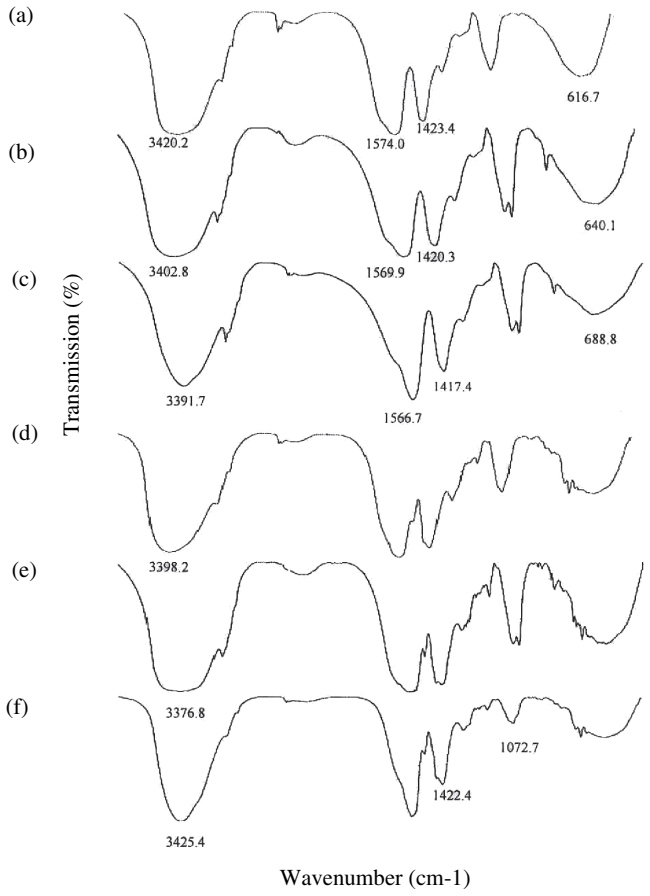

FIGURE 6 FTIR spectra of (a) blank beads and beads treated at 300 W for (b) 1 min 20 s and (c) 5 min 20 s, (d) drug loaded beads and beads treated at 300 W for (e) 1 min 20 s and (f) 5 min 20 s.

Analysis of blank polymeric beads by FTIR showed that the respective wavenumbers of O–H, as well as symmetric and asymmetric stretching transmission bands of COO^- / COOH at 3420.2 ± 0.2, 1423.4 ± 1.2, and 1574.0 ± 4.7 cm^{-1} decreased in the case of samples treated by microwave at 300 W for 1 min 20 s and 5 min 20 s (Fig. 6a, b, and c). On the other hand, the FTIR wavenumber of $(CH_2)_n$ moiety of the untreated blank beads at 616.7 ± 8.9 cm^{-1} was remarkably increased to 688.8 ± 11.7 cm^{-1} in the case of samples treated by microwave at 300 W for 5 min 20 s (Fig. 6a and c). The observation indicated that the irradiation of beads by microwave could enhance the polymer-polymer interaction via the O–H, COO^-, and COOH moieties, but reduced interaction at the $(CH_2)_n$ domain. The net effect on drug release was dependent on the balance between the strength and extent of polymer-polymer interaction via O–H, COO^-, COOH, and $(CH_2)_n$ moieties.

In contrast to drug loaded polymeric beads treated by microwave at 80 W, the treatment of the same batch of beads at 300 W for 1 min 20 s and 5 min 20 s did not bring about marked changes to the thermal profile of the samples (Fig. 5d, e, and f). As changes in the enthalpy values as well as peak, onset, and end temperatures of the endotherms were the net reflection of polymer-polymer and drug-polymer interaction, and the strength and propensity of polymer-polymer interaction was affected by microwave as inferred from the DSC study on the blank beads, an insignificant change in the thermogram of drug loaded beads treated by microwave at 300 W could mean that the profile of drug-polymer interaction varied in accordance to that of the polymer-polymer counterpart. The drug-polymer interaction could have been promoted through the irradiation of beads by microwave as a decrease in the extent of polymer-polymer interaction following the same condition of microwave irradiation could provide active polymeric sites at specific domains of matrix for drug-polymer interaction.

The FTIR spectroscopy of drug-loaded polymeric beads indicated that the wavenumber ascribing to O–H and N–H moieties of polymer and drug in the

untreated matrix at 3398.2 ± 5.0 cm^{-1} increased to 3425.4 ± 3.5 cm^{-1} in sample treated by microwave at 300 W for 5 min 20 s, unlike those of treated for 1 min 20 s of which the corresponding wavenumber was reduced to 3376.8 ± 13.8 cm^{-1} (Fig. 6d, e, and f). In the former, it was envisaged that the N–H moiety of drug was interacted markedly with COO^- and C–O moieties of the polymer instead of through the O–H functional group, thereby resulting in a marked increase in the transmission intensity of the FTIR bands at 1072.7 ± 0.4 and 1422.4 ± 0.2 cm^{-1} of such beads, and an increase in wavenumber of FTIR peak at 3425.4 ± 3.5 cm^{-1} (Fig. 6d and f). The interaction of drug with polymer via N–H, COO^-, and C–O moieties could have retarded the release of drug from beads to a greater extent than that of drug-polymer interaction via the N–H and O–H functional groups in beads treated by microwave at 300 W for 1 min 20 s since the beads treated by microwave at 300 W for 5 min 20 s exhibited the lowest extent of drug release after 4 hr of dissolution when compared to those of the untreated as well as treated samples at 300 W for 1 min 20 s.

Kinetics of Drug Release

Keeping the level of supplied irradiation energy identical, treatment of beads by microwave at 80 and 300 W led to an increase and a reduction in the rate of drug released from the polymeric beads respectively after 4 hr of dissolution, as inferred from the k and MDT values of untreated and treated samples (Table 1). The kinetics of drug released from both microwave-treated and untreated beads had a marked Case II release characteristic with a slight tendency to follow the anomalous release behavior in the case of samples treated by microwave at 80 W for 20 min, and Super Case II release behavior when others were concerned (Table 1; $r^2 \geq 0.95$). The good fit of drug dissolution data into these models suggested that drug release was 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.

CONCLUSIONS

The release property of drug was governed by the state of polymer-polymer and drug-polymer interaction in beads. Treatment of beads by microwave at varying intensities of irradiation did not bring about similar profiles of drug release despite the level of supplied irradiation energy was kept identical. The extent and rate of drug released from beads were markedly increased by treating the samples by microwave at 80 W as a result of loss of polymer-polymer interaction via the $(CH_2)_n$ moiety. Similar loss of polymer-polymer interaction via the $(CH_2)_n$ moiety was found in beads treated by microwave at 300 W. Nonetheless, these beads exhibited a higher level of drug release retardation capacity than those of treated by microwave at 80 W owing to polymer-polymer interaction via the O–H, COOH, and COO^- moieties as well as drug-polymer interaction via the N–H, O–H, COO^-, and C–O moieties. Using Korsmeyer-Peppas equation, it was found that the mechanism of drug release tends to follow the zero order kinetics. The drug release was 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. The poly(methyl vinyl ether-co-maleic acid) matrix, through the modification of its drug release property by microwave, is potentially useful as drug carrier for colonic delivery.

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