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Effects of microwave on drug release properties of matrices of pectin

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Abstract

The influence of microwave irradiation on the drug release properties of pectinate and pectinate–chitosonium beads was investigated. The beads were prepared with the highest possible concentration of polymer by an extrusion method. Sodium diclofenac was selected as a model water-soluble drug. The beads were subjected to microwave irradiation at 80 W for 5, 10, 21 and 40 min. The profiles of drug dissolution, drug content, drug stability, drug–polymer interaction and polymer–polymer interaction were determined by dissolution testing, drug content assay, differential scanning calorimetry (DSC) and Fourier transform infra-red spectroscopy (FTIR). The chemical stability of drug in beads was unaffected by the microwave irradiation. The drug release property of pectinate beads was mainly governed by the extent of polymer interaction in matrix. Treatment of pectinate beads by microwave led to an increase in the extent and rate of drug released owing to reduced pectin–pectin interaction via C=O of COOH and/or $COOCH_3$ of the polymer. The extent of drug released from the pectinate beads could not be reduced merely through the coacervation of pectinate matrix with chitosan. Treatment of pectinate–chitosonium beads by microwave was essential to reduce the rate and extent of drug released from the matrix, following an increase in drug–polymer and polymer–polymer interaction in beads. Treatment of chitosonium beads by microwave at 80 W for 5 min reduced the rate and extent of drug released from the matrix. Nonetheless, the degree of reduction in the extent of drug released from the chitosonium beads was lower than that of the pectinate–chitosonium matrix and the release of drug from the chitosonium samples was not markedly retarded through the treatment of beads by microwave for a period of duration longer than 5 min. The findings indicated that both pectin and chitosan were needed in the formulation of a controlled-release matrix using the microwave technology.

Keywords: Chitosan; Drug release; Drug–polymer interaction; Microwave; Pectin; Polymer–polymer interaction

1. Introduction

Carbohydrate polymers, such as pectin and alginate, have been widely employed in the formulation of pharmaceutical solid dosage forms (Acarturk & Takka, 1999; Adkin, Kenyon, Lerner, Landau, Strauss & Caron, 1997; Ashford, Fell, Attwood, Sharma, & Woodhead, 1994; Chan & Heng, 2002; Chan, Heng, & Wan, 1997; El-Gibaly, 2002; Fu Lu, Woodward & Burodkin, 1991; Fundueanu, Esposito, Mihai, Carpov, Desbrieres & Rinaudo, 1998; Gupta, Assmus, Beckert & Price, 2001; Liu & Krishnan, 1999; Macleod, Fell & Collett, 1997; Munjeri, Collett & Fell, 1997; Murata, Miyashita, Kofuji, Miyamoto & Kawashima, 2004; Pillay, Dangor, Govender, Moopanar & Hurbans, 1998a,b; Pillay & Fassihi, 1999; Sriamornsak & Nunthanid, 1998; Sriamornsak, Puttipipatkhachorn, & Prakongpan, 1997; Takka & Acarturk, 1999; Wan, Heng & Chan, 1993, 1994; Wong, Chan, Kho & Heng, 2002; 2005; Wong, Lee, Chan & Heng, 2002a,b). The wide application of these biopolymers is attributed to their biodegradability and low oral toxicity. As such, small molecule drugs are often embedded in matrix carrier made of these materials. 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.

Over the past 10 years, various formulation and processing approaches have been initiated to negate the rate of drug release from these biopolymeric matrices, but with varying degree of success. High concentrations of multivalent metallic or non-metallic cations have been employed as crosslinking agents for pectinate and alginate matrices (Acarturk & Takka, 1999; El-Gibaly, 2002;

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Fundueanu et al., 1998; Liu & Krishnan, 1999; Murata et al., 2004; Sriamornsak and Nunthanid, 1998; Sriamornsak et al., 1997; Wong et al., 2002a,b). The drug release property of the biopolymeric matrices has been examined in relation to the effects of drug:biopolymer ratio, molecular weight and chain conformation of pectin and alginate (Acarturk & Takka, 1999; Ashford et al., 1994; Takka & Acarturk, 1999; Pillay et al., 1998a). The pectin and alginate have been subjected to coacervation with chitosan to form the polyelectrolyte complex of which is envisaged to have a higher drug release retardation capacity than that of the individual substance (Munjeri et al., 1997; Takka & Acarturk, 1999; Wong et al., 2002). Attempts to coat or incorporate the biopolymeric matrix with hydroxypropylmethylcellulose and other excipients have taken place in view that such materials could serve to retard the release of small molecule drugs (Ashford et al., 1994; Chan et al., 1997; Fu Lu et al., 1991; Liu & Krishnan, 1999; Macleod et al., 1997; Murata et al., 2004; Pillay & Fassihi, 1999; Wan et al., 1993; 1994). Aldehyde, a reactive chemical agent, has also been used to crosslink the biopolymeric matrix in alleviation of the propensity of drug loss from the matrix (Chan & Heng, 2002).

Lately, Wong et al. (2002, 2005) utilized the microwave technology to modify the state of molecular interaction between the alginate, chitosan or alginate–chitosan chains, with the aim to delay the release of small molecule drugs from the formed matrix. Under the influence of microwave irradiation, it was found that the drug release could be further retarded in the matrix made of alginate. The drug release characteristics of the matrix were dependent on the extent of polymer crosslinkage and complexation brought about by microwave. In view that pectin resembles alginate in its structural backbone, the present study proposes to investigate the effects of microwave on the drug release property of pectinate matrix. The water-soluble sodium diclofenac is selected as a model drug unlike the previous study which employed a more hydrophobic sample (Wong et al., 2002, 2005). This provides a more rigorous formulation for testing the drug release retardation action of microwave.

2. Materials and methods

2.1. Materials

Pectin (methoxy content = 9.0%, galacturonic acid content = 87.6%, Sigma Aldrich, USA) and chitosan (Degree of deacetylation = 86%, Zulat Pharmacy, Malaysia) were employed as matrix or coating polymers in the preparation of gel beads, with calcium chloride dihydrate (Merck, Germany) and sodium tripolyphosphate (BDH, UK) as crosslinking agents. Sodium diclofenac (MP Biomedicals, Germany) was selected as a model drug. Other chemicals employed in this study included acetic acid and sodium hydroxide (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 at an off-centre position and rotated to achieve uniform irradiation.

2.3. Preparation of gel beads

Three types of gel beads were prepared using the extrusion method: pectinate, pectinate-chitosonium and chitosonium beads. All gel beads were prepared using the same processing conditions as those of pectinate beads, unless otherwise stated.

2.3.1. Pectinate beads

An aqueous dispersion containing 4% (w/w) of pectin and 1% (w/w) of sodium diclofenac was introduced dropwise into an aqueous solution containing 6% (w/w) 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, 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 15 min after the last addition of the pectin–sodium diclofenac dispersion. The formed pectinate beads were removed from the calcium chloride solution by filtration and washed with deionized water.

2.3.2. Pectinate–chitosonium beads

An aqueous dispersion containing 4% (w/w) of pectin and 1% (w/w) of sodium diclofenac was added dropwise into 1% (v/v) acetic acid solution containing 2% (w/w) of chitosan and 6% (w/w) of calcium chloride dihydrate, with pH adjusted to 5 using 0.5 M sodium hydroxide solution. The formed pectinate–chitosonium beads were washed with deionized water, followed by 4% (w/v) sodium tripolyphosphate solution and then deionized water again. Sodium tripolyphosphate solution was employed to wash the beads as it hardened the chitosan coat and thus prevented the adhesion of beads during drying.

2.3.3. Chitosonium beads

About 1% (v/v) acetic acid solution containing 4% (w/w) of chitosan and 1% (w/w) of sodium diclofenac was added dropwise into a 4% (w/v) sodium tripolyphosphate solution. The formed chitosonium beads were washed with deionized water.

For all formulations, the percentages of polymers employed were based on the maximum workable concentrations which were limited by the viscosity and extrudability of the polymeric solutions. Blank beads were prepared in the same manner for all formulations, except that no drug was incorporated. All beads were oven-dried at 40 ± 0.5 °C for 4 days and subsequently equilibrated to a constant weight by storing in a desiccator at 25 ± 1 °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. For each formulation, 10 beads were randomly selected for measurement and the results averaged.

2.5. Microwave treatment of beads

An accurately weighed amount of beads was contained in a lidless glass petri dish (internal diameter = 9 cm) and was subjected to microwave treatment at 80 W for 5, 10, 21 and 40 min, respectively. Microwave power higher than 80 W was not employed in avoidance of the degradation of matrix (Wong et al., 2005). The irradiation energy supplied was calculated as the product of power and time. 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 deionized water (pH 5.5) in simulation of the pH of the duodenum 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. An accurately weighed amount of sample was placed in 500 ml of dissolution medium (sink condition) and was agitated at 50 strokes/min (Memmert GmbH + Co. KG, Germany) at 37 ± 0.2 °C. Aliquots were withdrawn at various time intervals and assayed spectrophotometrically for sodium diclofenac at 276 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 sodium diclofenac. Each experiment was carried out in triplicate and the results averaged.

2.7. 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 zero order and Higuchi's dissolution models. An approximation of the Higuchi's equation can be obtained by plotting the fraction of drug released versus square-root of time as expressed by

$$W = kt^{1/2} \tag{1}$$

where W is the percentage of drug released at time t (min) and k is the Higuchi's release rate constant. The zero order equation is expressed as

$$Q = Q_0 - k_0 t \tag{2}$$

where Q is the percentage of drug remaining at time t (min), Q_0 is the percentage of drug at $t = 0$ min and k_0 is the zero order release rate constant.

The release rate constant was calculated by fitting the experimental drug release data into the dissolution models and the goodness-of-fit of the drug release data was evaluated by linear regression. For all statistical calculations, the level of significance was set at 0.05.

2.8. Fourier transform infra-red spectroscopy (FTIR)

About 2% (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, 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, Perkin Elmer, USA). About 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

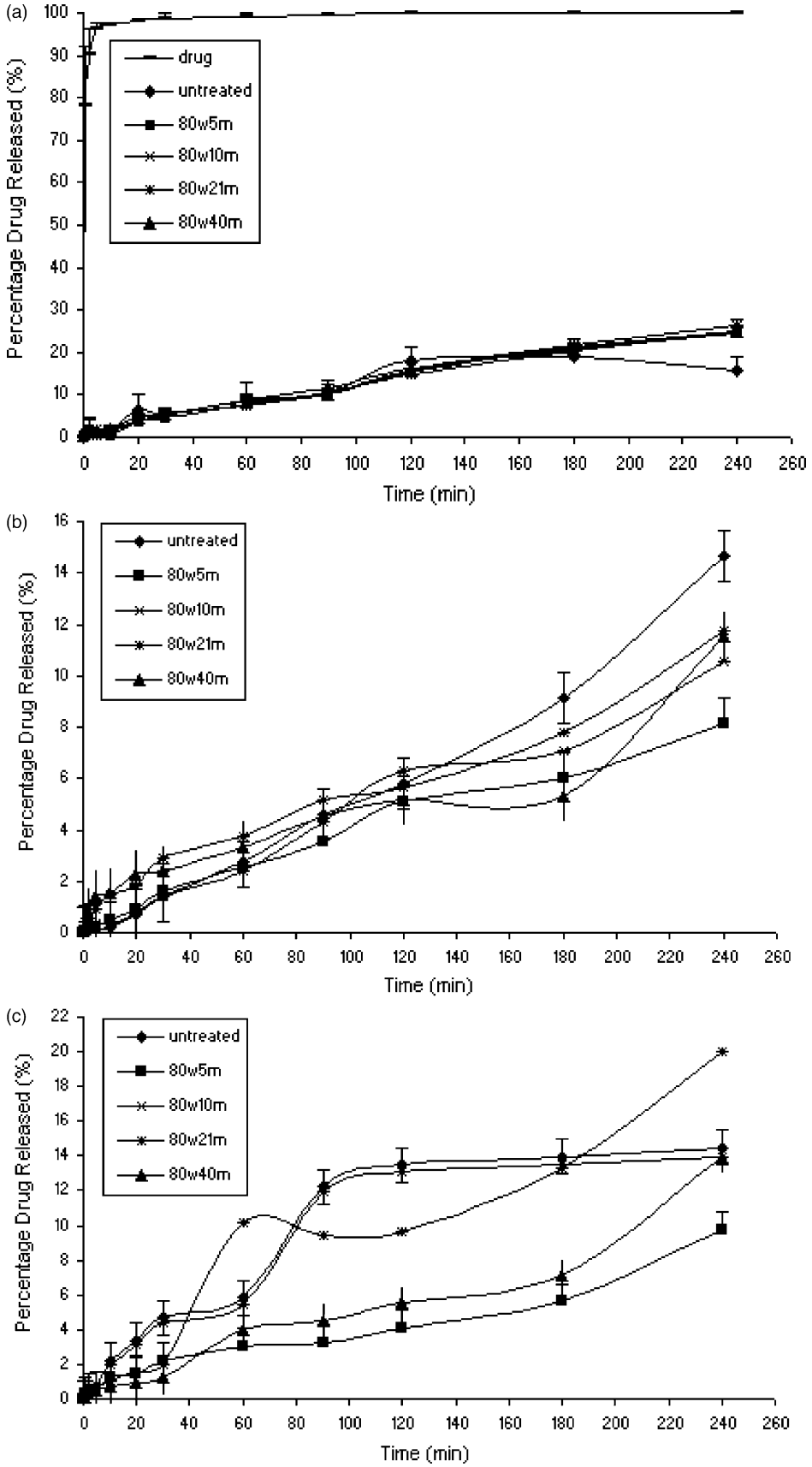

Fig. 1. Drug release profiles of (a) pectinate beads, (b) pectinate–chitosonium beads and (c) chitosonium beads, subjected to various microwave irradiation conditions, with dissolution profile of untreated free sodium diclofenac shown in (a).

carried out for each batch of sample and the results averaged.

3. Results and discussion

The formed pectinate, pectinate–chitosonium and chitosonium beads had sizes of 2.98±0.22, 3.54±0.27 and 2.14±0.15 mm, as well as elongation ratios of 1.14±0.11, 1.34±0.20 and 1.10±0.09 respectively. Irradiation of pectinate, pectinate–chitosonium and chitosonium 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 contents of pectinate, pectinate–chitosonium and chitosonium beads were amounting to 7.03±0.47, 8.39±0.17 and 7.02±0.38% (w/w). The drug contents of both treated and untreated pectinate, pectinate–chitosonium and chitosonium beads were not significantly different from each other (Student's *t*-test, $P > 0.05$). The chemical stability of sodium diclofenac in these beads was unaffected by the microwave conditions employed.

3.1. Pectinate beads

An average of 15.75±3.37% of sodium diclofenac was released from the untreated pectinate beads after 4 h of dissolution (Fig. 1a). The extent of drug dissolution was greatly reduced by 84.25% when the sodium diclofenac was encapsulated in the pectinate matrix. Interestingly, microwave irradiation of pectinate beads at 80 W for 5, 10, 21 and 40 min increased the percentage of drug released after 4 h of dissolution from 15.75±3.37% to 24.79±1.03, 26.43±1.45, 24.64±1.97 and 25.16±1.25%, respectively (Table 1, Student's *t*-test, $P < 0.05$). Unlike the case of alginate matrix (Wong et al., 2002), the extent of drug released from the pectinate beads was enhanced by microwave, in spite of the latter matrix was prepared with a high weight ratio of biopolymer to drug.

DSC analysis showed that the sodium diclofenac melted at 295.7±2.2 °C with a melting enthalpy of 110.9±19.6 J/g, as well as, onset and end temperatures of 292.6±4.8 and 296.6±1.8 °C, respectively (Fig. 2a). 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 pectin was characterized by two endothermic peaks at melting temperatures of 148.4±7.1 and 163.7±5.9 °C, and an exothermic peak at 233.9±0.4 °C (Fig. 2b). The endotherms had melting enthalpies of 21.2±2.8 and 136.4±31.5 J/g, respectively, and corresponding onset temperatures of 147.0±6.0 and 161.0±5.7 °C, as well as, end temperatures of 150.4±7.0 and 172.1±5.6 °C. The exothermic enthalpy of the unprocessed pectin was −145.2±23.9 J/g, with onset and end temperatures of 212.1±1.2 and 251.9±2.2 °C, respectively. Crosslinking of pectin with Ca^{2+} resulted in an increase in the endothermic melting peak temperatures from 148.4±7.1 to 158.1±1.5 °C and 163.7±5.9 to 172.1±1.6 °C (Fig. 2c). The onset and end temperatures of these endotherms were similarly raised to 156.7±1.4 and 167.0±2.1 °C, as well as, 161.3±1.6 and 189.2±2.7 °C respectively. In addition,

Table 1
Drug release kinetics of pectinate, pectinate–chitosonium and chitosonium beads treated under various microwave irradiation conditions.

Type of beads	Condition of microwave irradiation			Drug release kinetics				Percentage drug released after 4 h (%)
	Power (W)	Time (min)	Energy (kJ)	Zero order		Higuchi		
				k_0	r^2	k	r^2	
Pectinate	0	0	0	1.24	0.84	0.10	0.68	15.75
	80	5	24.0	1.38	0.90	0.11	0.97	24.79
	80	10	48.0	1.47	0.92	0.12	0.97	26.43
	80	21	100.8	1.36	0.92	0.11	0.98	24.64
	80	40	192.0	1.41	0.93	0.11	0.96	25.16
Pectinate–chitosonium	0	0	0	0.65	0.79	0.05	0.97	14.67
	80	5	24.0	0.44	0.91	0.04	0.97	8.17
	80	10	48.0	0.53	0.87	0.04	0.98	10.54
	80	21	100.8	0.60	0.92	0.05	0.93	11.78
	80	40	192.0	0.54	0.84	0.04	0.85	11.54
Chitosonium	0	0	0	1.02	0.93	0.08	0.81	14.50
	80	5	24.0	0.47	0.86	0.04	0.90	9.77
	80	10	48.0	0.98	0.93	0.08	0.80	13.98
	80	21	100.8	1.04	0.84	0.08	0.89	20.00
	80	40	192.0	0.61	0.81	0.05	0.95	13.94

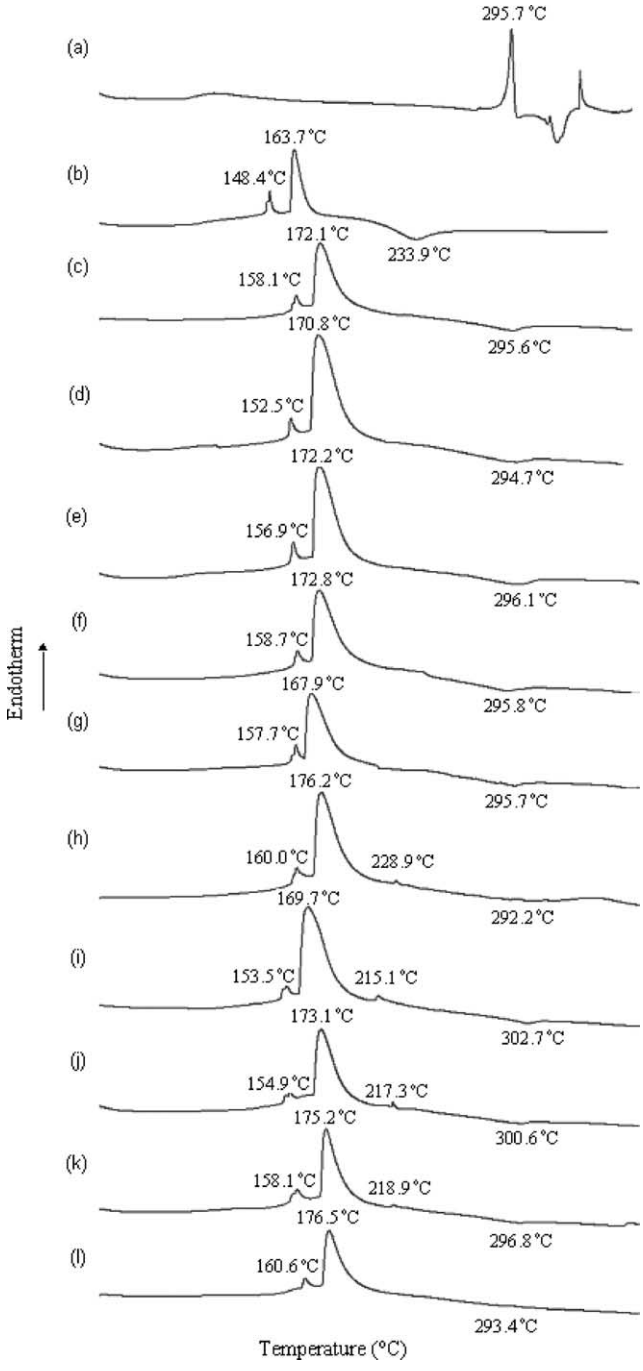

Fig. 2. DSC thermograms of (a) sodium diclofenac, (b) pectin powder, (c) blank pectinate beads and beads treated at 80 W for (d) 5 min, (e) 10 min, (f) 21 min and (g) 40 min, (h) drug loaded pectinate beads and beads treated at 80 W for (i) 5 min, (j) 10 min, (k) 21 min and (l) 40 min.

the melting temperature range became wider and an increase in melting enthalpy from 136.4 ± 31.5 to 303.8 ± 53.3 J/g was noted in the case of endotherm found at the melting peak temperature of 172.1 ± 1.6 °C. Nevertheless, a reduction in melting enthalpy from 21.2 ± 2.8 to 16.5 ± 1.2 J/g prevailed at melting peak of 158.1 ± 1.5 °C. The observation indicated that a crosslinked pectinate matrix was formed. The crosslinked matrix had a higher mechanical strength than that of the unprocessed pectin thereby leading to an increase in peak, onset and end temperatures, as well as, melting enthalpy. The Ca^{2+} could have crosslinked with pectin via different domains and at varying intensities as both melting endotherms of pectin were affected by the crosslinking process but in different manner with respect to the changes in melting enthalpy and temperature range. The reduction in melting enthalpy of endotherm at 158.1 ± 1.5 °C was probably ascribed to the loss of water molecules through oven and desiccator drying, in addition to the replacement of water molecules by Ca^{2+} in pectin–pectin crosslinkage and/or direct pectin–pectin interaction. The polymer–polymer interaction negated the propensity of pectin degradation. The peak, onset and end temperatures of exotherm were shifted to higher temperatures, from 233.9 ± 0.4, 212.1 ± 1.2 and 251.9 ± 2.2 °C to 295.6 ± 0.6, 263.8 ± 4.0 and 308.4 ± 2.4 °C, respectively, with a concurrent decrease in the exothermic enthalpy of pectin from −145.2 ± 23.9 to −48.0 ± 1.5 J/g.

Treatment of blank pectinate beads by microwave promoted the degradation propensity of matrix by heat. The exothermic enthalpy of untreated blank pectinate beads was lower than the corresponding enthalpies of the treated beads which were −63.1 ± 13.1, −60.4 ± 24.6, −83.1 ± 6.7 J/g in samples treated at 80 W for 10, 21 and 40 min, respectively (Fig. 2c, e, f and g), albeit there was a reduction in the exothermic enthalpy from −48.0 ± 1.5 to −28.7 ± 3.6 J/g and an increase in endothermic enthalpy from 303.8 ± 53.3 to 420.5 ± 30.7 J/g at peaks of 294.7 ± 3.2 and 170.8 ± 5.6 °C, respectively, in sample treated at 80 W for 5 min (Fig. 2c and d). In the latter, the endothermic melting peak temperature of untreated blank pectinate beads at 158.1 ± 1.5 °C decreased markedly to 152.5 ± 2.3 °C when beads were treated at 80 W for 5 min. The results suggested that the extent of drug released from the pectinate matrix can be enhanced by microwave through reducing the propensity or strength of pectin–pectin interaction. The drug release enhancement action of microwave was mediated via net changes in different domains of pectinate matrix, depending on the time length of microwave irradiation.

The incorporation of sodium diclofenac in pectinate matrix gave rise to an additional melting endotherm at 228.9 ± 9.2 °C of which was absent in thermogram of the untreated blank beads (Fig. 2c and h) and the melting peak temperature of this newly formed endotherm was lower than that of the pure drug by 66.8 °C (Fig. 2a and h). In addition, the exothermic enthalpy was greatly reduced from −48.0 ± 1.5 J/g of the untreated blank pectinate beads to −10.6 ± 3.6 J/g, 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–pectin interaction had taken place in the formed matrix. The interaction of drug with pectin was accompanied by a loss in pectin–pectin interaction. The latter observation was indicated by a reduction in

the enthalpy value of melting endotherm of untreated blank pectinate beads at 172.1 ± 1.6 °C to 243.8 ± 9.6 J/g in drug loaded matrix (Fig. 2c and h). Treatment of drug loaded pectinate beads by microwave at 80 W for 5 min brought about similar changes in melting temperature and enthalpy when compared to that of the blank pectinate beads. Practically, the melting peak temperatures of endotherms at 160.0 ± 2.9 and 176.2 ± 3.8 °C of untreated drug loaded pectinate beads were reduced to 153.5 ± 1.8 and 169.7 ± 3.4 °C, respectively, in microwave treated beads (Fig. 2h and i). On the other hand, the enthalpy value of endotherm at 176.2 ± 3.8 °C and exothermic peak temperature of untreated drug loaded pectinate beads increased from 243.8 ± 9.6 to 378.8 ± 122.7 J/g and 292.2 ± 0.4 to 302.7 ± 2.4 °C, respectively. The findings suggested that the strength of pectin-pectin interaction in matrix was negated in one domain though the extent of such interaction appeared to be enhanced to a greater extent, as well as, the strength of drug–pectin interaction could have been promoted in other domains of matrix via the introduction of microwave. In the case of sample treated by microwave at 80 W for 10 min, the peak temperatures of endotherm and exotherm of untreated drug loaded pectinate beads were reduced from 160.0 ± 2.9 to 154.9 ± 0.5 °C and increased from 292.2 ± 0.4 to 300.6 ± 1.3 °C, respectively (Fig. 2h and j). Similar to beads treated by microwave for 5 min, the strength of pectin–pectin interaction in matrix was reduced, but the strength of drug–pectin interaction was raised, under the influence of microwave irradiation. Treatment of drug loaded pectinate beads by microwave at 80 W for 21 and 40 min did not give rise to marked changes in the thermograms of matrices except a gradual disappearance of endotherm at 228.9 ± 9.2 °C of the untreated matrix following drug–pectin interaction (Fig. 2h, k and l). Generally, the enthalpy characteristics of exotherm were affected by microwave to a lesser extent in drug loaded pectinate beads than the blank matrix. Changes in exothermic enthalpy of blank pectinate beads could have minimized through the interaction between the drug and pectin. Apparently, loss of pectin–pectin interaction, as well as, gain in drug–pectin interaction was prevailed in pectinate matrix treated by microwave. On the basis that the extent of drug released was higher in microwave treated beads, pectin–pectin interaction would thus be expected to have a more significant bearing than drug–pectin interaction on the drug release property of pectinate matrix.

Examination of the FTIR spectroscopy indicated that the pectinate matrix was formed through crosslinking the pectin by Ca^{2+} via C=O and C–O moieties of the polymer. The wavenumber of FTIR peak ascribing the pectin at 1750.8 ± 0.9 was reduced to 1724.9 ± 2.3 cm^{-1}, and the transmission peaks at 1750.8 ± 0.9, 1444.7 ± 1.6, 1329.6 ± 1.5, 1266.0 ± 0.5, 1105.2 ± 0.7 and 1015.5 ± 0.7 cm^{-1} became inconspicuous in the spectrum of blank pectinate beads (Fig. 3b and c). The former observation showed that the Ca^{2+}-pectin interaction was mediated via the C=O moiety of COOH and/or $COOCH_3$ of pectin, while the latter suggested that the interaction between Ca^{2+} and pectin involved C–O moiety of the saccharide ring in addition to that of C=O group. Unexpectedly, the COO^- moiety of pectin appeared to have a comparatively minor role in Ca^{2+}-pectin crosslinkage. The wavenumber related to that of COO^- of pectin at 1634.7 ± 4.1 cm^{-1} decreased marginally to 1630.4 ± 0.5 cm^{-1} in blank pectinate beads (Fig. 3b and c).

Treatment of blank pectinate beads by microwave at 80 W brought about a reduction in the transmission intensity

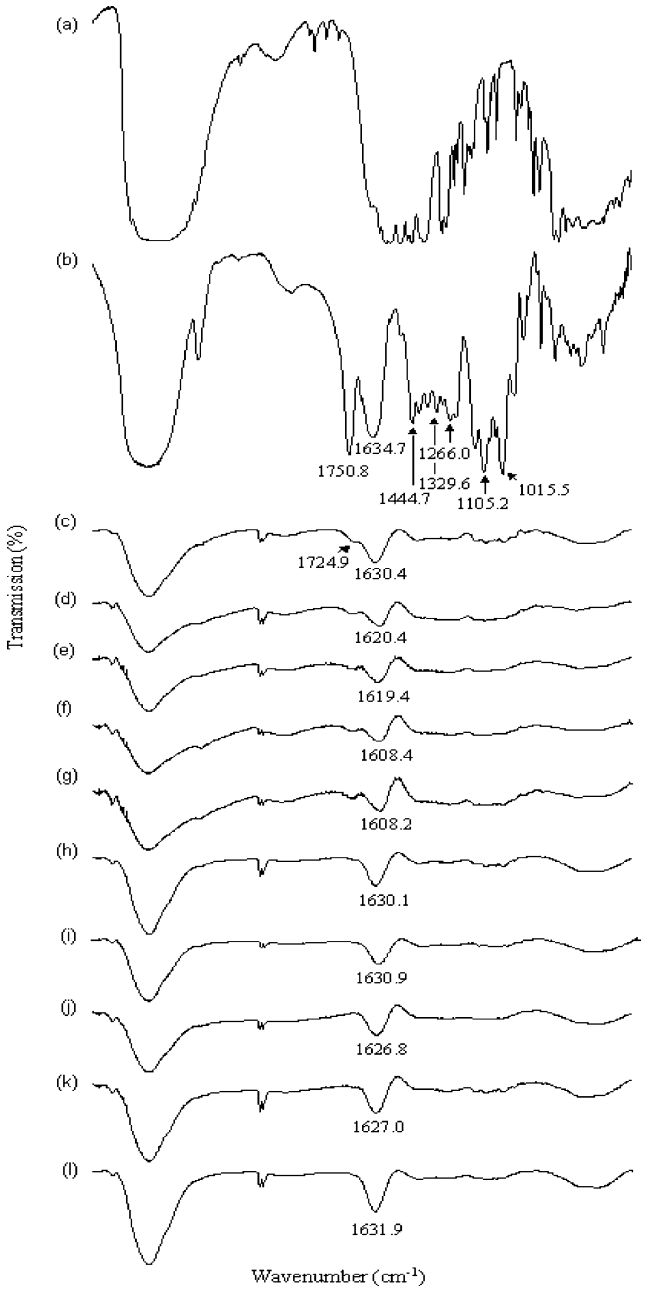

Fig. 3. FTIR spectra of (a) sodium diclofenac, (b) pectin powder, (c) blank pectinate beads and beads treated at 80 W for (d) 5 min, (e) 10 min, (f) 21 min and (g) 40 min, (h) drug loaded pectinate beads and beads treated at 80 W for (i) 5 min, (j) 10 min, (k) 21 min and (l) 40 min.

of FTIR peak at 1724.9±2.3 cm^{-1} (Fig. 3c–g). On the contrary, the transmission bands of pectin at 1444.7±1.6, 1329.6±1.5, 1266.0±0.5, 1105.2±0.7 and 1015.5±0.7 cm^{-1} became less prominent in microwave-treated blank pectinate beads than that of the untreated counterpart (Fig. 3b–g). In addition, the wavenumber of peak of untreated blank pectinate beads at 1630.4±0.5 cm^{-1} was higher than the corresponding wavenumbers of the treated beads which were 1620.4±10.3, 1619.4±1.8, 1608.4±2.5 and 1608.2±1.5 cm^{-1} in matrices treated by microwave at 80 W for 5, 10, 21 and 40 min, respectively (Fig. 3c–g). The findings indicated that an enhancement in the extent of drug released from the microwave-treated pectinate beads was attributed to reduced pectin–pectin interaction via C=O of COOH and/or $COOCH_3$. Pectin–pectin interaction via C–O of saccharide rings and COO^- moiety had a smaller influence on the drug release property of pectinate matrix in response to the irradiation of microwave. The incorporation of sodium diclofenac in the pectinate matrix resulted in disappearance of FTIR peak of untreated blank pectinate beads at 1724.9±2.3 cm^{-1} (Fig. 3c and h) as a result of drug–pectin interaction via the C=O moiety of COOH and/or $COOCH_3$. Treatment of drug loaded pectinate beads by microwave at 80 W did not negate drug–pectin interaction as proposed by the DSC investigation (Fig. 3h–l). The enhancement of drug released from the pectinate matrix by microwave was mainly governed by the state of polymer interaction in beads.

The rate of drug released was higher in microwave-treated pectinate beads than that of untreated counterpart (Table 1). The kinetics of drug released from the untreated pectinate beads followed the zero order model. The drug was released from the pectinate beads in accordance to the Higuchi's model (Table 1, $r^2 \geqq 0.96$) following the treatment of beads by microwave. In the latter, the drug was released from core to exterior of pectinate beads via diffusion through the pores of the matrix.

3.2. Pectinate–chitosonium beads

The extent and rate of drug released from beads made solely of pectin as the polymer were not reduceable through treating the beads by microwave. As such, the formed pectinate beads were coated with a second polymer, namely chitosan, using the coacervation technique. Coacervation of pectinate beads by chitosan did not bring about marked changes to the extent of drug released from the matrix after 4 h of dissolution (Fig. 1a and b), through the presence of chitosan and/or reduced specific surface area for drug dissolution due to an increase in size of the beads. Nevertheless, the extent of drug released from the pectinate–chitosonium beads was markedly reduced through treating the beads by microwave, unlike the cases of pectinate matrix. The extent of drug released at 4 h was reduced from 14.67±1.01% of the untreated pectinate–chitosonium beads to 8.17±0.24, 10.54±0.86, 11.78±0.24 and 11.54±0.47% in samples treated by microwave at 80 W for 5, 10, 21 and 40 min, respectively (Table 1, Student's *t*-test, $P < 0.05$).

The DSC investigation indicated that the endothermic enthalpy value of untreated blank pectinate–chitosonium beads at 168.2±5.6 °C was 122.0±37.3 J/g. It was aptly lower than the corresponding enthalpies of the treated beads which were 141.4±8.8, 166.7±21.9, 164.0±16.5 and 165.9±26.1 J/g in beads treated by microwave at 80 W for 5, 10, 21 and 40 min, respectively (Fig. 4a–e). There was an increase in the degree of polymer–polymer interaction both directly and/or indirectly through the crosslinking agent, thereby reducing the extent of drug released from the pectinate–chitosonium beads. The incorporation of sodium diclofenac in beads increased the melting peak temperatures of endotherms and exotherm of untreated blank matrix from 156.1±2.3, 168.2±5.6, 228.6±0.7 and 290.1±3.6 °C to

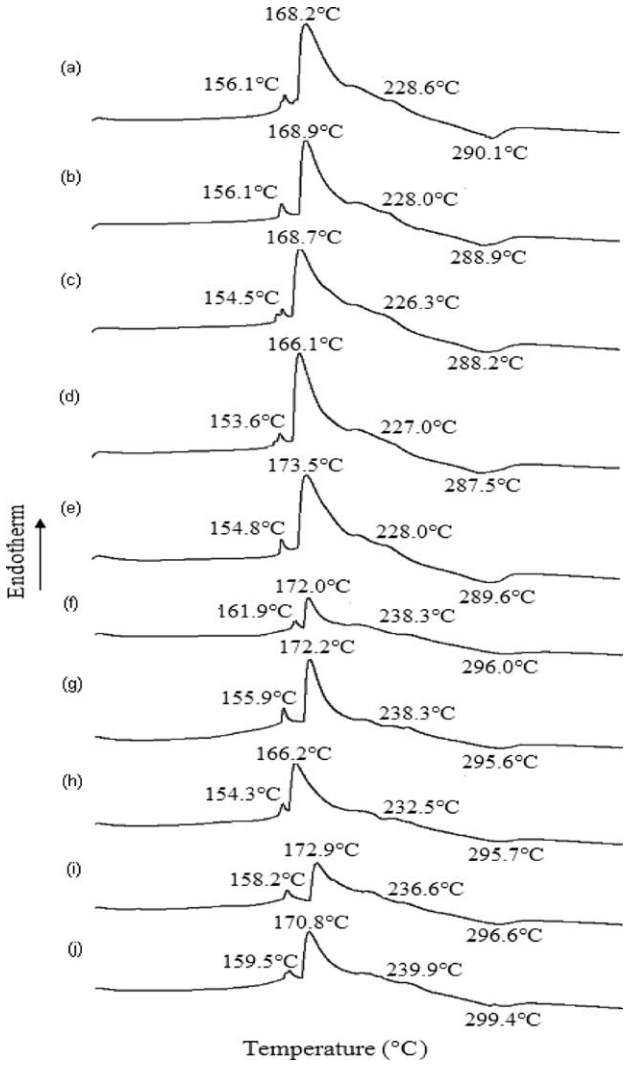

Fig. 4. DSC thermograms of (a) blank pectinate–chitosonium beads and beads treated at 80 W for (b) 5 min, (c) 10 min, (d) 21 min and (e) 40 min, (f) drug loaded pectinate–chitosonium beads and beads treated at 80 W for (g) 5 min, (h) 10 min, (i) 21 min and (j) 40 min.

161.9±0.9, 172.0±2.1, 238.3±2.5 and 296.0±2.9 °C respectively, with a corresponding rise in onset and end temperatures (Fig. 4a and f). Nonetheless, the endotherm at 172.0±2.1 °C of untreated drug loaded pectinate–chitosonium beads had an enthalpy value of 56.9±3.8 J/g of which was lower than the blank counterpart. It was envisaged that the incorporation of sodium diclofenac in pectinate–chitosonium beads induced drug–polymer interaction and the strength of polymer–polymer interaction was increased at the expense of its extent of interaction at specific domains of the matrix. Similar to that of blank pectinate–chitosonium beads, the extent of polymer–polymer interaction increased markedly upon subjecting the drug loaded beads to the treatment by microwave, thereby resulting in a remarkable rise of enthalpy value to 143.8±22.2, 116.4±2.1, 116.3±36.4 and 88.8±13.6 J/g in samples treated for 5, 10, 21 and 40 min, respectively (Fig. 4f–j). The extent of polymer–polymer interaction could have increased in one domain of pectinate–chitosonium matrix in response to microwave irradiation, but changes in the profiles of such interaction might be different in other domains of the same matrix. Typically, the melting peak temperature of untreated drug loaded pectinate–chitosonium beads at 161.9±0.9 °C had decreased to 155.9±0.8 and 154.3±0.5 °C in samples treated by microwave at 80 W for 5 and 10 min, respectively (Fig. 4f–h). The exothermic enthalpy of untreated drug loaded pectinate–chitosonium beads at 296.0±2.9 °C reduced markedly from −21.1±1.44 J/g to −5.2±2.19 J/g in beads treated for 40 min (Fig. 4f and j). The observation suggested that the strength of polymer–polymer interaction was negated, but the extent of polymer–polymer and drug–polymer interaction was markedly enhanced by microwave in other domains of pectinate–chitosonium matrix. Thus, the ability of microwave to retard the release of drug from pectinate–chitosonium beads was mainly governed by net changes in the state of drug–polymer and polymer–polymer interaction in various domains of beads. In contrast to samples treated by microwave at 80 W for 10, 21 and 40 min, drug loaded pectinate–chitosonium beads treated for 5 min exhibited the largest rise in the corresponding endothermic enthalpy in relation to that of the endotherm at 172.0±2.1 °C of the untreated matrix (Fig. 4f–j). The observation suggested that a large rise in the propensity of polymer–polymer interaction was taken place in drug loaded pectinate–chitosonium beads when they were subjected to treatment by microwave at 80 W for 5 min, unlike that of the blank pectinate–chitosonium beads (Fig. 4a, b, f and g). This led to a lower extent of drug released from these beads, at 8.17±0.24%, after 4 h of dissolution (Table 1).

The FTIR spectra showed that blank pectinate–chitosonium beads exhibited variable matrix interaction in response to the irradiation of microwave. There was a reduction in polymer-polymer interaction via the O–H and/or N–H moiety of polymers in microwave-treated beads and this was accompanied by an increase in FTIR wavenumber from 3426.4±4.9 cm^{-1} of untreated blank beads to 3431.4±5.4, 3443.2±7.1, 3438.0±6.8 and 3433.9±4.5 cm^{-1} in samples treated at 80 W for 5, 10, 21 and 40 min, respectively (Fig. 5a–e). Treatment of blank pectinate–chitosonium beads by microwave at 80 W brought about an increase in the transmission intensity of FTIR peaks at 1716.5±1.4, 1732.5±1.5 and 1747.2±1.1 cm^{-1} of the untreated matrix and a loss of tri-peak characteristics of the FTIR band in the case of beads treated for 40 min. The observation indicated that polymer–polymer interaction was effected by microwave via C=O of COOH and/or $COOCH_3$ of pectin. The propensity of polymer–polymer interaction was greater in blank pectinate–chitosonium beads treated by

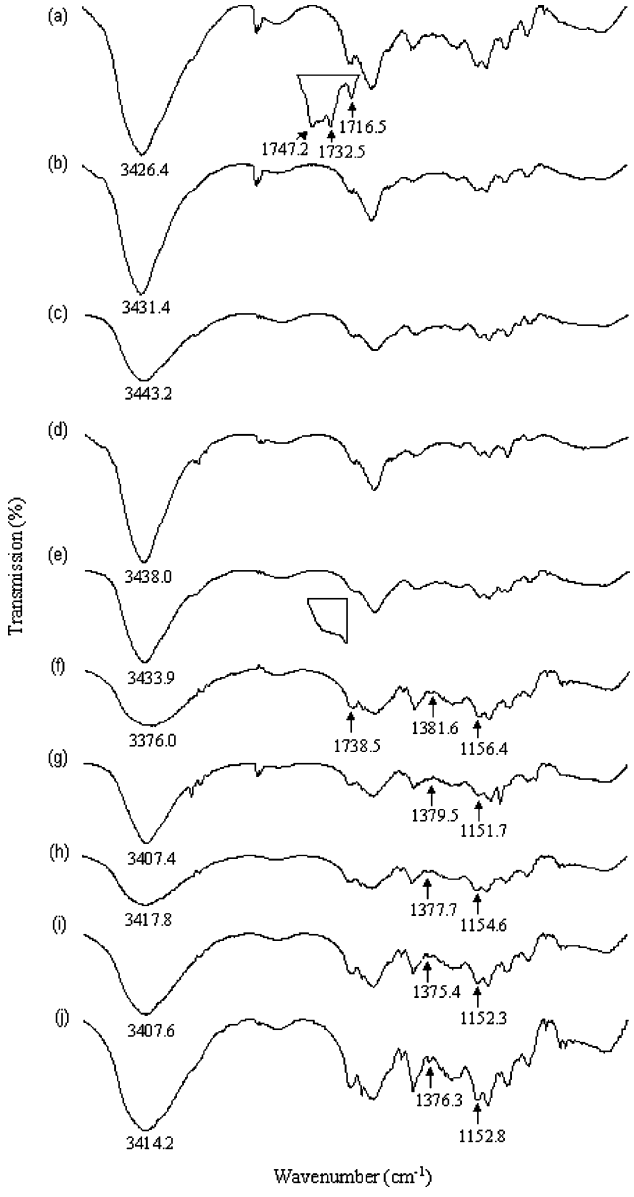

Fig. 5. FTIR spectra of (a) blank pectinate–chitosonium beads and beads treated at 80 W for (b) 5 min, (c) 10 min, (d) 21 min and (e) 40 min, (f) drug loaded pectinate–chitosonium beads and beads treated at 80 W for (g) 5 min, (h) 10 min, (i) 21 min and (j) 40 min.

microwave for a prolonged period of time, as previously shown by the DSC investigation.

Treatment of drug loaded pectinate–chitosonium beads by microwave gave rise to drug–polymer interaction in matrix. This was indicated by a reduction in FTIR wavenumber of untreated beads ascribed to benzyl and/or COO moiety of drug at $1381.6 \pm 1.5\ cm^{-1}$ to the lower corresponding values of the treated beads which were 1379.5 ± 2.7, 1377.7 ± 1.1, 1375.4 ± 1.4 and $1376.3 \pm 1.4\ cm^{-1}$ in samples treated by microwave at 80 W for 5, 10, 21 and 40 min, respectively (Fig. 5f–j). The drug–polymer interaction was possibly mediated via the association of drug with C–O moiety of polymers and/or C=O of COOH and/or $COOCH_3$ of pectin. The former observation was accompanied by a reduction in FTIR wavenumber of untreated drug loaded pectinate–chitosonium beads at $1156.4 \pm 2.9\ cm^{-1}$ to 1151.7 ± 5.2, 1154.6 ± 2.1, 1152.3 ± 2.5 and $1152.8 \pm 2.1\ cm^{-1}$ in samples treated by microwave at 80 W for 5, 10, 21 and 40 min, respectively (Fig. 5f–j), while the latter was marked by an increase in the transmission intensity of FTIR band at $1738.5 \pm 2.2\ cm^{-1}$ of untreated beads when the matrix was subjected to microwave irradiation at 80 W for 5 min (Fig. 5f and g). The interaction of drug with polymers induced conformational changes in polymer chains through rearrangement of O–H and/or N–H moiety which resulted in an increase in FTIR wavenumber of untreated drug loaded pectinate–chitosonium beads at $3376.0 \pm 13.6\ cm^{-1}$ to 3407.4 ± 7.1, 3417.8 ± 11.6, 3407.6 ± 4.9 and $3414.2 \pm 10.4\ cm^{-1}$ in samples treated by microwave at 80 W for 5, 10, 21 and 40 min, respectively (Fig. 5f–j). The drug release property of microwave-treated pectinate–chitosonium beads was governed by the summative effects of drug-polymer and polymer–polymer interaction in matrix. Treatment of drug loaded pectinate–chitosonium beads did not lead to an increase in transmission intensity of peaks ascribing to C=O of COOH and/or $COOCH_3$ of pectin except that of beads treated by microwave at 80 W for 5 min, unlike that of the blank counterpart. The observation suggested that the propensity of polymer–polymer interaction could have greatly enhanced in drug loaded pectinate–chitosonium beads through treating the beads by microwave at 80 W for 5 min via the C=O moiety of pectin, in addition to that of drug–polymer interaction, thereby leading to a greater extent of retardation in drug release in comparison to those of treated for a longer period of time.

Practically, irradiation of pectinate–chitosonium beads by microwave brought about a marked rise in drug–polymer and polymer–polymer interaction in matrix. This was attributed to reduced pectin–pectin interaction as previously described in Section 3.1, and reduced chitosan–chitosan interaction of which resulted in the availability of polymeric functional groups to interact with drug and polymer counterpart. The latter phenomenon was depicted by drug dissolution, DSC and FTIR profiles of blank and drug loaded chitosonium beads, both before and after the treatment by microwave. The DSC thermogram indicated that crosslinking of chitosan by tripolyphosphate ions gave rise to the formation of a thermally stable matrix. Apparently, the exotherm of chitosan at 314.4 ± 0.1 °C subsided in crosslinked matrix, and the melting peak temperatures of chitosan at 151.3 ± 1.2 and 176.4 ± 5.3 °C were increased to 202.6 ± 5.2 and 221.7 ± 1.5 °C, respectively (Fig. 6a and b). In addition, a multi-peak endotherm was formed at a temperature ranging between 226 and 249 °C. Treatment of blank chitosonium beads by microwave at 80 W for 5 min led to a reduction in melting peak temperature of blank matrix at 202.6 ± 5.2 to 174.2 ± 3.3 °C (Fig. 6b and c). Further treatment of beads by microwave for an additional period of time resulted in a decrease in both

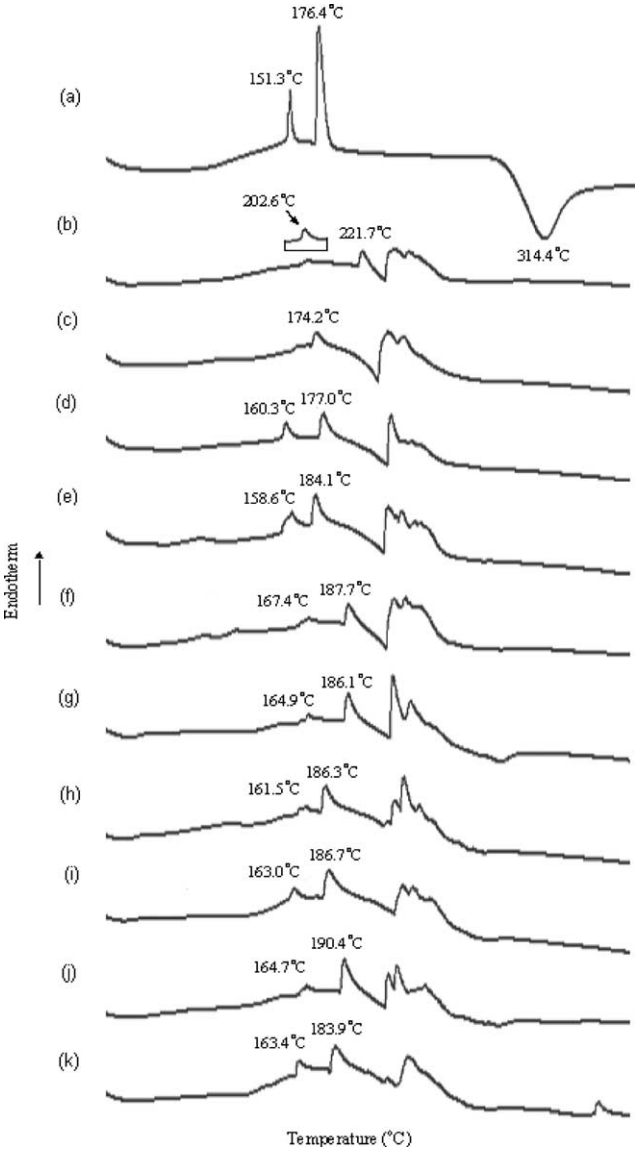

Fig. 6. DSC thermograms of (a) chitosan powder, (b) blank chitosonium beads and beads treated at 80 W for (c) 5 min, (d) 10 min, (e) 21 min and (f) 40 min, (g) drug loaded chitosonium beads and beads treated at 80 W for (h) 5 min, (i) 10 min, (j) 21 min and (k) 40 min.

melting peak temperatures of blank matrix at 202.6±5.2 and 221.7±1.5 °C to 160.3±7.9 and 177.0±10.1 °C, 158.6±3.6 and 184.1±14.5 °C, and 167.4±1.0 and 187.7±5.6 °C in samples treated for 10, 21 and 40 min, respectively (Fig. 6b, d, e and f). The reduction in melting peak temperatures of blank chitosonium beads indicated that the strength of chitosan–chitosan interaction could have been compromised via the application of microwave thereby leading to a rise in the propensity of drug–polymer and/or polymer–polymer interaction in pectinate–chitosonium beads and a reduction in the extent of drug released from these beads. In blank chitosonium beads, it was found that the endothermic enthalpy value of untreated matrix at 202.6±5.2 °C increased from 23.4±7.7 to 57.8±10.5 J/g in sample treated by microwave at 80 W for 5 min (Fig. 6b and c). The extent of chitosan–chitosan interaction in specific domain of matrix was markedly enhanced by microwave in spite of there was a reduction in strength. An enhancement in the propensity of chitosan–chitosan interaction could possibly account for reduced extent of drug released from the chitosonium beads (Table 1 and Fig. 1c), while partially responsible for reduced extent of drug released from the pectinate–chitosonium beads treated by microwave at 80 W for 5 min (Table 1 and Fig. 1b).

The FTIR investigation indicated that the treatment of blank chitosonium beads by microwave reduced the strength of chitosan–chitosan interaction in a matrix as the FTIR wavenumber of untreated beads at 1557.9±1.1 cm^{-1} was lower than the corresponding wavenumbers of the treated beads which were 1563.8±0.0, 1563.4±1.9, 1570.5±7.8 and 1564.8±0.9 cm^{-1} in samples treated by microwave at 80 W for 5, 10, 21 and 40 min, respectively (Fig. 7b–f). Nonetheless, treatment of blank chitosonium beads at 80 W for 5 min promoted the propensity of chitosan–chitosan interaction via the C=O moiety. Treatment of blank chitosonium beads by microwave for a period of time longer than 5 min negated the chitosan–chitosan interaction via C=O, N–H and O–H moieties. The former observation was marked by an increase in FTIR transmission intensity of untreated blank chitosonium beads at 1557.9±1.1 cm^{-1} after subjecting to the microwave treatment at 80 W for 5 min (Fig. 7b and c). The latter observation was reflected by a reduction in FTIR transmission intensity of untreated blank chitosonium beads at 1557.9±1.1 cm^{-1}, as well as, a change in FTIR peak characteristics from single to double crests at the wavenumber of 3423.5±11.1 cm^{-1} indicating the state of dissociation of N–H and/or O–H moieties of chitosan (Fig. 7b, d, e and f). The incorporation of sodium diclofenac into the chitosonium matrix was accompanied by drug–chitosan interaction as indicated by a reduction in the wavenumber of FTIR peak at 1702.0±0.1 cm^{-1} of the untreated blank beads to 1694.4±0.2 cm^{-1} in drug loaded matrix (Fig. 7b and g). Similar to that of the DSC investigation (Fig. 6g–k), treatment of drug loaded chitosonium beads by microwave

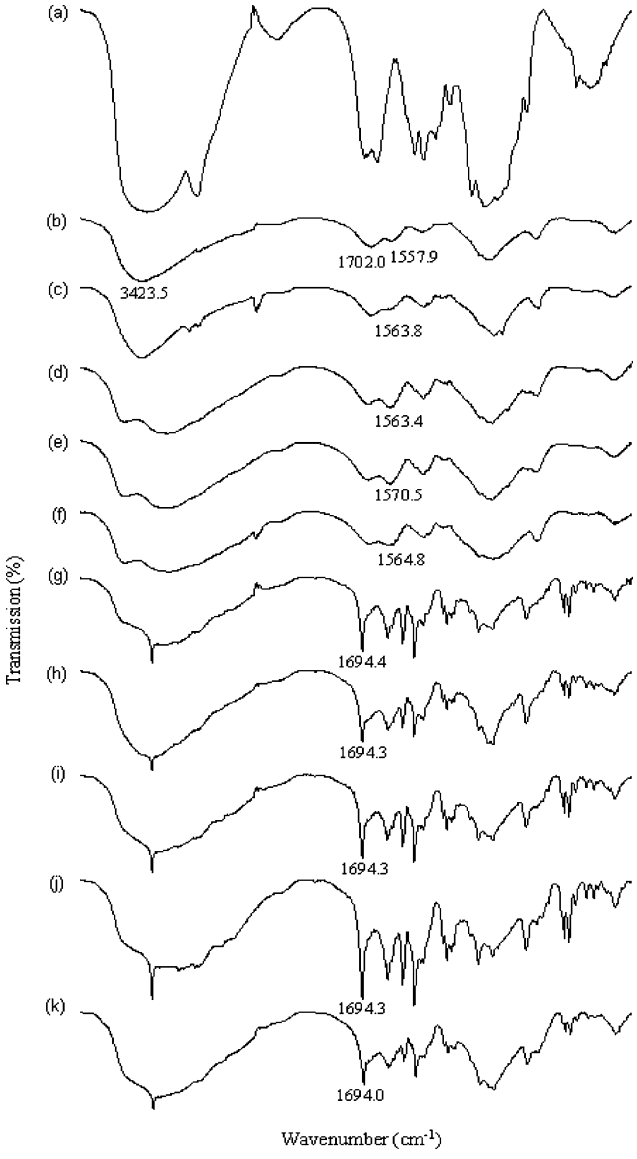

Fig. 7. FTIR spectra of (a) chitosan powder, (b) blank chitosonium beads and beads treated at 80 W for (c) 5 min, (d) 10 min, (e) 21 min and (f) 40 min, (g) drug loaded chitosonium beads and beads treated at 80 W for (h) 5 min, (i) 10 min, (j) 21 min and (k) 40 min.

brought about minor changes to the FTIR spectra of the matrix and had no clear trend in association with the drug release profile of beads (Fig. 7g–k). In chitosonium beads, the drug molecules were embedded in the chitosan matrix. The functional moieties of chitosan could have been saturated by drug molecules in chitosonium beads to a larger extent than that of the pectinate–chitosonium beads. In pectinate–chitosonium beads, the drug molecules were mainly embedded in the pectinate core. The chitosan molecules were deposited as coat onto the pectinate core. Thus, the state of drug–polymer and polymer–polymer interaction in drug loaded pectinate–chitosonium beads was more responsive to the irradiation of microwave than that of the chitosonium matrix.

Generally, the rate of drug released was lower in microwave-treated pectinate–chitosonium beads than that of the untreated counterpart (Table 1). The kinetics of drug released from both the untreated and treated pectinate–chitosonium beads fitted largely the Higuchi's model (Table 1, $r^2 \geqq 0.85$). The rate of drug released from the chitosonium beads was lower in samples treated by microwave at 80 W for 5 and 40 min when compared to that of untreated matrix. Nevertheless, the extent of drug released from the untreated chitosonium beads after 4 h of dissolution only markedly reduced in matrix treated by microwave for a short duration of time.

4. Conclusions

The chemical stability of drug embedded in beads was unaffected by the microwave irradiation. The drug release property of pectinate beads was mainly governed by the extent of polymer interaction in matrix. Treatment of pectinate beads by microwave led to an increase in the rate and extent of drug released owing to reduced pectin–pectin interaction via C=O of COOH and/or $COOCH_3$ of the polymer. The extent of drug released from the pectinate beads was unaffected by matrix coacervation with chitosan. The reduction in rate and extent of drug released from the pectinate beads required both matrix coacervation with chitosan and treatment of such beads by microwave in promotion of drug–polymer and polymer–polymer interaction in matrix, thereby retarding the drug release. Treatment of chitosonium beads by microwave at 80 W for 5 min reduced the rate and extent of drug released. Nonetheless, the degree of reduction in the extent of drug released from the chitosonium beads was lower than that of the pectinate–chitosonium counterpart. In addition, similar reduction in the rate and extent of drug release was not found in chitosonium samples treated by microwave for 10, 21 and 40 min. The findings indicated that the microwave could not effectively retard the release of drug from a matrix made of pectin or chitosan. Instead, both pectin and chitosan were needed in the formulation of a controlled-release matrix using the microwave technology.

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