Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 69 (2008) 176–188
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Drug release property of chitosan–pectinate beads and its changes under the influence of microwave

Tin Wui Wong [a,b,*], Sumiran Nurjaya [b]

[a] Non-Destructive Biomedical and Pharmaceutical Research Centre, Universiti Teknologi MARA, Selangor, Malaysia
[b] Particle Design Research Group, Faculty of Pharmacy, Universiti Teknologi MARA, Selangor, Malaysia

Received 10 June 2007; accepted in revised form 24 September 2007
Available online 1 October 2007

Abstract

The effects of microwave irradiation on the drug release property of pectinate beads loaded internally with chitosan (chitosan–pectinate beads) were investigated against the pectinate beads and beads coacervated with chitosan externally (pectinate–chitosonium beads). These beads were prepared by an extrusion method using sodium diclofenac as the 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–polymer interaction and polymer–polymer interaction were determined by drug dissolution testing, drug content assay, drug adsorption study, differential scanning calorimetry (DSC) and Fourier transform infra-red spectroscopy (FTIR) techniques. Treatment of pectinate beads by microwave did not lead to a decrease, but an increase in the extent of drug released at 4 h of dissolution owing to reduced pectin–pectin interaction via the C═O moiety of polymer. In addition, the extent of drug released from the pectinate beads could not be reduced merely through the coacervation of pectinate matrix with chitosan. The reduction in the extent of drug released from the pectinate–chitosonium beads required the treatment of these beads by microwave, following an increase in drug–polymer and polymer–polymer interaction in the matrix. The extent of drug released from the pectinate beads was reduced through incorporating chitosan directly into the interior of pectinate matrix, owing to drug–chitosan adsorption. Nonetheless, the treatment of chitosan–pectinate matrix by microwave brought about an increase in the extent of drug released unlike those of pectinate–chitosonium beads. Apparently, the loading of chitosan into the interior of pectinate matrix could effectively retard the drug release without subjecting the beads to the treatment of microwave. The microwave was merely essential to reduce the release of drug from pectinate beads when the chitosan was introduced to the pectinate matrix by means of coacervation. Under the influences of microwave, the drug release property of beads made of pectin and chitosan was mainly modulated via the C—H, O—H and N—H moieties of polymers and drug, with C—H functional group purported to retard while O—H and N—H moieties purported to enhance the drug released from the matrix.

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

1. Introduction

The control of small molecule drugs released from a polymeric matrix has remained a great challenge over the years. Practically, the drug molecules embedded in a polymeric matrix 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. Carbohydrate polymers, such as pectin and alginate, have been widely employed in design of drug delivery system for containment and release control of small molecule drugs. The wide application of these biopolymers is attributed to their biodegradability and low oral toxicity. Nonetheless, there is a varying degree of success with respect to the use of pectin and alginate to negate the extent and rate of drug released from the polymeric matrix [1–23]. Of all

* Corresponding author. Faculty of Pharmacy, Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia. Tel.: +60 3 55442771; fax: +60 3 55442725.
E-mail address: wongtinwui@salam.uitm.edu.my (T.W. Wong).

0939-6411/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2007.09.015

formulation and processing strategies for drug release modulation, the latest approach lies in the application of microwave technology to modify the state of molecular interaction between the polymer chains [24–27]. The use of microwave opens a new approach to control the physicochemical properties and drug delivery profiles of pharmaceutical dosage forms without the need for excessive heat, lengthy process and toxic reactants [27]. Under the influence of microwave irradiation, it was found that the drug release could be further retarded in the matrix made of alginate through changing the profiles of polymer–polymer interaction. Nevertheless, the treatment of pectinate matrix by microwave brought about a higher extent and rate of drug release.

The application of pectin as the carrier material for small molecule drugs requires the adoption of a new formulation approach. Frequently, the pectinate matrix was coacervated with chitosan at the external surfaces of matrix to further retard the drug release [12,19,24,27]. In the present study, the chitosan is directly filled into the pectinate core. The drug release property of chitosan–pectinate matrix and its changes against the influence of microwave are investigated with reference to those of pectinate matrix without and with externally coacervated chitosan.

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, filler or coating polymers in the preparation of 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 water-soluble 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 a uniform irradiation.

2.3. Preparation of beads

Three types of beads were prepared using the extrusion method: pectinate, pectinate–chitosonium and chitosan–pectinate beads. All 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. Chitosan–pectinate beads

An aqueous dispersion containing 4% w/w of pectin, 2% w/w of chitosan and 1% w/w of sodium diclofenac was added dropwise into 1% v/v acetic acid solution containing 6% w/w of calcium chloride dihydrate or an aqueous solution containing 6% w/w of calcium chloride dihydrate, with pH adjusted to 5 using 0.5 M sodium hydroxide solution whenever necessary. The formed chitosan–pectinate beads were washed with deionized water. The chitosan–pectinate beads were denoted as CPA in samples processed using the acetic acid solution containing calcium chloride dihydrate and CP in the case of aqueous calcium chloride solution without the addition of acetic acid.

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. At least five batches of beads were prepared for each type of matrix and these beads were pooled for subsequent physicochemical characterization.

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 [24,26]. The irradiation energy supplied was calculated as the product of power and time. The color and weight variations 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 [24,28]. An accurately weighed amount of sample was placed in 500 ml of dissolution medium (sink condition) and was agitated at 50 strokes/min in a shaker bath (Memmert GmbH + Co. KG, Germany) at 37 ± 0.2 °C. Aliquots were withdrawn at various time intervals and assayed spectrophotometrically for sodium diclofenac at wavelength maxima of 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 6 consecutive periods of 10 min before assaying for sodium diclofenac. Each experiment was carried out in triplicate and the results averaged. 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 reproducibility of the experimental data was expressed by means of standard deviation. Practically, the percentage of deviation from the average dissolution data varied between 2% and 25%, depending on the interplay between the extent of drug dissolution, type of matrix and condition of microwave irradiation (Table 1). The accuracy of these data was governed by the regression coefficient value derived from the plot of pure drug solution concentration against that of UV absorbance which was employed in the computation of drug release characteristics and drug content of beads ($r^2 \geqslant 0.98$).

2.7. Fourier transform infra-red spectroscopy (FTIR)

Two percentage 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.

2.8. Differential scanning calorimetry (DSC)

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

2.9. Drug–chitosan adsorption

Chitosan (0.10 g) was accurately weighed and dispersed in 3 ml of deionized water which contained 0.02 g of sodium diclofenac. The amounts of drug and chitosan were calculated on the basis of the polymeric beads containing a drug content amounting to 6%, expressed with respect to the weight of the matrix. The chitosan dispersion was subjected to agitation at 50 strokes/min for 4 h and at 37 ± 0.2 °C using a shaker bath (Memmert GmbH + Co. KG, Germany). The amount of drug adsorbed onto the chitosan was determined spectrophotometrically at 276 nm (Cary 50 Conc, Varian Australia Pty Ltd., Australia) using blank chitosan dispersion as the control and it was defined as the difference between the initial and final amounts of drug dissolved in the chitosan dispersion. At least triplicates were carried out and the results averaged.

3. Results and discussion

The formed pectinate, pectinate–chitosonium, CPA and CP beads had sizes of 2.98 ± 0.22, 3.54 ± 0.27, 3.40 ± 0.38 and 2.92 ± 0.09 mm, as well as elongation ratios of 1.14 ± 0.11, 1.34 ± 0.20, 1.14 ± 0.12 and 1.26 ± 0.13, respectively. Irradiation of pectinate, pectinate–chitosonium, CPA and CP beads by microwave did not result in significant color and weight variations of beads under all the

Table 1
Drug release profiles of pectinate, pectinate–chitosonium, CPA and CP beads treated under various microwave irradiation conditions

Type of beads	Condition of microwave irradiation			Percentage drug released after 4 h (%)
	Power (W)	Time (min)	Energy (kJ)	
Pectinate	0	0	0	15.75 ± 3.37
	80	5	24.0	24.79 ± 1.03
	80	10	48.0	26.43 ± 1.45
	80	21	100.8	24.64 ± 1.97
	80	40	192.0	25.16 ± 1.25
Pectinate–chitosonium	0	0	0	14.67 ± 1.01
	80	5	24.0	8.17 ± 0.24
	80	10	48.0	10.54 ± 0.86
	80	21	100.8	11.78 ± 0.24
	80	40	192.0	11.54 ± 0.47
CPA	0	0	0	4.51 ± 1.16
	80	5	24.0	9.31 ± 1.66
	80	10	48.0	13.39 ± 1.29
	80	21	100.8	10.07 ± 2.40
	80	40	192.0	17.15 ± 3.96
CP	0	0	0	5.63 ± 0.29
	80	5	24.0	7.79 ± 0.27
	80	10	48.0	9.31 ± 0.99
	80	21	100.8	9.76 ± 2.33
	80	40	192.0	4.78 ± 0.33

given experimental conditions. The observation of insignificant weight change in beads ($\leqslant$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, CPA and CP beads were amounting to 7.03 ± 0.47%, 8.39 ± 0.17%, 6.24 ± 0.25% and 5.79 ± 0.61% w/w, respectively. The drug contents of both treated and untreated pectinate, pectinate–chitosonium, CPA and CP beads were not significantly different from each other (Student's *t*-test, $P > 0.05$).

3.1. Drug dissolution

The extent of drug dissolution was greatly reduced by 84.25% when the sodium diclofenac was encapsulated in the pectinate matrix (Fig. 1a). An average of 15.75 ± 3.37% of sodium diclofenac was released from the untreated pectinate beads after 4 h of dissolution (Table 1). The percentage of drug released after 4 h of dissolution was increased from 15.75 ± 3.37% to 24.79 ± 1.03%, 26.43 ± 1.45%, 24.64 ± 1.97% and 25.16 ± 1.25% of pectinate beads subjected to microwave irradiation for 5, 10, 21 and 40 min, respectively (Table 1; Student's *t*-test, $P < 0.05$).

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, 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 for 5, 10, 21 and 40 min, respectively (Table 1; Student's *t*-test, $P < 0.05$).

The incorporation of chitosan directly into the core of pectinate beads brought about a marked reduction in the extent of drug released from the matrix after 4 h of dissolution (Fig. 1). The extents of drug released from CPA and CP beads at 4 h of dissolution were 4.51 ± 1.16% and 5.63 ± 0.29%, respectively (Table 1). Pearson correlation study of the extent of drug release after 4 h of dissolution with size, elongation ratio and drug content of pectinate, pectinate–chitosonium, CPA and CP beads indicated that the extent of drug dissolution of these beads was not significantly affected by the morphology and drug content of the matrix ($r \leqslant 0.80$, $P > 0.05$). Similar to those of pectinate beads, the treatment of CPA and CP beads by microwave generally induced a higher extent of drug dissolution except that of CP beads which underwent the irradiation of microwave for a period of 40 min (Table 1). There was no significant correlation between the irradiation energy of microwave supplied and the extent of drug release at 4 h of dissolution of all beads examined in the present study (Table 1; $P > 0.05$).

3.2. Pectinate beads

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 (Fig. 2). Further heating of sodium diclofenac beyond

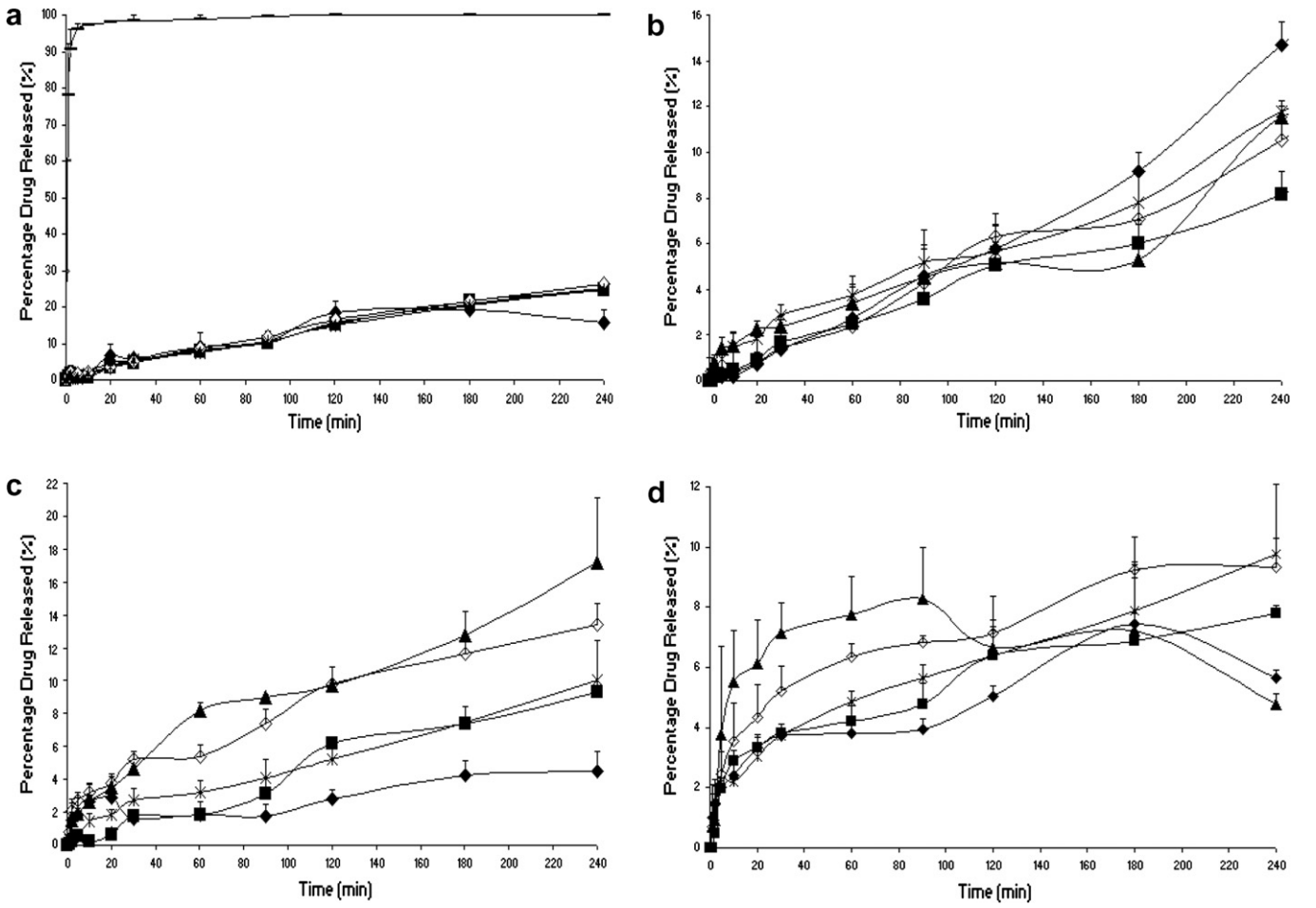

Fig. 1. Drug release profiles of (a) pectinate, (b) pectinate–chitosonium, (c) CPA and (d) CP beads, subjected to various microwave irradiation conditions, with dissolution profile of untreated free sodium diclofenac shown in (a). ▬, drug; ♦, untreated beads; ■, 80 W 5 min; ◇, 80 W 10 min, ×, 80 W 21 min; ▲, 80 W 40 min.

300 °C resulted in drug decomposition. 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. 2). Crosslinking of pectin with Ca^{2+} resulted in an increase in the melting peak temperatures of endotherms and exotherm with a concurrent decrease in the exothermic enthalpy of pectin from -145.2 ± 23.9 J/g to -48.0 ± 1.5 J/g (Table 2).

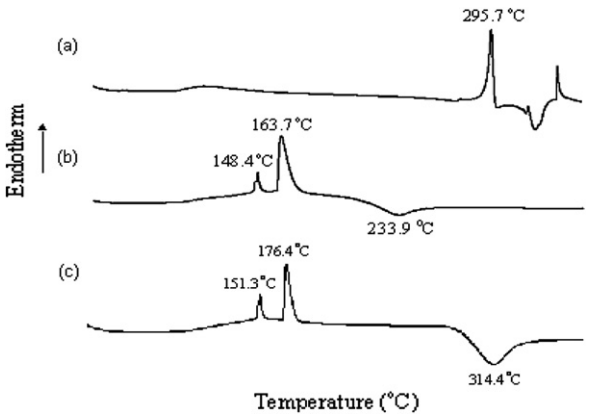

Fig. 2. DSC thermograms of (a) diclofenac sodium, (b) pectin powder and (c) chitosan powder.

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 beads treated by microwave for 10, 21 and 40 min (Table 2). The endothermic melting peak temperature of untreated blank pectinate beads at 158.1 ± 1.5 °C decreased markedly when beads were treated by microwave for 5 min (Table 2). 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 in different domains of matrix.

The incorporation of sodium diclofenac in pectinate matrix gave rise to an additional melting endotherm at 228.9 ± 9.2 °C which was absent in the thermogram of untreated blank beads (Table 2). Practically, the treatment of drug-loaded pectinate beads by microwave for 5 and 10 min reduced the strength of pectin–pectin interaction

Table 2
DSC peak temperatures and enthalpy values of (a) pectinate, (b) pectinate–chitosonium, (c) CPA and (d) CP beads treated under various microwave irradiation conditions

	Blank beads				Drug loaded beads			
	Endo	Endo	Endo	Exo	Endo	Endo	Endo	Exo
(a) Pectinate								
Untreated	158.1 ± 1.5 (16.5 ± 1.2)	172.1 ± 1.6 (303.8 ± 53.5)	–	295.6 ± 0.6 (−48.0 ± 1.5)	160.0 ± 2.9 (14.9 ± 2.7)	176.2 ± 3.8 (243.8 ± 9.6)	228.9 ± 9.2 (6.3 ± 4.2)	292.2 ± 0.4 (−10.6 ± 3.6)
80 W 5 min	152.5 ± 2.3 (13.2 ± 3.3)	170.8 ± 5.6 (420.5 ± 30.7)	–	294.7 ± 3.2 (−28.7 ± 3.6)	153.5 ± 1.8 (15.0 ± 3.0)	169.7 ± 3.4 (378.8 ± 122.7)	215.1 ± 3.5 (5.6 ± 2.1)	302.7 ± 2.4 (−14.4 ± 7.2)
80 W 10 min	156.9 ± 1.8 (21.7 ± 6.9)	172.2 ± 2.5 (323.6 ± 45.9)	–	296.1 ± 3.9 (−63.1 ± 13.1)	154.9 ± 0.5 (11.8 ± 2.2)	173.1 ± 3.0 (253.9 ± 26.3)	217.3 ± 2.9 (4.4 ± 3.1)	300.6 ± 1.3 (−14.2 ± 6.0)
80 W 21 min	158.7 ± 0.9 (15.5 ± 3.3)	172.8 ± 2.7 (294.6 ± 18.0)	–	295.8 ± 3.2 (−60.4 ± 24.6)	158.1 ± 1.0 (15.8 ± 2.7)	175.2 ± 2.3 (240.7 ± 54.2)	Gradual disappearance	296.8 ± 4.4 (−15.8 ± 12.9)
80 W 40 min	157.7 ± 0.7 (15.6 ± 1.7)	167.9 ± 0.8 (272.5 ± 26.7)	–	295.7 ± 0.5 (−83.1 ± 6.7)	160.6 ± 3.7 (15.1 ± 5.5)	176.5 ± 4.3 (222.6 ± 82.8)	Gradual disappearance	293.4 ± 6.1 (−5.2 ± 4.3)
(b) Pectinate–chitosonium								
Untreated	156.1 ± 2.3 (4.3 ± 0.9)	168.2 ± 5.6 (122.0 ± 37.3)	228.6 ± 0.7 (2.7 ± 0.6)	290.1 ± 3.6 (−33.8 ± 7.2)	161.9 ± 0.9 (5.4 ± 1.8)	172.0 ± 2.1 (56.9 ± 3.8)	238.3 ± 2.5 (2.6 ± 0.6)	296.0 ± 2.9 (−21.1 ± 1.4)
80 W 5 min	156.1 ± 0.9 (5.7 ± 2.4)	168.9 ± 4.2 (141.4 ± 8.8)	228.0 ± 3.8 (1.8 ± 0.5)	288.9 ± 1.7 (−46.8 ± 4.6)	155.9 ± 0.8 (7.3 ± 1.8)	172.2 ± 0.7 (143.8 ± 22.2)	238.3 ± 1.5 (5.2 ± 4.4)	295.6 ± 1.2 (−26.8 ± 4.8)
80 W 10 min	154.5 ± 2.0 (6.6 ± 0.9)	168.7 ± 1.2 (166.7 ± 21.9)	226.3 ± 3.7 (2.1 ± 0.9)	288.2 ± 2.1 (−48.2 ± 13.4)	154.3 ± 0.5 (5.5 ± 0.7)	166.2 ± 3.1 (116.4 ± 2.1)	232.5 ± 4.2 (3.0 ± 2.4)	295.7 ± 1.2 (−23.7 ± 4.8)
80 W 21 min	153.6 ± 1.0 (5.5 ± 1.1)	166.1 ± 3.5 (164.0 ± 16.5)	227.0 ± 5.5 (1.8 ± 0.4)	287.5 ± 1.3 (−47.2 ± 9.6)	158.2 ± 2.4 (8.3 ± 0.6)	172.9 ± 4.1 (116.3 ± 36.4)	236.6 ± 7.0 (7.5 ± 7.7)	296.6 ± 1.6 (−19.9 ± 5.9)
80 W 40 min	154.8 ± 0.7 (5.4 ± 0.8)	173.5 ± 1.8 (165.9 ± 26.1)	228.0. ± 1.2 (2.2 ± 1.8)	289.6 ± 1.8 (−35.6 ± 4.6)	159.5 ± 0.8 (5.9 ± 2.0)	170.8 ± 3.3 (88.8 ± 13.6)	239.9 ± 1.6 (3.5 ± 1.9)	299.4 ± 1.1 (−5.2 ± 2.2)
(c) CPA								
Untreated	158.5 ± 1.7 (16.4 ± 3.6)	171.9 ± 2.0 (165.3 ± 26.0)	222.0 ± 13.6 (4.8 ± 4.0)	293.0 ± 0.5 (−38.4 ± 4.8)	158.1 ± 0.7 (13.1 ± 3.5)	177.4 ± 4.3 (124.6 ± 15.5)	236.3 ± 2.6 (2.3 ± 1.2)	290.1 ± 6.0 (−29.4 ± 4.1)
80 W 5 min	155.3 ± 1.0 (16.3 ± 1.8)	176.7 ± 1.9 (201.6 ± 28.4)	231.8 ± 1.4 (4.7 ± 3.8)	293.0 ± 0.8 (−38.0 ± 7.3)	157.0 ± 1.1 (15.4 ± 2.4)	173.6 ± 8.6 (151.4 ± 6.4)	228.7 ± 1.0 (4.7 ± 0.4)	295.7 ± 1.5 (−27.8 ± 4.6)
80 W 10 min	157.0 ± 0.4 (12.4 ± 2.5)	177.0 ± 1.9 (176.0 ± 33.0)	229.2 ± 1.0 (5.5 ± 2.7)	291.8 ± 1.1 (−34.9 ± 4.0)	158.0 ± 0.3 (16.7 ± 2.0)	177.9 ± 2.2 (160.1 ± 27.1)	233.4 ± 2.1 (10.1 ± 1.7)	295.5 ± 2.4 (−29.3 ± 4.7)
80 W 21 min	159.1 ± 0.7 (12.0 ± 1.5)	181.6 ± 1.6 (150.0 ± 8.8)	230.0 ± 0.7 (5.5 ± 1.9)	292.4 ± 1.7 (−35.6 ± 1.8)	159.8 ± 1.2 (15.8 ± 2.1)	178.2 ± 1.1 (133.3 ± 8.5)	226.5 ± 4.1 (6.9 ± 2.4)	296.1 ± 0.6 (−27.2 ± 5.7)
80 W 40 min	162.2 ± 2.5 (16.4 ± 3.3)	186.1 ± 3.2 (125.3 ± 30.2)	225.4 ± 2.1 (3.2 ± 2.0)	292.6 ± 1.4 (−36.5 ± 4.2)	161.4 ± 1.4 (13.3 ± 3.1)	182.5 ± 2.2 (99.8 ± 15.5)	231.9 ± 2.5 (5.4 ± 2.7)	295.3 ± 1.7 (−31.0 ± 10.8)
(d) CP								
Untreated	157.3 ± 2.8 (18.1 ± 4.2)	169.2 ± 5.5 (194.6 ± 44.9)	220.8 ± 1.6 (11.4 ± 2.6)	297.5 ± 2.9 (−31.4 ± 1.4)	159.3 ± 1.7 (17.0 ± 1.2)	182.5 ± 2.5 (197.1 ± 29.4)	Disappearance	304.6 ± 3.5 (−19.9 ± 9.2)
80 W 5 min	154.3 ± 1.1 (19.1 ± 5.6)	173.4 ± 1.9 (300.0 ± 11.5)	219.4 ± 1.3 (11.2 ± 1.2)	300.0 ± 0.9 (−39.0 ± 3.2)	158.2 ± 1.5 (19.2 ± 1.8)	175.6 ± 1.7 (287.3 ± 110.0)	Disappearance	305.4 ± 2.4 (−24.7 ± 1.3)
80 W 10 min	152.3 ± 0.6 (21.3 ± 4.0)	170.8 ± 2.5 (401.2 ± 43.1)	217.7 ± 1.0 (7.7 ± 3.7)	299.1 ± 0.9 (−30.5 ± 3.0)	158.8 ± 0.3 (17.8 ± 1.6)	177.5 ± 4.6 (232.8 ± 7.6)	Disappearance	301.1 ± 3.8 (−24.3 ± 13.1)
80 W 21 min	161.5 ± 0.2 (20.9 ± 1.9)	176.7 ± 0.8 (196.5 ± 12.1)	223.0 ± 2.5 (11.5 ± 2.7)	300.0 ± 0.4 (−40.0 ± 7.9)	160.3 ± 0.7 (18.6 ± 2.6)	178.8 ± 4.2 (201.9 ± 38.1)	Disappearance	301.6 ± 4.8 (−16.2 ± 10.3)
80 W 40 min	164.3 ± 0.8 (19.2 ± 3.1)	182.5 ± 2.8 (169.7 ± 27.9)	227.5 ± 1.1 (10.5 ± 1.8)	299.5 ± 2.0 (−34.9 ± 3.7)	163.4 ± 0.6 (15.4 ± 2.2)	183.3 ± 3.6 (140.9 ± 17.2)	Disappearance	301.0 ± 3.1 (−22.1 ± 1.7)

The values in parentheses denote enthalpy (J/g).
Endo denotes endothermic peak.
Exo denotes exothermic peak.

of the matrix. The endothermic melting peak temperatures of untreated drug-loaded pectinate beads were reduced in sample treated by microwave for 5 min, albeit there was an increase in the enthalpy value of endotherm at 176.2 ± 3.8 °C (Table 2). In the case of drug-loaded pectinate beads treated by microwave for 10 min, a reduction in the endothermic melting peak temperature of untreated sample at 160.0 ± 2.9 °C was noted (Table 2). Generally, the exothermic characteristics of drug-loaded pectinate beads were less affected by microwave than the blank matrix, except an increase in exothermic temperature of samples treated by microwave for 5 and 10 min, and a gradual disappearance of endotherm at 228.9 ± 9.2 °C with respect to matrix treated by microwave for 21 and 40 min was noted following drug–pectin interaction. Apparently, loss of pectin–pectin interaction, as well as gain in drug–pectin interaction 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 expect to have a more significant bearing than drug–pectin interaction on the drug release property of pectinate matrix.

The previous FTIR spectroscopy study indicated that the treatment of blank pectinate beads by microwave brought about a reduction in the transmission intensity of FTIR peak at $1724.9 \pm 2.3\ cm^{-1}$ (Fig. 3c–g). On the contrary, it resulted in the less prominent transmission bands of pectin at 1444.7 ± 1.6, 1329.6 ± 1.5, 1266.0 ± 0.5, 1105.2 ± 0.7 and $1015.5 \pm 0.7\ cm^{-1}$ and a decrease in wavenumber of peak of untreated blank pectinate beads at $1630.4 \pm 0.5\ cm^{-1}$ (Fig. 3b–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 $1724.9 \pm 2.3\ cm^{-1}$ (Fig. 3c and h) following drug–pectin interaction via the C═O moiety of COOH and/or $COOCH_3$. Treatment of drug-loaded pectinate beads by microwave did not negate drug–pectin interaction (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.

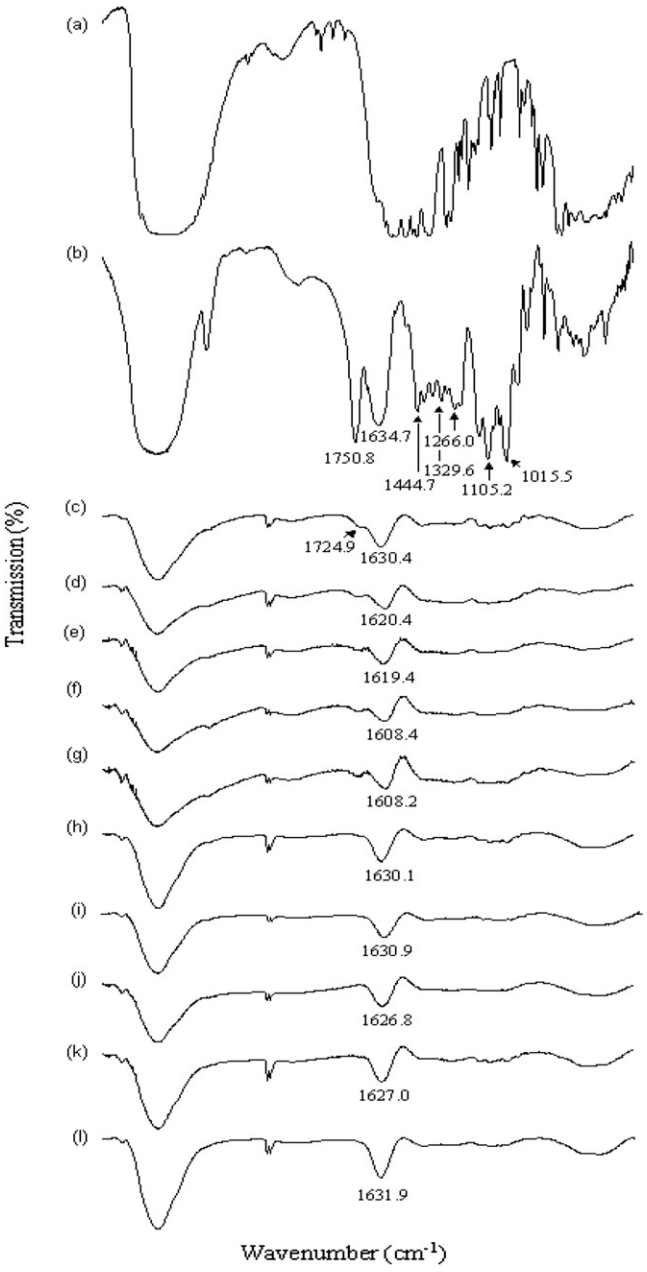

Fig. 3. FTIR spectra of (a) diclofenac sodium, (b) pectin powder, (c) blank pectinate beads and beads treated at 80 W for (d) 5 min, (e) 10 min, (f) 21 min and (g) 40 min, (h) drug-loaded pectinate beads and beads treated at 80 W for (i) 5 min, (j) 10 min, (k) 21 min and (l) 40 min. (Reprinted from Carbohydrate Polymers, 62 (3), Nurjaya Sumiran and Wong Tin Wui, Effects of microwave on drug release properties of matrices of pectin, 245–257, 2005, with permission from Elsevier.)

3.3. Pectinate–chitosonium beads

The DSC investigation indicated that the endothermic enthalpy value of untreated blank pectinate–chitosonium beads at 168.2 ± 5.6 °C increased in beads treated by microwave (Table 2). 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 microwave-treated pectinate–chitosonium beads. 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 values (Table 2). The extent of polymer–polymer interaction could have increased in one domain of pectinate–chitosonium matrix in response to microwave irradiation, but similar changes might not be applicable in other domains of the same

matrix as indicated by the reduction in melting peak temperature of endotherm at 161.9 ± 0.9 °C. In contrast to samples treated by microwave for 10, 21 and 40 min, the 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 (Table 2). A larger propensity of polymer–polymer interaction was taking place which in turn led to a lower extent of drug released from these beads (Table 1).

The FTIR spectra showed that the 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 wavenumbers of untreated beads ascribed to benzyl and/or COO moiety of drug at $1381.6 \pm 1.5\ cm^{-1}$ as well as C—O moiety of polymers at $1156.4 \pm 2.9\ cm^{-1}$ in samples treated by microwave (Fig. 4g–k). Similar to those of blank samples, 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 $3376.0 \pm 13.6\ cm^{-1}$ in samples treated by microwave (Fig. 4). Treatment of blank pectinate–chitosonium beads by microwave brought about an increase in the transmission intensity of FTIR peaks at 1716.5 ± 1.4, 1732.5 ± 1.5 and $1747.2 \pm 1.1\ cm^{-1}$ of the untreated matrix and a loss of tri-peak characteristics of the FTIR band in beads treated for 40 min (Fig. 4b–f). In the case of drug-loaded pectinate–chitosonium beads treated by microwave for 5 min, an increase in the transmission intensity of FTIR band at $1738.5 \pm 2.2\ cm^{-1}$ of untreated beads was noted (Fig. 4g and h). The observation suggested that the propensity of drug–polymer interaction could have greatly enhanced in these beads via the C═O moiety of COOH and/or $COOCH_3$ of pectin, in addition to that of polymer–polymer interaction, thereby leading to a greater extent of drug release retardation in comparison to those treated by microwave for a longer period of time.

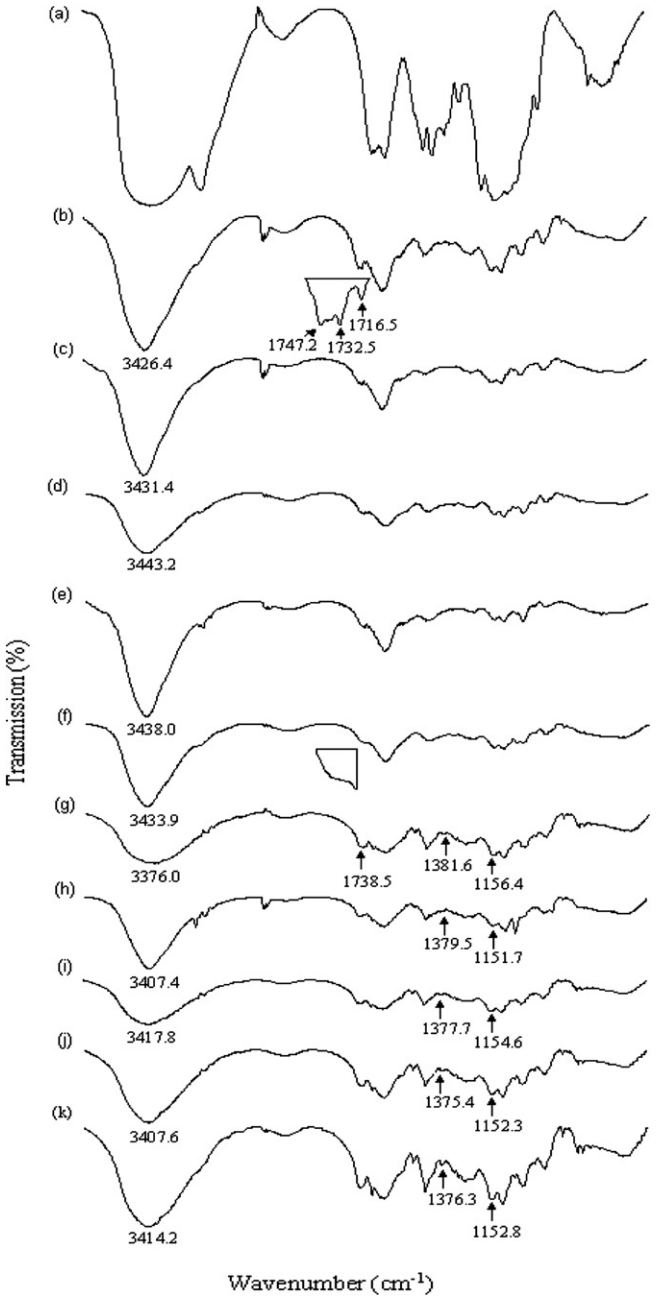

Fig. 4. FTIR spectra of (a) chitosan powder (b) blank pectinate–chitosonium beads and beads treated at 80 W for (c) 5 min, (d) 10 min, (e) 21 min and (f) 40 min, (g) drug-loaded pectinate–chitosonium beads and beads treated at 80 W for (h) 5 min, (i) 10 min, (j) 21 min and (k) 40 min. (Reprinted from Carbohydrate Polymers, 62 (3), Nurjaya Sumiran and Wong Tin Wui, Effects of microwave on drug release properties of matrices of pectin, 245–257, 2005, with permission from Elsevier.)

3.4. CPA beads

Unlike the pectinate matrix, the treatment of blank CPA beads by microwave gave no marked changes to the exothermic enthalpy of the matrix (Table 2). In response to microwave irradiation, there was no marked reduction in the extent of polymer–polymer interaction at the specific domain of matrix upon the introduction of chitosan into the core of pectinate beads. This could aptly explain the tendency of reduced extent of drug released from CPA beads when compared to that of pectinate matrix (Table 1). In contrast to pectinate–chitosonium beads, the introduction of chitosan into the pectinate core reduced the propensity of drug released from the pectinate matrix at 4 h of dissolution to a great extent (Table 1). Nonetheless, it did not have the capacity to prevent further release of drug in response to the influence of microwave (Fig. 1; Table 1). Unlike the blank pectinate–chitosonium beads, the extent of polymer–polymer interaction at the domain of matrix ascribed by the melting endotherm of untreated blank CPA beads at 171.9 ± 2.0 °C was not markedly promoted via the treatment of beads by microwave, particularly in sample treated for 40 min. The endothermic enthalpy of the untreated blank CPA beads was

165.3 ± 26.0 J/g. It had a tendency to be higher in sample treated by microwave for 5 min and reduced as the duration of microwave irradiation was increased to 40 min (Table 2). The endothermic enthalpy of untreated blank CPA beads at 158.5 ± 1.7 °C was reduced when the samples were treated by microwave for 10 and 21 min (Table 2). A decrease in endothermic melting peak temperature at 158.5 ± 1.7 °C of the untreated blank CPA beads in sample treated by microwave for 5 min was also noted (Table 2). The endothermic melting peak temperatures were increased from 158.5 ± 1.7 and 171.9 ± 2.0 °C of the untreated blank CPA beads to 162.2 ± 2.5 °C of beads treated by microwave for 40 min, and 181.6 ± 1.6 and 186.1 ± 3.2 °C of samples treated by microwave for 21 and 40 min, respectively (Table 2). The changes in the endothermic enthalpy and melting peak temperature of CPA beads were translated to a variation in the extent and strength of polymer–polymer interaction of matrix. Under the influence of microwave irradiation, the enhancement of drug released from the CPA beads was accounted by the net changes in strength and extent of polymer–polymer interaction of beads.

In response to microwave irradiation, both blank and drug-loaded CPA beads shared the similar thermal characteristics with respect to changes in endothermic enthalpies of the untreated samples at the melting peak temperatures of 171.9 ± 2.0 and 177.4 ± 4.3 °C, respectively (Table 2). Apparently, the treatment of drug-loaded CPA beads by microwave reduced the melting peak temperature of the untreated sample at 236.3 ± 2.6 °C (Table 2). The extent of melting peak temperature reduction was greater in samples treated by microwave for 5 and 21 min. The melting endotherm of the untreated sample at 236.3 ± 2.6 °C denoted the thermal characteristics of both drug and chitosan, as inferred from the DSC studies of pectinate and pectinate–chitosonium beads. The shift of melting peak towards the endotherm at a lower melting temperature range could mean that the drug and/or chitosan was interacted with pectin. Alternatively, the drug and/or chitosan was dissociated from the existing domain and interacted with another domain of chitosan. Following the changes in polymer–polymer and/or drug–polymer interaction of CPA beads, there was thus a rise in the extent of drug released from the matrix treated by microwave, and a lower extent of drug was released from beads treated by microwave for 5 and 21 min than those treated by microwave for 10 and 40 min.

There was a reduction in polymer–polymer interaction of blank CPA beads via the O—H and/or N—H moiety after subjecting them to microwave irradiation. The FTIR wavenumber of untreated blank CPA beads at $3408.4 \pm 4.7\ cm^{-1}$ became higher at the corresponding peaks of samples treated by microwave (Fig. 5a–e). Irradiation of blank CPA beads by microwave promoted polymer–polymer interaction via the C—H and C—O moieties in samples treated for 5, 21 and 40 min. The extent of interaction between the polymer chains of matrix via the C—H moiety was markedly enhanced in beads treated by microwave for 5 min. This was indicated by a subsidence of the FTIR peak at $2979.7 \pm 3.6\ cm^{-1}$ of untreated blank CPA beads in the spectrum of microwave-treated sample (Fig. 5a and b). In the case of beads treated by microwave for 21 and 40 min, a moderate level of polymer–polymer interaction via the C—H moiety was noted. The FTIR transmission intensities were visibly higher and the corresponding wavenumbers were lower notably with respect

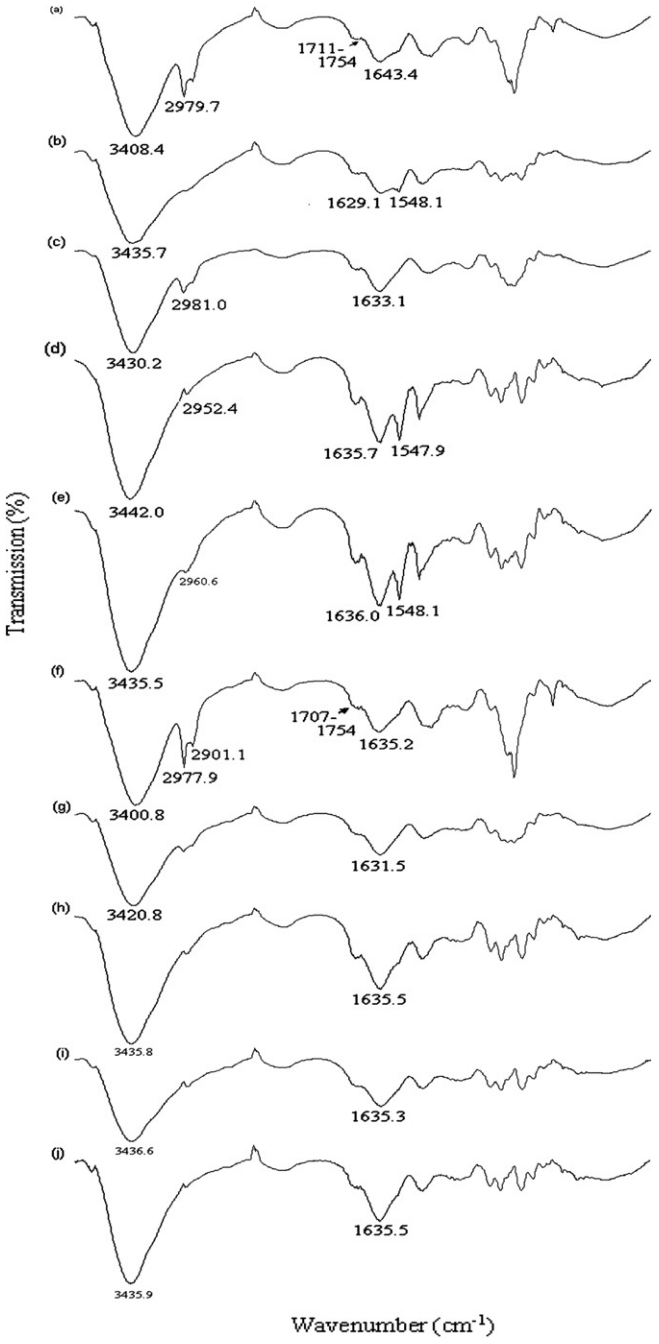

Fig. 5. FTIR spectra of (a) blank CPA beads and beads treated at 80 W for (b) 5 min, (c) 10 min, (d) 21 min and (e) 40 min, (f) drug-loaded CPA beads and beads treated at 80 W for (g) 5 min, (h) 10 min, (i) 21 min and (j) 40 min.

to blank CPA beads treated by microwave for 21 min than those of untreated sample at $2979.7 \pm 3.6\ cm^{-1}$ (Fig. 5a, d and e). On the contrary, the propensity of polymer–polymer interaction via the COO^- moiety was reduced in blank CPA beads treated by microwave. Apparently, a new FTIR peak ascribed to C=O of chitosan amide functional group at $1548.1 \pm 0.2\ cm^{-1}$ was derived from the band at $1643.4 \pm 0.0\ cm^{-1}$ of untreated blank CPA beads when the samples were treated by microwave for 5, 21 and 40 min (Fig. 5a, b, d and e). A higher level of peak demarcation was noted in beads treated by microwave for 21 and 40 min, indicating that these matrices were likely to undergo a higher level of dissociation between the pectin and chitosan chains via the respective COO^- and C=O moieties. The level of polymer–polymer interaction via the C=O of COOH and/or $COOCH_3$ of pectin was low in blank CPA beads treated by microwave for 21 and 40 min. The peak ascribed by C=O of COOH and/or $COOCH_3$ of pectin in untreated blank CPA beads at 1711 to $1754\ cm^{-1}$ had become apparent in these microwave-treated samples and was accompanied by a reduction in the intensity of IR transmission (Fig. 5a, d and e). Unlike the blank CPA beads treated by microwave for a shorter or longer duration of irradiation, the sample subjected to microwave treatment for 10 min experienced a lower propensity of changes with respect to polymer–polymer interaction via the C—H, C—O, C=O, COO^- and/or C=O of COOH and/or $COOCH_3$.

The treatment of drug-loaded CPA beads by microwave brought about a loss in drug–polymer and/or polymer–polymer interaction via the O—H and/or N—H moiety, but a gain via the C—H and C—O functional groups. The former was characterized by an increase in the FTIR wavenumber of untreated drug-loaded CPA beads at $3400.8 \pm 4.1\ cm^{-1}$, while the latter was described by a marked increase in the transmission intensities at $2977.9 \pm 0.2\ cm^{-1}$ and $900–1200\ cm^{-1}$ of the untreated matrix (Fig. 5f–j). Different from that of blank CPA beads, the treatment of drug-loaded samples by microwave was not accompanied by FTIR peak demarcation at $1635.2 \pm 7.2\ cm^{-1}$ as the drug interacted with the polymer via the COO^- moiety of the latter (Fig. 5). In the case of drug-loaded CPA beads treated by microwave for 21 and 40 min, the interaction between the polymer and drug was also effected via the C=O of COOH and/or $COOCH_3$ of pectin thereby resulting in the transmission intensity of FTIR peaks at $1707–1754\ cm^{-1}$ being unaffected by the irradiation of microwave when compared to those of the corresponding blank samples (Fig. 5). The changes of drug release profile of CPA beads in response to microwave were a complex interplay of various functional moieties of matrix, with drug release retardation effected subsequent to principally a gain in polymer–polymer and/or drug–polymer interaction via the C—H and C—O moieties and drug release enhancement followed by a loss in polymer–polymer and/or drug–polymer interaction via the C=O, O—H and/or N—H moiety. Under the influence of microwave irradiation, the drug release property of CPA beads was predominantly governed by the changes in matrix environment involving C=O, O—H and/or N—H moiety thereby leading to an increase in the extent of drug release after 4 h of dissolution when compared with the untreated samples. Among all batches of treated CPA samples, a lower extent of drug was released from beads treated by microwave for 5 and 21 min after 4 h of dissolution (Table 1). With reference to the FTIR findings, it was envisaged that the polymer–polymer interaction via the C—H moiety had markedly negated the propensity of drug released from these beads.

Practically, the extent of drug released from the microwave-treated and -untreated CPA beads after 4 h of dissolution was lower than those of the corresponding batches of pectinate samples. The incorporation of chitosan to the core of pectinate beads was expected to induce a rise in microviscosity of matrix and adsorption of drug onto the chitosan molecules, thus reducing the extent of drug released from the beads. The latter was marked by a reduction in the concentration of sodium diclofenac dissolved in a volume of aqueous chitosan dispersion by $12.75 \pm 0.02\%$ after 4 h of standing at 37 °C. In response to microwave irradiation, the level of drug–chitosan adsorption in matrix became higher. The FTIR peak of untreated drug-loaded CPA beads at $2901.1 \pm 0.0\ cm^{-1}$ was an attribute of chitosan and it had turned inconspicuous after the treatment of samples by microwave (Fig. 5).

3.5. CP beads

Different from those of CPA beads, the CP matrix treated by microwave for 40 min as well as the untreated matrix demonstrated an increase followed by a reduction in the extent of drug release over 4 h of dissolution (Fig. 1d). At drug dissolution time shorter than 100 min, all microwave-treated CP matrices exhibited a larger extent of drug released than the untreated counterpart. Similar to those of CPA beads, the extent of drug released from the CP beads treated by microwave for 5 and 21 min was lower than those of matrices treated for 10 and 40 min. Unexpectedly, the extent of drug released from the CP beads treated by microwave for 40 min became lower whilst the extent of drug released from the matrices treated by microwave for 5, 10 and 21 min remained higher than that of the untreated beads after 200 min of drug dissolution.

The DSC analysis indicated that the endothermic melting peak temperatures of the untreated blank CP beads were increased in matrix treated by microwave for 40 min (Table 2). There was an increase in the strength of polymer–polymer interaction at various domains of the matrix. Unlike the CPA beads, the endotherm between 182.5 ± 2.5 and 304.6 ± 3.5 °C of the untreated drug-loaded CP beads had subsided in both microwave-treated and -untreated samples (Table 2). In addition, the exothermic peak temperatures of both microwave-treated and -untreated drug-loaded CP beads were higher than those of blank counter-

parts, suggesting that the interaction strength between drug and polymers in the CP matrix was relatively high. A marked reduction in the extent of drug release from CP beads treated by microwave for 40 min at 4 h of dissolution in comparison to that of the untreated counterpart was likely to be a resultant effect of drug readsorption which was conferred by the presence of chitosan and a relatively strong polymeric matrix of beads.

In the case of CP beads treated by microwave for 5, 10 and 21 min, an increase in the exothermic enthalpy values of blank CP samples treated by microwave for 5 and 21 min, as well as a decrease in the melting peak temperature of endotherm at 157.3 ± 2.8 °C of blank CP matrix when it was subjected to microwave treatment for 5 and 10 min, were translated to a reduction in both extent and strength of polymer–polymer interaction of the matrix (Table 2). Consequently, there was an enhancement in the extent of drug released from these beads when compared to the untreated sample at 4 h of dissolution. The extent of drug released from the CP beads treated by microwave for 5 and 10 min was lower than that of sample treated for 21 min. In the former, there was a rise in the extent of polymer–polymer interaction via specific domains of the matrix. The endothermic enthalpy values of both untreated blank and drug-loaded CP beads at 169.2 ± 5.5 and 182.5 ± 2.5 °C, respectively, were markedly increased upon subjecting these beads to treatment by microwave for 5 and 10 min (Table 2). Further drug dissolution experiments indicated that a total of $9.42 \pm 0.48\%$, $10.67 \pm 1.30\%$, $15.30 \pm 1.59\%$, $5.18 \pm 0.51\%$ and $6.77 \pm 0.66\%$ of drug were released from CP beads treated by microwave for 5, 10, 21 and 40 min, as well as untreated matrix, respectively, after 300 min of dissolution. The results verified that the microwave could reduce the extent of drug release in samples treated by microwave for 40 min and enhance the dissolution degree of drug from CP beads treated by microwave for 5, 10 and specifically 21 min upon prolonged dissolution. At the early phase of drug dissolution, an unexpectedly higher extent of drug was released from the CP beads treated by microwave for 40 min than those of the untreated samples and matrices treated by microwave for a shorter duration of time. Analysis of the DSC thermogram indicated that the endothermic enthalpy values at 182.5 ± 2.8 and 183.3 ± 3.6 °C of both blank and drug-loaded CP beads treated by microwave for 40 min, respectively, were lower than those of the untreated samples and matrices treated for 5, 10 and 21 min (Table 2). There was a domain-specific reduction in the extent of polymer–polymer interaction of the former matrix which could possibly lead to an enhancement in the extent of drug release at the early phase of dissolution.

The FTIR analysis showed that the treatment of both blank and drug-loaded CP beads by microwave induced polymer–polymer and/or drug–polymer interaction via the C—H moiety of pectin and chitosan. This was indicated by an increase in the transmission intensity of FTIR peaks at 2978.0 ± 0.0 and $2897.0 \pm 2.7\ cm^{-1}$ of the untreated blank CP matrix, as well as 2976.2 ± 2.8 and $2913.9 \pm 3.2\ cm^{-1}$ of the untreated drug-loaded CP matrix, attributing to pectin and chitosan, respectively, following the irradiation of beads by microwave (Fig. 6). On the other hand, there was a reduction in polymer–polymer and/or drug–polymer interaction of blank and drug-loaded CP beads via the O—H and/or N—H moiety after subjecting them to microwave irradiation. This was shown by the FTIR wavenumbers of the untreated blank and drug-loaded CP beads at 3405.9 ± 3.5 and $3407.4 \pm 1.6\ cm^{-1}$,

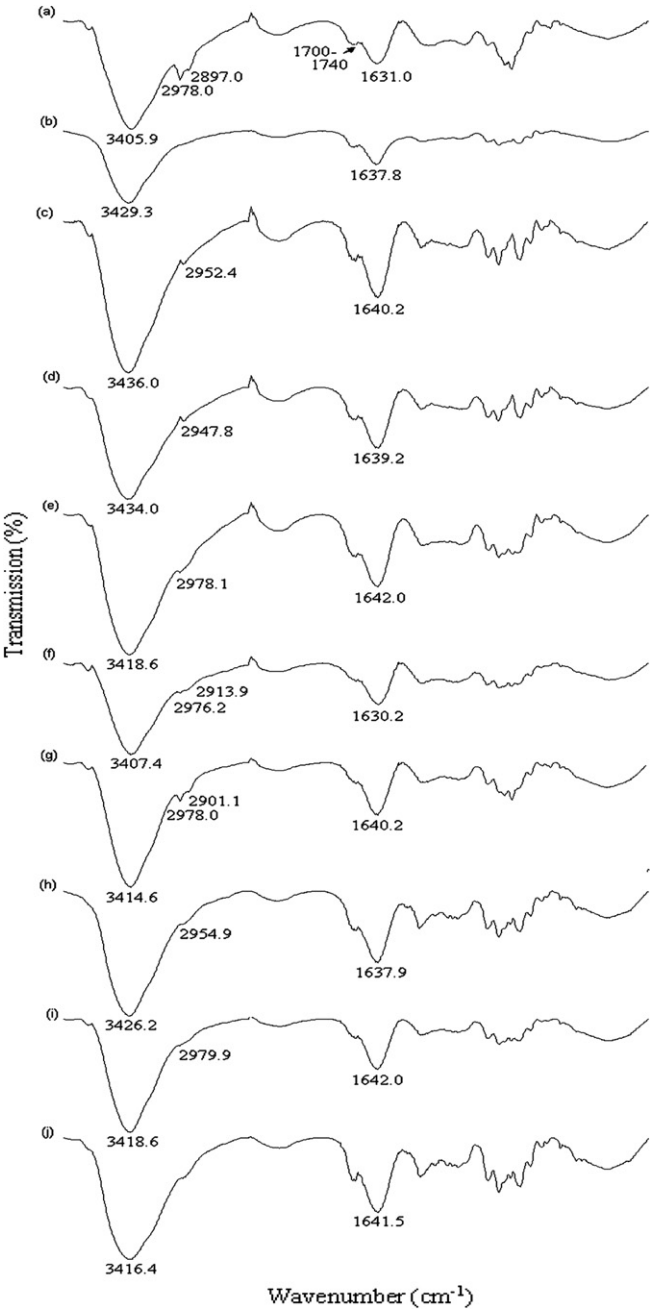

Fig. 6. FTIR spectra of (a) blank CP beads and beads treated at 80 W for (b) 5 min, (c) 10 min, (d) 21 min and (e) 40 min, (f) drug-loaded CP beads and beads treated at 80 W for (g) 5 min, (h) 10 min, (i) 21 min and (j) 40 min.

respectively, which became higher at the corresponding peaks of samples treated by microwave (Fig. 6). The incorporation of drug into the blank CP beads brought about drug–polymer interaction via the C═O moiety of COOH and/or $COOCH_3$ of pectin. The transmission intensity of FTIR peak at 1700–1740 cm^{-1} of the untreated blank CP beads was higher in drug-loaded matrix (Fig. 6). Nonetheless, the treatment of drug-loaded CP beads by microwave for 10 and notably 40 min could have resulted in a loss of drug–polymer interaction via the C═O moiety of COOH and/or $COOCH_3$ of pectin. Under the influence of microwave, the FTIR transmission intensities at 1700–1740 cm^{-1} of drug-loaded CP beads treated by microwave for 10 and 40 min became lower than those of the untreated counterparts, whereas there were no marked changes in the appearance of FTIR band when the drug-loaded CP beads were treated by microwave for 5 and 21 min (Fig. 6f–j). A gain in polymer–polymer interaction via the C—H moiety without a loss in drug–polymer interaction via the C═O of pectin in CP matrix treated by microwave for 5 and 21 min could aptly explain its lower extent of drug release at the early phase of dissolution than those treated for 10 and 40 min. Similar to CPA beads, the extent of drug released from the microwave-treated and -untreated CP beads at 4 h of dissolution was lower than those of corresponding batches of pectinate matrices. The incorporation of chitosan in the core of pectinate beads was expected to induce a rise in microviscosity of matrix and adsorption of drug onto the chitosan molecules, thus reducing the extent of drug released from the beads.

4. Conclusions

Treatment of pectinate beads by microwave did not lead to a reduction, but an increase in the extent of drug released at 4 h of dissolution owing to reduced pectin–pectin interaction via the C═O of COOH and/or $COOCH_3$ of the polymer. In addition, the extent of drug released from the pectinate beads would not reduce merely through the coacervation of pectinate matrix with chitosan. The reduction in the extent of drug released from the pectinate–chitosonium beads required the treatment of these beads by microwave for a specified period of irradiation time, following an increase in drug–polymer and polymer–polymer interaction in the matrix. The extent of drug released from the pectinate beads was reduced through incorporating chitosan directly into the interior of pectinate matrix, as a result of drug–chitosan adsorption. Nonetheless, the treatment of chitosan–pectinate matrix by microwave brought about an increase in the extent of drug released unlike those of pectinate–chitosonium beads. The present observation indicated that the loading of chitosan into the interior of pectinate matrix could effectively retard the drug release without the need to process the beads with microwave. The microwave was needed nevertheless to retard the release of drug from pectinate beads when the chitosan was introduced onto the matrix by means of coacervation. In response to the influences of microwave, the drug release property of beads made of pectin and chitosan was mainly modulated via the C—H, O—H and N—H moieties of polymers and drug, with C—H moiety purported to retard while O—H and N—H functional groups purported to enhance the extent of drug released from the matrix.

Acknowledgements

The authors thank Institute of Research, Development and Commercialization, UiTM, for funding of research grant.

References

[1] F. Acarturk, S. Takka, Calcium alginate microparticles for oral administration: II: effect of formulation factors on drug release and drug entrapment efficiency, J. Microencapsul. 16 (1999) 291–301.
[2] D.A. Adkin, C.J. Kenyon, E.I. Lerner, I. Landau, E. Strauss, D. Caron, A. Penhasi, A. Rubinstein, I.R. Wilding, The use of scintigraphy to provide "proof of concept" for novel polysaccharide preparations designed for colonic drug delivery, Pharm. Res. 14 (1997) 103–107.
[3] M. Ashford, J. Fell, D. Attwood, H. Sharma, P. Woodhead, Studies on pectin formulations for colonic drug delivery, J. Control. Release 30 (1994) 225–232.
[4] L.W. Chan, P.W.S. Heng, L.S.C. Wan, Effect of cellulose additive on alginate microspheres prepared by emulsification, J. Microencapsul. 14 (1997) 545–555.
[5] L.W. Chan, P.W.S. Heng, Effects of aldehydes and methods of cross-linking on properties of calcium alginate microspheres prepared by emulsification, Biomaterials 23 (2002) 1319–1326.
[6] I. El-Gibaly, Oral delayed-release system based on Zn-pectinate gel (ZPG) microparticles as an alternative carrier to calcium pectinate beads for colonic drug delivery, Int. J. Pharm. 232 (2002) 199–211.
[7] M. Fu Lu, L. Woodward, S. Burodkin, Xanthan gum and alginate-based controlled-release theophylline formulations, Drug Dev. Ind. Pharm. 17 (1991) 1987–2004.
[8] G. Fundueanu, E. Esposito, D. Mihai, A. Carpov, J. Desbrieres, M. Rinaudo, C. Nastruzzi, Preparation and characterization of Ca-alginate microspheres by a new emulsification method, Int. J. Pharm. 170 (1998) 11–21.
[9] V.K. Gupta, M.W. Assmus, T.E. Beckert, J.C. Price, A novel pH- and time-based multi-unit potential colonic drug delivery system. II. Optimization of multiple response variables, Int. J. Pharm. 213 (2001) 93–102.
[10] P. Liu, T.R. Krishnan, Alginate-pectin-poly-L-lysine particulate as a potential controlled release formulation, J. Pharm. Pharmacol. 51 (1999) 141–149.
[11] G.S. Macleod, J.T. Fell, J.H. Collett, Studies on the physical properties of mixed pectin/ethylcellulose films intended for colonic drug delivery, Int. J. Pharm. 157 (1997) 53–60.
[12] O. Munjeri, J.H. Collett, J.T. Fell, Hydrogel beads based on amidated pectins for colon-specific drug delivery: the role of chitosan in modifying drug release, J. Control. Release 46 (1997) 273–278.
[13] Y. Murata, M. Miyashita, K. Kofuji, E. Miyamoto, S. Kawashima, Drug release properties of a gel bead prepared with pectin and hydrolysate, J. Control. Release 95 (2004) 61–66.
[14] V. Pillay, C.M. Dangor, T. Govender, K.R. Moopanar, N. Hurbans, Drug release modulation from cross-linked calcium alginate microdiscs, 1: evaluation of the concentration dependency of sodium alginate on drug entrapment capacity, morphology and dissolution rate, Drug Deliv. 5 (1998) 25–34.
[15] V. Pillay, C.M. Dangor, T. Govender, K.R. Moopanar, N. Hurbans, Drug release modulation from cross-linked calcium alginate micro-

discs, 2: swelling, compression, and stability of the hydrodynamically-sensitive calcium alginate matrix and the associated drug release mechanisms, Drug Deliv. 5 (1998) 35–46.
[16] V. Pillay, R. Fassihi, In vitro release modulation from crosslinked pellets for site-specific drug delivery to the gastrointestinal tract I. Comparison of pH-responsive drug release and associated kinetics, J. Control. Release 59 (1999) 229–242.
[17] P. Sriamornsak, S. Puttipipatkhachorn, S. Prakongpan, Calcium pectinate coated pellets as an alternative carrier to calcium pectinate beads, Int. J. Pharm. 156 (1997) 189–194.
[18] P. Sriamornsak, J. Nunthanid, Calcium pectinate gel beads for controlled-release drug delivery. I. Preparation and in vitro release studies, Int. J. Pharm. 160 (1998) 207–212.
[19] S. Takka, F. Acarturk, Calcium alginate microparticles for oral administration: I: effect of sodium alginate type on drug release and drug entrapment efficiency, J. Microencapsul. 16 (1999) 275–290.
[20] L.S.C. Wan, P.W.S. Heng, L.W. Chan, Influence of hydrophile–lipophile balance on alginate microspheres, Int. J. Pharm. 95 (1993) 77–83.
[21] L.S.C. Wan, P.W.S. Heng, L.W. Chan, Surfactant effects of alginate microspheres, Int. J. Pharm. 103 (1994) 267–275.
[22] T.W. Wong, H.Y. Lee, L.W. Chan, P.W.S. Heng, Release characteristics of pectinate microspheres prepared by an emulsification technique, J. Microencapsul. 19 (2002) 511–522.
[23] T.W. Wong, H.Y. Lee, L.W. Chan, P.W.S. Heng, Drug release properties of pectinate microspheres prepared by emulsification method, Int. J. Pharm. 242 (2002) 233–237.
[24] S. Nurjaya, T.W. Wong, Effects of microwave on drug release properties of matrices of pectin, Carbohydr. Polym. 62 (2005) 245–257.
[25] T.W. Wong, L.W. Chan, S.B. Kho, P.W.S. Heng, Design of controlled-release solid dosage forms of alginate and chitosan using microwave, J. Control. Release 84 (2002) 99–114.
[26] T.W. Wong, L.W. Chan, S.B. Kho, P.W.S. Heng, Aging and microwave effects on alginate/chitosan matrices, J. Control. Release 104 (2005) 461–475.
[27] T.W. Wong, Use of microwave in processing of drug delivery systems, Curr. Drug Deliv., in press.
[28] T.W. Wong, S.A. Wahab, Y. Anthony, Effects of microwave on drug release property of poly(methyl vinyl ether-co-maleic acid) matrix, Drug Dev. Ind. Pharm. 33 (2007) 737–746.