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Properties of sustained release hot-melt extruded tablets containing chitosan and xanthan gum

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Abstract

The aim of this study was to investigate the influence of pH, buffer species and ionic strength on the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets containing chitosan and xanthan gum prepared by a hot-melt extrusion process. Drug release from hot-melt extruded (HME) tablets containing either chitosan or xanthan gum was pH and buffer species dependent and the release mechanisms were controlled by the solubility and ionic properties of the polymers. All directly compressed (DC) tablets prepared in this study also exhibited pH and buffer species dependent release. In contrast, the HME tablets containing both chitosan and xanthan gum exhibited pH and buffer species independent sustained release. When placed in 0.1N HCl, the HME tablets formed a hydrogel that functioned to retard drug release in subsequent pH 6.8 and 7.4 phosphate buffers even when media contained high ionic strength, whereas tablets without chitosan did not form a hydrogel to retard drug release in 0.1N HCl. The HME tablets containing both chitosan and xanthan gum showed no significant change in drug release rate when stored at 40 °C for 1 month, 40 °C and 75% relative humidity (40 °C/75% RH) for 1 month, and 60 °C for 15 days.

Keywords: Chitosan; Xanthan gum; Hot-melt extrusion; Sustained release; Hydrogel; pH independent release; Buffer species independent release

1. Introduction

The pH of the gastrointestinal tract (GI tract) varies from pH 1 to 3 in the stomach and increases to approximately pH 7–8 in the colon. Furthermore, the pH of the stomach can fluctuate with food intake, as well as with the age and health of the patient (Ogata et al., 1984; Dressman et al., 1990; Russell et al., 1993; Charman et al., 1997).

Sustained release dosage forms extend the duration time of drug therapy, reduce side-effects and increase safety and patient compliance by reducing the frequency of dosing. Multiple daily administration of an immediate release dosage form results in patient non-compliance. To control and modulate drug release properties of tablets, retardant polymers including hydrophilic polymers such as hydroxypropyl methyl cellulose (HPMC) (Siepmann et al., 1999a, 1999b, 2000; Roshdy et al., 2001; McConville et al., 2004; Sangalli et al., 2004), hydroxypropyl cellulose (HPC) (Roshdy et al., 2001), sodium alginate (Rubio and Ghaly, 1994; Kulkarni et al., 1999) and polyvinyl alcohol (PVA) (Peppas and Wright, 1998; Morita et al., 2000; Peppas and Simmons, 2004); as well as the ammonio methacrylate copolymers such as Eudragit® RL and RS (Eshra et al., 1994; Kidokoro et al., 2001; Zhu et al., 2002); or methacrylic acid copolymers like Eudragit® L and S (Palmieri et al., 2000; Bruce et al., 2003, 2005) have been utilized in solid dosage forms. For these retardants, hydrophilic polymers control drug release from tablets by hydrogelation (Lu et al., 1991; Dhopeshwarkar and Zatz, 1993; Peppas et al., 2000; El-Gazayerly, 2003; Peppas, 2004). The retardation mechanism is based on the intra-molecular hydrogelation of a hydrophilic polymer during dissolution and has been reported to be affected by the ionic strength of the dissolution medium (Talukdar and Plaizier-Vercammen, 1993; El-Gazayerly, 2003). Due to differences in ionic strength of gastric and intestinal fluids, as well as wide variations and fluctuations in its pH of the GI tract, the in vitro and in vivo data for sustained release dosage forms may not always correlate.

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The aim of our study was to investigate the influence of pH, buffer species and ionic strength on the release mechanism of chlorpheniramine maleate (CPM) from matrix tablets containing hydrophilic retardant polymers prepared by a hot-melt extrusion process. Chitosan and xanthan gum were investigated as the model hydrophilic retardant polymer.

Chitosan is a linear hydrophilic polysaccharide polymer of D-glucosamine. It is a non-toxic natural polycationic polymer that is degraded by the microflora in the colon. Chitosan is produced by the alkaline deacetylation of chitin. It is an abundant polymer in nature and is present in the exoskeleton of crustaceans such as crabs or shrimp. Chitosan has been widely researched for its potential use as a pharmaceutical ingredient. The characteristics of crosslinked chitosan with an anionic polymer (Takahashi et al., 1990), applications of chitosan in controlled release dosage forms (Chandy and Sharma, 1993; Tapia et al., 1993; Gupta and Ravi Kumar, 2000; Mitrevej et al., 2001; Agnihotri and Aminabhavi, 2004; Berger et al., 2004), evaluations of matrix tablets containing microcrystalline chitosan (Säkkinen et al., 2002) and applications of chitosan in thermo-sensitive chitosan-based hydrogels (Ruel-Gariépy et al., 2004) have been reported. In addition, the ability of chitosan to retard drug release depends on its molecular weight. High molecular weight chitosans function as matrix tablet retardants, whereas low molecular weight chitosans can function as drug release enhancers for poorly water-soluble drugs due to an improvement in wettability resulting from the solubility of low molecular weight chitosans in water (less than 10,000) (Shiraishi et al., 1990; Imai et al., 1991).

Xanthan gum is a polysaccharide consisting of a cellulose backbone and trisaccharide side chains containing glucuronic acids that give this polymer a negative charge. Although primarily used as a suspending agent, xanthan gum has been reported to function as a matrix retardant in solid dosage forms (Dhopeshwarkar and Zatz, 1993; Talukdar and Plaizier-Vercammen, 1993; El-Gazayerly, 2003; Mu et al., 2003; Rowe et al., 2003).

2. Materials and methods

2.1. Materials

Chitosan (deacetylation degree: 89.4%, powder) and chlorpheniramine maleate (CPM) were purchased from Spectrum Chemical Mfg. Corp. (Gardena, CA). Daichitosan® M (deacetylation degree: 87.4%, 75 μm pass powder) and Daichitosan® H (deacetylation degree: 84.8%, 150 μm pass powder) were donated by Dainichiseika Color and Chemicals Mfg. Co. Ltd. (Tokyo, Japan). PEO (SENTRY™ POLYOX™ WSR N80-LEO NF GRADE, Mw = 200,000) was purchased from Dow Chemical Co. (Midland, MI). Glyceryl monostearate (GMS) was purchased from Sasol Germany GmbH (Witten, Germany). Xanthan gum (XANTURAL® 180) was donated by CP Kelco U.S. Inc. (Chicago, IL). Microcrystalline cellulose (Avicel® PH-101) was supplied by FMC Corporation (Newark, DE). CPM was passed through a 250 μm screen prior to further processing.

2.2. Viscosity

The viscosity of 0.5% (w/v) chitosan solution in 0.5% (v/v) acetic acid solution was measured in triplicate with a Brookfield digital viscometer (LVDV-I+, Brookfield Engineering Laboratories Inc., Middleboro, MA) at 25 ± 1 °C after 1 min of rotation using a spindle #2. The rotation speed was 20 rpm.

2.3. Preparation of directly compressed (DC) tablets

A 200 g sample of powder containing 10% CPM as the model drug, functional polymers and excipients was blended using a mortar and pestle for 2 min. A 300 mg sample of the blended materials was then compressed using a hydraulic compactor (Fred S. Carver Inc., Menomonee Falls, WI) at the pressure of 2000 kg. The hardness of a DC tablet was measured in six replicates using a tablet hardness tester (WTP-3, Heberlein & Co. AG, Wattwil, Switzerland).

2.4. Preparation of hot-melt extruded (HME) tablets

The formulations used in this study are shown in Table 1. A 200 g sample of powder containing 10% CPM, functional polymers and excipients was first blended in a mortar and pestle for 2 min. The blended materials were then fed into the hopper of a single-screw Randcastle Extruder (Model RC 0750, Cedar Grove, NJ). The processing temperatures were 90 °C (zone 1), 95 °C (zone 2), 105 °C (zone 3) and 110 °C (die). The screw speed was 15 rpm and the processing time for the powders

Table 1
Tablet formulations used in the present study

	Composition (%)				
	Formulation #1	Formulation #2	Formulation #3	Formulation #4	Formulation #5
Chlorpheniramine maleate	10	10	10	10	10
Daichitosan® H	43	–	43	–	–
Daichitosan® M	–	–	–	43	–
Chitosan (spectrum)	–	–	–	–	43
Microcrystalline cellulose	17	43	–	–	–
Xanthan gum	–	17	17	17	17
PEO	27	27	27	27	27
GMS	3	3	3	3	3
Total	100	100	100	100	100

inside the barrel of the extruder was approximately 3–4 min. The extruded materials were stored at room temperature for at least 48 h and manually cut into tablets weighing approximately 300 mg.

2.5. Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was utilized to investigate the influence of hot-melt extrusion on the thermal properties of CPM, PEO and GMS, and to characterize the thermal properties of freeze-dried hydrogels formed in the dissolution media. The DSC instrument was a TA Instruments model 2920 (New Castle, DE). Ultra-high purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. Approximately 10 mg of powder was placed into aluminium pans and sealed. The temperature ramp speed and range for the measurement of samples were 5 °C/min and 25–180 °C, respectively. The temperature ramp speed and range on crosslinking studies were 10 °C/min and 0–400 °C, respectively.

2.6. Fourier transform infrared (FT-IR)

Fourier transform infrared (FT-IR) spectral studies were conducted on a Nicolet Magna-IR® system 560 FTIR Spectrophotometer (Nicolet Instrument Corporation Inc., Madison, WI) instrument using KBr pellets to investigate possible interactions between the respective polymers in the release media. All samples were crushed with potassium bromide. The weight ratio of a sample and potassium bromide was 2 mg to 300 mg. Crushed powders were compressed using a hydraulic compactor (Fred S. Carver Inc., Menomonee Falls, WI) at approximately 20,000 pounds under vacuum for 3 min. FT-IR measurements were performed under nitrogen atmosphere at a flow rate of 50 standard cubic feet per hour (SCFH). Spectral scanning was conducted from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

2.7. Scanning electron microscopy (SEM)

The cross sectional morphologies of HME tablets were examined using a Philips Model 515 scanning electron microscope (SEM) at an accelerating voltage of 17 kV. Images were captured using a SEMICAPS 2000A Imaging System. Tablets were extracted from vessels after dissolution testing. Thereafter, the tablets were fast frozen in liquid nitrogen and freeze-dried using a Labconco freeze dryer (Kansas City, MO) for at least 24 h. Prior to observation, samples were mounted on brass stages using double-sided adhesive tape and coated with gold–palladium for 60 s under an argon atmosphere using a Ladd Sputter Coater (Ladd Research Industries Inc., Burlington, VT).

2.8. In vitro drug release

In vitro release testing of tablets (300 mg) containing 30 mg CPM was carried out in the USP 27 Apparatus 2 using either a VanKel VK6010 or a VanKel Vanderkamp 600 Dissolution tester (Cary, NC), each equipped with a VanKel VK8000 auto sampler. The dissolution medium was 900 ml of either 0.1N HCl, pH 4.0 acetate buffer (100 mM), pH 4.0 citrate buffer (100 mM), pH 4.0 phosphate buffer (100 mM), pH 6.8 phosphate buffer (50 mM) or pH 7.4 phosphate buffer (50 mM). To evaluate the influence of ionic strength on CPM release from matrix tablets, 0.1N HCl, pH 4.0 acetate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer each containing 0.4 M NaCl were prepared. During dissolution testing, the media were maintained at 37 ± 0.5 °C and agitated at 100 rpm. A sample volume of 3 ml was taken at each sampling time point. All dissolution tests were conducted for 12 h. Samples were analyzed using a UV spectrometer (μQuant, BIO-TEK® Instruments Inc., Winooski, VT) at 261 nm. The data were collected using KC4 Version 3.1 software (BIO-TEK® Instruments Inc., Winooski, VT). All dissolution tests were performed in triplicate.

The experimental results were fitted to the following exponential equation proposed by Ritger and Peppas (1987a):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t is the amount of drug released at time t, M_∞ is the amount of drug released at infinity, k is a dissolution rate constant and n is the diffusional exponent characteristic of the release mechanism. The values of n were obtained by regression analysis. In the case of drug release from a swellable cylindrical device such as HME tablets containing hydrophilic polymers, the exponent n of Fickian diffusion is defined by $n = 0.45$, whereas anomalous (non-Fickian) transport is $0.45 < n < 0.89$ and Case-II transport is indicated by $n = 0.89$ (Ritger and Peppas, 1987b).

2.9. Crosslinking study

A crosslinking study, as seen in Fig. 1, was performed to investigate the potential for ionic interactions between the polymers in each dissolution medium, and to study the retardation mechanism of HME tablets containing chitosan and xanthan gum. Chitosan (Daichitosan® H) and xanthan gum were blended in a 1:1 ratio using a mortar and pestle for 2 min. Blended powders (300 mg) were compressed with 10 mm flat-face punches using a hydraulic compactor (Fred S. Carver Inc., Menomonee Falls, WI) at the pressure of 2000 kg. The tablet was then agi-

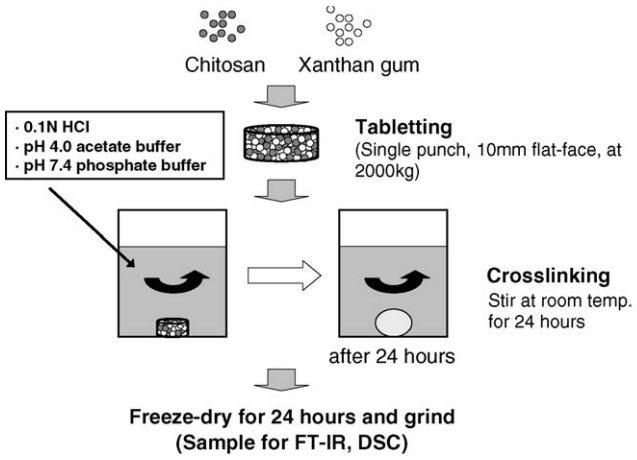

Fig. 1. Crosslinking study.

tated in either 200 ml of 0.1N HCl, pH 4.0 acetate buffer or pH 7.4 phosphate buffer for 24 h to form a hydrogel. Hydrogels were removed and washed twice using each dissolution medium. Without delay, the washed hydrogels were fast frozen in liquid nitrogen and freeze-dried using a Labconco freeze dryer (Kansas City, MO) for at least 24 h and then ground in a mortar and pestle. The properties of freeze-dried samples were determined using FT-IR and DSC.

2.10. Stability

The HME tablets prepared from formulation 3 containing both chitosan and xanthan gum were stored at 40 °C in aluminum induction sealed high density polyethylene (HDPE) bottles for 1 month, 40 °C and 75% relative humidity (40 °C/75% RH) in opened HDPE bottles for 1 month, and 60 °C in aluminum induction sealed HDPE bottles for 15 days. The CPM release profiles of the HME tablets and the DSC thermograms were determined and compared to initial data.

3. Results and discussion

3.1. The change in thermal properties following HME tablet preparation

The influence of hot-melt extrusion on the thermal properties of CPM, PEO and GMS was investigated using DSC. The DSC thermograms of CPM, physical mixture and hot-melt extrudate of formulation 3 are shown in Fig. 2. With the physical mixture, endothermic peaks were observed at approximately 60, 73 and 130 °C, which correspond to PEO, GMS and CPM, respectively. The peaks for CPM and GMS in the extrudate were not seen in the DSC profile because the crystal forms were changed to an amorphous state. CPM had dissolved and dispersed in the melted PEO from the high shear force of the rotating screw and the high temperature during the extrusion process. The GMS melted during the extrusion process, resulting in the melting point of PEO being reduced from 60.2 to 53.5 °C in the extrudate.

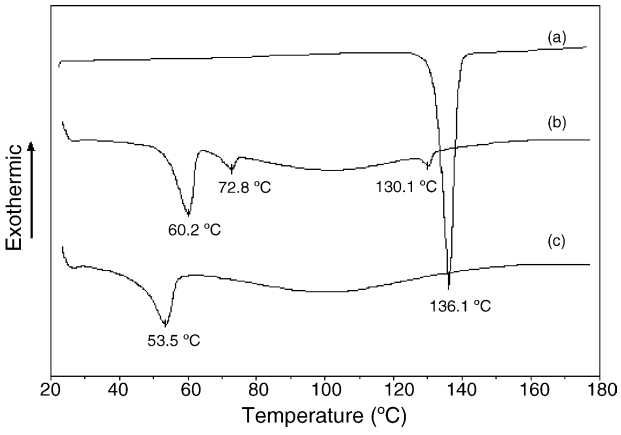

Fig. 2. DSC thermograms of: (a) CPM, (b) physical mixture of formulation 3 and (c) hot-melt extrudate of formulation 3.

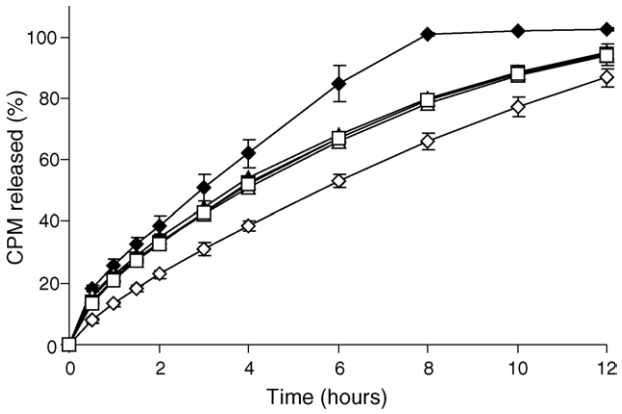

Fig. 3. CPM release profiles from DC tablets prepared by formulation 3 in 900 ml of either (♦) 0.1N HCl, (◊) pH 4.0 acetate buffer, (▲) pH 4.0 citrate buffer, (△) pH 4.0 phosphate buffer, (■) pH 6.8 phosphate buffer or (□) pH 7.4 phosphate buffer at 37 ± 0.5 °C (USP 27 Apparatus 2, 100 rpm). Each point represents the mean ± S.D., $n = 3$.

3.2. In vitro drug release studies

3.2.1. CPM release from DC tablets

Formulations 2 and 3 in Table 1 were used to investigate the CPM release properties from DC tablets. The hardness of DC tablets prepared from formulations 2 and 3 were both over 16 kg. Both the CPM release profiles of DC tablets prepared from formulation 2 (data not shown) and formulation 3 (Fig. 3) exhibited pH and buffer species dependent release. In Fig. 3, the CPM release rate in 0.1N HCl from DC tablets containing both chitosan and xanthan gum was faster than in other media. Almost 100% CPM released from DC tablets within 8 h in 0.1N HCl, suggesting that the hydrogel formed in 0.1N HCl during dissolution testing as a retardant mechanism did not function to retard drug release for 12 h.

3.2.2. CPM release from HME tablets

The CPM release profiles of HME tablets prepared from formulation 1 containing chitosan (Daichitosan® H) exhibited both pH and buffer species dependent release (Fig. 4). The CPM release rates in 0.1N HCl and pH 4.0 acetate buffer were slower than in other media. These results could be explained by both the solubility of chitosan and the difference in hydrogelation rate of chitosan in the respective dissolution media. Gelation of chitosan was visually observed during dissolution testing in 0.1N HCl and pH 4.0 acetate buffer, whereas no distinct hydrogel formulation in other media was observed. Highly deacetylated chitosan is soluble up to a pH of 6.5 (Hejazi and Amiji, 2003), therefore, retardation of drug release by intra-molecular hydrogel formation occurred in 0.1N HCl and pH 4.0 acetate buffer, but not in pH 6.8 and 7.4 phosphate buffers. In pH 4.0 buffers, the CPM release rate from HME tablets prepared from formulation 1 was buffer species dependent. This could be explained by the difference in the solubility of chitosan in dilute acids. Chitosan is soluble in dilute acetic acid and HCl, while it is slightly soluble in dilute H_3PO_4 and is partially soluble in dilute citric acid (Kanauchi et al., 1994). When the medium can dissolve chitosan completely, the solution will show a high viscosity,

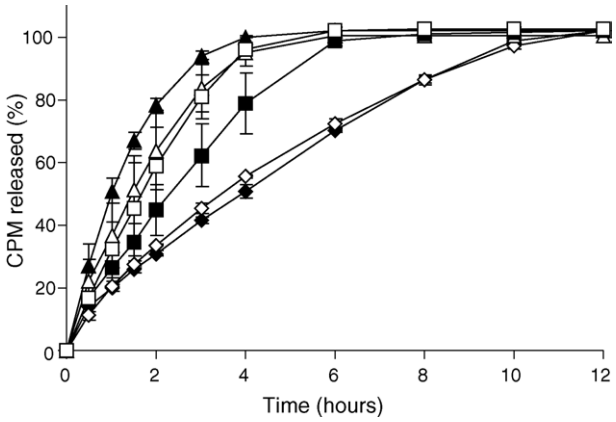

Fig. 4. CPM release profiles from HME tablets prepared by formulation 1 in 900 ml of either (♦) 0.1N HCl, (◊) pH 4.0 acetate buffer, (▲) pH 4.0 citrate buffer, (△) pH 4.0 phosphate buffer, (■) pH 6.8 phosphate buffer or (□) pH 7.4 phosphate buffer at 37 ± 0.5 °C (USP 27 Apparatus 2, 100 rpm). Each point represents the mean ± S.D., $n = 3$.

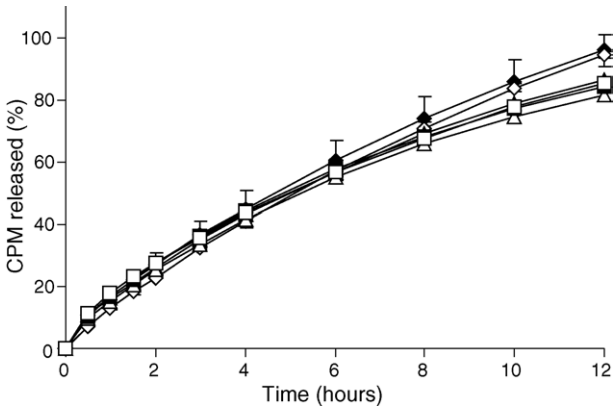

Fig. 6. CPM release profiles from HME tablets prepared by formulation 3 in 900 ml of either (♦) 0.1N HCl, (◊) pH 4.0 acetate buffer, (▲) pH 4.0 citrate buffer, (△) pH 4.0 phosphate buffer, (■) pH 6.8 phosphate buffer or (□) pH 7.4 phosphate buffer at 37 ± 0.5 °C (USP 27 Apparatus 2, 100 rpm). Each point represents the mean ± S.D., $n = 3$.

suggesting the solubility of chitosan in the dilute acidic media would affect the intra-molecular hydrogelation properties of chitosan. Thereby, in both pH 4.0 citrate and phosphate buffers, the hydrogel of chitosan could not form under the paddle rotation speed of 100 rpm, resulting in a rapid release of the CPM.

The CPM release rates from HME tablets prepared by formulation 2 containing xanthan gum were also pH dependent (Fig. 5) and were similar to those from DC tablets (data not shown). In 0.1N HCl, CPM release was especially rapid due to the difference in the ionization state of xanthan gum in the dissolution media. In general, xanthan gum is present predominantly in an unionized state at low pH, whereas xanthan gum is ionized under dilute acidic and alkaline conditions (Mu et al., 2003). This difference in the ionization state of xanthan gum in the dissolution media affected hydrogel formation and consequently, the retardation of drug release. When xanthan gum was present in an unionized state, an intra-molecular hydrogelation was prevented due to the absence of ionic bonds, resulting in a rapid release of CPM in 0.1N HCl.

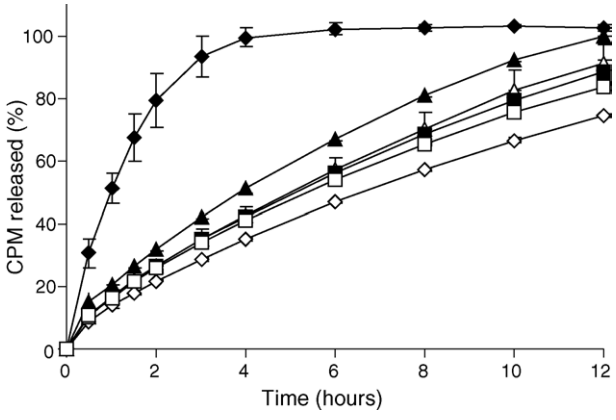

Fig. 5. CPM release profiles from HME tablets prepared by formulation 2 in 900 ml of either (♦) 0.1N HCl, (◊) pH 4.0 acetate buffer, (▲) pH 4.0 citrate buffer, (△) pH 4.0 phosphate buffer, (■) pH 6.8 phosphate buffer or (□) pH 7.4 phosphate buffer at 37 ± 0.5 °C (USP 27 Apparatus 2, 100 rpm). Each point represents the mean ± S.D., $n = 3$.

Interestingly, CPM release from HME tablets containing both chitosan and xanthan gum (formulation 3) showed pH and buffer species independent sustained release (Fig. 6), while CPM release from DC tablets exhibited pH and buffer species dependent release (Fig. 3). In pH 4.0 acetate buffer, CPM release rates from HME and DC tablets were almost the same, whereas in 0.1N HCl, the CPM release rate from DC tablets was faster than that from HME tablets. This could be attributed to the difference in media uptake speed into HME and DC tablets during dissolution test. The major difference between HME and DC tablets prepared in this study was the PEO state in the tablet. In the DC tablets, PEO is dispersed as a powder, whereas the PEO in HME tablets was present as a melt due to the melting which occurred during the hot-melt extrusion process. The media uptake speed into a DC tablet was faster than that for the HME tablet. This was visually observed in the cross sectional morphologies of freeze-dried HME and DC tablets extracted from vessels after 6 h during a dissolution test. The penetration rate (P) of media into a tablet was calculated by the following equation:

$$P\,(\%) = \frac{m}{d} \times 100 \qquad (2)$$

where m is the penetrated distance of 0.1N HCl from surface to center of tablets and d is the radius of tablets. The penetration of 0.1N HCl into HME tablets in 6 h was approximately 72%, whereas that into DC tablets was 100%, suggesting the media uptake speed for DC tablets was faster than HME tablets. This difference in media uptake speed into HME and DC tablets would affect the drug release rate from a tablet via a hydrogel of chitosan formed in 0.1N HCl since an intra-molecular hydrogel of chitosan could be sensitive due to the low viscosity property, resulting in the fast drug release in 0.1N HCl from a DC tablet.

In order to evaluate the release mechanism from a HME tablet, the CPM dissolution data up to 60% was taken and a linear fit was generated by a double logarithmic plot. The diffusional exponent (n), correlation coefficient (r^2) and dissolution rate constant (k) values are shown in Table 2. The CPM release profile from HME tablets prepared according to formulation 3 in

Table 2
Drug release kinetics from HME tablets

	Properties of dissolution medium		Drug-release characteristics		
	Medium	0.4 M NaCl	$n \pm$ S.D.	r^2	k ($h^{-n} \times 10^2$)
Formulation #1	0.1N HCl	Without	0.680 ± 0.019	0.9990	19.7
	0.1N HCl	With	0.633 ± 0.026	0.9985	21.1
Formulation #2	pH 4.0 acetate	Without	0.676 ± 0.018	0.9994	13.8
	pH 7.4 phosphate	Without	0.646 ± 0.012	0.9996	16.7
Formulation #3	0.1N HCl	Without	0.721 ± 0.012	0.9999	16.5
	0.1N HCl	With	0.655 ± 0.014	0.9995	18.9
	pH 4.0 acetate	Without	0.836 ± 0.006	0.9998	12.9
	pH 4.0 acetate	With	0.698 ± 0.007	0.9999	16.7
	pH 4.0 citrate	Without	0.702 ± 0.025	0.9997	16.5
	pH 4.0 phosphate	Without	0.728 ± 0.010	0.9998	15.5
	pH 6.8 phosphate	Without	0.691 ± 0.008	0.9999	16.9
	pH 7.4 phosphate	Without	0.649 ± 0.013	0.9998	17.7
	pH 7.4 phosphate	With	0.715 ± 0.010	0.9904	30.0

the dissolution media without 0.4 M NaCl followed an anomalous (non-Fickian) drug release with the exception of pH 4.0 acetate buffer. Drug release in pH 4.0 acetate buffer was close to Case-II transport, suggesting that the CPM release is controlled mainly by hydrogel matrix formation during dissolution, rather than by drug diffusion.

3.2.3. Influence of viscosity of chitosan on CPM release

In order to investigate the influence of the viscosity of chitosan on CPM release, three types of chitosan were formulated into tablets (Tables 1 and 3) and the CPM release properties from HME tablets were compared. The difference in chitosan viscosity especially affected the CPM release in 0.1N HCl since the retardation mechanism in this medium occurs primarily by the intra-molecular hydrogelation of chitosan. The CPM release rate in 0.1N HCl from HME tablets containing both chitosan and xanthan gum decreased with increasing viscosity of chitosan (data not shown). This result suggested that the intra-molecular hydrogelation rate of chitosan and the strength of hydrogel in 0.1N HCl were controlled by the viscosity of chitosan, thus affecting the retardation mechanism during dissolution in 0.1N HCl.

3.2.4. Effect of ionic strength on CPM release

To investigate the influence of ionic strength on CPM release, dissolution testing of the HME tablets prepared according to formulations 2 and 3 in 0.1N HCl, pH 4.0 acetate buffer and pH 7.4 phosphate buffer each containing 0.4 M NaCl was conducted and the data are shown in Fig. 7. The CPM release rates in pH 4.0 acetate buffer containing 0.4 M NaCl and pH 7.4 phosphate buffer containing 0.4 M NaCl from HME tablets prepared by formulation 2 containing xanthan gum were significantly faster than those without 0.4 M NaCl. These phenomena are due to the polymer configuration change of xanthan gum. It is known that the xanthan gum polymer is present as a random coil at low ionic strength since the anionic side chains are mutually repulsive. This repulsion is reduced when the electrolyte concentrations are greater than 0.15 M, and the polymer configuration is changed to a solid helical rod. As a solid helical rod, the side chains in the xanthan gum structure are under an electronic restraint status since the anionic side chains form hydrogen bonds with cellulose backbone. Due to this xanthan gum polymer configuration change, the intra-molecular hydrogelation retardation mechanism that occurs among the anionic side chains is prevented.

Alternatively, the CPM release profiles of HME tablets prepared from formulation 3 were not affected by an increase in the ionic strength of 0.1N HCl and pH 4.0 acetate buffer. This result demonstrated that the retardation mechanism in acidic media of HME tablets containing both chitosan and xanthan gum was not affected by the xanthan gum polymer configuration change. However, the CPM release rate from HME tablets prepared from formulation 3 in pH 7.4 phosphate buffer containing 0.4 M NaCl was much faster than that in pH 7.4 phosphate buffer. This can be explained by the solubility of chitosan and the polymer configuration change of xanthan gum caused by an increase in the ionic strength of the dissolution medium. The intermolecular hydrogelation between chitosan and xanthan gum did not occur since highly deacetylated chitosan was insoluble at a pH above 6.5. In addition, the intra-molecular hydrogelation of xanthan gum did not occur by the polymer configuration change with an increase of the ionic strength in dissolution medium. Moreover, the influence of the ionic strength on the CPM release mechanism was evaluated in terms of pharmaceutical kinetics. The n, r^2 and k values are shown in Table 2. When 0.4 M NaCl was present in the dissolution media, the diffusional exponent value changed slightly toward the value ($n = 0.45$) of a Fickian

Table 3
The properties of three chitosans used in the present study

	Viscosity[a] (mPa s)	Deacetylation degree (%)	Supplier
Chitosan (spectrum)	20 ± 1	89.4	Spectrum
Daichitosan® M	60 ± 0	87.4	Dainichiseika
Daichitosan® H	100 ± 1	84.8	Dainichiseika

[a] 0.5% (w/v) chitosan solution in 0.5% (v/v) acetic acid solution at 25 ± 1 °C. Each result represents the mean ± S.D., $n = 3$.

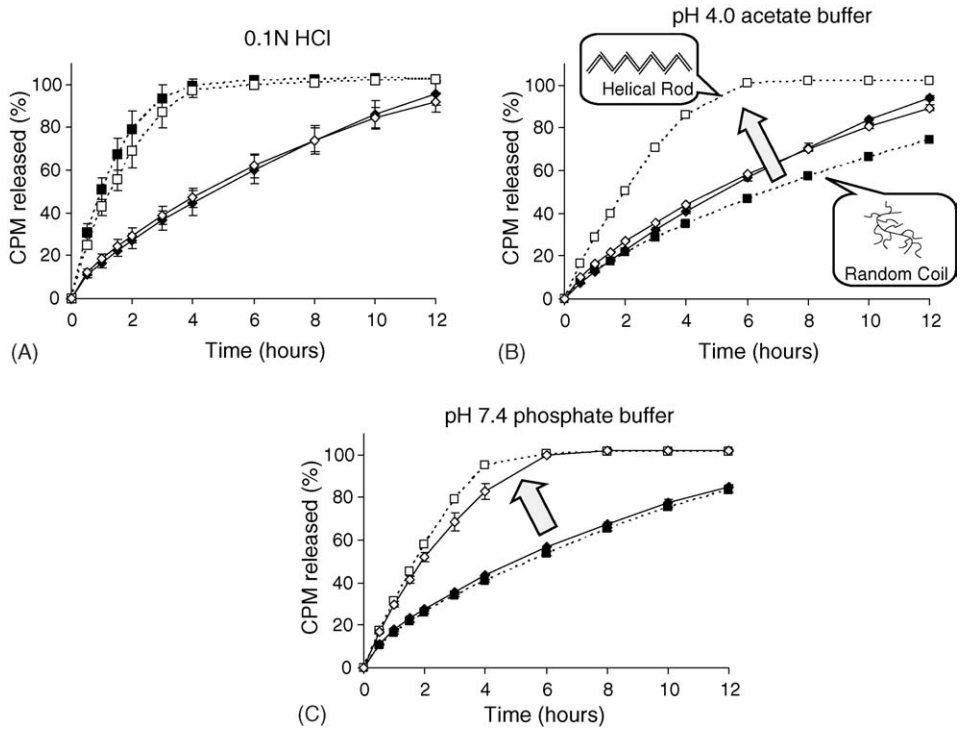

Fig. 7. Influence of the ionic strength on CPM release from HME tablets prepared by formulations 2 and 3 in: (A) 0.1N HCl, (B) pH 4.0 acetate buffer and (C) pH 7.4 phosphate buffer—(■) formulation 2, (□) formulation 2 in media containing 0.4 M NaCl, (♦) formulation 3, (◇) formulation 3 in media containing 0.4 M NaCl at 37 ± 0.5 °C (USP 27 Apparatus 2, 900 ml, 100 rpm). Each point represents the mean ± S.D., $n = 3$.

diffusion, and the dissolution rate constant increased. This could be due to the prevention of hydrogelation of xanthan gum according to an increase in the ionic strength of the dissolution medium.

3.2.5. *In vitro drug release profiles on media replacement*

To investigate the drug release properties from HME tablets under the variable pH environments, the dissolution medium was replaced every 3 h. The 0.1N HCl was used as the first medium, then the medium was replaced with pH 4.0 acetate buffer, pH 6.8 phosphate buffer and pH 7.4 phosphate buffer, continuously. Furthermore, to investigate the influence of ionic strength on CPM release, dissolution media containing 0.4 M NaCl were also used in this study.

In a media replacement study (Fig. 8), the CPM release profile of the HME tablets prepared from formulation 3 containing both chitosan and xanthan gum exhibited the same release profile with that in the respective dissolution media and this sustained release property was not affected by the ionic strength. This is due to the formation of a hydrogel in the first medium, 0.1N HCl, which then functioned to retard drug release in all media. However, the CPM release profile of HME tablets prepared from formulation 2 containing xanthan gum showed significantly rapid release due to the prevention of intra-molecular hydrogelation of the xanthan gum in 0.1N HCl.

3.2.6. *Retardation mechanism of CPM from HME tablets in respective media*

The retardation mechanism in each dissolution medium of CPM from HME tablets containing both chitosan and xanthan gum (formulation 3) was investigated by performing a crosslinking study.

It is known that the amino group of chitosan can interact with the carboxyl group of an anionic polymer such as xanthan gum (Takahashi et al., 1990; Chellat et al., 2000; Mitrevej et al., 2001). Due to this interaction, an inter-molecular hydrogel forms and functions as a retardant to drug release during dissolution testing. Theoretically, this inter-molecular hydrogel occurs in the medium up to a pH of 6.5 since both chitosan and xanthan gum are soluble. Crosslinking studies were performed to investigate the ionized state of chitosan and xanthan gum in each

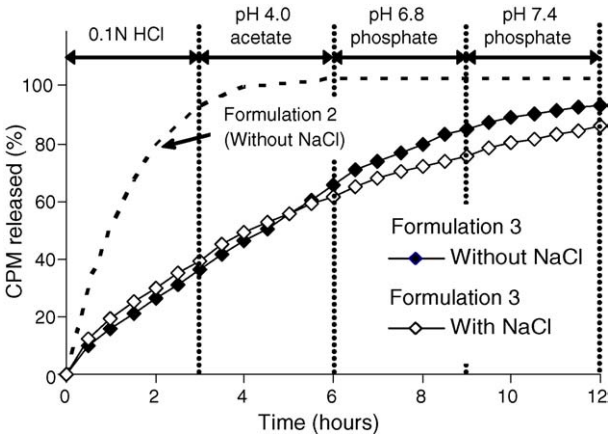

Fig. 8. Media replacement study of HME tablets prepared from formulations 2 and 3 in media with and without 0.4 M NaCl at 37 ± 0.5 °C (USP 27 Apparatus 2, 900 ml, 100 rpm), $n = 3$.

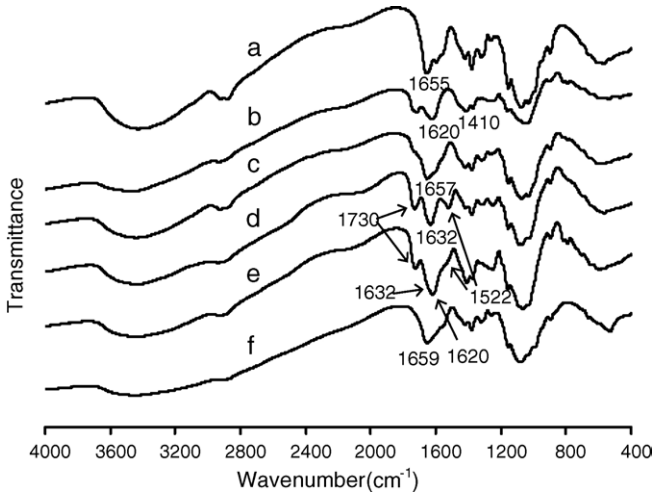

Fig. 9. FT-IR spectra of: (a) Daichitosan® H, (b) xanthan gum, (c) physical mixture of Daichitosan® H/xanthan gum (1:1), (d) freeze-dried hydrogel formed in 0.1N HCl, (e) freeze-dried hydrogel formed in pH 4.0 acetate buffer and (f) freeze-dried hydrogel formed in pH 7.4 phosphate buffer.

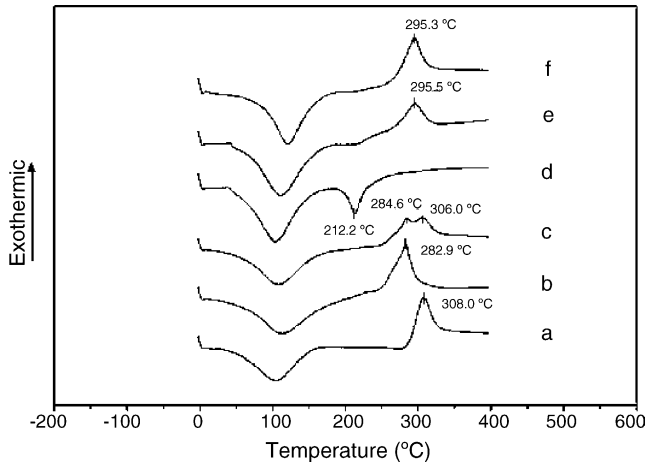

Fig. 10. DSC thermograms of: (a) Daichitosan® H, (b) xanthan gum, (c) physical mixture of Daichitosan® H/xanthan gum (1:1), (d) freeze-dried hydrogel formed in 0.1N HCl, (e) freeze-dried hydrogel formed in pH 4.0 acetate buffer and (f) freeze-dried hydrogel formed in pH 7.4 phosphate buffer.

dissolution medium by using FT-IR. Fig. 9 shows the IR spectra of: (a) Daichitosan® H, (b) xanthan gum, (c) physical mixture of Daichitosan® H/xanthan gum (1:1), (d) freeze-dried hydrogel formed in 0.1N HCl, (e) freeze-dried hydrogel formed in pH 4.0 acetate buffer and (f) freeze-dried hydrogel formed in pH 7.4 phosphate buffer. A peak at 1655 cm^{-1}, which corresponds to amino groups, was observed with the chitosan sample. IR spectra of a freeze-dried hydrogel formed in 0.1N HCl and pH 4.0 acetate buffer exhibited peaks of 1730, 1632 and 1522 cm^{-1} that correspond to carboxyl groups (C=O stretch), asymmetric NH_3^+ (N–H bend) and symmetric NH_3^+ (N–H bend), respectively. IR spectrum of a freeze-dried hydrogel formed in pH 4.0 acetate buffer exhibited a peak corresponding to an ionized carboxyl group (COO^-) on xanthan gum at 1620 cm^{-1}, whereas the IR spectrum of a hydrogel prepared in 0.1N HCl showed no peak corresponding to ionized carboxyl groups since xanthan gum was present predominantly in an unionized state at low pH. On the other hand, the IR spectrum of the freeze-dried hydrogel formed in pH 7.4 phosphate buffer exhibited the complete ionization of carboxyl groups since no peak at 1730 cm^{-1} was observed.

DSC thermograms of freeze-dried hydrogels were also investigated. Fig. 10 shows the DSC thermograms of: (a) Daichitosan® H, (b) xanthan gum, (c) physical mixture of Daichitosan® H/xanthan gum (1:1), (d) freeze-dried hydrogel formed in 0.1N HCl, (e) freeze-dried hydrogel formed in pH 4.0 acetate buffer and (f) freeze-dried hydrogel formed in pH 7.4 phosphate buffer. The thermogram of the physical mixture showed two exothermic peaks at 284.6 and 306.0 °C that correspond to the decompositions of xanthan gum and chitosan, respectively. In a thermogram of the freeze-dried hydrogel formed in 0.1N HCl, a new endothermic peak appeared at 212.2 °C, which corresponds to the endothermic peak of chitosan hydrochloride (Bogataj et al., 2000). This result suggested that the inter-molecular hydrogelation between chitosan and xanthan gum was minimal in 0.1N HCl, suggesting the main retardation mechanism in 0.1N HCl of HME tablets containing both chitosan and xanthan gum is according to the intra-molecular hydrogelation of chitosan.

In the drug release profiles in 0.1N HCl, the averages of CPM release in 6 and 10 h of HME tablets prepared from formulation 1 containing chitosan were 70.2% and 98.9%, respectively. On the other hand, those of HME tablets prepared from formulation 3 containing both chitosan and xanthan gum were 60.3% and 85.9%, respectively. The CPM release rate from HME tablets prepared from formulation 3 was slower than formulation 1. These results suggested that the retardation mechanism in 0.1N HCl is a function of both an intra-molecular hydrogel of chitosan and an inter-molecular hydrogel between chitosan and xanthan gum, although the main retardation mechanism was due to an intra-molecular hydrogel formed by chitosan.

In pH 4.0 acetate buffer, the dissolution profiles of HME tablets prepared from formulations 1–3 were all similar. When 0.4 M NaCl was present in pH 4.0 acetate buffer, the dissolution profile of HME tablets prepared from formulations 1 (data not shown) and 3 were unchanged, whereas that of HME tablets prepared from formulation 2 containing xanthan gum was affected by an increase in the ionic strength of media (Fig. 7). These results indicate that the retardation mechanism in pH 4.0 acetate buffer was according to the intra-molecular hydrogelation of chitosan itself and/or the inter-molecular hydrogelation between chitosan and xanthan gum. In the case of pH 4.0 citrate and phosphate buffers, the retardation mechanisms were mainly according to inter-molecular hydrogelation between chitosan and xanthan gum, because the CPM release rates in pH 4.0 citrate and pH 4.0 phosphate buffers from HME tablets prepared from formulation 1 containing chitosan were rapid, whereas the release profiles of HME tablets prepared from formulation 3 containing both chitosan and xanthan gum showed sustained release and the CPM release properties were not affected by the ionic strength (data not shown). These results suggested that the retardation mechanism in pH 4.0 citrate and phosphate buffers of HME tablets prepared from formulation 3 occurred primarily

Table 4
Retardation mechanism in dissolution media of CPM from HME tablets prepared from formulation 3

Dissolution media	In each medium		Media replacement study		Ionization state	
	Without 0.4 M NaCl	With 0.4 M NaCl	Without 0.4 M NaCl	With 0.4 M NaCl	Chitosan	Xanthan gum
0.1N HCl	A, C	A, C	A, C	A, C	Ionized	Unionized
pH 4.0 acetate	A, B, C	A, C	A, C	A, C	Ionized	Ionized
pH 6.8 phosphate	B	Rapid release	A, C	A, C	Unionized	Ionized
pH 7.4 phosphate	B	Rapid release	A, C	A, C	Unionized	Ionized

A: intra-molecular hydrogelation of chitosan; B: intra-molecular hydrogelation of xanthan gum; C: inter-molecular hydrogelation between chitosan and xanthan gum.

by the inter-molecular hydrogelation between chitosan and xanthan gum.

The CPM release profiles in pH 6.8 and 7.4 phosphate buffers of HME tablets prepared from formulation 3 were controlled by only an intra-molecular hydrogelation of xanthan gum because chitosan is insoluble at a pH above 6.5. In fact, when 0.4 M NaCl was present in pH 6.8 phosphate buffer (data not shown) and pH 7.4 phosphate buffer (Fig. 7C), the CPM release rates were significantly faster due to the polymer configuration change of xanthan gum.

Based on these investigations, the retardation mechanism for HME tablets containing chitosan and xanthan gum in the respective dissolution media was summarized in Table 4.

3.3. Cross sectional morphologies

The cross sectional morphologies of HME tablets containing chitosan and xanthan gum (formulation 3) before and after dissolution tests in pH 4.0 acetate buffer, pH 4.0 acetate buffer containing 0.4 M NaCl and pH 7.4 phosphate buffer are shown in Fig. 11. The cross sectional morphologies of freeze-dried hydrogels formed in pH 4.0 acetate buffer and pH 7.4 phosphate buffer were observed as three-dimensional porous structures. When 0.4 M NaCl was present in pH 4.0 acetate buffer, no porous structure was observed and no change in the sustained release properties of HME tablets was observed, which suggested that the main retardation mechanism from drug release in the pH 4.0 acetate buffer containing 0.4 M NaCl resulted from the intra-molecular hydrogelation of chitosan, whereas in pH 4.0 acetate buffer, retardation was attributable to the inter-molecular hydrogelation between chitosan and xanthan gum. In the drug release study in 0.1N HCl, it was visually observed that the chitosan did not significantly swell. While the HME tablets formed a swellable hydrogel in pH 4.0 acetate buffer, the hydrogel formed in the medium containing 0.4 M NaCl was similar to that in 0.1N HCl, suggesting the main retardation mechanism of CPM in pH 4.0 acetate buffer containing 0.4 M NaCl could be attributable to the intra-molecular hydrogelation

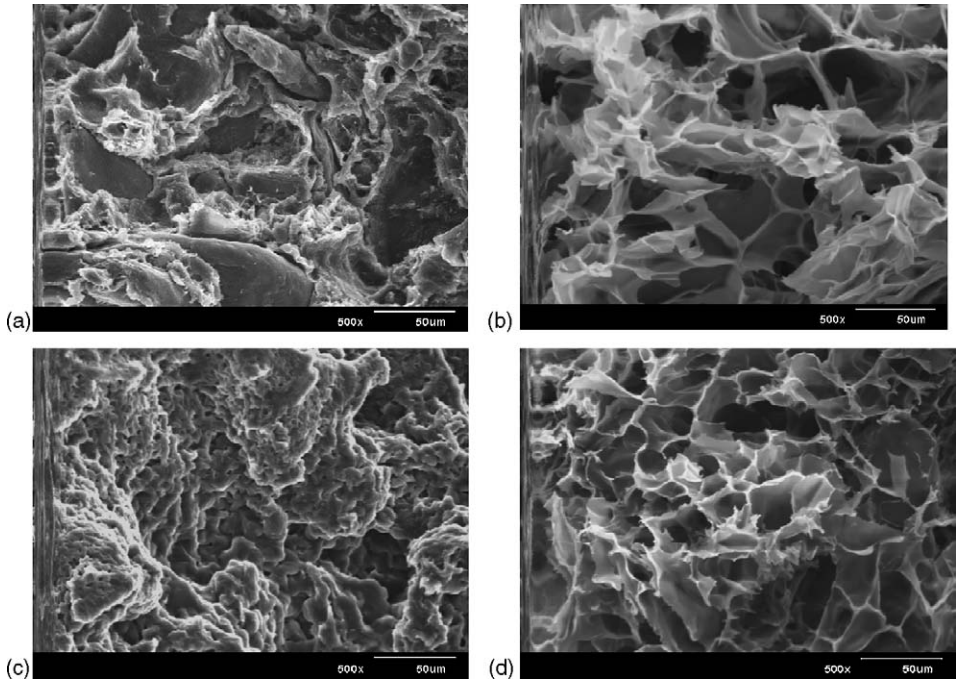

Fig. 11. Morphologies of cross sectional HME tablets prepared from formulation 3 of: (a) before dissolution test, (b) after dissolution test in pH 4.0 acetate buffer, (c) after dissolution test in pH 4.0 acetate buffer containing 0.4 M NaCl and (d) after dissolution test in pH 7.4 phosphate buffer, 500×.

properties of chitosan. Therefore, the cross sectional morphology of the hydrogel formed in pH 4.0 acetate buffer containing 0.4 M NaCl did not exhibit a distinct porous structure.

3.4. Stability

To evaluate the stability of HME tablets prepared by formulation 3 containing chitosan and xanthan gum, tablets were stored at 40 °C for 1 month, 40 °C/75% RH for 1 month, and 60 °C for 15 days. Under these storage conditions, no significant change in CPM release profiles from HME tablets was observed (data not shown). In DSC thermograms, no recrystallization of CPM occurred during stability tests (data not shown). The result of stability tests suggested that the CPM release properties from HME tablets containing chitosan and xanthan gum were stable under the above storage conditions.

4. Conclusions

CPM release from HME tablets containing both chitosan and xanthan gum exhibited pH and buffer species independent sustained release attributable to the combination of the property of slow media uptake speed into a tablet due to the melt state of PEO by a hot-melt extrusion process, the intra-molecular hydrogelation properties of chitosan at a pH below 6.5, the intra-molecular hydrogelation properties of xanthan gum at pH 4.0, 6.8 and 7.4, and the inter-molecular hydrogelation properties of chitosan and xanthan gum under acidic conditions.

In acidic media, the sustained release property of the HME tablets containing both chitosan and xanthan gum was not affected by the ionic strength in media. Furthermore, in a media replacement study, the hydrogel that was formed in acidic media functioned to retard drug release in subsequent pH 6.8 and 7.4 phosphate buffers even when media contained 0.4 M NaCl. In addition, the HME tablets showed no significant change in drug release rate when tablets were stored at 40 °C for 1 month, 40 °C/75% RH for 1 month, and 60 °C for 15 days.

It is proposed that the pH and buffer species independent sustained release HME tablet may exhibit the same release profile in the GI tract since a hydrogel is formed in acidic media similar to stomach fluid, and the resulting hydrogel would function to retard drug release in neutral and slightly alkaline media, irrespective of ionic strength.

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