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RESEARCH ARTICLE

In situ gelling formulation based on methylcellulose/pectin system for oral-sustained drug delivery to dysphagic patients

Kunihiko Itoh[1], Tomoaki Hatakeyama[1], Tetsuya Shimoyama[1], Shozo Miyazaki[1], Antony D'Emanuele[2], and David Attwood[3]

[1]Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido, Japan, [2]School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, UK and [3]School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, UK

Abstract

Background: Oral-sustained release gel formulations with suitable rheological properties have been proposed as a means of improving the compliance of dysphagic and geriatric patients who have difficulties with handling and swallowing oral dosage forms.

Aim: We have modified the rheological and release properties of thermally reversible methylcellulose solutions by admixture with pectin, the gelation of which is ion-responsive, with the aim of formulating an *in situ* gelling vehicle suitable for oral-sustained drug delivery.

Method: Gels formed by solutions containing methylcellulose (1.0–2.0%) and pectin (0.5–2.0%) were assessed for suitable gel strength, and *in vitro* and *in vivo* release of paracetamol.

Results: Addition of 1.5% pectin to a 2.0% methylcellulose formulation containing 20% D-sorbitol and calcium ions in complexed form increased the gel strength and provided a formulation with a suitable viscosity for ease of swallowing by dysphagic patients. Gels formed *in situ* after oral administration of this formulation retained their integrity in the rat stomach for sufficient time for sustained release to be achieved. *In vitro* release of paracetamol from methylcellulose, pectin, and methylcellulose/pectin gels was diffusion-controlled. Plasma levels of paracetamol after oral administration to rats (gastric pH 2.6 and 5.5) of a solution including 2.0% methylcellulose/1.5% pectin showed improved sustained release compared with that from both 2.0% methylcellulose and 1.5% pectin solutions.

Conclusions: The addition of suitable concentrations of pectin to methylcellulose solutions produces *in situ* gelling formulations with suitable viscosity for administration to dysphagic patients and improved sustained release characteristics.

Keywords: Methylcellulose, pectin, oral drug delivery, controlled release, dysphagia, gels, paracetamol

Introduction

Dysphagic and geriatric patients often have problems with handling and swallowing typical oral dosage forms such as tablets and capsules, but compliance is higher with thickened liquid formulations, which are generally easier to swallow[1,2]. *In situ* gelling oral liquid formulations present a novel and interesting approach to obtain sustained release of drugs[3] and several *in situ* forming hydrogels have been developed for drug delivery[4–7].

Methylcellulose is a water-soluble polysaccharide derived from cellulose and is commercially available in partially methylated forms (degree of methylation = 1.4–2.0), solutions of which can form thermoreversible hydrogels in water on heating above 55°C[8]. The gelation temperature may be reduced to a more suitable level (i.e. to below body temperature) by the addition of metal salts[9–15], citrate[10,16], sugars (sucrose[9,16], fructose[17], and sorbitol[9,18]), and glycerol[9,19], the effectiveness of which is consistent with their ability to change

Address for Correspondence: Kunihiko Itoh, Faculty of Pharmaceutical Sciences, Health Sciences University of Hokkaido, Ishikari-Tobetsu, Hokkaido 061-0293, Japan. E-mail: itou@hoku-iryo-u.ac.jp

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water structure[20] according to the Hofmeister series[21]. Recently, *in situ* gelling ophthalmic drug delivery using the thermosetting gelation property of methylcellulose with these additives has been examined[10,14,15,17,19]. In particular, an *in situ* gelling ophthalmic solution based on a methylcellulose–polypropylene glycol–citric acid ternary system[22–24] is marketed in Japan (Rysmon® TG) for the long-acting release of timolol maleate.

However, the electrolyte concentration required to reduce the gelation temperature to a suitable value to enable the methylcellulose to be used as an *in situ* gelling vehicle is generally too high for oral administration to the patients. We have previously reported a methylcellulose formulation in which the gelation temperature was reduced to below body temperature by the addition of 20–25% D-sorbitol and demonstrated its ability to control the *in vitro* release of drug[18].

Pectins are anionic polysaccharides present in the cell walls of most plants, which are used as gelling and thickening agents, and as stabilizers for application in the food, pharmaceutical, and cosmetics industries[25]. The low methoxy pectins (degree of esterification <50%) form hard gels in the presence of divalent ions such as Ca^{2+}, and can also form soft gels in the absence of Ca^{2+} when the pH is below about 3.3[26]. We have previously investigated the potential of *in situ* gelling pectin gels for oral-sustained drug delivery[27–33]. Pectin solutions undergo ion-responsive gelation, and this is achieved in our formulations through the presence of a calcium complex (calcium citrate, prepared by adding sodium citrate and calcium chloride to the pectin solution) that releases Ca^{2+} in the gastric environment below pH 3, which cross-link the galacturonate chains of the pectin to form gels.

An appropriately blended mixture of two or more different polymers can often produce a new system with the desirable features of its constituents[34]. For example, a mixture of methylcellulose and κ-carrageenan shows a double gel transition gel–sol–gel upon heating[35]. Similarly, *in situ* gelling mixtures of methylcellulose with alginate[10] or carbopol[36–38] have been examined for use in ophthalmic drug delivery.

We have recently reported an *in situ* gelling polysaccharide formulation composed of a mixture of xyloglucan, which has thermoresponsive gelling properties, and pectin[39] or alginate[40], which have ion-responsive gelling properties, and demonstrated its potential as a thermo/ion-responsive vehicle for oral-sustained drug delivery. In the present study, we have investigated the potential for oral-sustained drug delivery of a thermo/ion-responsive *in situ* gelling vehicle formed from a methylcellulose/pectin mixture. The formulations have been optimized to produce gelling and rheological properties suitable for oral administration to dysphagic patients and the *in vitro*/*in vivo* drug release characteristics have been examined.

Materials and methods

Materials

Methylcellulose (MCE-400, Lot. 7105564) was supplied by Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Pectin (LM-104-ASJ, DE = 31%, Lot 23001-7) was supplied by Sansho Co., Ltd. (Osaka, Japan). Paracetamol (acetaminophen) was obtained from Choseido Pharmaceutical Co., Ltd. (Tokushima, Japan). CALONAL® Syrup 2%, which is a paracetamol syrup marketed in Japan, was obtained from Showa Yakuhin Kako Co., Ltd. (Tokyo, Japan) and was diluted with ultra pure water to a paracetamol content of 1.0% before use. D-Sorbitol, calcium chloride dihydrate, sodium citrate trihydrate, and Brilliant Blue were obtained from Wako Pure Chemical Ind., Ltd. (Osaka, Japan). Gaster® injection 10 mg, which is a famotidine injection, was obtained from Astellas Pharma Inc. (Tokyo, Japan). Ultra pure water was prepared by Barnstead NANOpure® UV (Thermo Fischer Scientific Inc., Waltham, MA). All other reagents were of analytical grade.

Preparation of polysaccharide solutions

Pectin solutions were prepared by dispersing the required amount of pectin and paracetamol in ultra pure water containing 0.5% sodium citrate and 0.1% calcium chloride, and heating to 40–50°C while stirring. Methylcellulose solutions were prepared by gradually adding with constant stirring weighed quantities of methylcellulose and D-sorbitol to about half of the required quantity of ultra pure water preheated at 70–80°C. The solutions were cooled to 50°C, stirred thoroughly for 1 h at 50°C and for a further 1 h at 5°C with ice-cooling, before making up to the final volume with water. The methylcellulose/pectin solutions were prepared by gradually adding with constant stirring weighed quantities of methylcellulose, pectin, 20% D-sorbitol, 0.5% citric acid, and 0.1% calcium chloride to about two-thirds of the required quantity of ultra pure water preheated at 70–80°C. The solutions were then cooled and stirred as described for the methylcellulose solutions. To prepare the polysaccharide solutions containing 1.0% paracetamol, the required amount of paracetamol was added when the methylcellulose and methylcellulose/pectin were dispersed at 70–80°C. All percentage concentrations are given as w/v.

Measurement of gelation temperature of polysaccharide solutions

Gelation temperatures of 1.0%, 1.5%, and 2.0% methylcellulose solutions containing 0.5%, 1.0%, 1.5%, and 2.0% pectin were measured by a sine-wave vibro viscometer (SV-10; A&D Co., Ltd., Tokyo, Japan) equipped with a water jacket through which water from a controlled temperature bath (NCB-1200; Tokyo Rikakikai Co., Ltd., Tokyo, Japan) could be circulated.

Ten milliliters of the solution was gradually heated from 10°C to 70°C, and the gelation temperature was

determined from the sharp inflection point in the curve of viscosity versus temperature resulting from the sudden increase of viscosity accompanying gel formation.

Measurement of viscosity of polysaccharide solutions

The viscosities of a 2.0% methylcellulose solution and 2.0% methylcellulose pectin solutions containing 0.5%, 1.0%, 1.5%, and 2.0% pectin were determined at 5°C with a cone and plate rotational viscometer with a cone angle of 1°34′ (TV-20H, model E; Tokyo Keiki Inc., Tokyo, Japan) using 1 mL aliquot of the sample. Measurements on each sol were performed in triplicate over a shear rate range of approximately 23–230 sec^{-1}, each shear rate sweep taking 30 sec.

Measurement of stress–strain curves of polysaccharide gels

The stress–strain curves of 2.0% methylcellulose and 2.0% methylcellulose/1.5% pectin gels were measured using a rheometer (CR-500DX; Sun Scientific Co., Tokyo, Japan) by the method reported previously[41]. Cylindrical gels (33 mm diameter and 10 mm height) were prepared as described above in a glass Petri dish (10 mL) and stored at 37°C for 24 h. The gels were placed in the rheometer and raised at a rate of 60 mm/min, so pushing a probe slowly through the gel. The change in the load on the probe was measured as a function of the depth of immersion of the probe below the gel surface.

Measurement of in vitro drug release

Measurement of the *in vitro* release of paracetamol from 2.0% methylcellulose, 1.5% pectin, and 2.0% methylcellulose/1.5% pectin gels was carried out using plastic dialysis cells similar to that described previously[42]. The capacity of each half-cell was 4 mL and the surface area of the membranes was 2.67 cm^2. The polysaccharide solutions initially containing 1.0% paracetamol were placed in the donor compartment, and an equal volume of simulated gastric (pH 1.2) or intestinal (pH 6.8) fluid (as specified for the JP XV disintegration test) was placed in the receptor compartment. The gel donor phase and the aqueous receptor phase were separated by a dialysis membrane (Viskase® Co., Inc., Darien, IL). The assembled cell was shaken horizontally at the rate of 60 strokes per minute in an incubator at 37°C. The total volume of the receptor solution was removed at intervals and replaced by fresh release medium. The concentration of paracetamol in the samples was determined from the absorbance at a wavelength of 244 nm using a spectrophotometer (UV-1200; Shimadzu Co., Kyoto, Japan).

Measurement of in vivo drug release

Male Wister rats, weighing 250–320 g, were provided by Hokudo Co., Ltd. (Sapporo, Japan). The rats were fasted for 24 h with free access to water. They were anesthetized with an intraperitoneal injection of urethane, 1 g/kg, and the jugular vein was cannulated to facilitate removal of blood samples. One milliliter solutions of polysaccharide containing 10 mg paracetamol were orally administrated using a stomach sonde needle for rats (KN-349D; Natsume Seisakusho Co., Ltd., Tokyo, Japan). At given intervals, a blood sample was taken from the jugular vein and analyzed as described below.

For experiments involving gastric acid-controlled rats, the gastric acidity was controlled at pH 5.0 by i.p. injection of 3 mg/0.5 mL of famotidine solution, prepared by diluting 0.3 mL of Gaster® with 0.2 mL saline, and the rats were then used for the *in vivo* experiments after 30 min. The intragastric pH was measured directly on the surface of stomachs removed from anesthetized (urethane 1g/kg by i.p. injection) rats, using a pH composite electrode for surface measurement (SE-1600GC; Chemical Instruments Co., Ltd., Tokyo, Japan) attached to a pH meter (F-22; Horiba Ltd., Tokyo, Japan).

The protocols for the animal experiments were previously approved by the Animal Ethics and Research Committee of the Health Sciences University of Hokkaido.

The statistical significance of the results was assessed by the Student's *t*-test, and results are presented as the mean ± standard error of the mean.

Determination of paracetamol concentration in rat plasma

The plasma samples were separated by centrifugation and assayed by HPLC. The HPLC chromatographic system consisted of a pump (LC-10AS; Shimadzu), with a UV detector (SPD-10A; Shimadzu) at a wavelength of 254 nm.

The assay of paracetamol was based on the methods described by Ameer et al.[43] with minor modifications. To 100 µL of plasma was added 200 µL of water, 100 µL of 2-acetamidophenol (100 µg/mL in 20% methanol) as internal standard, and 7 mL of ethyl acetate. The sample was shaken and centrifuged. Five milliliters of the ethyl acetate layer were evaporated to dryness under a nitrogen stream. The residue was reconstituted with 200 µL of 50% methanol and an aliquot of 20 µL was injected onto an analytical column (150 × 4.6 mm), packed with Inertsil-ODS (GL Sciences Inc., Tokyo, Japan). Elution was carried out with 0.1M sodium acetate buffer (pH 4.0): acetonitrile = 85 : 15 at a rate of 0.8 mL/min at 40°C.

Assessment of in situ gel-forming property in rat stomach

One milliliter samples of 1.5% pectin and 2.0% methylcellulose/1.5% pectin including 0.02% Brilliant Blue as a marker dye but no drug were orally administered to fasted rats as described above. The stomach was excised after 0.5 and 3 h and gels were removed and weighed after removal of surface dirt.

Results and discussion

Gelation of methylcellulose/pectin formulations

Figure 1 shows the effect of pectin on the gelation temperature of 1.0%, 1.5%, and 2.0% methylcellulose solutions containing 20% D-sorbitol. The gelation temperature of 1.0% and 1.5% methylcellulose solutions was decreased from approximately 41°C to 37.5°C and 35.6°C, respectively, in the presence of 0.5% pectin. At low concentrations, pectin may act like an electrolyte and enhance the thermal aggregation of methylcellulose by removing hydration water that is bound to the methylcellulose molecule. However, higher pectin concentrations produced an increase from these minimum values, suggesting obstruction of the thermal aggregation of the methylcellulose by the pectin chains. A more appreciable decrease of gelation temperature was noted following the addition of pectin to 2.0% methylcellulose solutions, with a minimum gelation temperature of 30.1°C observed in the presence of 1.5% pectin.

The ion-responsive gel-forming properties of solutions of 2.0% methylcellulose (containing 20% D-sorbitol), 1.5% pectin (containing calcium complex), and mixtures of the 2.0% methylcellulose solutions with pectin solutions of concentrations of 0.5% to 2.0% were observed visually when these solutions were poured into simulated gastric fluid at pH 1.2 and 37°C. There was no visible evidence of gel formation in the 2.0% methylcellulose solutions in the simulated gastric fluid. The 1.5% pectin solutions gelled immediately when added to the gastric fluid; Ca^{2+} ions are released when the calcium complex is broken down in the acidic conditions and these cross-link the galacturonate chains of the pectin to form a gel. Soft gels were formed by methylcellulose/pectin mixtures containing 0.5% pectin; more rigid gels were formed by mixtures containing 1.0–2.0% pectin. When the pH of the gastric fluid was increased to 3.0 and 5.0 at 37°C (to simulate low acidity conditions), no gelation was observed for either 2.0% methylcellulose or 1.5% pectin solutions. The absence of gels in pectin solutions at pH > 3 has been noted previously[31] and is a consequence of incomplete release of complexed Ca^{2+}. However, a 2.0% methylcellulose/1.5% pectin solution formed a soft gel, showing that pectin addition enhanced the thermoresponsive gelation of methylcellulose even at high pH, although these gels are too soft to be of use as vehicles for controlled drug delivery.

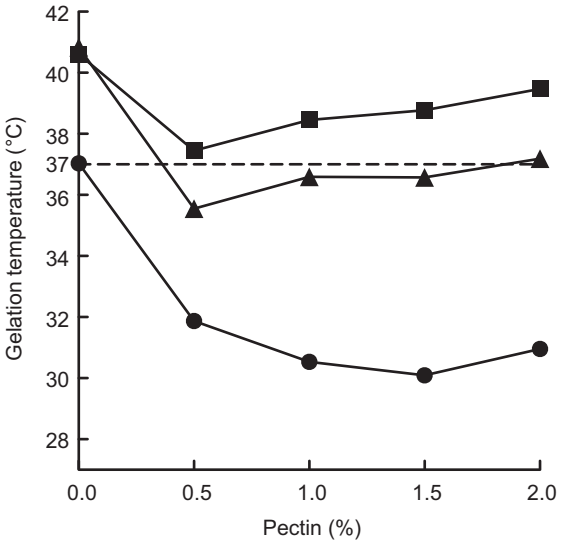

Figure 1. Effect of pectin at concentrations (%) of 1.0 (■), 1.5 (▲), and 2.0 (●) on the gelation temperature of 2.0% methylcellulose solutions. Each value is the mean ± SE of four determinations.

Rheological behavior of the polysaccharide solutions

Figure 2 shows the shear dependency of the viscosity at 5°C of the 2.0% methylcellulose solution and 2.0% methylcellulose/pectin solutions with pectin concentrations of between 0.5% and 2.0%. All solutions showed shear-thinning non-Newtonian flow characteristics, similar to those in previous reports[44,45]. It is interesting to note that although 1.0–2.0% pectin solutions have viscosities below 100 mPa·sec at shear rates of between 23 and 230 per second[28], the addition of these concentrations of pectin to the methylcellulose solutions caused a marked increase of viscosity suggesting significant interaction between the two polysaccharides. Although it is generally difficult for dysphagic patients to take low-viscosity liquids, too great an increase in viscosity as observed for 2.0% methylcellulose/2.0% pectin can produce a dosage form that is difficult to swallow. For this reason, it is suggested that 2.0% methylcellulose/pectin formulations containing <1.5% pectin may be more suitable for administration to dysphagic patients.

The enhancement of methylcellulose gel strength in the presence of 1.5% pectin is clearly shown by the stress–strain curves of Figure 3. Curves for gels of both 2.0% methylcellulose and 2.0% methylcellulose/1.5%

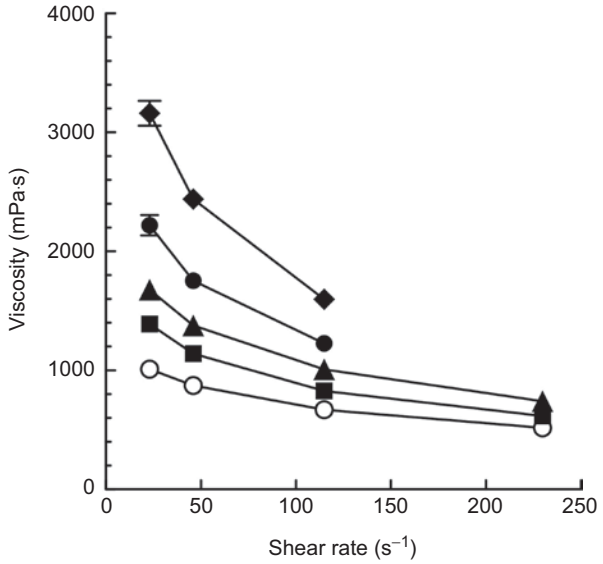

Figure 2. The viscosity at 5°C of 2.0% methylcellulose/pectin solutions with pectin concentrations (%) of 0 (○), 0.5 (■), 1.0 (▲), 1.5 (●), and 2.0 (◆). Each value is the mean ± S.E. of three determinations.

pectin showed typical elastic behavior. Values of the gel strength, taken as the stress at the point of collapse of the gel structure, were 3.1 and 5.8 kN/m^2 for the methylcellulose and methylcellulose/pectin gels, respectively. Thus, the durability of the gel formed *in situ* in the stomach may be increased by co-formulation of the methylcellulose solution with a suitable concentration of pectin.

In vitro drug release

Figure 4 compares *in vitro* release of paracetamol from gels of 2.0% methylcellulose, 1.5% pectin, 2.0% methylcellulose/1.5% pectin, and from a commercially available syrup. The receptor solution of the diffusion cell was changed after 1 h from simulated gastric fluid at pH 1.2 to a simulated intestinal fluid at pH 6.8 to mimic gastrointestinal transit at two extremes of gastric acidity in the fasting state in Figure 4A, and kept at pH 5.0 for 6 h as a hypoacidic model in Figure 4B. The pK_a of paracetamol is 9.5[46] and consequently this drug will be in the fully ionized form over this pH range.

The methylcellulose, pectin, and methylcellulose/pectin solutions formed gels in the donor cell within 30 min and remained in the gel state for 6 h despite the change of pH. The release profiles of these formulations were similar (Figure 4A) and indicated a much slower release compared with that from the syrup. When the receptor solution was maintained at pH 5.0 (Figure 4B), the 1.5% pectin solutions showed no evidence of gelation over a 6-h period, drug release was rapid with a similar profile to that of the syrup in Figure 4A. In contrast, because of their thermoresponsive rather than ion-selective gelation characteristics, 2.0% methylcellulose and 2.0% methylcellulose/1.5% pectin solutions gelled in the donor cell at pH 5.0 and showed sustained release characteristics similar to those of Figure 4A.

The release data over the whole time period of release for these formulations were analyzed using the Higuchi equation[47] for drug release from semisolid vehicles including dissolved drug:

$$Q = 2C_0\left(\frac{Dt}{\pi}\right)^{1/2} \quad (1)$$

where Q is the cumulative amount of drug released per unit surface area, C_0 is the initial drug concentration, and t is the time. Plots of Q versus $t^{1/2}$ for the release of paracetamol from the gels at pH 1.2 are shown in Figure 5.

Release from gels at each of the polysaccharide concentrations conformed to Equation (1) after a short lag period indicating diffusion-controlled release. The diffusion coefficients, D, calculated from the gradients of Higuchi plots of Figure 5 are shown in Table 1.

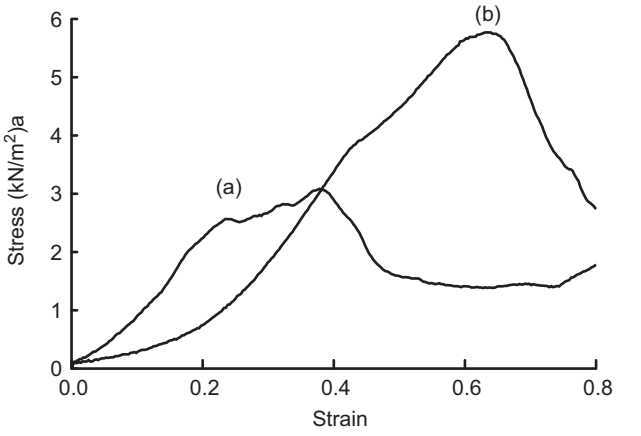

Figure 3. Stress–strain curves of (a) 2.0% methylcellulose gel and (b) 2.0% methylcellulose/1.5% pectin gel prepared at 37°C.

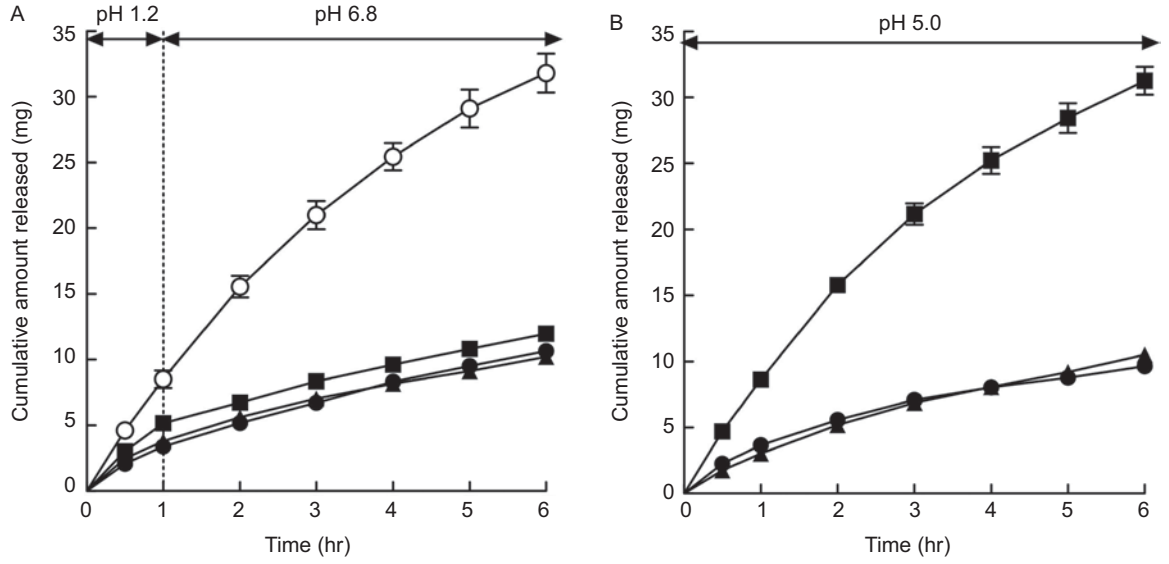

Figure 4. Cumulative *in vitro* release of paracetamol as a function of time from commercial syrup (○), 2.0% methylcellulose gel (▲), 1.5% pectin gel (■), and 2.0% methylcellulose/1.5% pectin gel (●). Release was into simulated gastric fluid at (A) pH 1.2, for a period of 1 h and subsequently at pH 6.8; and (B) at pH 5.0. Each value is the mean ± SE of four determinations.

In vivo drug release

Plasma drug levels following oral administration of paracetamol (10 mg/mL) to rats (gastric pH 2.6) from commercial syrup, 2.0% methylcellulose, 1.5% pectin, and 2.0% methylcellulose/1.5% pectin solutions, are compared in Figure 6A. In addition, the area under the plasma concentration–time curve (AUC) and the mean residence time (MRT) obtained from the plasma concentration–time data of each animal using a computer program for model-independent analysis[48] are compared in Table 2.

A rapid release of paracetamol from the commercial syrup was observed, with a peak plasma drug concentration of 9.01 μg/mL at 0.5 h (Figure 6A and Table 2). The *in vivo* release profiles of the three polysaccharide formulations show a more sustained release of paracetamol, particularly that of the methylcellulose/pectin gel, which shows an almost constant release rate for 2 h after administration. The release profiles may be correlated with visual observations of gels formed in the rat stomach following administration of 1 mL solutions of 1.5% pectin and 2.0% methylcellulose/1.5% pectin (Figure 7). The sustained release achieved over a 3-h period from the methylcellulose/pectin formulations is seen to be a consequence of well-formed gels that remain intact in the rat stomach over this time interval; the more rapid release from the pectin formulation corresponds to an erosion of more than half of the pectin gel after 3 h.

Figure 6B compares the plasma drug levels following oral administration of paracetamol from solutions of 1.5% pectin and 2.0% methylcellulose/1.5% pectin to gastric acid-controlled rats (pretreated with the H_2 blocker, famotidine). As expected from the *in vitro* release experiments (Figure 4B), the absorption of drug from the 1.5% pectin solution was rapid because of a failure of the solution to gel at high pH. In contrast, a more sustained release of paracetamol was achieved with the methylcellulose/pectin formulation as might be expected since the gelation of this formulation is not solely dependent on the presence of free

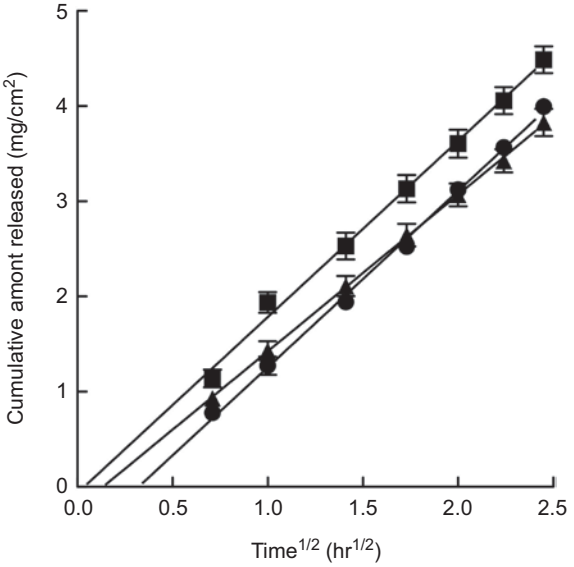

Figure 5. Cumulative *in vitro* release at pH 1.2 of paracetamol per unit area, *Q*, as a function of square root of time from the gels of 2.0% methylcellulose (▲), 1.5% pectin (■), and 2.0% methylcellulose/1.5% pectin (●). Each value is the mean ± SE of four determinations.

Table 1. Diffusion coefficients, *D*, for *in vitro* release of paracetamol from methylcellulose, pectin, and methylcellulose/pectin gels.

	10^6 *D* (cm²/sec)	
Formulations	pH 1.2 → 6.8	pH 5.0
2.0% Methylcellulose	5.95 ± 0.52	5.52 ± 0.24
1.5% Pectin	7.49 ± 0.43	No gelation
2.0% Methylcellulose/1.5% pectin	7.49 ± 0.16	7.71 ± 0.47

Each value is the mean ± SE of four determinations.

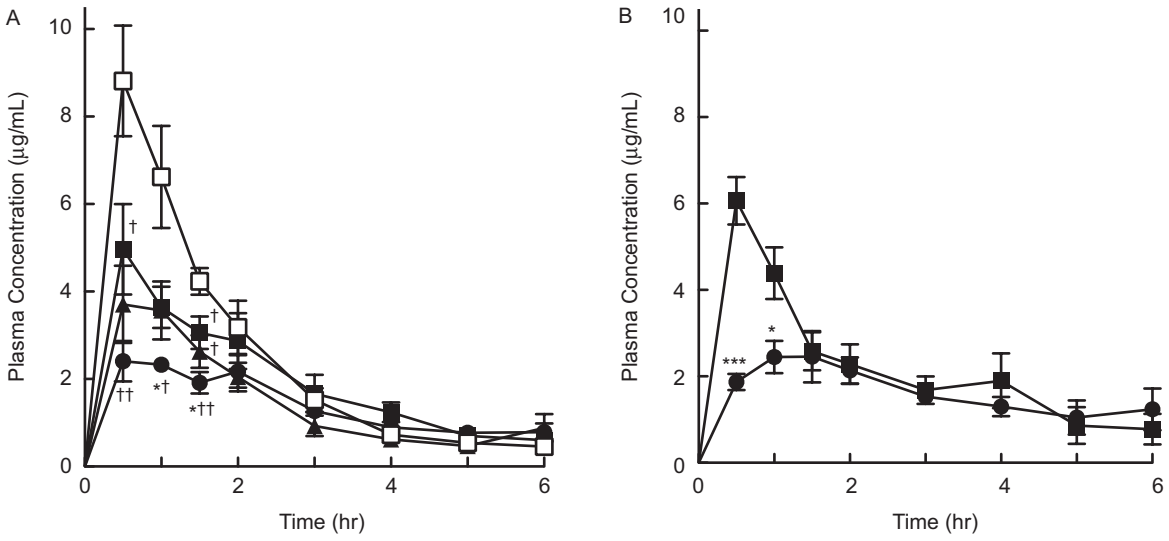

Figure 6. Plasma concentrations of paracetamol in (A) normal and (B) gastric acid-controlled rats after oral administration of commercial syrup (□), 2.0% methylcellulose (▲), 1.5% pectin (■), and 2.0% methylcellulose/1.5% pectin (●). Each value is the mean ± SE of four determinations. $^{\dagger}P < 0.05$, $^{\dagger\dagger}P < 0.01$, compared with commercial syrup. $^{*}P < 0.05$, $^{***}P < 0.001$, compared with 1.5% pectin.

Table 2. Pharmacokinetic parameters of paracetamol administrated from commercial syrup, methylcellulose gel, pectin gel, and methylcellulose/pectin gels formed *in situ* in rat stomach.

Gastric pH	Formulation	C_{max} (μg/mL)	t_{max} (h)	$AUC_{(0-6h)}$ (μg·h/mL)	MRT (h)
2.58	Commercial syrup	9.01 ± 1.30	0.50 ± 0.00	15.23 ± 1.28	1.64 ± 0.14
	2.0% Methylcellulose	3.88 ± 0.81	1.00 ± 0.20	8.94 ± 1.15	2.05 ± 0.27
	1.5% Pectin	5.06 ± 0.97	0.75 ± 0.25	11.89 ± 1.60	2.11 ± 0.15
	2.0% Methylcellulose/1.5% pectin	2.75 ± 0.30	1.00 ± 0.35	8.28 ± 0.77	2.42 ± 0.09
5.48	1.5% Pectin	6.06 ± 0.30	0.50 ± 0.35	13.10 ± 1.22	2.13 ± 0.23
	2.0% Methylcellulose/1.5% pectin	2.78 ± 0.48**	2.50 ± 1.17	9.48 ± 0.77	2.68 ± 0.23

Each value is the mean ± SE of four determinations.
**$P < 0.01$, compared with 1.5% pectin at pH 5.48.

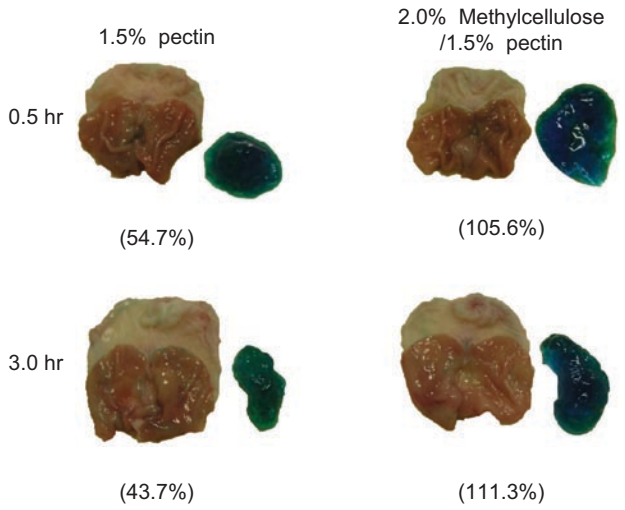

Figure 7. Photographs showing presence of gels in rat stomach (gastric pH 2.5) 0.5 and 3 h after oral administration of solutions of 1.5% pectin and 2.0% methylcellulose/1.5% pectin. Numbers in parenthesis indicate percentage of gel remaining.

Ca^{2+}. Observations of gel formation in the rat stomach showed that 80.0% and 43.3% of the amount of solution administered remained in gel form after 0.5 and 3 h, respectively (figures not shown).

Concluding remarks

This study has demonstrated the potential of mixtures of methylcellulose, which has thermoresponsive gelation characteristics, and pectin, the gelation of which is ion-responsive, for use in the development of suitable *in situ* gelling formulations for oral administration. The addition of pectin (and complexed calcium ions) to methylcellulose solutions (containing D-sorbitol) led to a reduction of gelation temperature to below body temperature enabling *in situ* gelation of the formulations, and an improvement of the rheological characteristics such that the formulations were of suitable viscosity for swallowing by dysphagic patients. Gels formed *in situ* in the rat stomach from the methylcellulose/pectin solutions were sufficiently rigid to remain intact for at least 3 h and to sustain the release of paracetamol over a 6-h period. More effective sustained release was achieved from the methylcellulose/pectin formulations in both normal and gastric acid-controlled rats than from either methylcellulose or pectin formulations. The results of this study suggest that the methylcellulose/pectin solutions have application in the development of sustained release formulations with potential to improve compliance for elderly and dysphagic patients.

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Declaration of interest

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