Drug Development and Industrial Pharmacy, 2009; 35(7): 780–787

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healthcare

RESEARCH ARTICLE

Preparation and evaluation of gel formulations for oral sustained delivery to dysphagic patients

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Abstract

Background: Oral sustained release gel formulations may provide a means of administering drugs to dysphagic and geriatric patients who have difficulties with handling and taking oral dosage forms. *Aim*: We have designed gel formulations for the oral administration of paracetamol with suitable rheological characteristics for ease of administration to patients with swallowing difficulties and sufficient integrity in the acidic environment of the stomach to achieve a sustained release of this drug. *Method*: Gels formed by gelatin, agar, gellan, pectin, and xyloglucan were assessed for suitable gel strength and in vitro and in vivo release characteristics. *Results*: Gellan (1.5% w/v) and xyloglucan gels (1.5% w/w) had acceptable gel strengths for ease of swallowing and retained their integrity in the rat stomach sufficiently well to sustain the release of paracetamol over a period of 6 hours. Comparison of 1.5% xyloglucan gels with a commercially available preparation with identical paracetamol concentrations demonstrated improved sustained release properties of the xyloglucan gels. *Conclusions*: Gels formed by gellan and xyloglucan have suitable rheological and sustained release characteristics for potential use as vehicles for oral delivery of drugs to dysphagic patients.

Key words: *Controlled release; dysphagia; gels; oral drug delivery; paracetamol*

Introduction

Gel (jelly-like) formulations for oral drug administration have been proposed as a means of improving the compliance of dysphagic and geriatric patients who have difficulties with handling and taking oral dosage forms. These gel preparations are preferred by the elderly, particularly in Japan, because of their ease of handling and swallowing compared to more conventional oral dosage forms such as tablets and powders and have been prepared with various materials, including agar[1,2], gelatin[3,4], carrageenan[5], carrageenan and gelatin mixtures[6], sodium caseinate[7,8], glycerogelatin [9], and silk fibroin[10–12]. Kazepitan™ jelly (150 mg/30 g) is commercially available in Japan for the oral administration of paracetamol. These preparations are not, however, primarily intended as vehicles for sustained release of drugs and are frequently designed to melt at body temperature for easy swallowing rather than to retain their integrity in the gastrointestinal tract. There have been only limited pharmacokinetic evaluations of these gel formulations[6].

We have recently described in situ gelling formulations of the polysaccharides gellan[13–15], pectin[16–22], and xyloglucan[15,23–25], which were designed to be administered in liquid form and to form gels in the acidic environment of the stomach from which a sustained release of drug could be achieved. The xyloglucan formulation was administered as a chilled solution which gelled in the stomach on attaining body temperature. In situ gelation of gellan and low methoxy pectin solutions was achieved by including a soluble nonionized calcium complex in the solution which was optimized to release free Ca^{2+} ions when the orally administered liquid formulation reached the acidic environment of the stomach, so ensuring instantaneous gelation. Our experience with these polysaccharide gels has shown a

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(Received 9 Jul 2008; accepted 31 Oct 2008)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.1080/03639040802592443

strong dependency of their rheological properties on gel concentration over the range 0.5%–2.5%, which suggests that formulations of these polysaccharides could be optimized to provide gels that were sufficiently rigid to retain their integrity in the stomach over several hours and thus provide vehicles suitable for sustained drug delivery, but sufficiently soft to facilitate ease of swallowing by patients with swallowing difficulties. The properties of these formulations have been compared with those produced using agar and gelatin and with the commercial product Kazepitan^{TM} jelly.

Materials and methods

Materials

Agar (Lot 9071300, JP XV Powdered Agar) was obtained from Konishi Pharmaceutical Co., Ltd. (Higashi-Osaka, Japan). Gelatin (porcine skin, Type A) was obtained from Sigma-Aldrich Inc. (St. Louis, MO, USA). Gellan gum, Kelcogel (Lot 1L1966A), and xyloglucan with a percentage of galactose removal of 45% wt/vol (Lot 3603) was supplied by Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan). Pectin (LM-104-ASJ, DE = 31% wt/vol, Lot 34329) was supplied by SANSHO Co., Ltd. (Osaka, Japan). A commercial paracetamol gel formulation for oral administration, Kazepitan^{TM} jelly (150 mg/30 g) that contains agar, was obtained from Kobayashi Pharmaceutical Co., Ltd. (Osaka, Japan). Paracetamol (acetaminophen) was obtained from Astellas Pharma Inc. (Tokyo, Japan). All other reagents were of analytical grade.

Preparation of gels

Gels of gelatin, gellan, pectin, and xyloglucan of concentrations 1.0%, 1.5%, and 2.0% containing paracetamol (1.0%) were prepared in the following ways (the concentrations of xyloglucan gels are expressed as % (wt/wt); all other concentrations are % (wt/vol)). Gelatin gels were prepared by dispersing the required amount of gelatin and paracetamol in ultra pure water and heating to 40°C–50°C with stirring; the resulting solution was stored at 20°C for 24 hours before use. Gellan gels were prepared by dispersing the required amount of gellan in ultra pure water, heating to 90°C while stirring. After cooling to below 40°C–50°C, appropriate amounts of paracetamol were then dissolved in the resulting solution. Pectin gels were prepared by dispersing the required amount of pectin and paracetamol in ultra pure water containing 0.05% calcium chloride, heating to 40°C–50°C while stirring, and storing the resulting solution at 20°C for 24 hours. Xyloglucan gels were prepared by dispersing the required amount of the xyloglucan and paracetamol in ultra pure water at 65°C–70°C and mixing completely using a homogenizer (CM-200, AS ONE Corp., Osaka, Japan) at 2000 rpm for about 10 minutes at room temperature, a further 10 minutes at 2000 rpm with ice-cooling, and finally 50 minutes at 3000 rpm with ice-cooling. Agar gels were prepared by dispersing the required amount of the powdered agar in ultra pure water, heating to 90°C–95°C with stirring and storing the resulting solution at 20°C for 24 hours.

Measurement of rheological properties of gels

The influence of polymer content on gel strength was measured at 20°C using a rheometer (CR-500DX, Sun Scientific Co., Tokyo, Japan) by the method described previously[9]. Cylindrical gels (approximately 33 mm diameter and 10 mm height) were prepared as described above in a glass Petri dish (10 mL) and stored at 20°C for 24 hours. 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 selected gels and from the commercial preparation (Kazepitan^{TM} jelly) was carried out using the JP XV paddle method at 37°C. A 500 mL portion of simulated gastric (pH 1.2) or intestinal (pH 6.8) fluid (as specified for the JP XV disintegration test) was used as the release medium, and the paddle rotation speed was 50 rpm. Gels were prepared from 10 mL of the polymer solution containing drug in a 50 mL disposable syringe and stored at 20°C for 24 hours. The head of the disposable syringe was cut off and a fixed weight of the cylindrical gel (diameter, 29 mm; height, 16 mm) was pressed out through the syringe into the release test fluid. A 5.0 mL portion of the fluid was removed at suitable intervals and the volume was kept constant by adding the same amount of release medium at the same temperature. The concentration of paracetamol in the samples was determined by high performance liquid chromatography (HPLC) as described below.

In vivo drug release

Male Wistar rats, weighing 230–330 g, were provided by Hokudo Co., Ltd. (Sapporo, Japan). The rats were fasted for 24 hours 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 gram samples of gels of 1.5% polymer containing 5 mg or 10 mg paracetamol were orally administrated using a stomach sonde needle for rats (KN-349D, Natsume Seisakusho Co., Ltd., Tokyo, Japan).

A stomach sonde needle was also used for oral administration of the commercial paracetamol gel formulation (5 mg in 1 g). At given intervals, a blood sample was taken from the jugular vein and analyzed as described below. 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 ± SEM.

Determination of paracetamol concentration in rat plasma

The plasma samples were separated by centrifugation and assayed by HPLC. The HPLC system consisted of a pump (LC-10AS, Shimadzu, Kyoto, Japan), 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.[26], with minor modifications. 200 μL of water, 100 μL of 2-acetamidophenol (100 μg/mL in 20% methanol) as internal standard, and 7 mL of ethyl acetate were added to 100 μL of plasma. The sample was shaken and centrifuged. 5 mL of the ethyl acetate layer was 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 acetonitrile:0.1 M acetate buffer (pH 4.0; 15:85) at a rate of 0.8 mL/min at 40°C.

Visualization of gels in rat stomach

Gels (1 g) of 1.5% polymers containing 0.02% brilliant blue as a marker dye but no drugs were orally administered to fasted rats as described previously. The stomach was excised after 0.5, 1.0, or 3 hours and gels were removed and weighed after removing surface dirt.

Results and discussion

Rheological properties

Gel behavior under applied stress was determined using a simple method that measured the change in load of a probe pushed slowly through the gel. Figure 1 and Table 1 compare the rheological properties of gels formed by gelatin, agar, gellan, pectin, and xyloglucan. Gels of the commercial formulation were too soft to be measured by this method. Agar gels (1.5% and 1.0%) were hard and friable with gel strengths in excess of 40 kN/m^2, suggesting possible difficulty of swallowing by dysphagic patients. Similarly, the gel strengths of 2.0% gellan gels (31 kN/m^2) and 2.0% gelatin gels (14 kN/m^2) were considerably higher than those of xyloglucan and pectin at this concentration (4–5 kN/m^2), the rheological behavior of which is typical of that of soft, elastic gels. Consequently, a concentration of 1.5% was selected for further studies on gels of gelatin, gellan, xyloglucan, and pectin; agar gels were used at a concentration of 0.5%. At these concentrations the gel strengths of all formulations were within the recommended range of 3–9 kN/m^2 [27].

In vitro release

Figure 2 shows the percentage release of paracetamol at 37°C as a function of time at pH 1.2 and 6.8 from 1.5% gels of gelatin, gellan, xyloglucan, and pectin and from the 0.5% agar gel. The rapid dissolution of gelatin gels observed at both pH values was a consequence of their rapid melting at 37°C. Agar is digested in simulated gastric fluid at pH 1.2 resulting in the rapid release of drug as seen in Figure 2a. Although pectin gels retain their structure at pH 1.2, they revert to sol form at pH 6.8 and drug release is rapid at this pH (Figure 2b). A more sustained release at both pH values was observed from gels of xyloglucan and gellan and these gels retained their structure over the period of observation.

In vivo release

Plasma drug levels following oral administration of paracetamol (10 mg) from gels of gellan, pectin, xyloglucan, and gelatin (1.5%) and agar (0.5%) to rats are compared in Figure 3. The absorption of paracetamol from the gelatin and agar gels was rapid with peak plasma drug concentrations at 0.5 hour. Absorption from the pectin gels was initially higher than from the gellan and xyloglucan gels; the pH of the rat stomach has been reported to be in the range 3.2–3.9[28] and hence the more rapid release may be a consequence of solubility of the pectin which is approximately 50% ionized (pK_a 3.5) over this pH range. Evidence for pectin solubility in the stomach is seen from the disappearance of gel from the stomach over a 3-hour period as discussed below. A more sustained release of drug was observed from the other polysaccharide gels; release from 1.5% xyloglucan gels, for example, was maintained at levels of between 0.9 and 1.7 μg/mL for 6 hours after administration.

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[29] are summarized in Table 2. Gels of agar, gellan, pectin, and xyloglucan produced a greater sustained release compared to that of the gelatin as evidenced by the lower C_{max}, higher t_{max}, and longer mean retention times.

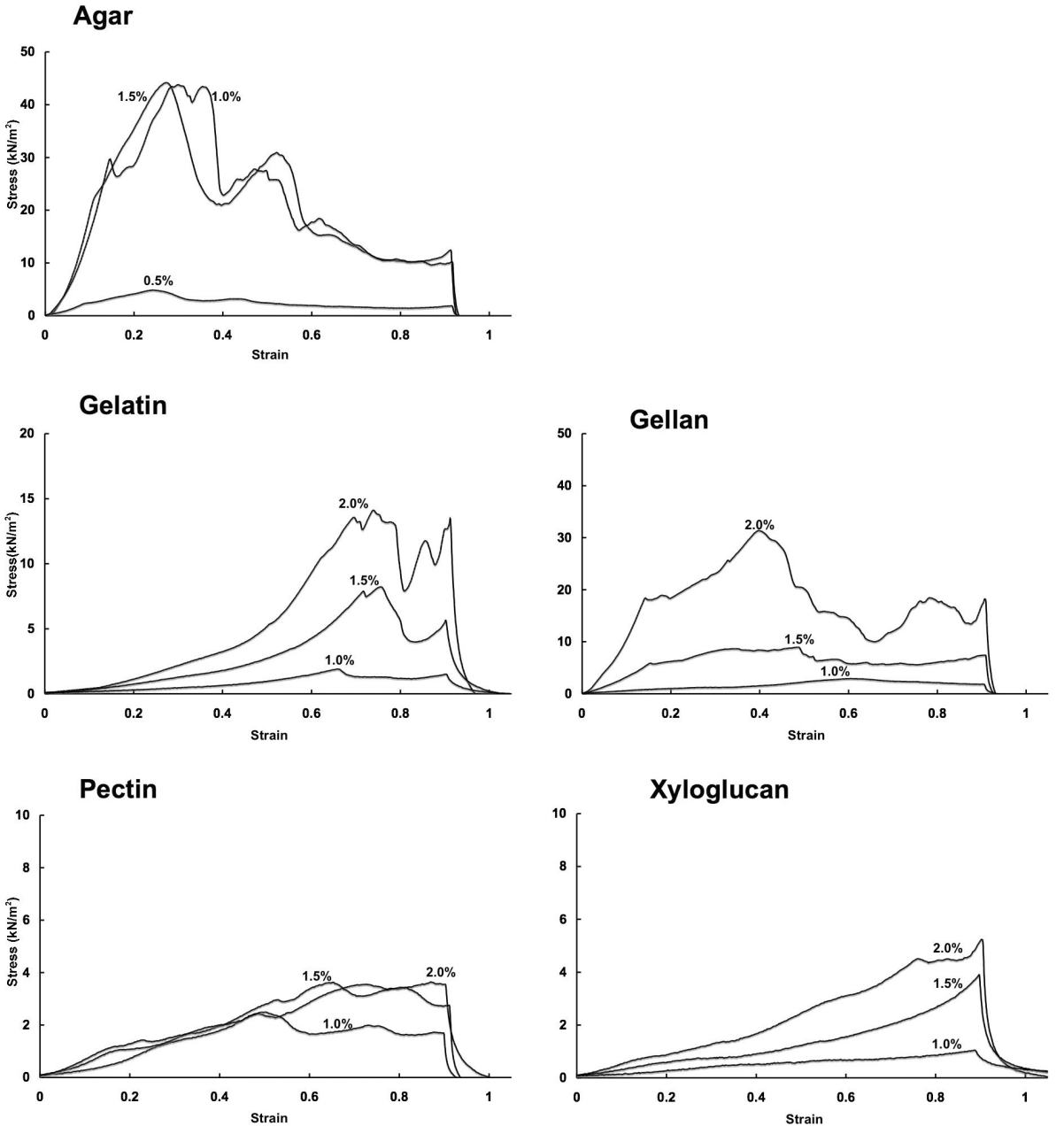

Figure 1. Rheological properties of gels with concentrations indicated at 20°C.

Table 1. Comparison of gel strengths (kN/m^2).

Conc (%)	Agar	Gelatin	Gellan	Pectin	Xyloglucan
0.5	4.88	—	—	—	—
1.0	43.82	1.90	2.93	2.50	1.05
1.5	44.19	7.91	8.96	3.64	3.90
2.0	—	13.57	31.40	3.65	5.25

Visual observation of the contents of the stomach following administration of 1 g of 1.5% xyloglucan gel containing a marker dye (but without drug) showed the gradual erosion of the gel to about 59% of the amount administered, over a period of 3 hours (Figure 4a). A similar rate of erosion of 1.5% gellan gels was observed after 3 hours (Figure 4b). The maintenance of the integrity of the gel in the stomach over this time period is probably the cause of the prolongation of the release of paracetamol from these gels. In contrast, only about 9% of a 1.5% pectin gel and 28% of 0.5% agar gel remained in the stomach at 3 hours after administration and complete disappearance of the 1.5% gelatin gel was observed, in agreement with the rapid release from this vehicle.

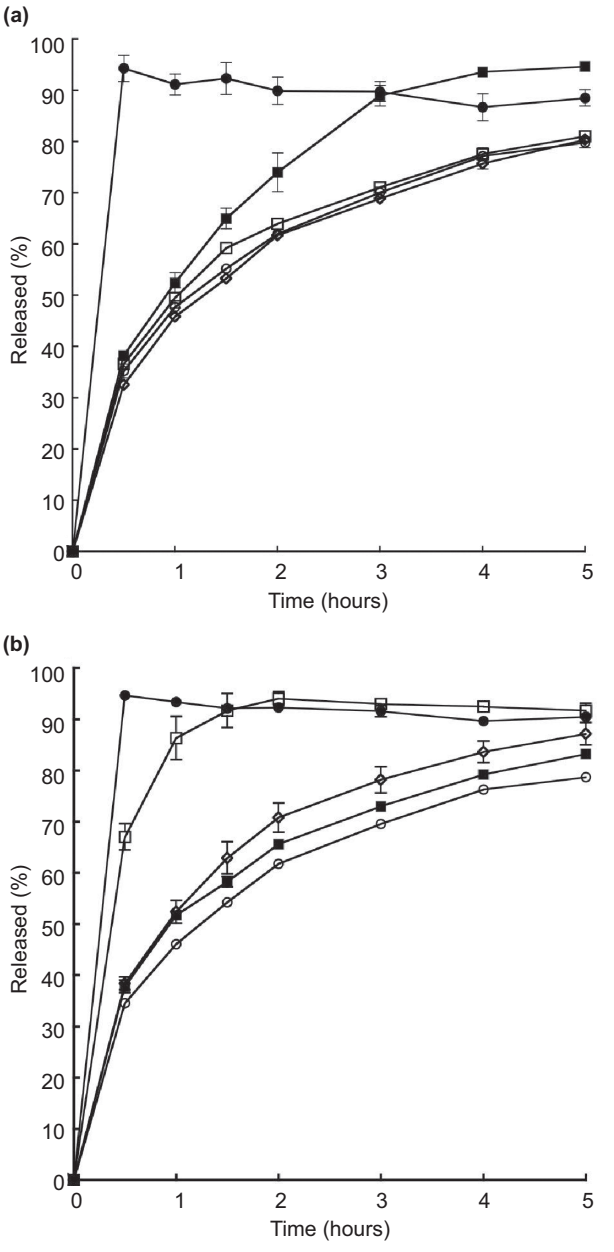

Figure 2. In vitro release at 37°C of paracetamol from polysaccharide gels as a function of time at (a) pH 1.2 and (b) pH 6.8. 0.5% agar (■), 1.5% gelatin (●), 1.5% gellan (○), 1.5% pectin (□), 1.5% xyloglucan (◇). All formulations contained 100 mg drug. Each value is the mean ± SE of three determinations.

Comparison of in vitro and in vivo release of paracetamol from 1.5% xyloglucan gels and a commercial formulation

Figure 5 compares the in vitro release of paracetamol as a function of time from 1.5% xyloglucan gels loaded with an initial drug concentration of 0.5% and from the commercial formulation, Kazepitan™ jelly, containing an identical paracetamol concentration. The release from

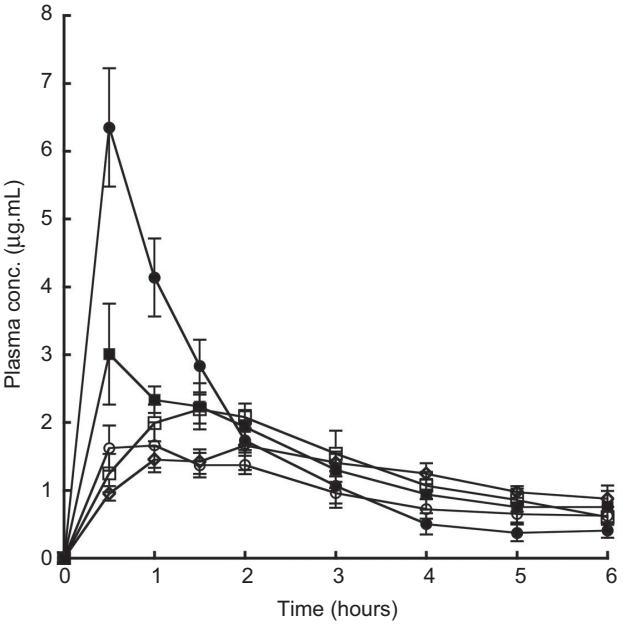

Figure 3. Plasma concentrations of paracetamol after oral administration of polysaccharide gels in rats. 0.5% agar (■), 1.5% gelatin (●), 1.5% gellan (○), 1.5% pectin (□), 1.5% xyloglucan (◇). All formulations contained 10 mg drug. Each value is the mean ± SE of 4–5 determinations.

the commercial formulation was rapid and complete after about 3 hours; a more sustained release from the xyloglucan gel was observed with approximately 75% release in 5 hours.

Plasma drug levels following oral administration to rats of paracetamol (5 mg) from 1.5% xyloglucan gel and from the commercial gel formulation (5 mg in 1 g) are compared in Figure 6. Rapid absorption from the commercial gel produced a peak plasma drug concentration at 0.5 hour. Plasma levels achieved from the 1.5% xyloglucan gel formulation were maintained at 0.6–1.1 μg/mL for 6 hours after administration. Table 3 shows a more prolonged retention of paracetamol when released from the xyloglucan gels compared to the commercial gel. The bioavailability of paracetamol when released from 1.5% xyloglucan gel was 1.35 times that from the commercial gel. Visual observation of the contents of the stomach showed that no gel remained at 3 hours after administration of the commercial gel.

Concluding remarks

The objective of this study was to assess the suitability of the gels of selected materials in the formulation of sustained release vehicles for the oral administration of paracetamol to dysphagic patients. As anticipated, gelatin gels rapidly dissolved at pH values approximating to

Table 2. Comparison of bioavailability parameters in rats of paracetamol (1%) administered orally from gel formulations.

Dosage form	C_{max} (μg/mL)	t_{max} (hours)	AUC (0–6 hours) (μg hour/mL)	MRT (hours)	AUC test/ AUC gelatin
0.5% agar	3.19 ± 0.67[a]	1.10 ± 0.29	8.61 ± 1.40	2.28 ± 0.18[a]	0.85 ± 0.14
1.5% gelatin	6.35 ± 0.87	0.50 ± 0.00	10.11 ± 7.40	1.65 ± 0.16	1
1.5% gellan	1.83 ± 0.31[b]	0.88 ± 0.24	6.01 ± 0.91[a]	2.53 ± 0.10[b]	0.59 ± 0.09
1.5% pectin	2.40 ± 0.19[b]	1.88 ± 0.43	8.05 ± 0.82	2.60 ± 0.12[b]	0.80 ± 0.08
1.5% xyloglucan	1.89 ± 0.31[b]	2.00 ± 0.71	7.22 ± 0.64[a]	2.94 ± 0.11[c]	0.71 ± 0.06

Each value represents the mean ± SE of 4–5 determinations. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ compared with 1.5% gelatin.

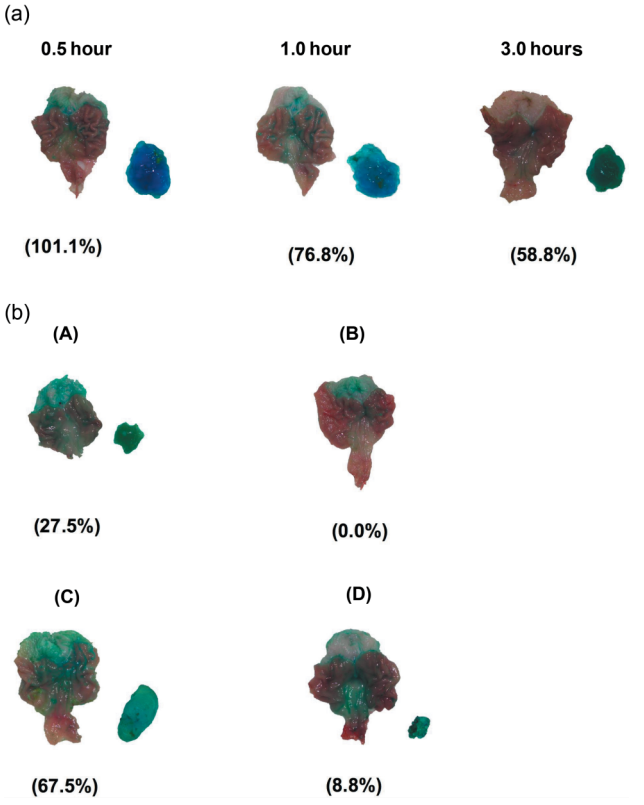

Figure 4. Photographs showing presence of gels in rat stomach (a) at 0.5, 1.0, and 3.0 hours after oral administration of 1.5% xylogulcan gels and (b) at 3.0 hours after oral administration of (A) 0.5% agar, (B) 1.5% gelatin, (C) 1.5% gellan, (D) 1.5% pectin gels. Numbers in parenthesis indicate percentage of gel remaining.

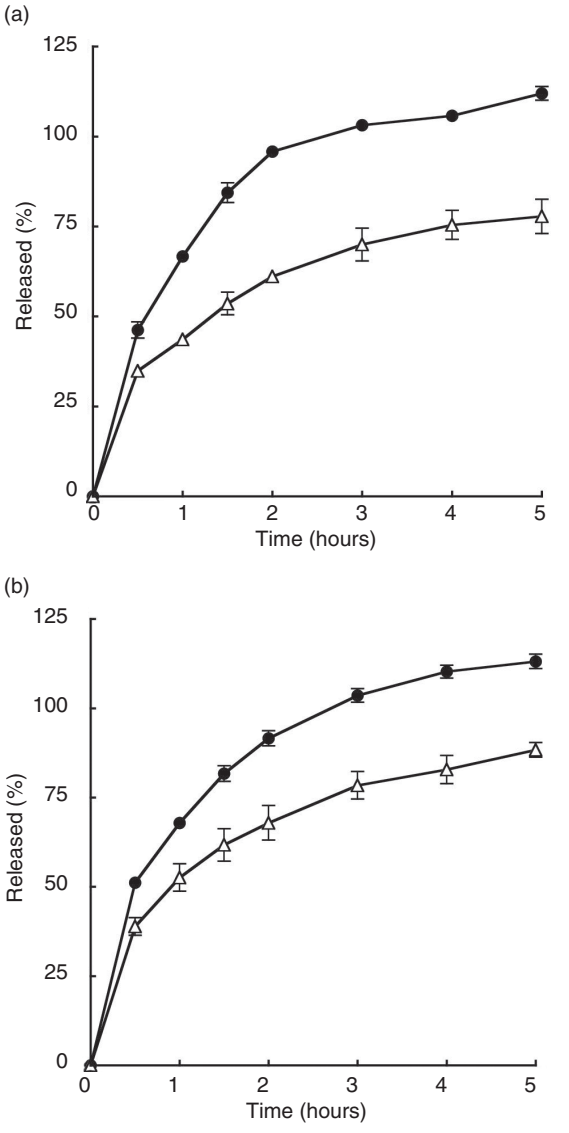

Figure 5. In vitro release at 37°C of paracetamol from commercial gel formulation and xyloglucan gels as a function of time at (a) pH 1.2 and (b) pH 6.8. Commercial gel formulation (●), 1.5% xyloglucan (△). All formulations contained 50 mg drug. Each value is the mean ± SE of three determinations.

those of both the human stomach and small intestine leading to a rapid in vitro release of drug. Visualization of the rat stomach contents revealed the absence of gel 3 hours after administration, in agreement with its poor in vivo sustained release characteristics. Consequently, gels of this material were used for comparative purposes only.

Gels formed using low concentrations of agar (0.5%) had satisfactory gel strengths for oral administration but showed a rapid in vitro dissolution rate at pH 1.2 and poor retention of integrity after 3 hours in the rat stomach leading to correspondingly poor sustained release of drug. Although 1.5% pectin gels exhibited a satisfactory in vitro release profile at pH 1.2, our results show solubility in the rat stomach. It is known that in healthy young Caucasians the gastric

Table 3. Comparison of bioavailability parameters in rats of paracetamol (0.5%) administered orally from xyloglucan gels and a commercial formulation.

Dosage form	C_{max} (μg/mL)	t_{max} (hours)	AUC (0–6 hours) (μg hour/mL)	MRT (hours)	AUC xyloglucan/ AUC commercial
Commercial gel[a]	1.59 ± 0.26	1.10 ± 0.24	3.74 ± 0.20	2.35 ± 0.14	1
1.5% xyloglucan[b]	1.21 ± 0.12	1.63 ± 0.13	5.06 ± 0.25[c]	2.87 ± 0.09[d]	1.35 ± 0.07

[a]Each value represents the mean ± SE of five determinations. [b]Each value represents the mean ± SE of four determinations. [c]$P < 0.01$, [d]$P < 0.05$, compared with commercial gel formulation.

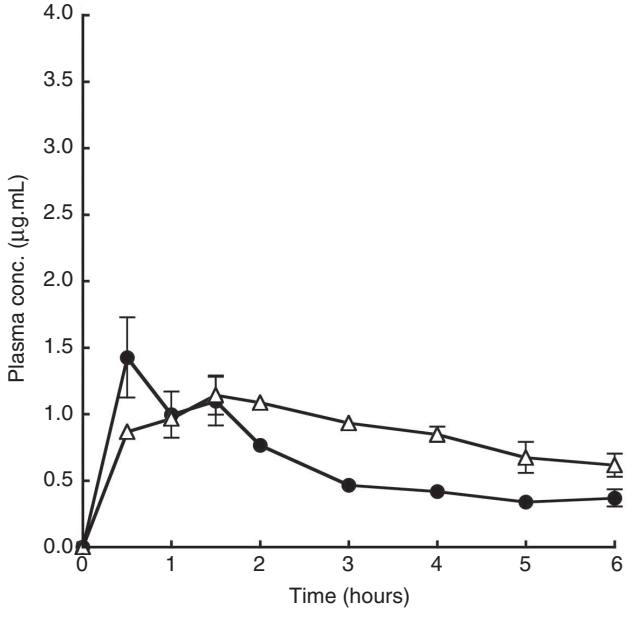

Figure 6. Plasma concentrations of paracetamol after oral administration of commercial gel formulation and xyloglucan gels in rats. Commercial gel formulation (●), 1.5% xyloglucan (△). All formulations contained 5 mg drug. Each value is the mean ± SE of 4–5 determinations.

pH is less than pH 3 during 90% of the fasted state, although on a minute-to-minute basis may reach as high as pH 7[30]. After ingestion of a meal the gastric acidity can vary over a wide range depending on the composition of the meal but is typically in the range pH 3–7. This wide variation of gastric pH in humans may restrict the applicability of the pectin gel because of its high solubility at the higher end of this pH range.

Optimization of the concentration of gellan and xyloglucan formulations produced gels that retained their integrity in the stomach and exhibited good in vitro and in vivo release characteristics with potential as sustained release vehicles. Comparison of 1.5% xyloglucan gels with Kazepitan™ jelly with identical paracetamol concentrations further demonstrated the sustained release properties of the xyloglucan gels compared to a commercially available gel formulation for the oral administration of paracetamol.

Acknowledgments

This work was supported in part by a Grant-in-Aid for High Technology Research Program from Ministry of Education, Culture, Sports, Sciences, and Technology of Japan.

Declaration of interest: The authors report no conflicts of interest.

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