Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 258 (2003) 55–64
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations

Wataru Kubo [a], Shozo Miyazaki [a], David Attwood [b,*]

[a] *Faculty of Pharmaceutical Sciences, Health Science University of Hokkaido, Ishikari-Tohbetsu, Hokkaido 061-0293, Japan*
[b] *School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK*

Received 9 October 2002; received in revised form 17 February 2003; accepted 24 February 2003

Abstract

The purpose of this study was to evaluate the potential for the oral sustained delivery of paracetamol of two formulations with in situ gelling properties. Oral administration of aqueous solutions of either gellan gum (1.0%, w/v) or sodium alginate (1.5%, w/v) containing calcium ions in complexed form resulted in the formation of gel depots in rabbit and rat stomachs as a consequence of the release of the calcium ions in the acidic environment. In vitro studies demonstrated diffusion-controlled release of paracetamol from the gels over a period of 6 h. The bioavailability of paracetamol from the gels formed in situ in the stomachs of rabbits following oral administration of the liquid formulations was similar to that of a commercially available suspension containing an identical dose of paracetamol.

Keywords: In situ gelation; Paracetamol; Oral drug delivery; Sustained release; Gellan gels; Alginate gels

1. Introduction

Paracetamol (acetaminophen) is usually administered orally in tablet and liquid form, following which its absorption is rapid, predominantly from the small intestine. A gel formulation for the oral delivery of paracetamol containing κ-carrageenan and gelatin as gelling agents has recently been reported by Endo et al. (2000), which achieved a high (90%) bioavailability in rabbits. In the present paper, we assess the potential of two formulations comprising solutions of gellan gum or sodium alginate as vehicles for the sustained delivery of paracetamol, both of which are designed to be administered in liquid form and to form gels in situ in the acidic environment of the stomach.

Gellan gum (commercially available as Gelrite™ or Kelcogel™) is an anionic deacetylated exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucose. Aqueous solutions of gellan gum form gels on warming to body temperature and in the presence of cations (Crescenzi et al., 1990), the mechanism of gelation involving the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water (Grasdalen and Smidsroed, 1987; Chanrasekaran et al., 1988; Chanrasekaran and Thailambal, 1990). Gellan gels have previously been examined for application in ophthalmic drug delivery

* Corresponding author. Tel.: +44-161-2752328; fax: +44-161-2752396.
E-mail address: david.attwood@man.ac.uk (D. Attwood).

0378-5173/03/$ – see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0378-5173(03)00163-7

(Rozier et al., 1989, 1997; Sanzgiri et al., 1993); gelation occurring when the aqueous solutions of the polysaccharide encounter the ions of the tear fluid at body temperature. The gellan formulation examined in the present study is similar to that which we have previously examined for the oral sustained delivery of theophylline (Miyazaki et al., 1999) and cimetidine (Miyazaki et al., 2001). To ensure reproducible gelation we include a source of Ca^{++} ions in the solution, but delay the gelation until the administered solution is in the acidic environment of the stomach by complexing the free calcium ions with sodium citrate. Gelation is then instantaneous as the complex breaks down and the Ca^{++} ions are released. The optimum quantities of calcium chloride and sodium citrate that maintained fluidity of the formulation before administration and resulted in gelation when the formulation was added to simulated gastric fluid (pH 1.2) were determined previously (Miyazaki et al., 1999).

The other in situ gelling compound examined, sodium alginate, is widely used in pharmaceutical formulation. Gelation of dilute solutions of sodium alginate occurs on addition of di- and trivalent metal ions by a co-operative process involving consecutive guluronic residues in the α-L-guluronic acid (G) blocks of the alginate chain (Morris et al., 1973, 1978; Grant et al., 1973; Liang et al., 1980). When formulated for use in sustained drug delivery, the alginate is usually in the form of a matrix (Johnson and Medlin, 1985; Nakano and Ogata, 1984; Nicholson et al., 1990; Segi et al., 1989; Stockwell et al., 1986; Yotsuyanagi et al., 1987), and there have been only a few studies on the use of alginates in liquid sustained release preparations for oral administration (Zatz and Woodford, 1987; Katayama et al., 1999). The formulation described by Zatz and Woodford gelled when in contact with simulated gastric fluid; gelation of that reported by Katayama et al. was achieved by the separate oral administration of a solution of a calcium salt immediately following that of the sodium alginate solution. The strategy for ensuring gelation of the alginate formulation of the present study is similar to that described above for the gellan solutions, involving a supply of complexed calcium ions that are released in the acidic environment of the stomach. We have recently reported the use of such a formulation for the oral delivery of cimetidine (Miyazaki et al., 2001) and have determined optimum amounts of calcium chloride and sodium citrate for effective gelation.

2. Materials and methods

2.1. Materials

Deacetylated gellan gum, Kelcogel™ (Lot 7501), was supplied by Dainippon Pharmaceutical Co., Osaka. Sodium alginate (Duck Algin™, Lot 34691, 350 ± 50 cP for a 1% solution, M/G ratio 0.8–1.0) was supplied by Kibun Food Chemifa Co., Tokyo. Paracetamol (acetaminophen) was obtained from Yamanouchi Pharmaceutical Co., Tokyo. A commercially available product, Children's 3 Months Plus Pain Relief Suspension, was purchased from The Boots Co., UK. All other reagents were of analytical grade.

2.2. Preparation of sols and suspension

Gellan gum solutions of concentrations 0.25, 0.5 and 1.0% (w/v) were prepared by adding the gum to ultrapure water containing 0.17% (w/v) sodium citrate and heating to 90 °C while stirring. After cooling to below 40 °C appropriate amounts of calcium chloride (0.016%, w/v) and paracetamol (1%, w/v) were then dissolved in the resulting solution. Sodium alginate solutions of concentrations 1.0, 1.5 and 2.0% (w/v) were prepared by adding the alginate to ultrapure water containing 0.25% (w/v) sodium citrate and 0.075% (w/v) calcium chloride and heating to 60 °C while stirring. Paracetamol was then dissolved in the resulting solution after cooling to below 40 °C. A 1% (w/v) control suspension (for use in the in vitro release experiments) was prepared by dispersing paracetamol in a 0.6% (w/v) aqueous solution of sodium alginate. A 1% (w/v) solution of paracetamol was prepared in ultrapure water.

2.3. Measurement of rheological properties of sols and gels

A comparison of the gel strengths of gellan and alginate gels was carried out at 20 °C using a rheometer (CR-200D, Sun Scientific Co., Tokyo) by the method described previously (Miyazaki et al., 1998;

Watanabe et al., 1994). Cylindrical gels of either 1.0% (w/v) gellan or 1.5% (w/v) alginate were prepared by placing a 20 ml sample of the solution into a cellulose tube (Viskase Sales Co., size 36/32), immersing the tube in 100 ml of pH 1.2 simulated gastric fluid (as specified for the JP XIV disintegration test) and allowing to equilibrate for 24 h. The cylindrical gels (15 mm diameter and 15 mm height) were placed in the rheometer and raised at a rate of 60 mm min^{-1} so pushing a probe slowly through the gel. The changes in the load on the probe were measured as a function of the depth of immersion of the probe below the gel surface.

The viscosity of sols (drug-free) prepared in water was determined at 20 °C with a cone and plate viscometer with cone angle 1°34′ (TV-20H, model E, Tokimec Co., Tokyo) using a 1 ml aliquot of the sample. Measurements on each sample were performed in triplicate each taking approximately 30 s. Comparison was made with the viscosity of the commercial suspension of paracetamol under the same conditions.

2.4. Measurement of drug release rate from gels

The release rates of paracetamol were measured by using plastic dialysis cells similar to that described previously (Miyazaki et al., 1984). The capacity of each half-cell was 4 ml and the surface area of the membranes was 2.67 cm^2. Gels of gellan or sodium alginate loaded with 1% (w/v) of drug, were placed in the donor compartment. An equal volume of simulated gastric (pH 1.2) or intestinal (pH 6.8) fluid (as specified for the JP XIV disintegration test) was placed in the receptor compartment. The donor phase and the aqueous receptor phase were separated by a cellulose membrane (Viskase Sales Co., Chicago, USA, size 36/32). The assembled cell was shaken horizontally at the rate of 60 strokes min^{-1} in an incubator. The total volume of the receptor solution was removed at intervals and replaced by fresh release medium. The drug concentration of the samples was determined using a spectrophotometer at a wavelength of 244 nm.

2.5. Animal experiments

2.5.1. Rabbits

White male rabbits weighing 3.1–3.6 kg were fasted for 24 h prior to the experiments but allowed free access to water. The possibility of coprophagy was minimized by the fasting process, which ensured that very little food was present in the stomach (from visual observation), and also through the use of a yoke. The sol preparation (5 ml) containing 50 mg paracetamol was orally administered using a stomach sonde needle for rabbits (Natume Seisakusho, KN-342). A stomach sonde needle was also used for oral administration of the commercial paracetamol suspension (50 mg in 2.1 ml) and aqueous solution (50 mg in 5 ml). For intravenous administration, 50 mg doses of the drug in 5 ml saline solution were injected through the ear vein. At given intervals, a blood sample was taken from the ear vein and analysed as described below.

2.5.2. Rats

Male Wistar rats, weighing 250–340 g, were fasted for 24 h with free access to water. The rats were anaesthetised with an i.p. injection of urethane and divided into two groups of four rats. One group received paracetamol gel preparation given orally as 1 ml sol preparation containing the drug (10 or 15 mg) through a stomach sonde needle for rats (Natume Seisakusho, KN-348). A second group was dosed in a similar manner with a paracetamol aqueous solution (10 or 15 mg in 1 ml). At predetermined intervals, a blood sample was taken from the jugular vein of rats in each group.

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 mean.

2.6. Paracetamol assay

The plasma samples were separated by centrifugation and assayed by HPLC (Shimazu LC-10A with a Shimazu SPD-10A detector at a wavelength of 254 nm). The assay of paracetamol was based on the methods described by Ameer et al. (1981) with minor modifications. To 100 μl of plasma was added 300 μl of water, 100 μl of 2-acetoaminophenol solution (100 μg ml^{-1} in 20% methanol) as internal standard and 7 ml of ethyl acetate. The sample was vortex mixed and centrifuged after which 5 ml of the organic layer was evaporated to dryness under a nitrogen stream. The residue was reconstituted

with 200 μl of 50% methanol, and aliquots of 20 μl were injected onto a 150 mm × 46 mm i.d. column, packed with Inertsil-ODS. Elution was carried out with acetonitrile-pH 4.0 sodium acetate buffer (2:8) at a rate of 1.0 ml min^{-1} at 40 °C.

3. Results and discussion

3.1. Rheological properties of sols and gels

Fig. 1 compares the rheological properties of gels of gellan gum and sodium alginate; values of gel strength calculated from these data are 190.8 and 79.9 kN m^{-2} for 1.0% (w/v) gellan and 1.5% (w/v) sodium alginate, respectively. The values determined by this method are relative rather than absolute values but nevertheless serve to show the significant difference in gel strengths of these two gels.

Fig. 2 compares the shear dependency of the viscosity of 1.0% (w/v) gellan and 1.5% (w/v) sodium alginate solutions with that of the commercial suspension. All formulations showed evidence of shear thinning behaviour, with higher viscosities being observed with the commercial suspension at all shear rates.

The rheological properties of the sols are of importance in view of their proposed oral administration. The results obtained here show that solutions of both polysaccharides are of lower viscosity than the commercial product and should not present difficulties in swallowing. Of the two compounds, gellan gum produces gels of higher strength, which may be an advantage for their proposed use as delivery vehicles.

3.2. In vitro drug release

The release profiles of paracetamol from gellan and sodium alginate gels of a range of concentrations loaded with 1.0% (w/v) drug are compared with that from an aqueous solution in Figs. 3(a) and 4(a), respectively. Because of osmotic effects in the apparatus used it was not possible to measure the release characteristics of the commercial suspension, and the control suspension of paracetamol (1%, w/v) in 0.6% (w/v) sodium alginate was substituted for the purposes of comparison. No discontinuities of the plots were observed when the receptor solution was changed from simulated gastric fluid (pH 1.2) to simulated intestinal fluid at pH 6.8 to mimic passage through the gastrointestinal tract. This was expected since there will be no change in the state of ionization of this acidic drug (pK_a of paracetamol is 9.5, Florey, 1974) accompanying the pH change. Although a pH of 1.2 was used as a representation of the gastric acidity, there is evidence that the pH of the rabbit stomach may not be as low as this, and consequently inferences from in vitro to in vivo data should be tempered with caution.

The release data from gels and suspension over the whole time period were analysed according to the treatment proposed by Higuchi (1962) for drug release from semisolid vehicles containing dissolved drug. For the initial 50–60% release the cumulative amount Q of drug released per unit surface area from

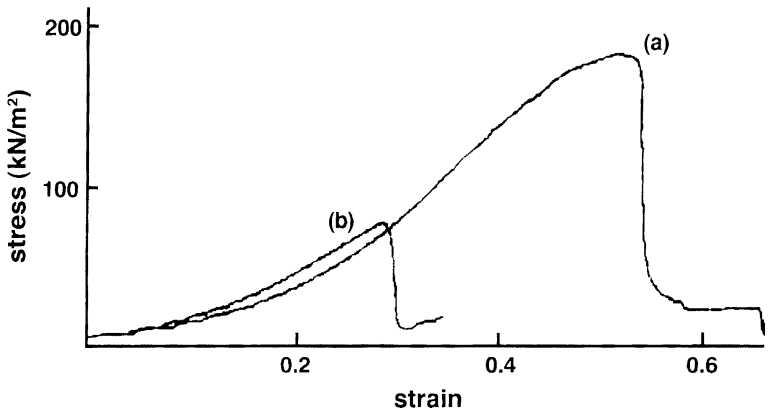

Fig. 1. Rheological properties of (a) 1.0% (w/v) gellan gels and (b) 1.5% (w/v) alginate gels in simulated gastric fluid at pH 1.2 and 20 °C.

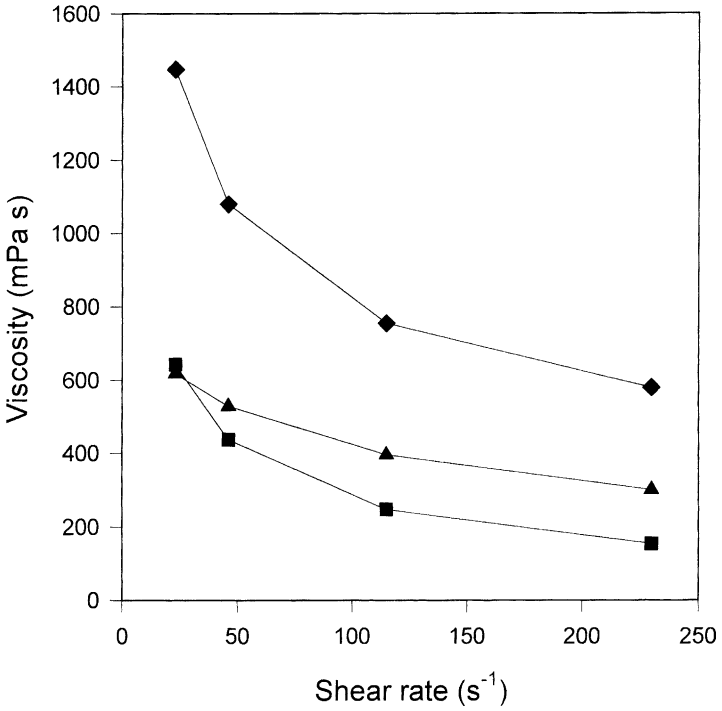

Fig. 2. Comparison of the shear rate dependency of the viscosities of (◆) commercial suspension of paracetamol, (■) 1.0% (w/v) gellan sol, and (▲) 1.5% (w/v) alginate sol at 20 °C.

gels of initial drug concentration C_0 is proportional to the square root of time t:

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

Figs. 3(b) and 4(b) show linear plots of Q versus $t^{1/2}$ for the release of paracetamol from the gels (C_0 = 1%, w/v) after a short lag period, indicative of diffusion-controlled release. Diffusion coefficients, D, calculated from the gradients of the plots of Fig. 3(b) were 1.22 ± 0.05, 1.03 ± 0.04 and 0.90 ± 0.01 × 10^{-5} cm^2 s^{-1} for 0.25, 0.5 and 1.0% (w/v) gels, respectively; those from the gradients of Fig. 4(b) were 1.13 ± 0.02, 1.01 ± 0.03 and 0.95 ± 0.05 × 10^{-5} cm^2 s^{-1} for 1.0, 1.5 and 2.0% (w/v) gels, respectively. Release from the suspension did not conform to Eq. (1) as expected. There is evidence from these values of a tendency for a decreasing release rate with increasing gel concentration presumably as a consequence of increased resistance to drug diffusion through the gel matrix. It is interesting to note that diffusion coefficients through gellan gels were of similar magnitude to those through alginate gels despite the lower concentration range involved reflecting differences in the gel structure of these gels.

3.3. In vivo release

3.3.1. Rabbit

The release of paracetamol from 1.0% (w/v) gellan and 1.5% (w/v) alginate gels formed in situ in the rabbit stomach following oral administration of 5 ml of sol containing 50 mg of paracetamol was monitored by the determination of plasma drug levels. Gelation of these formulations was confirmed by visual observation of the stomach contents, which showed the presence of distinct gel blocks of regular shape (as discussed below). Fig. 5 compares paracetamol levels from the gels with those following oral administration of the commercial suspension (50 mg in 2.1 ml) and an aqueous solution of paracetamol (50 mg in 5 ml). The in vivo release curves from the gels had a similar profile to that of the commercial suspension.

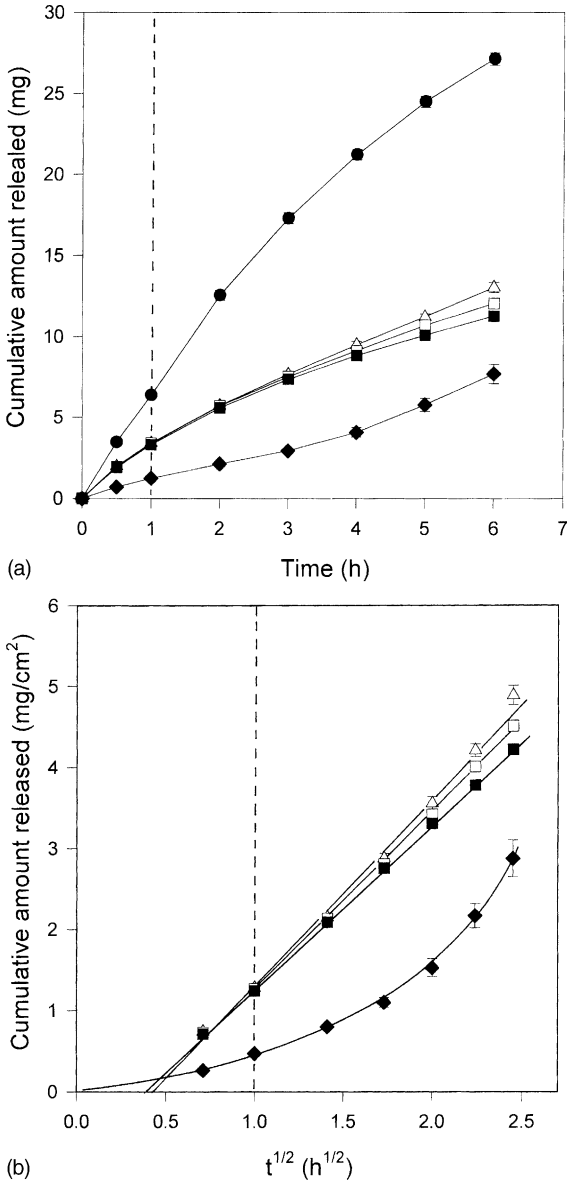

Fig. 3. In vitro release of paracetamol from gellan sols of concentrations (△) 0.25% (w/v), (□) 0.5% (w/v) and (■) 1.0% (w/v); (●) the paracetamol aqueous solution and (◆) the control suspension of paracetamol, plotted as (a) cumulative release as a function of time and (b) cumulative release per unit area as a function of square root time. All formulations contain 1% (w/v) paracetamol. Release was into simulated gastric fluid pH 1.2 for a period of 1 h and subsequently into simulated intestinal fluid pH 6.8. Each value is the mean ± S.E. of four determinations.

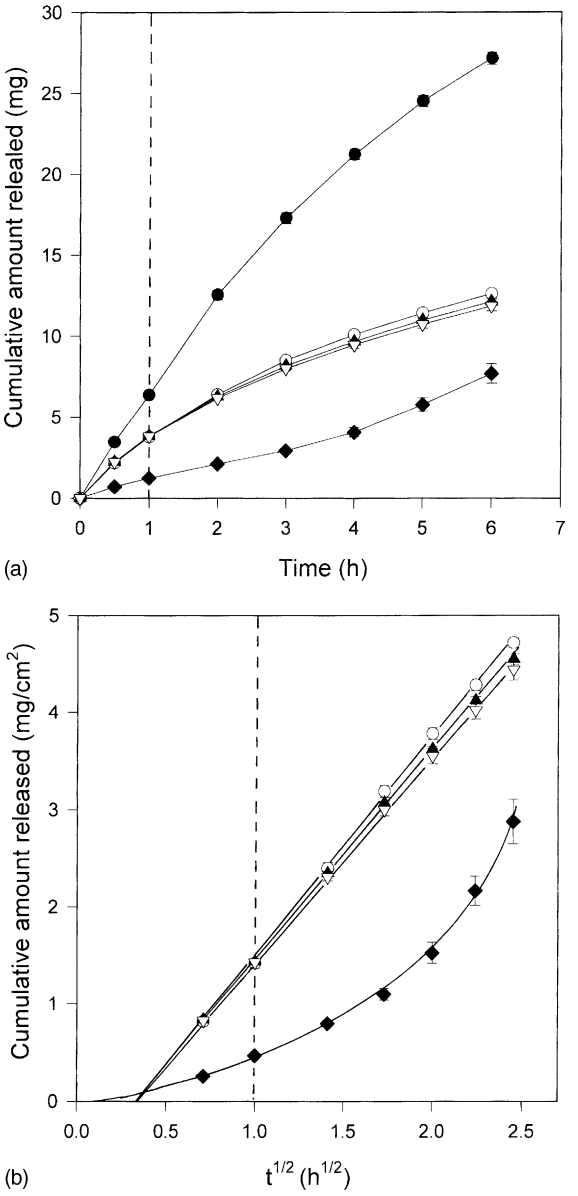

Fig. 4. In vitro release of paracetamol from alginate sols of concentrations (○) 1.0% (w/v), (▲) 1.5% (w/v) and (▽) 2.0% (w/v); (●) the paracetamol aqueous solution and (◆) the control suspension of paracetamol, plotted as (a) cumulative release as a function of time and (b) cumulative release per unit area as a function of square root time. All formulations contain 1% (w/v) paracetamol. Release was into simulated gastric fluid pH 1.2 for a period of 1 h and subsequently into simulated intestinal fluid pH 6.8. Each value is the mean ± S.E. of four determinations.

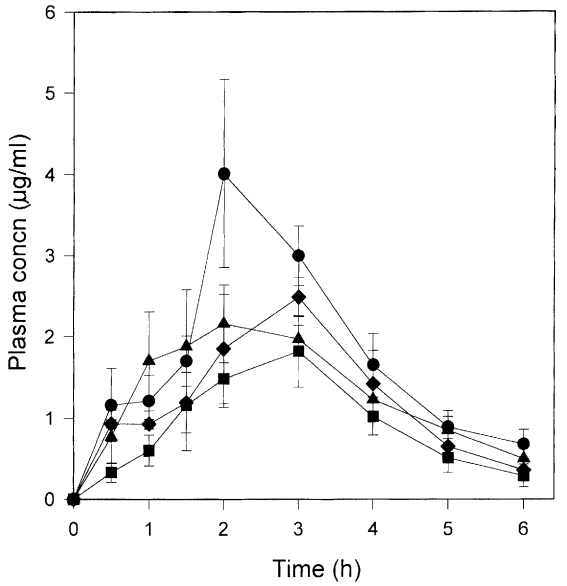

Fig. 5. Plasma concentrations of paracetamol in rabbits after oral administration of (■) 1.0% (w/v) gellan sols, (▲) 1.5% (w/v) alginate sols, (◆) the commercial suspension of paracetamol and (●) the paracetamol aqueous solution. All formulations contained 50 mg paracetamol. Each value represents mean ± S.E. of four determinations.

The areas under the plasma concentration–time curve (AUC) and the mean residence times (MRT) were obtained from the plasma concentration–time data for each animal using a computer program for model-independent analysis (Yamaoka et al., 1981) and are summarized in Table 1 together with values of the C_{max} and t_{max}. The $t_{1/2}$ value was 2.91 ± 1.24 h which compares with a value of 2.6 h following i.v. injection of paracetamol to human volunteers (Ameer et al., 1981). The values of MRT, C_{max} and t_{max} for release from the gel formulations and the commercial suspension were similar. Although the MRT and t_{max} values of all three oral formulations were similar, the C_{max} values for release from gels were significantly lower than from the paracetamol solution, which is of relevance when considering their potential use as delivery vehicles. Bioavailabilities have been expressed in Table 1 as both the ratio AUC [(gel,suspn/soln)] and as AUC [(oral/i.v.)]. The latter values may be compared with values for bioavailabilities of paracetamol reported for the same animal model when released from conventional tablets (70 ± 2%) and rapidly disintegrating tablets (59 ± 4%) (Ishikawa et al., 2001), and from gels prepared from κ-carrageenan and gelatin (89%) (Endo et al., 2000). Namiki et al. (1997)

Table 1
Comparison of bioavailability parameters of paracetamol administered from the commercial suspension, aqueous solution and i.v. injection of paracetamol, and from gellan (1.0%, w/v) and alginate (1.5%, w/v) gels formed in situ in rabbit and rat stomach

Dosage form	C_{max} (μg ml^{-1})	t_{max} (h)	AUC[a] (μg h ml^{-1})	MRT (h)	$AUC_{oral}/AUC_{i.v.}$	$AUC_{gel,suspn}/AUC_{soln}$
Rabbit						
Alginate gel	2.55 ± 0.44	2.38 ± 0.38	8.10 ± 1.10	2.81 ± 0.21	0.69 ± 0.09	0.74 ± 0.10
Gellan gel	2.48 ± 0.25	2.13 ± 0.31	5.65 ± 0.23[b]	2.89 ± 0.19	0.48 ± 0.02	0.52 ± 0.02
Aqueous solution	4.33 ± 0.96	2.25 ± 0.25	10.93 ± 1.74	2.80 ± 0.09	0.93 ± 0.15	1.0
Commercial suspension	2.93 ± 0.36	3.00 ± 0.41	7.65 ± 0.57	2.86 ± 0.15	0.65 ± 0.05	0.70 ± 0.05
i.v. injection	–	–	11.75 ± 1.20	1.32 ± 0.19	1.0	–
Rat						
Alginate gel (10)	7.19 ± 1.88	1.50 ± 0.61	16.23 ± 2.22	1.95 ± 0.26	–	0.77 ± 0.11
Alginate gel (15)	8.08 ± 0.92	1.88 ± 0.13[c]	22.79 ± 3.40	2.32 ± 0.06[c]	–	0.72 ± 0.11[d]
Gellan gel (10)	4.30 ± 0.99[e]	1.00 ± 0.35	10.87 ± 2.54	2.11 ± 0.14	–	0.52 ± 0.12
Gellan gel (15)	5.96 ± 0.94[b]	1.63 ± 0.55	18.18 ± 2.78	2.25 ± 0.09[b]	–	0.58 ± 0.09[d]
Aqueous solution (10)	11.89 ± 1.64	0.75 ± 0.14	21.05 ± 3.32	1.66 ± 0.14	–	1.0

Each value represents the mean ± S.E. of four experiments. A dose of 50 mg was administered to rabbits, and either 10 or 15 mg administered to rats as indicated in parenthesis.

[a] Rabbits: AUC (0–6 h); rats: AUC (0–5 h).

[b] $P < 0.05$ compared with paracetamol solution.

[c] $P < 0.005$ compared with paracetamol solution.

[d] Calculated from $(AUC_{gel}/15)/(AUC_{soln}/10)$.

[e] $P < 0.01$ compared with paracetamol solution.

reported relative bioavailabilities of 73% for paracetamol released from a gel confectionary from sugars and gelatin, compared with that from paracetamol powder administered orally using a dog model.

It is interesting to note the similarity of mean residence times of the gel and the commercial suspension. The sustained release effect of the gel formulation is a consequence of the resistance of the gel structure to the diffusion of drug, whereas that of the suspension arises from the reservoir effect of the suspension particles as they slowly dissolve in the intestine. Visual observation of the contents of the rabbit stomach following administration of a 1.0% (w/v) gellan sol (without drug) containing a marker dye (Fig. 6(a)) showed that approximately 82% of the soft gel remained at 5 h after administration. A similar study of the contents of the rabbit stomach after administration of a 1.5% (w/v) alginate sol (Fig. 6(b)) showed approximately 51% of gel remaining after the same time period. The maintenance of the integrity of the gel over this time period is probably the cause of the prolongation of the release of paracetamol from the gel. No evidence of suspension particles, also marked with dye, could be detected at this time period following administration of the commercial suspension.

3.3.2. Rat

A comparison of the release profiles of paracetamol from 1.0% (w/v) gellan and 1.5% (w/v) alginate gels formed in situ in the rat stomach following oral administration of 1 ml of sol containing 10 mg of paracetamol is shown in Fig. 7. Values of the pharmacokinetic values derived from these data are given in Table 1. It is interesting to note the similarity of the bioavailabilities expressed as the ratio AUC [(gel/soln)] obtained in the rat and rabbit models for the corresponding gels. Visual observation of the contents of the rat stomach following administration of a 1.0% (w/v) gellan gel and 1.5% (w/v) alginate gel containing a marker dye showed the presence of a gel block immediately after administration, approximately 87 and 41%, respectively, of which remained 5 h after administration.

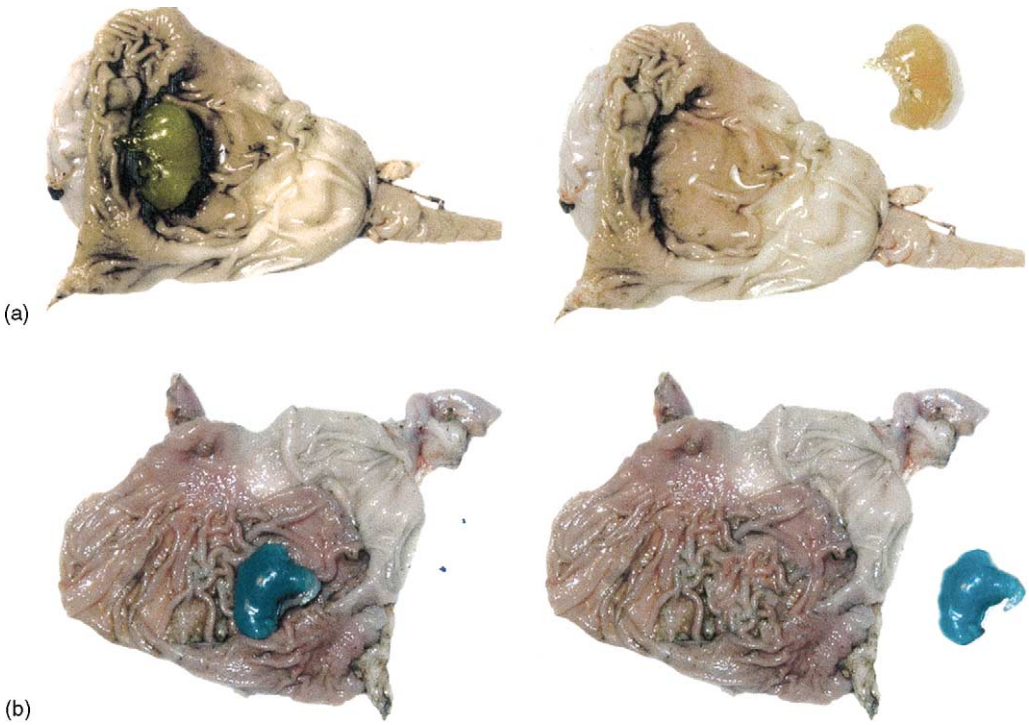

Fig. 6. Photographs showing presence of gels in rabbit stomach 5 h after oral administration of (a) a 1.0% (w/v) gellan sol and (b) a 1.5% (w/v) alginate sol.

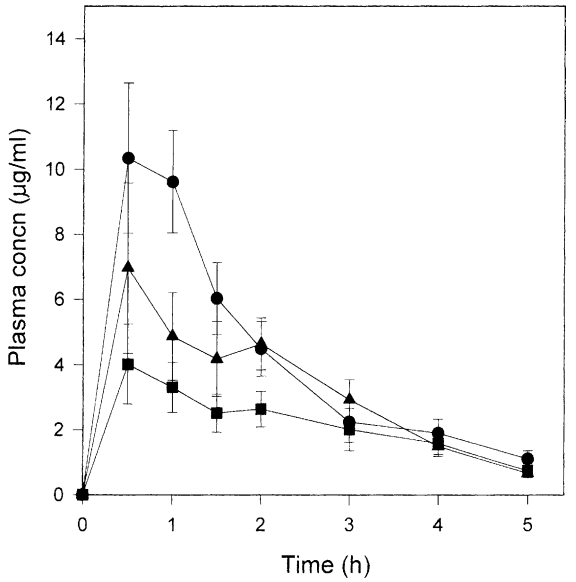

Fig. 7. Plasma concentrations of paracetamol in rats after oral administration of (■) 1.0% (w/v) gellan sols, (▲) 1.5% (w/v) alginate sols and (●) the paracetamol aqueous solution. Formulations contained 10 mg paracetamol. Each value represents mean ± S.E. of four determinations.

Table 1 shows that increasing the dosage of paracetamol from 10 to 15 mg had little effect on the bioavailability of paracetamol relative to that from the aqueous solution containing 10 mg, after correction of the data obtained for the higher paracetamol dose for the difference in dosage using the ratio $[(AUC_{gel}/15)/(AUC_{soln}/10)]$. It is interesting, however, to note a corresponding increase of the MRT by approximately 19% when release is from the alginate gels, compared to only 6–7% with the stronger gellan gels.

4. Concluding remarks

We have demonstrated that oral administration of aqueous solutions containing either gellan gum or sodium alginate and calcium in complexed form results in the formation of gels in rabbit and rat stomachs, which function as depots for the release of paracetamol over a period of 6 h. Similar bioavailabilities in rabbit to those of a commercial suspension for the oral administration of paracetamol can be achieved with these in situ gelling formulations, with the advantage that such formulations are homogeneous liquids when administered orally and do not have the problems that may be associated with the formulation and administration of suspensions. In addition, peak plasma levels of paracetamol following administration from the gelling formulations are similar to those from the suspension and are appreciably lower than those following oral administration of an aqueous solution of this drug.

Acknowledgements

The authors are grateful to Ms. K. Endo, Ms. N. Kawasaki and Dr. H. Watanabe, of the Health Science University of Hokkaido for assistance. We also wish to thank Dainippon Pharmaceutical Co. and Kibun Food Chemifa Co. for the generous supply of gellan gum and sodium alginate, respectively.

References

Ameer, B., Greenblatt, D.J., Divoll, M., Abernethy, D.R., Shargel, L., 1981. High-performance liquid chromatographic determination of acetominophen in plasma: single dose pharmacokinetic studies. J. Chromatogr. 226, 224–230.

Chanrasekaran, R., Thailambal, V.G., 1990. The influence of calcium ions, acetate and L-glycerate groups on the gellan double helix. Carbohydr. Polym. 12, 431–442.

Chanrasekaran, R., Puigjaner, L.C., Joyce, K.L., Arnott, S., 1988. Cation interaction in gellan: an X-ray study of the potassium salt. Carbohydr. Res. 181, 23–40.

Crescenzi, V., Dentini, M., Coviello, T., 1990. Solution and gelling properties of microbial polysaccharides of industrial interest: the case of gellan. In: Dawes, E.A. (Ed.), Novel Biodegradable Microbial Polymers. Kluwer Academic Publishers, The Netherlands, pp. 227–284.

Endo, H., Watanabe, Y., Matsumoto, M., Shirotake, S., 2000. Preparation and evaluation of heat-sensitive melting gel–acetaminophen gel. Jpn. J. Hosp. Pharm. 26, 250–258.

Florey, K. (Ed.), 1974. Analytical Profiles of Drug Substances, vol. 3. Academic Press, New York.

Grant, G.T., Morris, E.R., Rees, D.A., Smith, P.J., Thom, D., 1973. Biological interactions between polysaccharides and divalent cations: the egg-box model. FEBS Lett. 32, 195–198.

Grasdalen, H., Smidsroed, O., 1987. Gelation of gellan gum. Carbohydr. Polym. 7, 371–393.

Higuchi, W.I., 1962. The analysis of data on the medicament release from ointments. J. Pharm. Sci. 51, 802–804.

Ishikawa, T., Koizumi, N., Mukai, B., Utoguchi, N., Fujii, M., Matsumoto, M., Endo, H., Shirotake, S., Watanabe, Y., 2001.

Pharmacokinetics of acetominophen from rapidly disintegrating compressed tablet prepared using microcrystalline cellulose (PH-M-06) and spherical sugar granules. Chem. Pharm. Bull. 49, 230–232.

Johnson, M., Medlin, J., 1985. Attempts to control the release of the dyestuff proflavine hemisulphate from calcium alginate gels. I. Physical co-entrapment of polymers. Eur. Polym. J. 21, 147–150.

Katayama, H., Nishimura, T., Ochi, S., Tsuruta, Y., Yamazaki, Y., Shibata, K., Yoshitomi, H., 1999. Sustained release liquid preparation using sodium alginate for eradication of *Helicobacter pylori*. Biol. Pharm. Bull. 22, 55–60.

Liang, J.N., Stevens, E.S., Frangou, S.A., Morris, E.R., Rees, D.A., 1980. Cation-specific vacuum ultraviolet circular dichronism behavior of alginate solutions, gels and solid films. Int. J. Biol. Macromol. 2, 204–208.

Miyazaki, S., Takeuchi, S., Yokouchi, C., Takada, M., 1984. Pluronic F 127 gels as a vehicle for topical administration of anticancer agents. Chem. Pharm. Bull. 32, 4205–4208.

Miyazaki, S., Suisha, F., Kawasaki, N., Shirakawa, M., Yamatoya, K., Attwood, D., 1998. Thermally reversible xyloglucan gels as vehicles for rectal drug delivery. J. Control. Release 56, 75–83.

Miyazaki, S., Aoyama, H., Kawasaki, N., Kubo, W., Attwood, D., 1999. In situ gelling gellan formulations as vehicles for oral delivery. J. Control. Release 60, 287–295.

Miyazaki, S., Kawasaki, N., Kubo, W., Endo, K., Attwood, D., 2001. Comparison of in situ gelling formulations for the oral delivery of cimetidine. Int. J. Pharm. 220, 161–168.

Morris, E.R., Rees, D.A., Thom, D., 1973. Characterisation of polysaccharide structure and interaction by circular dichronism: order–disorder transition in the calcium alginate system. J. Chem. Soc. Chem. Commun. 9, 245–246.

Morris, E.R., Rees, D.A., Thom, D., Boyd, J., 1978. Chiroptical and stoichiometric evidence of a specific, primary dimerisation process in alginate gelation. Carbohydr. Res. 66, 145–154.

Nakano, M., Ogata, A., 1984. Examination of natural gums as matrices for sustained release of theophylline. Chem. Pharm. Bull. 32, 782–785.

Namiki, N., Takagi, N., Yuasa, H., Kanaya, Y., 1997. Studies on development of dosage form for pediatric use (no. 4). Time courses of plasma concentration of acetominophen after oral administration of gummi drug and powder preparation in dogs. Yakuzaigaku 57, 215–219.

Nicholson, S.J., Horder, R., Attwood, D., Collett, J.H., 1990. Investigation of drug release from sodium alginate–sodium calcium alginate matrices. J. Pharm. Pharmacol. 42, 2.

Rozier, A., Mazuel, C., Grove, J., Plazonnet, B., 1989. Gelrite^{TM}: a novel, ion-activated, in situ-gelling polymer for ophthalmic vehicles. Effect on bioavailability of timolol. Int. J. Pharm. 57, 163–168.

Rozier, A., Mazuel, C., Grove, J., Plazonnet, B., 1997. Functionality testing of gellan gum, a polymeric excipient material for ophthalmic dosage forms. Int. J. Pharm. 153, 191–198.

Sanzgiri, Y.D., Maschi, S., Crescenzi, V., Callegaro, L., Topp, E.M., Stella, V.J., 1993. Gellan-based systems for ophthalmic sustained delivery of methylprednisolone. J. Control. Release 26, 195–201.

Segi, N., Yotsuyanagi, T., Ikeda, K., 1989. Interaction of calcium-induced alginate gel beads with propranolol. Chem. Pharm. Bull. 37, 3092–3095.

Stockwell, A.F., Davis, S.S., Walker, S.E., 1986. In vitro evaluation of alginate gel systems as sustained release drug delivery systems. J. Control. Release 3, 167–176.

Watanabe, A., Hanawa, R., Sugihara, M., 1994. Application of glyserogelatin as oral dosage form for the elderly. Yakuzaigaku 54, 77–87.

Yamaoka, K., Tanigawa, Y., Nakagawa, T., Uno, T., 1981. Pharmacokinetic analysis program (MULTI) for micro-computer. J. Pharmacobio. Dyn. 4, 879–885.

Yotsuyanagi, T., Ohkubo, T., Ohhashi, T., Ikeda, K., 1987. Calcium-induced gelation of alginic acid and pH sensitive re-swelling of dried gels. Chem. Pharm. Bull. 35, 1555–1563.

Zatz, J.L., Woodford, D.W., 1987. Prolonged release of theophylline from aqueous suspensions. Drug. Dev. Ind. Pharm. 13, 2159–2178.