Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 271 (2004) 233–240
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Oral sustained delivery of ambroxol from in situ-gelling pectin formulations

Wataru Kubo [a], Shozo Miyazaki [a], Masatake Dairaku [b], Mitsuo Togashi [b], Ryozo Mikami [b], David Attwood [c,*]

[a] *Faculty of Pharmaceutical Sciences, Health Science University of Hokkaido, Ishikari-Tohbetsu, Hokkaido 061-0293, Japan*
[b] *Research Laboratory, Ohta Pharmaceutical Co. Ltd., Saitma-Shi, Saitama 331-0056, Japan*
[c] *School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, UK*

Received 22 September 2003; accepted 13 November 2003

Abstract

Gels formed in situ following oral administration of dilute aqueous solutions of pectin (1.0 and 1.5%, w/v) to rats were evaluated as vehicles for the sustained release of the expectorant drug ambroxol hydrochloride. The solutions contained calcium ions in complexed form, which on release in the acidic environment of the stomach caused gelation of the pectin. In vitro studies demonstrated diffusion-controlled release of ambroxol from the gels over a period of 6 h. A bioavailability of ambroxol of approximately 64% of that of a commercially available formulation could be achieved from gels containing an identical dose of ambroxol formed in situ in the stomachs of rats, with appreciably lower peak plasma levels and a sustained release of drug over a period of at least 6 h. The influence of added sorbitol (17%, w/v) on the rheological and drug release properties of the formulations has been examined.

Keywords: In situ gelation; Oral drug delivery; Sustained release; Pectin gels; Ambroxol

1. Introduction

Ambroxol is an active metabolite of the mucolytic agent bromhexine and is used in the treatment of bronchitis to improve expectoration. It is rapidly absorbed after oral administration followed by an elimination with a half-life of 3–4 h requiring three dosings per day for optimum therapeutic efficacy (Vergin et al., 1985). Several sustained release formulations have been developed to improve patient compliance that are based on tablet, pellet or capsule dosage forms allowing once daily administration. For example, Alighieri et al. (1988) reported sustained release capsules containing lipid matrices, the release from which was controlled by a dialyzing membrane.

In the present study, we examine the potential for the sustained delivery of ambroxol of a liquid formulation comprising a dilute aqueous solution of pectin that is designed to form gels in situ in the acidic environment of the stomach. Pectins are a family of polysaccharides in which the polymer backbone mainly comprises α-(1 → 4)-D-galacturonic acid residues. Low methoxy pectins (degree of esterification <50%) such as those used in the present study readily form gels in aqueous solution in the presence of free calcium ions, which cross-link the galacturonic acid chains in a

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

0378-5173/$ – see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2003.11.027

manner described by the 'egg-box' model (Dumitriu et al., 1996). The procedure by which gelation is achieved is similar to that described previously in the design of in situ-gelling formulations of the polysaccharides gellan (Miyazaki et al., 1999, 2001; Kubo et al., 2003) and sodium alginate (Miyazaki et al., 2000, 2001; Kubo et al., 2003), aqueous solutions of which also readily form gels in the presence of Ca^{2+} ions. Reproducible gelation of these polysaccharides is ensured by including a source of Ca^{2+} ions in the formulation, but gelation is delayed until the administered solution reaches the stomach by complexing the calcium with sodium citrate. Here the acidic environment causes breakdown of the complex, releasing free Ca^{2+} ions and causing instantaneous gelation.

2. Materials and methods

2.1. Materials

Pectin (LM-104AS, DE = 31%, Lot 03113-5) was supplied by SANSHO Co., Osaka, Japan. Ambroxol hydrochloride (Lot YT-13) was supplied by YIA Co., Shiga, Japan and a commercially available product, Broami® solution, by Ohta Pharmaceutical Co., Saitama, Japan. Propranolol hydrochloride and D-sorbitol were obtained from Wako Pure Chemical Ind. Ltd., Osaka, Japan. All other reagents were of analytical grade.

2.2. Preparation of sols

Pectin solutions of concentrations 1.0, 1.5 and 2.0% (w/v) were prepared by adding the pectin to ultrapure water containing 0.25% (w/v) (9.69 mmol l^{-1}) sodium citrate and 0.075% (w/v) (6.76 mmol l^{-1}) calcium chloride and heating to 40–50 °C while stirring. Appropriate amounts of ambroxol hydrochloride (0.3%, w/v) and D-sorbitol (17%, w/v) were then dissolved in the resulting solution.

2.3. Measurement of rheological properties of sols and gels

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. Although these formulations contain sodium citrate and calcium chloride, the hydrogen ion concentration is not sufficiently high to release calcium ions from the complex and gelation does not occur. Measurements on each sol were performed in triplicate each taking approximately 30 s.

A comparison of the gel strengths of pectin with and without 17% (w/v) D-sorbitol 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). A cylindrical gel of 1.5% (w/v) pectin was prepared by placing 20 ml of the sol into Visking tubing (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 equilibrating for 24 h. The cylindrical gels (15 mm diameter and 15 mm height), formed as a result of the release of complexed calcium ions in the acidic environment, 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.

2.4. Measurement of in vitro drug release

The release rates of ambroxol hydrochloride 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. Sols of pectin (1.0 and 1.5%, w/v) loaded with 0.3% (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. Comparison was made with the commercial solution of ambroxol hydrochloride and also with a 0.3% (w/v) solution of ambroxol hydrochloride under the same conditions. The concentration of ambroxol in the samples was determined by HPLC as described below.

2.5. Animal experiments

Male Wistar rats, weighing 250–350 g, were fasted for 24 h with free access to water. The sol preparation (1 ml) containing 3 or 9 mg ambroxol hydrochloride was orally administered using a stomach sonde needle for rats (Natume Seisakusho, KN-349D). A stomach sonde needle was also used for oral administration of the commercial ambroxol hydrochloride solution (3 mg in 1 ml). At given intervals, a blood sample was taken from the jugular vein and analysed as described below. 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.

2.6. Determination of ambroxol

The plasma samples were separated by centrifugation and assayed by HPLC (Shimazu LC-10A with a Shimazu SPD-10A detector at a wavelength of 210 nm) using the method described by Botterblom et al. (1987) with minor modifications. To 0.5 ml of plasma was added 100 μl of propranolol hydrochloride solution (0.2 μg ml^{-1}) as internal standard, 100 μl of 1 M sodium hydroxide and 5 ml of diethyl ether and the sample was vortex-mixed and centrifuged. To supernatant was added 150 μl of 0.01 M hydrochloric acid. After shaking and centrifugation, the diethyl ether layer was discarded and 50 μl of the acid layer were injected onto the analytical column (300 mm × 3.9 mm i.d.), packed with Waters μBondapak C_{18}. A column (20 mm × 3.9 mm i.d.) packed with Waters μBondapak C_{18} was used as guard column. Elution was carried out with acetonitrile–methanol–0.05 M phosphate buffer (0.65:1:3) at a rate of 0.8 ml min^{-1} at 40 °C.

3. Results and discussion

3.1. Gelling properties

Although gelation of pectin will occur in the presence of H^+ ions, the soft gels that are formed are not generally suitable as vehicles for drug delivery. In this study Ca^{2+} ions were included in the formulation for induction of pectin gelation. However, for ease of administration we required the formulation to be in the fluid (sol) state. This was achieved by addition of sufficient sodium citrate to the formulation to form a complex with all of the Ca^{2+} ions present in the formulation and hence to effectively remove them from solution. In the acidic environment of the stomach the complex is broken down and the Ca^{2+} ions released cause gelation to occur.

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, were determined by preliminary tests in which pectin sols (1%, w/v) containing sodium citrate concentrations in the range 0–0.50% (w/v) and calcium chloride concentrations of 0.025, 0.050 and 0.075% (w/v) were added dropwise to 50 ml simulated gastric fluid (pH 1.2, 37 °C). Of the sodium citrate concentrations examined, the minimum concentration required for gelation of sols with these three calcium chloride concentrations was 0.25% (w/v). Gelation occurred without exposure to acidic conditions in formulations containing either 0.050 or 0.075% (w/v) $CaCl_2$ and sodium citrate concentrations of 0.125% (w/v) or less; these formulations were not therefore of interest for the present study. The optimum formulation for maximum gel strength was 0.075% (w/v) calcium chloride and 0.25% (w/v) sodium citrate; increase of calcium chloride content to 0.10% (w/v) with the same sodium citrate concentration caused gelation of the formulation before contact with simulated gastric fluid.

Sorbitol (17%, w/v) was included in the in situ gelling formulation for improvement of the taste and stability of the formulations and for comparison with the commercial solution of ambroxol hydrochloride. Preliminary studies of the influence of this excipient on gelling properties in which sols containing 1.0, 1.5 or 2.0% (w/v) pectin, 0.25% (w/v) sodium citrate, 0.075% (w/v) $CaCl_2$ and 0.3% (w/v) drug were added dropwise to simulated gastric fluid (pH 1.2) showed that it was possible to form sols with these pectin concentrations in the presence of sorbitol that gelled in the gastric fluid. In the absence of sorbitol, formulations containing pectin contents of 1.5 and 2.0% (w/v) gelled at room temperature before contact with acid.

The influence of sorbitol (17%, w/v) on the rheological properties of pectin sols in water at 20 °C is shown in Fig. 1. Sols containing 1.0 and 0.75% (w/v) pectin and no sorbitol showed shear thinning characteristics;

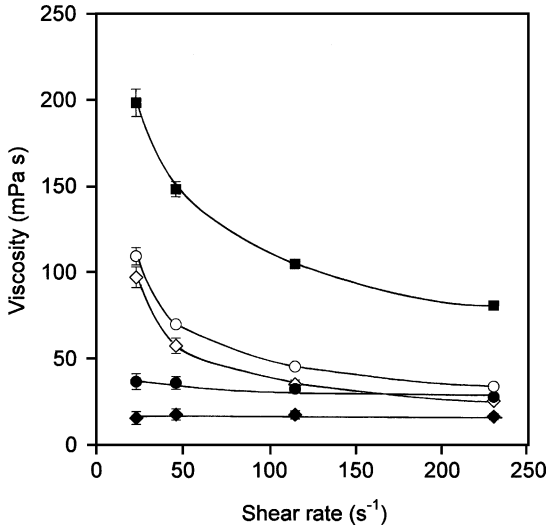

Fig. 1. Viscosity of pectin sols of concentrations (■) 1.5% (w/v), (○) 1.0% (w/v) and (◇) 0.75% (w/v) at 20 °C; closed symbols refer to pectin sols containing 17% (w/v) sorbitol, open symbols refer to sols with no added sorbitol. Each value is the mean ± S.E. of three determinations.

addition of sorbitol to these sols caused a reduction of viscosity and a change to flow properties approximating to Newtonian behaviour. These changes in viscosity resulting from sorbitol addition have implications for the administration of the sols of this formulation; the lower viscosity improving the ease of swallowing of the solutions. Shear thinning characteristics were observed for a 1.5% (w/v) pectin sol containing sorbitol; in the absence of sorbitol this formulation existed as a soft gel.

The addition of sorbitol to the formulations was also observed to affect their rheological properties in the gel state. The influence of 17% (w/v) sorbitol on the gel strengths of 1.5% (w/v) pectin gels containing 0.25% (w/v) sodium citrate and 0.075% (w/v) $CaCl_2$ in simulated gastric fluid at 37 °C was determined using a simple method that measured the change in load of a probe pushed slowly through the gel. Stress–strain plots (Fig. 2) were typical of those for elastic gels showing a sudden decrease of stress after the maximum, indicative of a brittle system. Although values of gel strength (taken as the stress at the point of collapse of the gel structure) were almost identical for both formulations, the inclusion of sorbitol produced gels that were able to withstand a higher strain before collapse, possibly because of hydrogen bonding of sorbitol molecules between the polysaccharide chains.

3.2. In vitro drug release

Fig. 3 shows the release of ambroxol as a function of time from 1.5 and 1.0% (w/v) pectin gels (containing

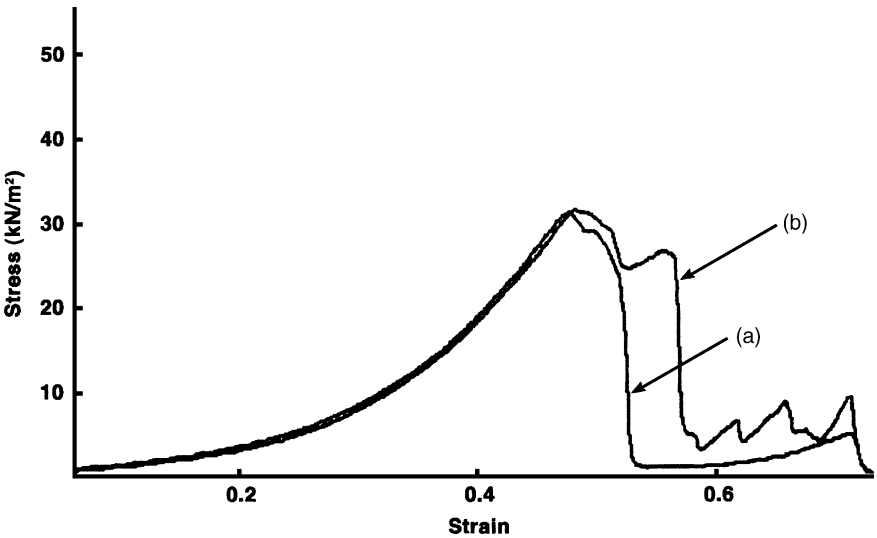

Fig. 2. Rheological properties of 1.5% (w/v) pectin gels (a) with no added sorbitol and (b) containing 17% (w/v) sorbitol, in simulated gastric fluid at pH 1.2 and 20 °C.

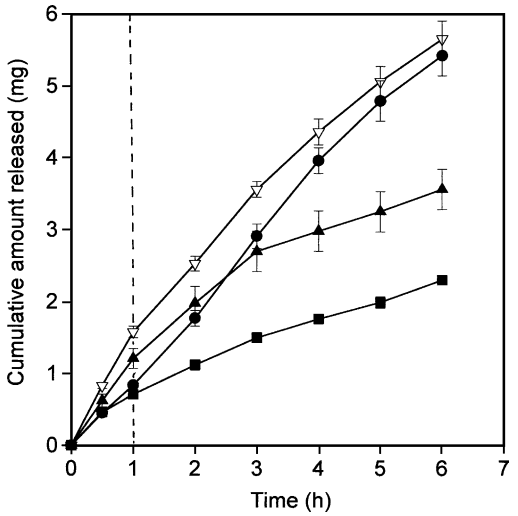

Fig. 3. In vitro release of ambroxol hydrochloride at 37 °C from (●) 1.0% (w/v), and (■) 1.5% (w/v) pectin sols containing 17% (w/v) sorbitol; (▲) the commercial formulation and (▽) the control solution, plotted as cumulative release as a function of time. All formulations initially contain 0.3% (w/v) ambroxol hydrochloride. 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.

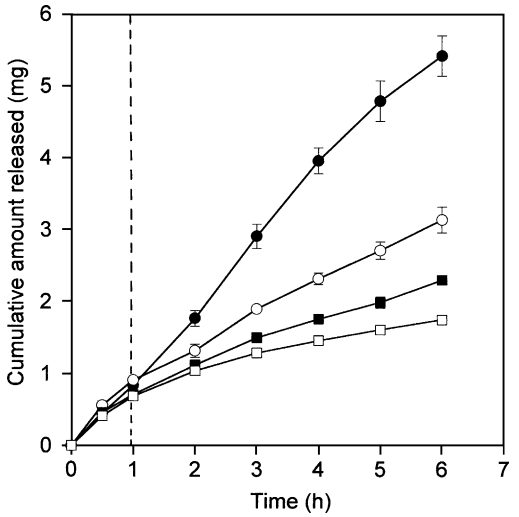

Fig. 4. In vitro release of ambroxol hydrochloride at 37 °C from (○) 1.0% (w/v), and (□) 1.5% (w/v) pectin sols; closed symbols refer to pectin sols containing 17% (w/v) sorbitol, open symbols refer to sols with no added sorbitol, plotted as cumulative release as a function of time. All formulations initially contain 0.3% (w/v) ambroxol hydrochloride. 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.

17%, w/v sorbitol) loaded with an initial drug concentration, C_0, of 0.3% (w/v) and from aqueous solutions of ambroxol hydrochloride and the commercial formulation (Broami®) both also containing 0.3% (w/v) of drug. The receptor solutions were changed after 1 h from simulated gastric fluid at pH 1.2 to a simulated intestinal fluid at pH 6.8 to mimic gastro-intestinal transit. Except in the case of the 1.0% (w/v) pectin gels, which showed a pronounced increase in the amount released after 1 h, there were no significant inflections in the release curves for the gels in the region of the pH change despite a reduction in ionisation of the basic group of ambroxol ($pK_b = 7.16$, Heinanen and Barbas, 2001) to approximately 50% at pH 6.8. Observation of the contents of the donor cells during release measurements showed that the inflection in the plots for release from 1.0% (w/v) pectin gels coincided with a reversion of these gels back to the sol phase as the pH in the receptor cell was changed from pH 1.2 to pH 6.8. After 3 h the cumulative amount released exceeded that from the commercial formulation eventually becoming identical to that from the ambroxol solution, as expected for release from sol phase. No such change occurred with the 1.5% (w/v) pectin formulation, which remained as a gel throughout the release experiment. Fig. 4 compares the influence of sorbitol on the release characteristics of the gels of these two concentrations. In formulations of 1% (w/v) pectin not containing sorbitol, the gel structure is retained at the higher pH and the release profile does not show the increase of release that is noted in formulations containing sorbitol. Fig. 1 shows that sorbitol decreases the viscosity of the sols formed by 1% (w/v) pectin and the release studies suggest that this formulation produced gels with insufficient strength to withstand a large decrease of hydrogen ion concentration. In contrast, the presence of sorbitol had relatively small effects on release from 1.5% (w/v) gels.

The release data from the 1.5% (w/v) pectin gels 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 is

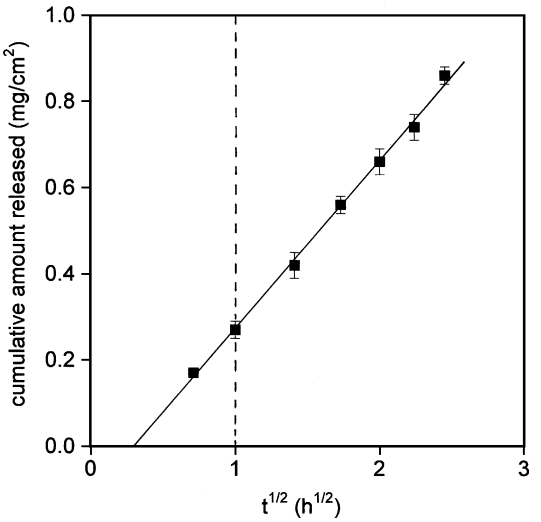

Fig. 5. In vitro release of ambroxol hydrochloride at 37 °C from 1.0% (w/v) pectin sols containing 17% (w/v) sorbitol, plotted as cumulative release as a function of square root time. The formulations initially contain 0.3% (w/v) ambroxol hydrochloride. Release was into simulated gastric fluid pH 1.2 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.

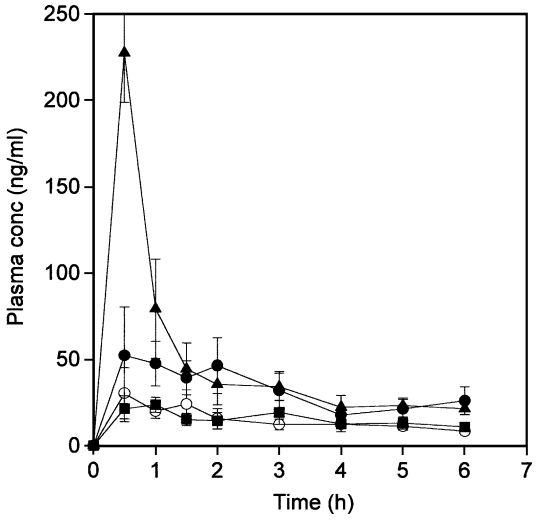

Fig. 6. Plasma concentrations of ambroxol in rats after oral administration of (○) 1.0% (w/v) pectin sols with no added sorbitol, (●) 1.0% (w/v) pectin sols containing 17% (w/v) sorbitol, (■) 1.5% (w/v) pectin sols containing 17% (w/v) sorbitol, and (▲) the commercial formulation. All formulations initially contain 0.3% (w/v) ambroxol hydrochloride. Each value is the mean ± S.E. of four to five determinations.

proportional to the square root of time t:

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

The plot of Q versus $t^{1/2}$ for the release of ambroxol from the pectin gels was linear after a short lag period (Fig. 5) indicating diffusion-controlled release. The diffusion coefficient, D, calculated from the gradient of the plot was $3.73 \pm 0.31 \times 10^{-6}$ cm^2 s^{-1} ($n = 4 \pm$S.E.).

3.3. In vivo release of ambroxol

Plasma drug levels following oral administration to rats of ambroxol (3 mg) from 1.0 and 1.5% (w/v) pectin sols (1 ml) containing 17% (w/v) sorbitol, from a 1.0% (w/v) pectin gel without sorbitol, and from the commercial solution of ambroxol (3 mg in 1 ml), are compared in Fig. 6. All pectin formulations contained the optimum levels of sodium citrate and calcium chloride and formed gels in the stomach at 37 °C. Rapid absorption from the commercial solution produced a peak plasma drug concentration of 230 ng ml^{-1} at 0.5 h. A sustained release of drug from the gels was evident from the concentration–time profiles of Fig. 6. For example, release of ambroxol from the 1.5% (w/v) pectin formulation containing 3 mg of drug produced plasma concentrations decreasing gradually from about 22–11 ng ml^{-1} over the 6 h period following administration. Plasma levels achieved from the 1.5% (w/v) pectin formulation containing 9 mg drug (not shown) were maintained at approximately 50 ng ml^{-1} for the first 3 h after administration, decreasing to approximately 15 ng ml^{-1} at 6 h.

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 personal computer program for model-independent analysis (Yamaoka et al., 1981) are summarised in Table 1. The mean residence times of ambroxol when released from the gels are significantly longer than that following the oral administration of this drug in solution. It is interesting to note that increase of dose from 3 to 9 mg had little effect on bioavailability or mean residence times of this drug. The bioavailability of ambroxol when released from 1.0% (w/v) pectin gels (64%) was very much higher than that from 1.5% (w/v) pectin gels

Table 1
Comparison of bioavailability parameters of ambroxol hydrochloride administered from the commercial solution and from pectin gels (1.0 and 1.5%, w/v) formed in situ in rat stomach

Dosage form	C_{max} ($\mu g\,ml^{-1}$)	t_{max} (h)	AUC (0–6 h) ($\mu g\,h\,ml^{-1}$)	MRT (h)	AUC_{gel}/AUC_{soln}
1.0% (w/v) pectin (3)	32.71 ± 13.98[a]	0.63 ± 0.13	89.35 ± 21.53[b]	2.70 ± 0.22[b]	0.31 ± 0.07
1.0% (w/v) pectin with sorbitol (3)	82.02 ± 23.27[c]	1.10 ± 0.29	188.57 ± 40.10	2.57 ± 0.15[c]	0.64 ± 0.14
1.5% (w/v) pectin with sorbitol (3)	29.34 ± 5.16[a]	0.75 ± 0.14	91.56 ± 22.92[b]	2.82 ± 0.04[a]	0.31 ± 0.08
1.5% (w/v) pectin with sorbitol (9)	71.61 ± 8.20[d]	1.38 ± 0.55	242.93 ± 31.08	2.62 ± 0.21[b]	0.28 ± 0.04[e]
Commercial solution (3)	222.36 ± 28.78	0.50 ± 0.00	292.41 ± 53.73	1.91 ± 0.06	1.00

Each value represents the mean ± S.E. of four to five experiments. A dose of 3 or 9 mg was administered to rats as indicated in parenthesis.
[a] $P < 0.001$ compared with commercial solution.
[b] $P < 0.05$ compared with commercial solution.
[c] $P < 0.01$ compared with commercial solution.
[d] $P < 0.005$ compared with commercial solution.
[e] Calculated from (AUC gel (9 mg))/(AUC commercial solution (3 mg)).

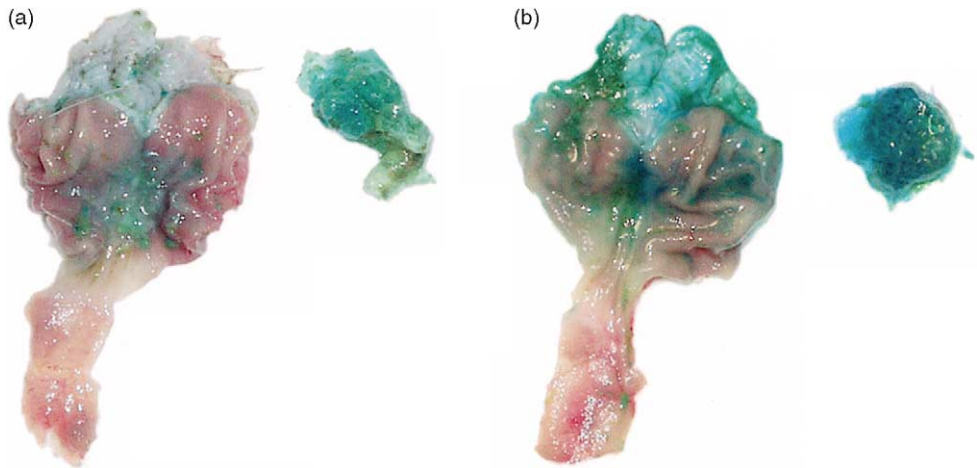

Fig. 7. Photographs showing presence of gels in rat stomach 5 h after oral administration of (a) 1.0% (w/v) pectin sol and (b) 1.5% (w/v) pectin sol. Both formulations contained 17% (w/v) sorbitol but no drug.

(31%); formulation of the 1.0% w/v pectin gels without the sorbitol, however, considerably reduced the bioavailability (31%).

Visual observation of the contents of the stomach following administration of 1 ml of 1.0% (w/v) pectin sol containing sorbitol and a marker dye (but without drug) showed that approximately 32% of the gel remained at 5 h after administration (Fig. 7a). A similar study in which 1.5% (w/v) pectin sols were administered showed approximately 27% of gel remaining after the same time period (Fig. 7b). 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 ambroxol from the gel. The in vitro measurements have shown gel-to-sol transition of the 1.0% (w/v) pectin gels containing sorbitol at pH 6.8 (Fig. 3); Fig. 7a shows that this gel-transition has not occurred at the low pH of the rat stomach.

4. Concluding remarks

This study has demonstrated the feasibility of forming pectin gels in the stomach of rats by the oral administration of dilute aqueous solutions containing pectin and a source of calcium in complexed form.

The gels formed when the calcium ions were released in the acidic environment of the stomach functioned as depots for the release of ambroxol. Peak plasma levels of ambroxol following administration from the gelling formulations were appreciably lower than those following oral administration of a commercial solution of this drug of the same concentration and drug release was sustained over a period of 6 h. A bioavailability in rat of approximately 64% of that from the commercial product was achieved from a 1% (w/v) pectin gel containing 17% (w/v) sorbitol.

Acknowledgements

The authors are grateful to Ms. N. Kawasaki and Mr. Y. Konno of the Health Science University of Hokkaido for assistance. We also wish to thank SANSHO Co. Ltd. and YIA Ltd. for the generous supply of pectin and ambroxol hydrochloride, respectively.

References

Alighieri, T., Avanessian, S., Berlini, S., Bianchi, S.G., Deluigi, P., Valducci, R., Guelen, P.J.M., 1988. Bioavailability of ambroxol sustained release preparations. Part 1: dissolution studies. Arzneim-Forsch./Drug Res. 38, 92–94.

Botterblom, M.H.A., Janssen, T.J., Guelen, P.J.M., 1987. Rapid and sensitive determination of ambroxol in human plasma and urine by high-performance liquid chromatography. J. Chromatogr. 421, 211–215.

Dumitriu, S., Vidal, P.F., Chornet, E., 1996. Hydrogels based on polysaccharides. In: Dumitriu, S. (Ed.) Polysaccharides in Medical Applications. Marcel Dekker, Inc., New York, pp. 125–242.

Heinanen, M., Barbas, C., 2001. Validation of an HPLC method for the quantification of ambroxol hydrochloride and benzoic acid in a syrup as pharmaceutical form stress test for stability evaluation. J. Pharm. Biomed. Anal. 24, 1005–1010.

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

Kubo, W., Miyazaki, S., Attwood, D., 2003. Oral sustained delivery of paracetamol from in situ-gelling gellan and sodium alginate formulations. Int. J. Pharm. 258, 55–64.

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.

Miyazaki, S., Kubo, W., Attwood, D., 2000. Oral sustained delivery of theophylline using in situ gelation of sodium alginate. J. Control. Release 67, 275–280.

Miyazaki, S., Nakamura, T., Yokouchi, C., Takada, M., 1984. Effect of Pluronic gels on the rectal absorption of indomethacin in rabbits. Chem. Pharm. Bull. 32, 1243–1248.

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.

Vergin, H., Bishop-Freundling, G.B., Micka, M., Nitsche, V., Strobel, K., Matzkies, F., 1985. Untersuchungen zur pharmakokinetik und bioaquivalenz unterschiedlicher darreichungsformen von ambroxol. Arzneim-Forsch./Drug Res. 35, 1591–1595.

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 microcomputer. J. Pharmacobiol. Dyn. 4, 879–885.