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Drug release from oral mucosal adhesive tablets of chitosan and sodium alginate

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Abstract

Oral mucosal bioadhesive tablets of diltiazem were prepared by directly compressing the drug with a mixture of chitosan and sodium alginate. In vitro adhesion studies indicated adhesion properties comparable to those of a commercial formulation. In vitro release of diltiazem was rapid and could be modified by changing the mixing ratio of chitosan and sodium alginate; increasing the chitosan content in the tablets and/or the viscosity grade of the alginate resulted in a decrease in the in vitro release rate. The bioavailability of diltiazem was 69.6% from tablets with a 1:4 chitosan/alginate weight ratio when administered sublingually to rabbits compared with 30.4% by oral administration.

Keywords: Bioadhesive tablet; Sublingual administration; Chitosan; Sodium alginate; Diltiazem

1. Introduction

Diltiazem is a calcium channel blocker which has been useful in the treatment of various cardiovascular disorders, particularly angina and systemic hypertension. It has been reported to be rapidly absorbed from the gastrointestinal tract, and to be extensively metabolized in the liver, mainly by deacetylation (Clozel et al., 1984; Chaffman and Brogden, 1985). The bioavailability of oral diltiazem is approx. 40% in humans (Chaffman and Brogden, 1985; Yeung et al., 1990) and the absolute bioavailability of diltiazem in rabbits was reported to be 30% (Yeung et al., 1990, 1991). Because of its low bioavailability and short half-life, attempts have been made to develop sustained release preparations with extended clinical effects and a reduced dosing frequency (Murata et al., 1989).

Recently, there has been much interest expressed in the use of oral cavity membranes as sites of drug administration (Harris and Robinson, 1992). Both the buccal and sublingual sites have advantages compared with other routes (Rathbone and Hadgraft, 1991), including rapid onset of action, high blood levels, avoidance of the first-pass effect and the exposure of the drug to the gastrointestinal tract. There is of course

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excellent accessibility and the drug can be applied, localized and removed easily.

A variety of drugs have been shown to be absorbed by the mucosal epithelium of the oral cavity, mainly by the buccal or sublingual mucosa (Harris and Robinson, 1992). The in situ absorption of diltiazem from solution through the oral mucosa of dog has been reported recently (Yamahara et al., 1990) and it was concluded that the drug absorption proceeded by passive diffusion according to the pH-partition theory. The results of this study indicated that diltiazem could be rapidly and readily absorbed across the oral mucosa and it is suggested, therefore, that intraoral administration of diltiazem may present an alternative route of administration which avoids oral first-pass metabolism so providing significantly greater bioavailability than oral administration. The present study was designed to evaluate intraoral (sublingual) diltiazem bioavailability in rabbits, and to compare the results to oral bioavailability.

Bioadhesion appears to be especially attractive for the development of controlled drug delivery systems to improve intraoral administration of drugs systemically or locally (Hunt et al., 1987). The adhesive mucosal dosage forms which have been suggested for oral delivery, include adhesive tablets and adhesive patches (Vries et al., 1991), the strong adhesive contact to the mucosa generally being achieved by the use of mucoadhesive polymers.

Several synthetic polymers including cellulose derivatives, plant gums and polyacrylic acid have been described as bioadhesive polymers. A typical preparation is an oral mucosa adhesive tablet developed for the treatment of aphtha, which is now commercially available in Japan under the brand name of Aftach (Teijin Ltd, 1980). Hydroxypropyl cellulose and carboxyvinyl polymer have been used as principal excipients of this tablet in order to obtain the appropriate adhesion properties to the oral mucous membrane and to control the drug release from the tablet. The use of natural polymers as drug carriers has received much attention in the pharmaceutical field from the viewpoint of safety. In particular, natural polysaccharides such as chitosan (Miyazaki et al., 1981) and sodium alginate (Nicholson et al., 1989) have been studied for broad applications and usages in the design of dosage forms for controlled release. However, most of these studies using chitosan and alginate have been limited to oral dosage forms. One of the properties of alginate is its ability to cause significant bioadhesion with the mucosal membrane (Hunt et al., 1987) and in a previous paper (Miyazaki et al., 1994) we prepared oral mucosal adhesive tablets by combining these polysaccharides, and examined the bioadhesive properties and release characteristics of a model drug (ketoprofen) by in vitro and in vivo methods. The results of this study suggested that such tablets are potential candidates for intraoral drug delivery. In the present work, we have prepared tablets containing diltiazem by directly compressing the drug with a mixture of chitosan and sodium alginate and have examined the influence of alginate content and viscosity grade on both the in vitro release characteristics and the bioavailability of diltiazem following sublingual administration to rabbits.

2. Materials and methods

2.1. Materials

Chitosan of 80% degree of deacetylation was supplied by Katakura Chikkarin Co., Tokyo, and used after grinding in a ceramic ball mill and subsequent passage through a 150 mesh screen. Sodium alginates of a range of viscosity grades (1000 ± 100, 350 ± 50 and 45 ± 5 cP for 1% solution), were used as received from Kibun Food Chemifa Co., Tokyo. Diltiazem hydrochloride and saline solution for injection (Herbesser®) were obtained from Wako Pure Chemical Ind. Ltd, Osaka and Tanabe Pharmaceutical Co. Ltd, Osaka, respectively. Other chemicals were of reagent grade.

2.2. Preparation of compressed tablets

Weighed amounts of chitosan, alginate and drug were mixed in their dry powder forms in a mortar. Flat-faced tablets with a diameter of 10

mm were prepared by compressing 100 mg of a mixture of chitosan and alginate in mixing ratios of 1:4, 1:1 and 4:1 by weight at a pressure of 300 kg cm^{-2} for 3 min using a hydraulic press. Each tablet (100 mg) contained 25 mg of the drug.

2.3. In vitro bioadhesion test

Bioadhesion of the tablets was examined by the method of Ishida et al. (1981) and Satoh et al. (1989) with slight modifications (Miyazaki et al., 1994). The peritoneal membrane was removed from male Wistar rats weighing 200–300 g and washed with saline solution. A piece of the fresh membrane was glued to a support with cyanoacrylate adhesive and the test tablet was glued with the same adhesive to a polypropylene cap (38 mm × 19 mm i.d.). The tablet was wetted with saline solution, placed in contact with the mucosal surface of rat peritoneal membrane and a constant force of 2 N was maintained for 1 min. The maximum force of adhesion was measured using a calibrated strain gauge (Tublar Scale, Kamoshita Co., Tokyo) by lowering the tablet mounting device at a constant rate of 90 mm min^{-1} until the tablet became detached from the tissue.

2.4. Determination of drug release

Drug release from the tablets was examined using a JP XII dissolution test apparatus. One surface of the tablets was moistened and the tablet was attached to the inside of the glass dissolution vessel at height of 7.5 cm. 1 l of distilled water at 37°C was placed in the vessel and stirred at 150 rpm. 5 ml samples were collected at pre-determined intervals for analysis and replaced with 5 ml of fresh water after each sample collection. The drug concentration of the sample was determined spectrophotometrically at 237 nm. All experiments were carried out in triplicate and average values were plotted.

2.5. Animal studies

Rabbits weighing 3.0–3.8 kg were fasted for 24 h before drug administration and anaesthetized with pentobarbital (25 mg kg^{-1}). A bioadhesive tablet containing 25 mg diltiazem hydrochloride was inserted sublingually and located with the tablet surfaces in contact with the ventral tongue and floor of the mouth. At given intervals, 1 ml blood samples were taken from the ear vein and analysed as described below. For intravenous administration, 25 mg doses of the drug in 12.5 ml saline solution were injected through the ear vein. For oral administration, 25 mg doses in 25 ml of aqueous solution were administered by a stomach tube.

2.6. Determination of diltiazem

The plasma samples were separated by centrifugation and assayed for diltiazem by HPLC (Shimazu LC-10A with a Shimazu SPD-10A detector at a wavelength of 237 nm) using the method described by Wiens et al. (1984) with minor modifications. To 0.5 ml of plasma was added 100 μl of verapamil solution (3 μg/ml) as internal standard. The drug was extracted with 4 ml of hexane-isoamyl alcohol (98:2). The drug organic phase was separated by centrifugation and mixed with 100 μl of 0.01 M HCl. After shaking and centrifugation, 10 μl of the aqueous phase was directly injected onto a 25 cm × 46 mm i.d. column, packed with Inertsil-ODS. Elution was carried out with acetonitrile-methanol-0.05 M dihydric ammonium phosphate (pH 3.75) containing 0.2% triethylamine (3:1:6) at a rate of 1.0 ml min^{-1} at 40°C.

Table 1
Maximum force of adhesion of chitosan/alginate tablets to rat peritoneal membrane

Chitosan/alginate ratio	Viscosity grade of alginate [a] (cP)	Maximum adhesion force [b] (g/cm^2)
1:4	350	97.4 ± 5.9
1:1	350	85.9 ± 1.2
4:1	350	80.2 ± 4.0
1:1	45	82.1 ± 1.9
1:1	1000	100.6 ± 7.9

[a] Supplier's specification. Viscosity of a 1% w/v solution at 20°C.
[b] Each value represents the mean ± S.E. of four determinations.

3. Results

3.1. Bioadhesive properties of the tablets

The bioadhesive properties of tablets consisting of chitosan and alginate with weight ratios of 1:4, 1:1 and 4:1 and containing 25 mg of diltiazem hydrochloride were measured using the rat peritoneal membrane. The maximum force of adhesion of these tablets to the membrane increased with increasing alginate content of the tablets (Table 1), demonstrating the strong adhesive properties of the alginate (Hunt et al., 1987). The magnitude of the adhesive force of the chitosan/alginate tablets was observed to be similar to that (85.1 ± 1.9 g cm^{-2}, as mean $\pm$ S.E. of four determinations) obtained with Aftach® which is a typical commercial oral mucosal adhesive tablet (Teijin Ltd., 1980), containing hydroxypropyl cellulose and carboxyvinyl polymer.

Measurements of the in vitro bioadhesion of tablets prepared using different viscosity grades of alginate (45, 350 and 1000 cP) with a chitosan and alginate weight ratio of 1:1 showed an increase of the adhesion force with increase in the viscosity of alginate (Table 1).

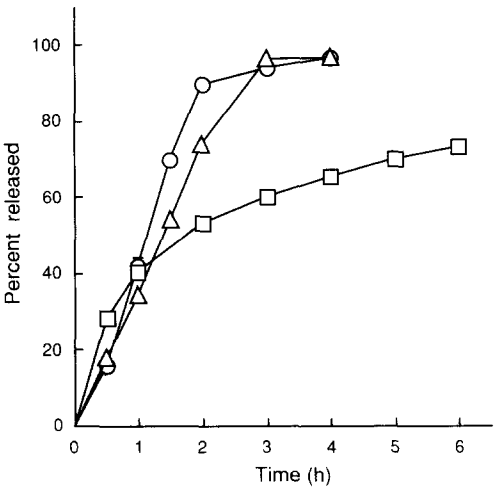

Fig. 1. Release profile of diltiazem at 37°C from the bioadhesive tablets prepared from 1:4 (○), 1:1 (△), and 4:1 (□) mixtures of chitosan and alginate (viscosity grade 350 cP). Each value represents the mean ± S.E. of three experiments (error bars are within symbols).

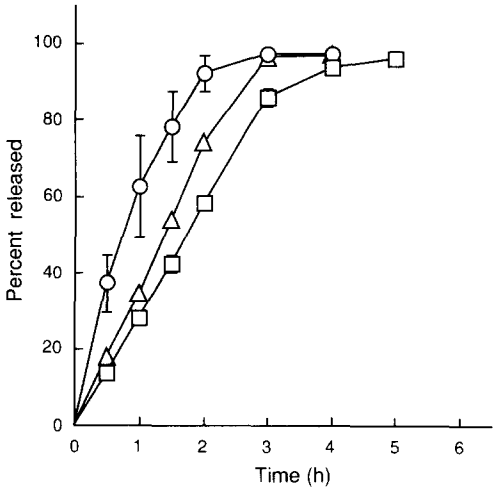

Fig. 2. Release profile of diltiazem at 37°C from chitosan/alginate (1:1 weight ratio) tablets prepared using alginate viscosity grade of (○) 45, (△) 350 and (□) 1000 cP. Each value represents the mean ± S.E. of three experiments.

3.2. In vitro release studies

The influence of the chitosan/alginate weight ratio on the release of diltiazem from the bioadhesive tablets is shown in Fig. 1. The release from tablets composed of 1:4 and 1:1 chitosan/alginate was rapid with almost 100% release within 3 h. In contrast, the release from the tablet composed of 4:1 chitosan/alginate was significantly slower with only 70% released within the 6 h period of measurement. The effect of the viscosity grade of the alginate on the drug release from tablets consisting of chitosan and alginate in a weight ratio of 1:1 is demonstrated in Fig. 2. The release rate decreased with increase of the viscosity grade as a consequence of the more rapid hydration, swelling and dissolution of the lower viscosity grades of alginate.

3.3. Bioavailability of diltiazem after sublingual administration

Fig. 3 shows the mean plasma level profile of diltiazem obtained from sublingually administered tablets with 1:4, 1:1 and 4:1 weight ratios of chitosan and alginate (viscosity grade 350 cP). The pharmacokinetic parameters derived from

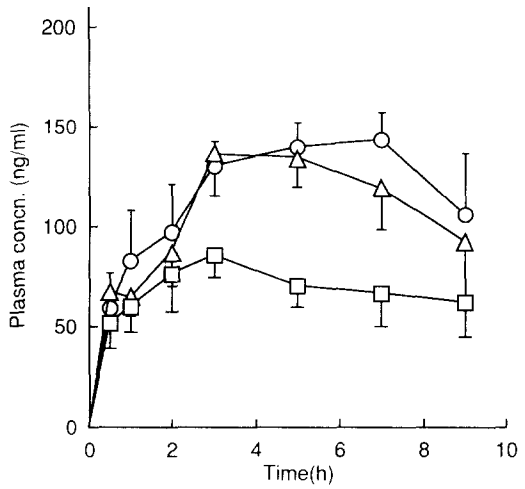

Fig. 3. Plasma concentration of diltiazem as a function of time after sublingual administration to rabbits of bioadhesive tablets prepared from (○) 1:4, (△) 1:1 and (□) 4:1 mixtures of chitosan and alginate (viscosity grade 350 cP). Each value represents the mean ± S.E. of four experiments.

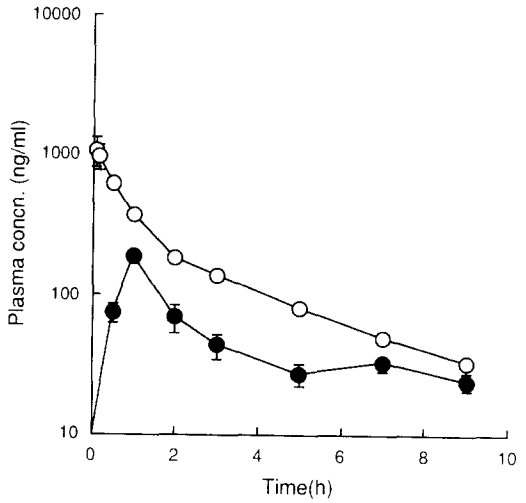

Fig. 4. Plasma concentration of diltiazem as a function of time after intravenous (○) and oral (●) administration to rabbits. Each value represents the mean ± S.E. of four to five experiments.

the data of Fig. 3 using moment analysis (Yamaoka et al., 1981) are given in Table 2.

For comparison, plasma concentration-time curves were determined after a single i.v. injection and after oral administration. Fig. 4 shows that diltiazem was rapidly absorbed after oral dosing with a peak plasma concentration at 1 h. The oral bioavailability calculated from the ratio of the AUC [(oral/i.v.) × 100] was 30.4% which is in good agreement with the literature value of approx. 30% in rabbits (Yeung et al., 1991). The plasma decay curves after i.v. and oral dosings showed biexponential kinetics, and the apparent terminal half-life ($t_{1/2}$) of elimination for the i.v. route found in this study was 3.0 h which is comparable to the 3.6 h reported by Yeung et al. (1991).

Comparison of the concentration-time profiles for orally administered diltiazem with those obtained following sublingual administration shows the absence of sharp peaks in the latter and a more sustained plasma level profile. The mean maximum plasma concentrations, C_{max}, of diltiazem from sublingual tablets were less than those from orally administered solutions and decreased with decrease in the alginate content of the tablets (Table 2). No significant difference in the AUC

Table 2
Bioavailability parameters after intravenous, oral and sublingual administration of diltiazem in rabbits

Route of administration	Chitosan/alginate ratio	Viscosity grade of alginate (cP)	n	C_{max} [a] (ng ml^{-1})	T_{max} (h)	AUC (0–9 h) [a] (ng h ml^{-1})	AUC oral, sublingual/ AUC i.v.
Intravenous	–	–	4	–	–	1521.6 ± 99.8	–
Oral	–	–	5	192.42 ± 7.5	1	462.3 ± 38.9	0.304
Sublingual	1:4	350	4	144.0 ± 13.8	7	1058.7 ± 72.2 [b]	0.696
	1:1	350	4	136.3 ± 20.5	3	975.2 ± 79.5 [b]	0.641
	4:1	350	4	86.2 ± 11.0	3	611.0 ± 41.6 [d]	0.402
	1:1	45	4	118.6 ± 18.5	3	732.3 ± 34.6 [c]	0.481
	1:1	1000	4	118.7 ± 22.9	7	740.2 ± 103.5 [d]	0.486

[a] Each value represents the mean ± S.E.
Probability level [b] $p < 0.001$; [c] $p < 0.01$; [d] $p < 0.05$.

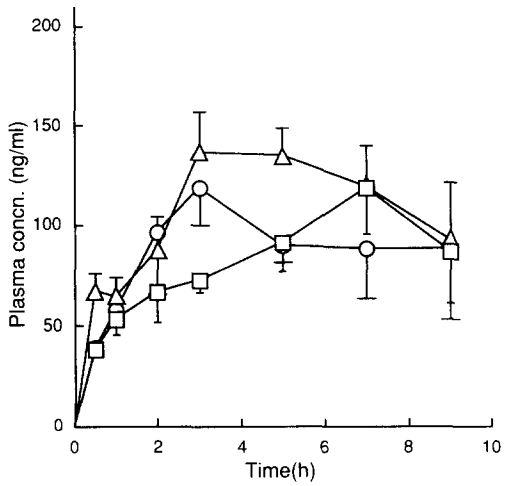

Fig. 5. Plasma concentration of diltiazem as a function of time after sublingual administration to rabbits of chitosan/alginate (1:1 weight ratio) tablets prepared using alginate viscosity grades of (○) 45, (△) 350, and (□) 1000 cP. Each value represents the mean ± S.E. of four experiments.

(0–9 h) was noted between tablets with 1:4 and 1:1 weight ratios of chitosan/alginate. The sublingual bioavailability, calculated from the ratio of the AUC [(sublingual/i.v.) × 100], was 69.6% for the 1:4 mixture and 64.1% for the 1:1 mixture, respectively, which are more than twice the value of oral solution (30.4%). In the case of tablets with 4:1 weight ratio of chitosan and alginate, a low, almost constant plasma concentration of diltiazem was maintained for over 9 h. The bioavailability was reduced to 40.2% of that from i.v. administration, probably as a consequence of the slow rate of release (Fig. 1). However, the mean AUC (0–9 h) value (611.0 ng h ml^{-1}) after administration of the tablet was still higher than that of the oral solution (462.3 ng h ml^{-1}).

The effect of the viscosity grade of alginate on the drug absorption for the tablets consisting of chitosan and alginate in a weight ratio of 1:1 is shown in Fig. 5. The peak time for drug in plasma, T_{max}, is approx. 3 h for the tablets with both low (45 cP) and medium (350 cP) viscosity grades of alginate, but is closer to 7 h for tablets with the high (1000 cP) viscosity grade of alginate. The mean C_{max} and AUC values after administration of the tablets with low- and high-viscosity grades of alginate were slightly lower than those of the tablets with the medium-viscosity grade.

4. Discussion

The in vitro bioadhesion study indicated that the magnitude of the adhesive force of the chitosan/alginate tablets was similar to that of a commercial oral mucosal dosage form, suggesting their potential for use as a bioadhesive drug delivery system. Preliminary experiments to examine the adhesion of tablets to human cheek mucosa, showed that they adhered within a few seconds and remained in place for at least 1 h.

The in vitro drug release study showed a rapid release rate of diltiazem from the bioadhesive tablets which could be modified by changing the mixing ratios of chitosan and alginate and/or the viscosity grade of the alginate. On contact of the tablets with water, the sodium alginate rapidly hydrates and swells to form a visible gel layer over the tablet surface. The rate of penetration of the medium into the tablets, and hence the rate of release of dissolved drug, are a function of the amount of the hydrophilic sodium alginate dispersed throughout the matrix. Tablets with low alginate content or high viscosity grade of alginate hydrate less readily resulting in a slower release rate. The tablet with a 4:1 mixture was still intact in the dissolution vessel after 6 h.

The results of this study show a significant improvement of bioavailability of diltiazem administered sublingually (69.6 and 64.1% bioavailability from tablets consisting of 1:4 and 1:1 chitosan/alginate mixtures) compared to that achieved by oral administration (30.4% bioavailability). Furthermore, the plasma concentration-time curves for sublingual tablets showed evidence of sustained-release of drug which was particularly apparent for tablets prepared using the high viscosity grade of alginate. The lower bioavailability achieved from tablets with a 4:1 mixture of chitosan/alginate is a consequence of the slower rate of drug release. However, even with these tablets, sublingual administration achieves a significantly greater bioavailability than oral administration suggesting that the intraoral

route may be of potential value for administration of this calcium channel blocker.

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