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Oral mucosal bioadhesive tablets of pectin and HPMC: in vitro and in vivo evaluation

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Abstract

The potential of tablets containing 1:4, 1:1 and 4:1 weight ratios of pectin and hydroxypropyl methylcellulose (HPMC) for the sustained release of diltiazem by sublingual administration has been investigated. Measurements of maximum adhesive force to rat peritoneal membrane indicated a satisfactory bioadhesive strength. An in vitro sustained release of diltiazem over 5 h was achieved with bilayer tablets composed of a drug-free ethylcellulose layer in addition to the pectin/HPMC layer containing drug. Plasma concentration-time curves obtained following sublingual administration to rabbits of single and bilayer tablets with 1:1 weight ratios of pectin and HPMC showed evidence of sustained release of diltiazem. Bioavailability of diltiazem was 2.5 times that achieved by oral administration for single layer tablets and 1.8 times for the bilayered tablets. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Sublingual drug delivery; Pectin/HPMC tablets; Diltiazem; Sustained release

1. Introduction

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; Nagai and Machida, 1993), including rapid onset of action, high blood levels, avoidance of the first-pass effect and possible degradation of drug as a result of its exposure to the gastrointestinal tract. In addition, there is 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 absorp-

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tion of diltiazem from solution through the oral mucosa of dog has been reported (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 main requirement of a vehicle for buccal delivery is good bioadhesive properties, and the many bioadhesive polymers examined for the fabrication of buccal devices have included Carbopols™, polycarbophil, and the cellulose derivatives sodium carboxymethylcellulose, hydroxypropylcellulose and hydroxypropyl methylcellulose. (Nagai and Machida, 1993; Merkle and Wolany, 1996; Taylan et al., 1996). We previously investigated the use of mixtures of chitosan and sodium alginate for the fabrication of tablets for sustained release by the buccal route (Miyazaki et al., 1994, 1995). Chitosan has also recently been used by Remuñán-López et al. (1998) as the adhesive material in bilayered mucoadhesive devises for buccal delivery.

In the present work we have designed and evaluated both single and bilayer tablets of pectin and hydroxypropyl methylcellulose (HPMC) for the sublingual delivery of diltiazem. Pectin is a non-toxic, heterogeneous polysaccharide present in the cell wall of most plants, which has a wide range of applications in pharmaceutical formulation. It was selected for use in the sublingual tablets because of its mucoadhesive properties (Smart et al., 1984). Bilayered tablets are of interest for buccal delivery because they provide unidirectional drug release towards the mucosa. Bioadhesive properties have been evaluated by in vitro measurements and the influence of the ethylcellulose backing layer of the bilayered tablets on the in vitro and in vivo release characteristics has been investigated. Diltiazem bioavilability in rabbits from the pectin/HPMC sublingual tablets has been compared to its oral bioavailability.

2. Materials and methods

2.1. Materials

Pectin from apple (Classic AF701) was supplied by Dainippon Pharmaceutical Co., Osaka, Japan. Hydroxypropyl methylcellulose (HPMC, TC-5) and ethylcellulose (N-10-F) were supplied by Shinetsu Chemical Co. Ltd., Tokyo, Japan. Diltiazem hydrochloride was obtained from Wako Pure Chemical Ind. Ltd., Osaka, Japan. Other chemicals were of reagent grade.

2.2. Preparation of compressed tablets

2.2.1. Single-layer tablets

Weighed amounts of pectin, HPMC and drug were mixed in their dry powder forms in a mortar. Flat-faced tablets, 10 mm diameter and 0.9 mm thickness, were prepared by compressing 100 mg of the mixture of pectin and HPMC in mixing ratios of 1:4, 1:1 and 4:1 by weight using a hydraulic press at a pressure of 200 kg/cm for 2 min. Each tablet (100 mg) contained 25 mg of drug.

The mean hardness value of 100 mg tablets composed of equal weights of pectin and HPMC and containing 25 mg of diltiazem was 6.6 ± 0.4 kg ($n = 3$). This is a similar value to that of the alginate/chitosan tablets selected for comparison (5.3 ± 0.2 kg ($n = 3$)), and indicates an acceptable hardness (exceeding 5 kg).

2.2.2. Bilayer tablets

Bilayer tablets (consisting of a backing layer and adhesive/drug reservoir layer) were made by covering one side of the single-layer tablet with an inert ethylcellulose layer. Ethylcellulose was selected as a backing material because this hydrophobic polymer has very low water permeability thus providing an impermeable backing layer that prevents drug loss. Ethylcellulose powder was compressed into flat-faced tablets by applying a pressure of 200 kg/cm for 10 s. 100 mg of a mixture of pectin, HPMC and drug was then added to the die and re-compressed at a pressure of 200 kg/cm for 2 min. The resulting bilayer tablets were 10 mm in diameter and 1.3 mm in thickness.

2.3. Measurement of bioadhesion

Measurements were carried out at room temperature using a rheometer (CR-200D, Sun Scientific Co. Ltd., Tokyo) modified for adhesion measurement by the method described previously (Serizawa et al., 1999). The tablet was attached by adhesive tape to the upper steel rod (1 cm diameter) which was connected to a strain gauge. The tablet surface was wetted with 40 μl of water. After 30 s the lower motor driven platform, to which was attached a rat peritoneal membrane (previously stored in frozen saline and defrosted), was raised slowly (10 mm/s) until in contact with the tablet. Contact between tablet and membrane was maintained at a loading of 200 g for 30 s, after which time the lower platform was lowered at a rate of 90 mm/min until separation. The maximum adhesive force was determined from a recorder trace of the output of the strain gauge during the separation process.

2.4. Measurement of in vitro drug release

Drug release from the tablets was examined by the paddle method using a JP XIII dissolution test apparatus (Toyama Sangyo Co.). One surface of the tablet was moistened and attached at a height of 7.5 cm to the inside of the glass dissolution vessel containing 1 l of distilled water at 37°C and the vessel was stirred at 150 rpm. Five millilitres of samples were collected at pre-determined intervals and replaced with 5 ml of fresh water after each sample collection. The diltiazem content of the samples was determined spectrophotometrically (Shimadzu UV-visible spectrophotometer, UV-1200) at 237 nm. All experiments were carried out in triplicate and average values plotted.

2.5. Animal studies

White male rabbits weighing 3.0–4.0 kg were fasted for 24 h before drug administration and anaesthetised with pentobarbital (25 mg/kg). A bioadhesive tablet containing 1:1 pectin/HPMC and 25 mg diltiazem hydrochloride was inserted sublingually and positioned with the tablet surfaces in contact with the ventral tongue and the floor of the mouth. At given intervals, 1 ml blood samples were taken from the ear vein and analysed by HPLC (see Section 2.6). For intravenous administration, 25 mg doses of 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 μl/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 on to a 25 cm × 46 mm i.d. column packed with Inertsil-ODS. Elution was 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 at 40°C.

3. Results and discussion

3.1. Bioadhesive properties

The values of maximum adhesive force (g/cm) to rat peritoneum, of tablets containing pectin and HPMC (but no drug) in weight ratios of 1:4, 1:1 and 4:1, were 28.9 ± 4.3, 42.3 ± 7.2 and 66.0 ± 4.0, respectively ($n = 6$). The increase with increase of the pectin content indicates the greater adhesive properties of this component.

Comparison of the bioadhesive properties of these formulations with values reported in the literature for bioadhesive materials is not meaningful unless measurements are carried out using similar methods and experimental conditions. For example, it has been shown (Martini et al., 1995)

that the bioadhesion between hydrated block copolymer matrices and tissues increases with increase in the initial applied force. Similar findings have been reported by Park and Robinson, (1985) and Park and Park, (1990) and attributed to enhanced interaction between the hydrogel and the substrate. In addition, different types of mucosal tissue may exhibit markedly different behaviour in bioadhesion experiments (Lejoyeux et al., 1988) and identical tissues should be used for valid comparison with literature values. However, we have shown previously (Miyazaki et al., 1995) that alginate/chitosan tablets have comparable bioadhesive properties to commercial oral mucosal adhesive tablets containing hydroxypropyl cellulose and carboxyvinyl polymer (Aftach™, Teijin Ltd.) when measured under identical conditions and hence are useful for the purpose of comparison. Values of maximum adhesive force of the pectin/HPMC tablets were similar to those for alginate/chitosan measured under identical conditions, (for example, tablets formed from 1:1 mixtures of alginate/chitosan had a maximum adhesive force of 44.8 ± 5.6 g cm^{-2} ($n = 6$)), suggesting their potential use in the fabrication of bioadhesive drug delivery systems.

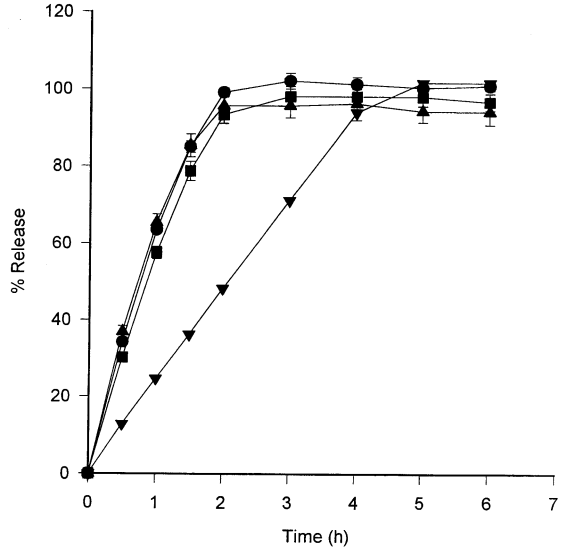

Fig. 1. Percentage release of diltiazem hydrochloride as a function of time at 37°C from pectin/HPMC single-layer tablets with pectin/HPMC weight ratios of ▲ 1:4, ● 1:1 and ■ 4:1, and from ▼ pectin/HPMC bilayer tablets with a pectin/HPMC weight ratio of 1:1. Each value represents mean ± S.E. of three experiments.

3.2. In vitro release studies

Fig. 1 shows release profiles of diltiazem hydrochloride from pectin/HPMC tablets with pectin/HPMC weight ratios of 1:4, 1:1 and 4:1. Release was rapid with almost 100% release within 2 h and no significant dependency on composition. The release profile of the 1:1 pectin/HPMC tablet is compared in Fig. 1 with that for tablets composed of a layer of pectin and HPMC (1:1 weight ratio) containing the drug, and a second layer of ethyl cellulose. A much slower release is achieved from the bilayer tablet, total release being noted only after 5 h. The slower release is presumably a consequence of the reduced surface area of drug-containing layer exposed to the release medium.

3.3. Bioavailability of diltiazem after sublingual administration

The mean plasma level profiles of diltiazem obtained following sublingual administration to rabbits of single-layered and bilayer pectin/HPMC tablets (1:1 weight ratio) containing 25 mg drug, and from an oral diltiazem solution of the same concentration (data from Miyazaki et al., 1995, determined under identical conditions) are compared in Fig. 2. Absorption of diltiazem following oral administration was rapid with a peak plasma concentration at 1 h. The plasma–concentration curves for both single-layered and bilayer sublingual tablets showed evidence of a more sustained release of diltiazem, the C_{max} for the bilayer tablets being lower than that of the single layer tablets.

The pharmacokinetic parameters derived from these data using moment analysis (Yamaoka et al., 1981) and from plasma–concentration curves obtained after a single i.v. injection (Miyazaki et

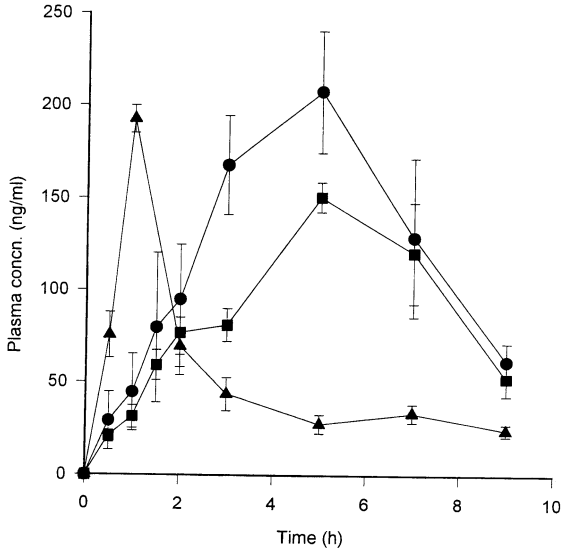

Fig. 2. Plasma concentrations of diltiazem hydrochloride in rats after ▲ oral administration and after sublingual administration of ● single-layer tablet and ■ bilayer tablet. All tablets had pectin/HPMC weight ratios of 1:1. Each value represents the mean ± S.E. of four to five experiments.

al., 1995) are given in Table 1. The bioavailability of diltiazem calculated from the ratio AUC [(oral/i.v.) × 100] was 75.4% for the single-layer tablets, which compares favourably with a value of 30.4% calculated for oral bioavailability. The equivalent value for the bilayer tablets in which drug release is restricted to one surface by the backing layer, was lower (54.5%), although still exceeded that of the oral solution.

4. Conclusion

The results of this study show a significant improvement of bioavailability of diltiazem administered sublingually to rabbits from tablets containing equal weights of pectin and HPMC compared to that achieved by oral administration. Furthermore, the plasma concentration–time curves for sublingual tablets showed evidence of sustained-release of drug (t_{max} of 5 h for sublingual tablets compared to 1 h for oral administration). The sublingual tablets were of satisfactory hardness and showed good bioadhesion to rat peritoneal membrane. A more sustained in vitro release of diltiazem was achieved from bilayer tablets composed of a layer of pectin and HPMC (1:1 weight ratio) containing the drug and a second layer of ethyl cellulose.

Acknowledgements

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Table 1
Bioavailability parameters of diltiazem administered from single and bilayer tablets of 1:1 pectin/HPMC[a]

	T_{max} (h)	C_{max} (ng/ml)	AUC (0–9 h) (ng/h per ml)	$\frac{AUC_{oral}}{AUC_{IV}}$
I.V. injection[b]	—	—	1521.6. ± 99.8	—
Oral[b]	1.0	192.4	462.3 ± 38.9	0.304
Single layer	5.0	207.4	1133.0 ± 84.0*	0.754
Bilayer	5.0	150.6	828.6 ± 60.7**	0.545

[a] Each value represents the mean ± S.E. of four to five experiments.
[b] From Miyazaki et al., 1995.
* $P < 0.001$.
** $P < 0.005$.

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