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Adhesive and in vitro release characteristics of propranolol bioadhesive disc system

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Summary

For the study of bioadhesive systems used in the controlled delivery of drugs through the oral mucosal membrane, direct compressed disc systems containing either 10, 15 or 20 mg of propranolol HCl (PL) with a mixture of hydroxypropyl cellulose and poly(acrylic acid) were prepared. The release data were fitted to the simple power equation, and it was found that the release characteristics of PL from these systems were not affected by the amounts of the drug loaded and followed behavior conforming to a non-Fickian mechanism of release. The diffusion exponents for the drug released in pH 6.8 medium were higher than those in pH 3.5 medium. However, the fraction of PL released in pH 6.8 medium was less than that in pH 3.5 medium. The adhesive bond strength of the systems to the porcine buccal mucosa was evaluated by the tensile strength test and the result showed no significant difference in adhesive bond strength to the porcine buccal mucosa among the three PL-containing discs and drug-free discs.

Introduction

Recently, many researchers have focused their attention on the use of bioadhesive hydrophilic polymers to control the delivery of biologically active agents systemically or locally (Lenaerts and Gurny, 1990). These bioadhesive systems are useful for the administration of drugs, which are susceptible to extensive gastrointestinal degradation and/or first-pass metabolism, via buccal, nasal and/or rectal mucosae. Buccal bioadhesive systems appear to be especially attractive because of the easy accessibility and the robust nature of the oral mucosa. It is less prone to irritation or irreversible damage by a dosage form, therefore, it may lead to better patient acceptance and compliance (Anders and Merkle, 1989).

Among various bioadhesive polymers, poly(acrylic acid) has been found to have the property of significant bioadhesion with the mucosal membrane (Nagai et al., 1979). Due to the hydrophilic nature of the bioadhesive polymers, they tend to swell upon hydration. The release of a drug from these polymeric matrixes is often represented by a simple power equation:

$$M_t/M_\infty = kt^n \quad (1)$$

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(Korsmeyer et al., 1983; Sinclair and Peppas, 1984; Lee, 1985; Peppas, 1985; Ponchel et al., 1987b; Ritger and Peppas, 1987; Ranga Rao and Pamalatha Devi, 1988; Ranga Rao et al., 1990), where M_t/M_∞ is the fraction of the drug released at time t, k denotes the constant incorporating structural and geometric characteristics of the drug/polymer system and n is the diffusion exponent related to the mechanism of the release. For non-Fickian release the n value falls between 0.5 and 1.0, while for Fickian (case I) diffusion, $n = 0.5$, and for zero-order release (case II transport), $n = 1.0$.

The in vitro permeation of propranolol through porcine buccal mucosa from the solution has been reported recently (Le Brun et al., 1989). In an attempt to optimize the buccal absorption of propranolol, bioadhesive disc systems were prepared by directly compressing the drug with a mixture of poly(acrylic acid) (PAA) and hydroxypropyl cellulose (HPC), and the adhesive and release characteristics of the prepared systems were evaluated.

Materials and Methods

Preparation of direct compressed discs

HPC (average mol. wt 3×10^5, particle size 190–460 μm, Aldrich) and PAA (Carbopol 940, particle size 2–6 μm, B.F. Goodrich) were triturated and mixed in their dry powder forms in a 1:2 ratio. Different amounts of PL (propranolol HCl, Sigma) were added to the polymer mixture to make three different kinds of discs so that each disc (150 mg) contained either 10, 15 or 20 mg of PL. The control disc contained only 150 mg of the polymer mixture without PL. The discs were prepared by compressing the powder mixtures in a die of 9.5 mm in diameter (0.71 cm^2) under a force of 2×10^4 N for 15 s.

Release study of the direct compressed discs

It has been reported that the normal pH of human saliva varies from 5.8 to 7.8 with an average of 6.8 (Kreuser et al., 1972; Dawes, 1974; Ferguson and Fort, 1974). However, various aqueous solutions such as pH 1 (Ponchel et al., 1987b), pH 7.38 (Ishida et al., 1981) and normal saline (Ishida et al., 1983) as well as chloroform (Ishida et al., 1982) have been used to study the in vitro release kinetics of drugs from the bioadhesive buccal delivery systems. Our preliminary study of the hydration of the bioadhesive disc by 0.2 ml of pH 6.8 phosphate buffer showed that the pH of the hydrated gel layer was between 3 and 4 based on pH-indicating paper. Thus, the release studies were conducted at both pH 3.5 and 6.8 to investigate the release characteristic and the effects of pH on the release kinetics of PL from the bioadhesive discs.

250 ml of phosphate buffer (ionic strength, 0.015 M, pH 3.5 or 6.8) at 37°C was placed in a USP Type II dissolution apparatus (Pharma test) with a paddle stirring rate of 75 rpm. To ensure that the PL was released only from one side of the disc in a fixed area, each disc was placed in a glass cylinder closed at one end and submerged in the dissolution medium. 5 ml of sample was collected at 1-h intervals up to 10 h, and replaced with 5 ml of fresh buffer after each sample collection. The PL concentration was measured by a UV spectrophotometer (Hitachi 139) at 282 nm for pH 3.5 medium and 288 nm for pH 6.8 medium. Ten discs of each formulation were tested.

Tensile strength test

The tensile strength test was used in order to determine the force and work of adhesion of bioadhesive discs on the oral mucosa. These parameters are commonly used to study the rupture of adhesive joints (Wu, 1982; Kammer, 1983) and can be used for quantification of the bioadhesive bond strength (Ch'ng et al., 1985; Ponchel et al., 1987a,b).

The adhesive bonding of the discs, containing 10, 15 and 20 mg of PL as well as the drug-free disc, to porcine buccal mucosa was studied in quadruplicate in a tensile tester assembled by the engineering department. The procedure of the test was modified from the method described by Ponchel et al. (1987a,b).

In the test, one side of the disc was firmly glued to a metal screw nut which can be joined to

a screw attached to the upper arm of the tensile tester. The porcine buccal mucosa was held on the perforated platform of the tensile tester by vacuum and further secured by clamping a metal ring on the top of the tissue. During the test, 10 μl of pH 3.5 phosphate buffer was evenly spread on the surface of the disc, and the disc was immediately brought into contact with the buccal mucosa. A 20 g weight was placed on the top of the screw nut, which was glued to the disc, for 5 min to enhance the contact of the disc with the mucosa. Then the weight was removed and the disc was attached to the upper arm of the tester. The extension rate of the upper arm, which was controlled by a gearbox (The Ohio Gear Co.) and a programmable power supply (Regatran®, Electronic Measurements Co.), was set at 7.25 mm/min. The increase in the tension at the disc-mucosa interface along with the rise of the upper arm of the tensile tester was transformed into analog signals by a strain indicator (P-3500, Measurements Group) and recorded on a chart recorder (Fisher Recordall series 5000). The force required for the detachment of the disc from buccal mucosa was recorded as a function of elongation until the breaking point.

The bioadhesive bond strength of the disc to buccal mucosa was evaluated from its fracture stress and work of adhesion. The fracture stress can be calculated using F_M/A_0, where F_M is the maximum detachment force and A_0 represents the surface area of the disc. The work of adhesion can be found from the area under the force/elongation curve (Ponchel et al., 1987a,b).

To determine whether the elastic stretch occurred at the disc-mucosa interface or in the disc itself, tensile strength tests were conducted to evaluate the force/elongation behavior of the discs. All PL-containing and drug-free discs were tested in pairs of the same kind. One disc from each pair was glued to a metal screw nut and the other was glued to a stationary platform; the unglued sides of the two discs were hydrated with 10 μl of phosphate buffer and brought into contact with each other. The procedures for the rest of the test were similar to that for determining the bioadhesive bond strength between the disc and the buccal mucosa.

Results and Discussion

Figs 1 and 2 show that, at both pH values, the cumulative amounts of PL released from the discs increase with increasing amount of PL loaded in the discs, while the fraction of PL released from the discs (M_t/M_∞), as shown in Fig. 3, is independent of the loading of PL. On the other hand, the fraction of PL released at pH 3.5 is about 15–20% higher than that at pH 6.8. This may be due to the increased degree of ionization of carboxyl groups of PAA at higher pH, which may lead to more complex formation between the cationic drug and the anionic polymer (Ranga Rao et al., 1990).

To examine further the release mechanism of PL from bioadhesive discs, the results were analyzed according to Eqn 1. The values of k and n were estimated by linear regression of $\log(M_t/M_\infty)$ on $\log(t)$. As shown in Fig. 3 and Tables 1 and 2, the release profiles of the three PL-containing disc systems, at both pH values, fitted well

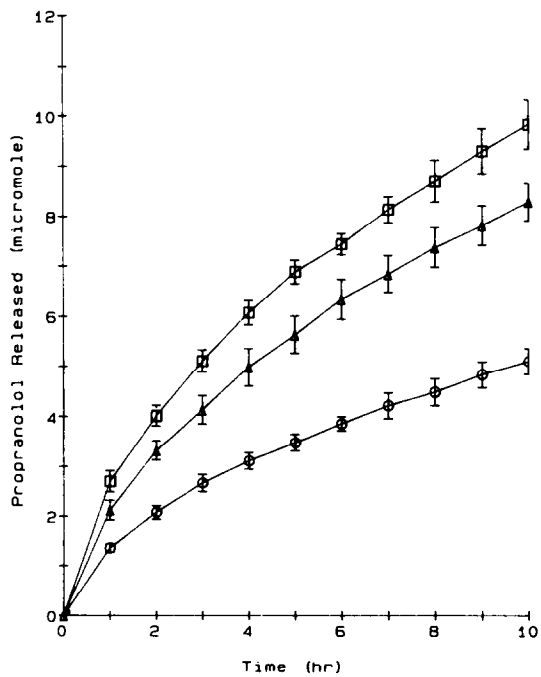

Fig. 1. Cumulative amount of propranolol released from bioadhesive discs vs time (pH 3.5). Dose loaded (mg): 10 (○), 15 (△), 20 (□).

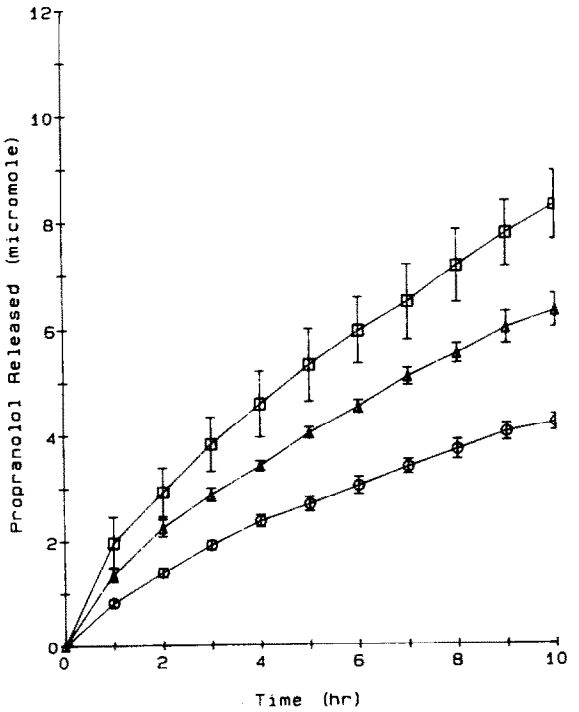

Fig. 2. Cumulative amount of propranolol released from bioadhesive discs vs time (pH 6.8). Dose loaded (mg): 10 (○), 15 (△), 20 (□).

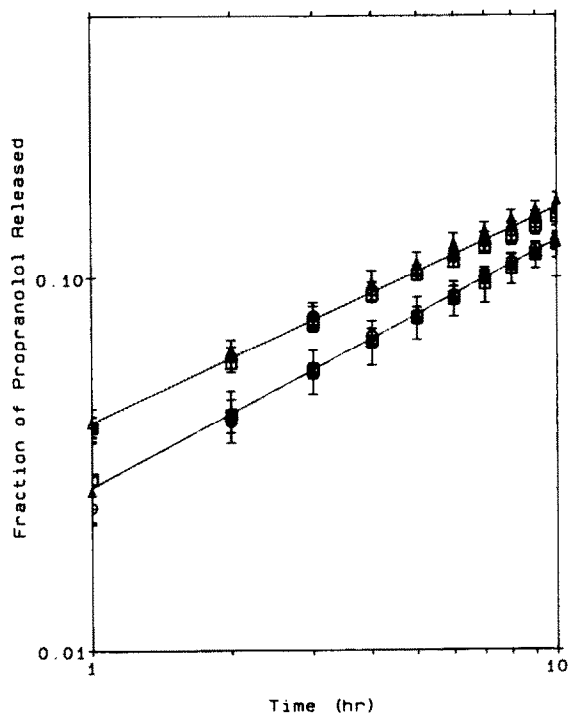

Fig. 3. Fraction of propranolol released from bioadhesive discs vs time on logarithmic grids. Dose loaded (mg): 10 (○), 15 (△), 20 (□). (· · · · · ·) pH 3.5, (———) pH 6.8.

to the model (correlation coefficients > 0.99). The values of n were greater than 0.5 in all cases exhibiting non-Fickian release behavior controlled by a combination of diffusion and chain relaxation mechanisms as suggested by Ponchel et al. (1987b). Furthermore, the value of n increased from 0.57 at pH 3.5 to 0.67 at pH 6.8, suggesting a more significant contribution of the polymer relaxation processes, besides the ionization of PAA, to the drug released in the pH 6.8 medium. The n values for the drug released in medium at the same pH were not significantly different among the systems ($F < 3.00$, $p > 0.05$), indicating that the release mechanism was not affected by the loading dose of PL in the system.

A typical force/elongation profile of the adhesion of the bioadhesive disc to the porcine buccal mucosa is shown in Fig. 4. A linear portion from the beginning of the curve to the maximum force value is observed in the tensile curve. Along the linear portion, the force is directly propor-

TABLE 1

Estimated values of k and n by linear regression of $\log(M_t / M_\infty)$ on log(t) at pH 3.5

PL loaded (mg)	k	n	r [a]
10	0.0413 ± 0.0022	0.5672 ± 0.0202	0.9994
15	0.0413 ± 0.0036	0.5898 ± 0.0218	0.9995
20	0.0417 ± 0.0030	0.5603 ± 0.0388	0.9995

[a] Correlation coefficient.

TABLE 2

Estimated values of k and n by linear regression of $\log(M_t / M_\infty)$ on log(t) at pH 6.8

PL loaded (mg)	k	n	r
10	0.0264 ± 0.0014	0.6850 ± 0.0209	0.9990
15	0.0278 ± 0.0027	0.6560 ± 0.0574	0.9996
20	0.0286 ± 0.0071	0.6409 ± 0.0761	0.9996

tional to the elongation indicating the elastic behavior of the adhesive bond according to Hooke's law (Merkle et al., 1990). Beyond the maximum value, the force declines rapidly due to the detachment of the disc from the mucosa. The same profile was seen in all PL-containing and drug-free discs.

The forces required to separate the partially hydrated disc pairs in contact with each other (for all PL-containing and drug-free discs) were greater than 19.6 N (equivalent to the fracture stress of 276.1 kPa) which is the maximum limit that can be detected by the instrument. This value is about 10-times greater than the forces required to separate the disc from the buccal mucosa as shown in Table 3. The result suggests that the cohesive bond strength of either the hydrated or unhydrated disc itself is much stronger than the adhesive bond strength of the disc to the mucosa. Hence, the results listed in Table 3 represent the fracture stress and work of adhesion between the disc and the mucosa.

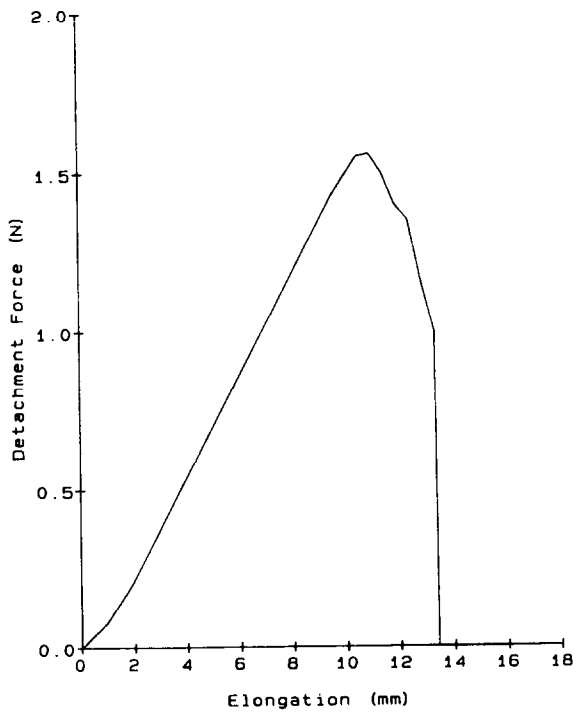

Fig. 4. Force/elongation profile of the tensile strength test between the bioadhesive discs and porcine buccal mucosa.

TABLE 3

Effects of propranolol loading on the fracture stress (F_M / A_0) and the work of adhesion (W_a) between bioadhesive discs and porcine buccal mucosa

PL loaded (mg)	F_M / A_0 (kPa)	W_a (J) ($\times 10^3$)
0	21.97 ± 5.22 [a]	17.065 ± 5.430 [b]
10	24.37 ± 5.60 [a]	19.203 ± 5.400 [b]
15	19.35 ± 1.29 [a]	13.291 ± 1.122 [b]
20	21.75 ± 2.62 [a]	14.631 ± 3.091 [b]

[a] Not significantly different among the systems ($F = 1.00$, $p = 0.43$).

[b] Not significantly different among the systems ($F = 1.58$, $p = 0.25$).

A comparison of the fracture stress and the work of adhesion among different discs provides a good measurement of the adhesiveness of discs to the mucosa. As shown in Table 3, there is no significant difference in fracture stress and work of adhesion among these four kinds of discs. The values of the work of adhesion of the bioadhesive discs prepared in this study are comparable to those observed by Ponchel et al. (1987b).

In conclusion, at low loading doses of PL, the release mechanism of PL from bioadhesive discs depends only on the physicochemical nature of the drug/polymer system as well as the environment in which the drug is released. The adhesiveness of the discs to porcine buccal mucosa is independent of the small amount of the drug loaded.

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