Drug Development and Industrial Pharmacy, 22(3), 243-253 (1996)

Development of Anticandidal Delivery Systems: (II) Mucoadhesive Devices for Prolonged Drug Delivery in the Oral Cavity

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ABSTRACT

Conventional dosage forms designed for drug delivery in the oral cavity suffer from the disadvantage of an initial burst of activity followed by a rapid decrease in concentration to subtherapeutic levels. To counter this effect, two prolonged-release dosage forms were devised for the treatment of oral candidiasis. These devices were to contain the antifungals, chlorhexidine and clotrimazole, for therapy against Candida albicans, *and also benzocaine and hydrocortisone to combat the pain and inflammation secondary to a candidal infection. Release studies demonstrated that only chlorhexidine and clotrimazole could be delivered in a controlled manner from the mucoadhesive patches. On the other hand, release of all four drugs could be controlled from the mucoadhesive tablets, with optimum release of the drugs in 24 hr achieved using sodium carboxymethylcellulose and polyethylene oxide (85:15) combination tablets.*

INTRODUCTION

A conventional lozenge, mouthwash, or gel would be the simplest dosage form for the delivery of drugs through the mucosa or to the oral cavity. But these conventional dosage forms have the disadvantage of an initial burst of activity followed by a rapid decrease in concentrations to below therapeutic levels. A lozenge produces effective drug levels for <1 hr and repeated administration is restricted due to systemic toxicity that might result due to the large quantity of drug ingested. The action of mouthwashes is even more transient than that of lozenges, and gels/pastes are difficult to retain in the mouth (1). Therefore, oral mucosal sustained-release devices may prove to be a viable alternative to the conventional local oral medications.

Oral candidal infections require prolonged therapy with antifungal agents and hence it may be advantageous to deliver these drugs in a sustained manner. The choice of antifungal agent used depends on the severity of in-

fection, and usually polyenes, azoles, chlorhexidine, and flucytosine are preferred (2–4). Previous reports have documented prolonged release of antifungal agents from buccal devices (1,5). However, oral candidiasis is a painful condition (6), and hence medication containing antifungals in combination with anesthetics and/or anti-inflammatory agents might help alleviate the pain and inflammation associated with the candidal infection.

On prior comparison of the minimum inhibitory concentrations of various antifungals, clotrimazole was found to be the most effective topically used agent against two strains of *Candida albicans* (7). In addition, chlorhexidine, which is prescribed for the therapy of a variety of oral diseases including oral cancer, gingivitis, plaque, and denture stomatitis, was found to have a synergistic effect in combination with clotrimazole. Therefore, a sustained-release device containing chlorhexidine and clotrimazole in addition to benzocaine and hydrocortisone was formulated.

Two different mucoadhesive devices were designed. The first was a bioadhesive patch for localized, unidirectional delivery of drugs for therapy of isolated lesions. The second was a bioadhesive tablet for delivery of the drugs in the oral cavity. This device would be more applicable for treatment of oral candidiasis, which typically spreads over the entire oral mucosal surface.

Five different polymers, all of which have been characterized to be excellent bioadhesives (8,9), were chosen for the initial screening of drug release from the polymers. Also, combinations of different polymers were tried in order to achieve optimum sustained-release profiles of the drugs.

MATERIALS

Clotrimazole, chlorhexidine (diacetate salt), benzocaine, and hydrocortisone were all obtained from Sigma Chemical Co. (St. Louis, MO). Sodium carboxymethylcellulose 7H3SF was obtained from Aqualon (Wilmington, DE), carbopol 974P from BF Goodrich (Breckville, OH), polyethylene oxide (MW 4,000,000) and polymethylvinylether/maleic anhydride (MN 67,000) from Polysciences (Warrington, PA), and gum tragacanth from Sigma Chemical Co. (St. Louis, MO). The backing laminate, scotchpack #1109, for the patches was obtained from 3M Corp. (St. Paul, MN). The fungi *Candida albicans* was obtained from American Type Culture Collection (Rockville, MD). Talc, disodium hydrogen orthophosphate, potassium dihydrogen orthophosphate, sodium chloride, polyethylene glycol 400, glycerol, sodium acetate, sodium hydroxide, triethylamine, glacial acetic acid, acetonitrile, and methanol were purchased from Fisher Scientific (Fair Lawn, NJ).

METHODS

Polymer Swelling

The degree of polymer swelling was determined by adding 25 ml of isotonic phosphate buffer (pH 6.8) to the respective polymer (0.5 g) in a 25 ml measuring cylinder. The cylinders were covered to prevent loss of water due to evaporation and were kept in an oven at 37°C. The degree of swelling was read directly from the cylinder at regular intervals until no further polymer hydration occurred (10).

Viscosity of Polymer Solutions

Viscosities of the polymer solutions were determined using a cone-plate viscometer (Brookefield Ins., Stoughton, MA). Polymer solutions were made by dispersing 1.5% w/w of the polymer in methanol (49.25% w/w, containing the drugs), and adding to this solution 49.25% w/w water. The resulting mucilage was stirred and 0.5 ml was placed on the plate of the viscometer. The viscometer was then run at 10 rpm and the percent reading was obtained. In the case of polymethylvinylether/maleic anhydride a speed of 100 rpm was required to obtain a reading.

Mucoadhesive Patch

Patch Preparation

The polymer (1% w/w) was first dispersed in glycerol (1% w/w), added as a plasticizer. A stock solution of the active ingredients was made in methanol and the amount required to obtain the desired loading (2 mg/g of polymer solution, in the case of benzocaine and hydrocortisone, and 1 mg/g in the case of chlorhexidine and clotrimazole) was added to the polymeric dispersion. The required quantity of water was then added to the dispersion and the resultant mucilage was stirred.

The mucilage obtained was cast onto the backing laminate and films (with a wet thickness of 1000 μm) were made using a laboratory coating machine (Werner Mathis, Zurich, Switzerland). After drying, the coated films were cut into circular patches (9 mm diameter each) and assayed for content uniformity and drug release.

Content Uniformity of Patches

Representative patches were immersed in a test tube containing 3.5 ml of methanol/water. The tubes were sealed and shaken in a wrist-action shaker (Burrell Corp., Pittsburgh, PA) for 6 hr. The concentration of each drug was determined by HPLC.

Drug Release from Patches

Release kinetics of the drugs from patches were studied in the Valia-Chien permeation cells at 37°C. Patches were fixed between the two half-cells with the backing membrane facing the donor half-cell and the drug adhesive layer facing the receptor half-cell. Isotonic phosphate buffer (pH 6.8) containing 20% PEG 400 (3.5 ml), to ensure that sink conditions were maintained for the released drugs, served as the receptor medium. The surface area of each patch exposed for drug release was 0.64 cm^2.

Release studies were carried out for a duration of 4 hr and samples (200 μl each for HPLC and growth inhibition assays) were withdrawn at preset time intervals.

Inoculum Preparation

Inocula were prepared using the spectrophotometric method. The organism pellet (ATCC #44505) was suspended in 5 ml of RPMI 1640 medium, and a loopful of this suspension was inoculated onto the Sabouraud's dextrose agar and incubated at 35°C for 48 hr. Five colonies, at least 1 mm in diameter, were picked from the medium using a disposable plastic loop (10 μl), and were suspended in 5 ml of sterile saline solution (0.85%). The resulting yeast suspension was vortexed for 15 sec and its turbidity was adjusted to 85% transmission at 530 nm using sterile saline. This procedure yields a cell suspension containing $1–5 \times 10^6$ organisms/ml. The solution was then diluted 1:20 with the RPMI 1640 medium to provide a working inoculum of $1–5 \times 10^4$ organisms/ml (2,11,12). Colony counts were performed to confirm the number of organisms in each ml of inoculum.

Growth Inhibition Assay

Samples (100 μl each) of the receptor solution (from release studies) were added to a 24-well microtiter plate (3 ml/well). To each well 0.9 ml of sterile RPMI 1640 medium and 100 μl of inoculum were added. The initial amount of organism in the suspension at zero time was determined by similarly adding 100 μl of inoculum to 1 ml of medium devoid of any drug. The plates were incubated at 35°C for 24 hr and growth of organisms was determined spectrophotometrically, using disposable microcuvettes (Fisher Scientific), at 530 nm. The growth profile was plotted and correlated to the release of the antifungal drugs.

Mucoadhesive Tablet

Tablet Preparation

Tablets were prepared using a Carver Laboratory Press (Fred S. Carver Inc., Menomonee Falls, WI) with a compression force of 10,000–11,000 lb (~5 metric tons) for 5 sec. The diameter of the die cavity was 8 mm and 100 mg of the tablet mixture was used. Clotrimazole, chlorhexidine, benzocaine, and hydrocortisone were each weighed at a 5% (w/w) concentration. Talc, as a lubricant and glidant, was also added at 5% (w/w) level to the tablet mixture. Thus, the four therapeutic agents and talc accounted for a total of 25% (w/w) of the tablet mixture, with the remaining 75% being the polymer. The powders were mixed well prior to weighing each tablet.

Content Uniformity of Tablets

Representative tablets were crushed using a mortar and pestle. Aliquots of the crushed tablets were weighed and the required amount of methanol was added to extract the drugs. This suspension was shaken in a wrist-action shaker (Burrell Corp., Pittsburgh, PA) for 6 hr. Samples were withdrawn, diluted as required, and analyzed by HPLC.

Physical Characteristics of Tablets

Tablet thickness was determined using a Micrometer and tablet hardness using a Tablet Hardness Analyzer (VK 2000) (Vankel Industries Inc., Edison, NJ).

Bioadhesive Strength of Tablets

Bioadhesive strength of tablets prepared from the polymers was estimated by the adhesion force and the work of adhesion-shear required to separate the tablet from a mucosal membrane specimen (rabbit ileum), with mucin solution (0.25%) as the interstitial medium.

The membrane specimen was adhered to a disposable microcuvette, which in turn was clamped to the inside wall of a beaker kept on an electronic jack. The

microcuvette was filled with water at 37°C. The tablet was adhered on a plexiglass slide using cyanoacrylate glue. The slide was hung from the underside of a semi-microbalance and was brought in contact with the vertically placed membrane (which had previously been wet with 0.25% mucin solution) such that the two were in exact parallel position (Figure 1). The membrane specimen and tablet were kept in contact for 5 min, subsequent to which the jack was lowered at a constant rate (0.225 mm/sec). The adhesion force vs. time profile was monitored on a computer interfaced with the balance. The maximum adhesion force and the area under the force/time curve (work of adhesion-shear) were determined for each polymer (modified from ref. 13).

Drug Release from Tablets

Drug release from tablets was determined using a dissolution apparatus (Vankel Industries Inc., Edison, NJ). Isotonic phosphate buffer containing 40% PEG 400 was used as the dissolution medium. PEG was used in order to maintain sink conditions for the released drugs. A total of 200 ml of the dissolution medium was used and studies were performed at 37°C with paddle rotation at 50 rpm. Samples (100 µl each) were withdrawn at preset time intervals for a period of 12 hr, and amount of drug in the samples was determined by HPLC.

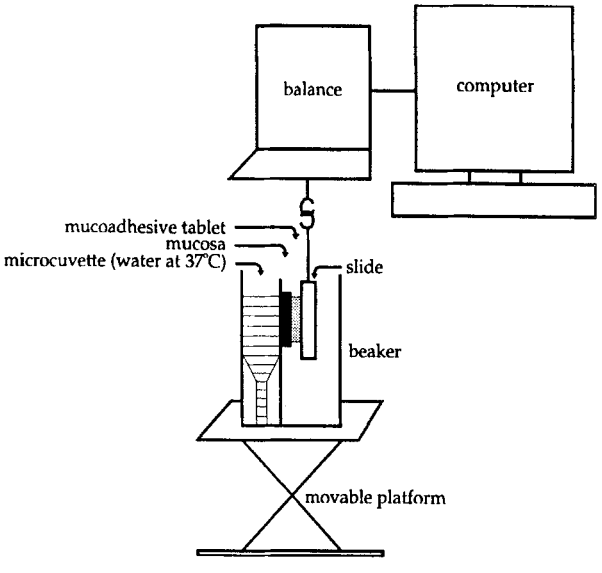

Figure 1. Experimental setup for measurement of mucoadhesive strength.

Drug Loading Effect

To determine the effect of increasing antifungal agent loading on drug release profiles, in addition to the 5% loading, two additional loading levels were tried. Chlorhexidine and clotrimazole were each added at 7.5% and 10% of the tablet weight, while the concentrations of benzocaine and hydrocortisone were maintained at 5%. A polymer combination of sodium carboxymethylcellulose:polyethylene oxide—80:20—was used, the total respective polymer concentration being 70% and 65%.

Transmucosal Permeation

Buccal and alveolar mucosae were surgically excised from freshly sacrificed pigs (Dealaman Enterprises, Warren, NJ) and cleaned off the underlying muscle and connective tissue. Buccal mucosa was mounted on one half-cell of the Valia-Chien permeation cell, with its serosal surface facing the receptor solution compartment. Alveolar mucosa was secured on the inner side of a mucoadhesive tablet-holding device (14), and the tablet was then adhered directly onto the alveolar mucosa surface. The device was then clamped between the two half-cells, such that the other side of the tablet was in close contact with the buccal mucosa. The exposed surface area for buccal membrane permeation was 0.64 cm^2, while that for the alveolar membrane permeation was 0.03 cm^2. An aliquot (100 µl) of the receptor medium was added into the device to initiate tablet dissolution. Isotonic phosphate buffer (pH 6.8, 3.5 ml) containing 40% PEG 400 was added, as the receptor medium, in the solution compartment of both half-cells, and permeation experiments carried were out at 37°C for a period of 24 hr. Samples (50 µl each) were withdrawn at preset intervals and analyzed by HPLC.

Analytical Method

A method for the analysis of chlorhexidine (15) was modified so as to simultaneously detect all four drugs. Quantitation of the drugs was done by injecting samples (10 µl each) into an HP 1050 system (Hewlett Packard, Avondale, PA). An ODS-Hypersil column (5 µm, 100 mm × 2.1 mm; Hewlett Packard) was used and gradient elution was carried out. The mobile phase was comprised of acetonitrile and acetate buffer, with the gradient varying from 90% and 10% to 40% and 60% respectively, over a period of 20 min.

Acetate buffer was made by dissolving sodium acetate (0.2% w/w) in water and adding triethylamine (0.4% w/w) to it. The pH of the buffer was adjusted to 5 with glacial acetic acid.

The elution sequence followed the order benzocaine, succeeded by hydrocortisone, then chlorhexidine, and finally clotrimazole. The limit of detection for benzocaine and hydrocortisone was <1 μg/ml and that for chlorhexidine and clotrimazole was ~ 2 μg/ml.

Data Treatment

Triplicate experiments were run for all studies performed. Statistical analyses were conducted on the data generated to obtain the arit etic mean and standard deviation of the triplicate data.

RESULTS AND DISCUSSION

Polymer Swelling

It was observed that carbopol swelled rapidly within the first 5 min and expanded to more than six times its original volume in 48 hr. Sodium carboxymethylcellulose and tragacanth followed similar swelling patterns, their extent of swelling followed closely by that of polyethylene oxide. Polymethylvinylether/maleic anhydride did not swell much but rather became a translucent suspension within 24 hr.

When bioadhesives come in contact with an aqueous medium, they swell and form a gel (16). The rate and extent of water uptake by a polymer has been reported to be an important factor in determination of its relative bioadhesive strength. Uptake of water results in relaxation of the originally stretched, entangled, or twisted polymer chains, resulting in exposure of all polymer bioadhesive sites for bonding to occur. The faster this phenomenon occurs, more rapidly will the polymer adhere to its substrate (17,18).

Since carbopol exhibits very good swelling properties, it is expected that carbopol would be a good candidate for bioadhesive applications. However, it must be noted that in a previous study no correlation was established between water uptake by the polymer and its relative bioadhesive strength (19).

Viscosity of Polymer Solution

The average viscosities of polymer solutions (1.5% w/w in a 50:50 methanol:water solution with all four drugs) were 15.77 ($\pm$0.07) poise for sodium carboxymethylcellulose, 6.29 ($\pm$0.43) poise for carbopol, 4.22 ($\pm$0.18) poise for polyethylene oxide, 1.78 ($\pm$0.11) poise for tragacanth, and 0.22 ($\pm$0.01) poise for polymethylvinylether/maleic anhydride.

One of the most important properties of a mucoadhesive polymer is its aqueous viscosity (16). Since the interactive forces between a polymer and mucin, which are required for mucoadhesion to occur, are similar to those demonstrated by the polymer in aqueous solution during viscosity measurement, knowledge of the relative viscosities could provide some insight about their expected mucoadhesive strength (20).

Thus, sodium carboxymethylcellulose solution, which was most viscous among the polymer solutions evaluated, would be expected to yield good mucoadhesion. On the other hand, polymethylvinylether/maleic anhydride solution exhibited the lowest viscosity and hence would be expected to be the poorest mucoadhesive among the five polymers tested.

Mucoadhesive Patch

Content Uniformity

Drug loading in the patches was 96.3 ($\pm$18.2) μg for benzocaine, 79.9 ($\pm$14.4) μg for hydrocortisone, 22.9 ($\pm$4.4) μg for chlorhexidine, and 24.7 ($\pm$3.8) μg for clotrimazole. In addition to interpatch uniformity of content, intrapatch uniformity was also seen.

Drug Release

All patches were found to release 100% of benzocaine and hydrocortisone within the first 15 min. This could be due to the relatively higher solubility of both drugs in the receptor fluid. The release of chlorhexidine and clotrimazole from the patches is shown in Figure 2. It is evident that among the polymers studied, polymethylvinylether/maleic anhydride patches released both drugs in the most sustained manner. This was followed by patches made from sodium carboxymethyl-cellulose, which released both drugs at similar rates, with almost 100% release occurring at 4 hr. The patches made from carbopol released chlorhexidine in a sustained manner similar to carboxymethylcellulose patches, but release of clotrimazole was more rapid. On the other hand, patches made from tragacanth and polyethylene oxide released 100% of chlorhexidine within the first 15 min, but resulted in prolonged release of clotrimazole. Carbopol, polyethylene oxide, and tragacanth patches thus released

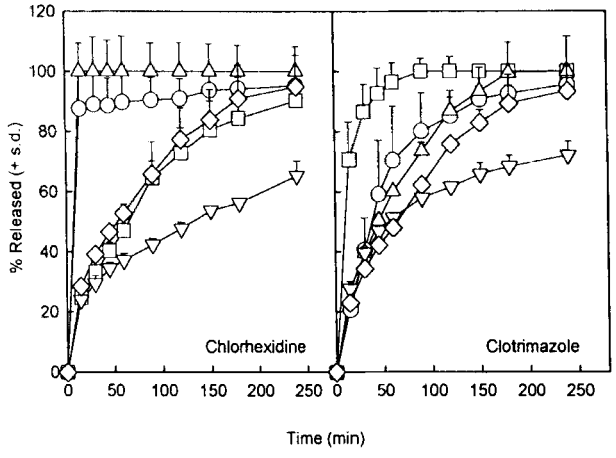

Figure 2. Release of chlorhexidine and clotrimazole from mucoadhesive patches prepared using various candidate polymers. Δ tragacanth, ○ polyethylene oxide, □ carbopol, ◇ sodium carboxymethylcellulose, ▽ polymethylvinylether/maleic anhydride.

at least one of the two drugs prematurely and hence did not yield optimum release of the two drugs.

Microbiological Assay of the Drugs Released

Percent transmission of the samples was spectrophotometrically determined against a blank. The sample at zero time, i.e., devoid of any antifungal drug, had a transmission value of 1.64%, indicating presence of turbidity as the result of microorganism growth. But the 15 min release samples from patches made from the polymers had a transmission value of almost 100%, indicating absence of microbial growth. This proved that a sufficient amount of antifungal drug had been released from the patches within a period of 15 min, so as to achieve a level of drug concentration above the MIC of the drug combination (0.015 μg/ml) (7) effective against the microorganism ($1–5 \times 10^4$ colonies/ml).

Mucoadhesive Tablet

Content Uniformity

The average content of all drugs in the tablets was 4.74 ± 0.59 mg. The individual drug loading was 4.53 (±0.58) mg for benzocaine, 4.46 (±0.34) for hydrocortisone, 4.75 (±0.72) for chlorhexidine, and 5.20 (±0.44) for clotrimazole. Thus, the amount of drugs in the tablets was very close to the theoretical 5 mg value.

Tablet Characteristics

The thickness and hardness values of the tablets are tabulated in Table 1. It can be seen that tablet thickness did not vary much from one polymer to another, except in the case of polyethylene oxide. These tablets were thicker than the others. Tablet hardness did vary substantially from one polymer to another. Tablets prepared from sodium carboxymethylcellulose and tragacanth had very low values for hardness and hence would be expected to disintegrate rapidly. Carbopol and polymethylvinylether/maleic anhydride tablets, on the other hand, were very hard and hence would result in slow disintegration and thus slow release of drugs. This difference could be attributed to the effect of polymer density, with sodium carboxymethylcellulose and tragacanth being free-flowing, high-density powders and carbopol and polymethylvinylether/maleic anhydride having low density. It has been previously demonstrated that carboxymethylcellulose tablets have high porosity values and consequently low mechanical strength (19).

Table 1

Tablet Characteristics: Thickness and Hardness

Polymer	Thickness[a] (mm)	Hardness[a] (kp)
Sodium carboxymethylcellulose	1.478 (0.003)	2.1 (0.3)
Carbopol	1.439 (0.062)	19.8 (2.0)
Polyethylene oxide	1.734 (0.003)	6.6 (0.4)
Polymethylvinylether/maleic anhydride	1.514 (0.008)	21.0 (2.1)
Tragacanth	1.571 (0.033)	1.8 (0.0)

[a]Mean of three determinations (±one standard deviation).

Bioadhesive Strength of Tablets

In situ methods for determination of bioadhesive strength are based on measuring the force or work of fracture of the adhesive bond. Depending on the direction in which the adhesive is being removed from the substrate, peel, shear, or tensile forces can be measured. Shear tests are considered to be a good simulation of the predominantly tangential forces in the in vivo situation as far as buccal mucoadhesion is concerned (21). Shear forces have thus far been mainly designed for gels, films, and patches, but recently a method for shear force measurement of tablets has been developed (13).

Force vs. time profiles for the polymers are shown in Figure 3, while the adhesion force and work of adhesion-shear (area under curve) obtained from these profiles is tabulated in Table 2. Sodium carboxymethylcellulose, carbopol, and polyethylene oxide demonstrated excellent bioadhesion to the model rabbit ileal membrane.

While sodium carboxymethylcellulose, polyethylene oxide, and carbopol all demonstrated comparable maximum adhesion force, the profiles obtained for these polymers were different. In the case of carboxymethylcellulose and polyethylene oxide tablets there was a rapid linear increase in the force experienced by the tablet as the mucosa was gradually pulled away from it. This was followed by a clean break when the tablet was detached, with a subsequent swift decline in the force experienced by the tablet. This phenomenon suggested that for these two polymers, the formation of secondary chemical bonds had not yet occurred, but that the bioadhesion was still a surface phenomenon. On the other hand, for carbopol, the increase in the force experienced by the tablet was more gradual, indicating the formation of secondary bioadhesive bonds due to the rapid swelling of carbopol. The resultant area under the curve (work of adhesion-shear) was greater for carbopol.

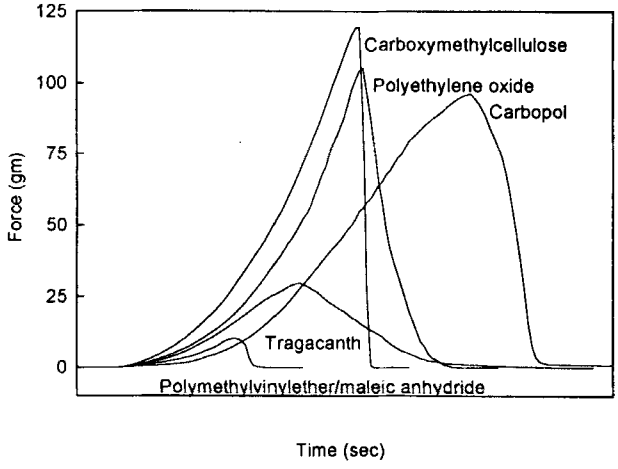

Figure 3. Typical adhesion force vs. time profile for the five polymeric tablets.

The results obtained are in very good agreement with the results of polymer swelling and polymer solution viscosity experiments performed, both of which have been said to be indicators of polymer bioadhesion. Thus, for mucoadhesive formulations, either sodium carboxymethylcellulose, or carbopol, or polyethylene oxide, or any combination of the three, should serve as excellent polymeric bases to achieve prolonged adhesion of the dosage form to the substrate.

Drug Release

Release profiles of the drugs from the five polymeric tablets are illustrated in Figure 4. As predicted from tablet hardness, sodium carboxymethylcellulose- and tragacanth-based tablets disintegrated rapidly in the dissolution medium and thus resulted in an instantaneous release of all four drugs. Polymethylvinylether/maleic

Table 2

Tablet Strength: Adhesion Force and Work

Polymer	Adhesion Force[a] (g)	Work[a] (g·cm)
Sodium carboxymethylcellulose	119.85 (0.21)	684.75 (18.75)
Carbopol	102.83 (6.50)	1343.00 (250.74)
Polyethylene oxide	109.73 (4.48)	694.28 (7.27)
Polymethylvinylether/maleic anhydride	10.97 (0.57)	242.89 (2.62)
Tragacanth	34.75 (4.96)	307.46 (26.33)

[a]Mean of three determinations (±one standard deviation).

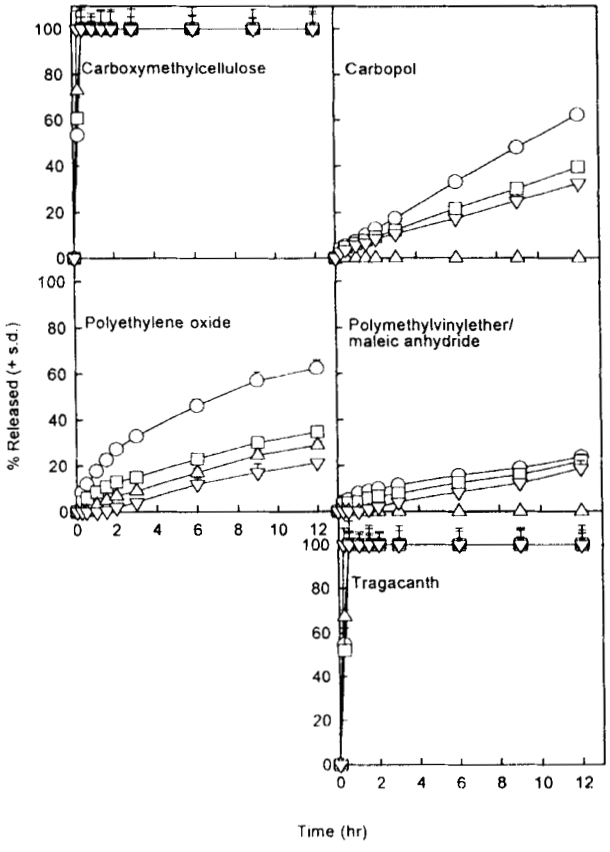

Figure 4. Release profile of the four drugs from the mucoadhesive tablets prepared using the five candidate polymers. ○ benzocaine, □ hydrocortisone, Δ chlorhexidine, ∇ clotrimazole.

anhydride-based tablets, on the other hand, released only about 20% of the drug content in the 12 hr study period. In the case of polyethylene oxide-based tablets, the release rate was fastest for benzocaine, followed by hydrocortisone and chlorhexidine, and finally clotrimazole. On complete dissolution of polyethylene oxide tablets, the consistency of the dissolution medium was found to become more slimy. This has been previously reported to be the case with polyethylene oxide tablets (19). For both carbopol- and polymethylvinylether/maleic anhydride-based tablets, the release pattern was similar to that observed with polyethylene oxide, with the exception that the release of chlorhexidine was negligible in both cases.

In order to obtain 100% release in 12 hr, sodium carboxymethylcellulose and polyethylene oxide combinations were tried. The two were combined at 75:25, 50:50, and 25:75 ratio, and tablets were prepared as described above.

As seen in Figure 5, no significant difference in drug release was observed when the ratio of polymers was varied from 75:25 to 25:75. The 75:25 combination had a slightly higher rate of release, indicating that an even higher percentage of carboxymethylcellulose in the tablets may promote drug release.

Further studies were carried out by combining carboxymethylcellulose and polyethylene oxide at 80:20, 85:15, 90:10, and 95:5 ratios. The release profiles are also illustrated in Figure 5. While the 90:10 and 95:5 polymer combinations resulted in instantaneous release of the drugs, similar to that observed with 100% sodium carboxymethylcellulose tablets, the 80:20 polymer combination released 100% of only bezocaine and about 40–50% of the other three drugs. Increasing the weight fraction of carboxymethylcellulose from 80% to 85% resulted in 80–100% release of all the four drugs in 12 hr; hence it was concluded that the optimum ratio between sodium carboxymethylcellulose and polyethylene oxide for the simultaneous release of the four drugs was around 85:15.

The release profiles of the drugs from carboxymethylcellulose:polyethylene oxide (85:15) tablets have been plotted as a function of square root of time, assuming

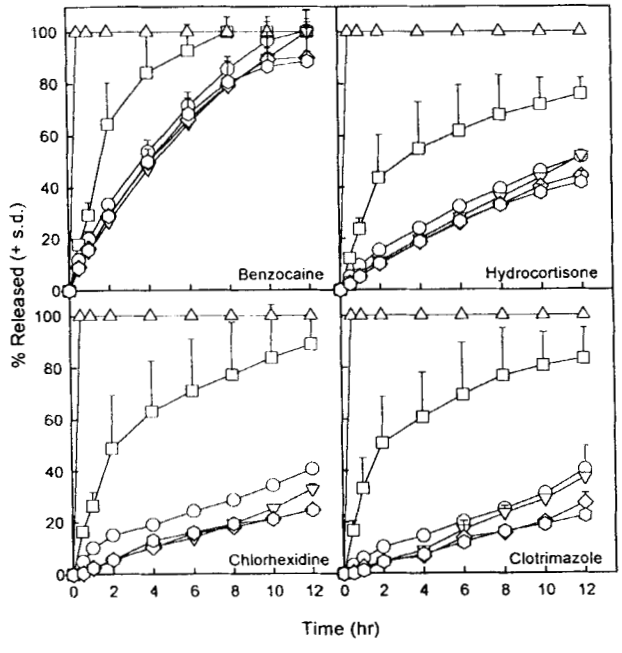

Figure 5. Release profile of the four drugs from tablets fabricated using various combinations of sodium carboxymethylcellulose and polyethylene oxide. ○ 25:75, ◇ 50:50, ∇ 75:25, ○ 80:20, □ 85:15, Δ 90:10, and 95:5.

that the polymer matrix-diffusion controlled process is in operation (Figure 6). It can be seen that release from the bioadhesive tablets is biphasic in nature due to the eventual swelling of the polymers. This phenomenon has been described in earlier reports (22,23) that state it is unreasonable to expect a kinetic behavior expressed by a dependence of release on the square root of time, as would have been the case with conventional nonswelling tablets.

Drug Loading Effect

To evaluate the effect of variation in drug loading on release, the amount of both chlorhexidine and clotrimazole was increased to 7.5 mg and 10 mg, respectively. Lower loadings could not be investigated due to the detection limit of drug assay by HPLC.

Benzocaine and hydrocortisone concentrations were maintained at 5 mg. This variation of drug loading was done in the 80:20 carboxymethylcellulose:polyethylene oxide tablets, since upon increasing the drug loading, release rates are expected to increase. This effect would not be evident in the 85:15 ratio tablets due to 100% drug release from these tablets in 12 hr.

The effect of varying antifungal drug loading on release is shown in Figure 7. As expected, an increase in the loading of the antifungals (and hence a decrease in the total polymer concentration) resulted in faster release of these drugs.

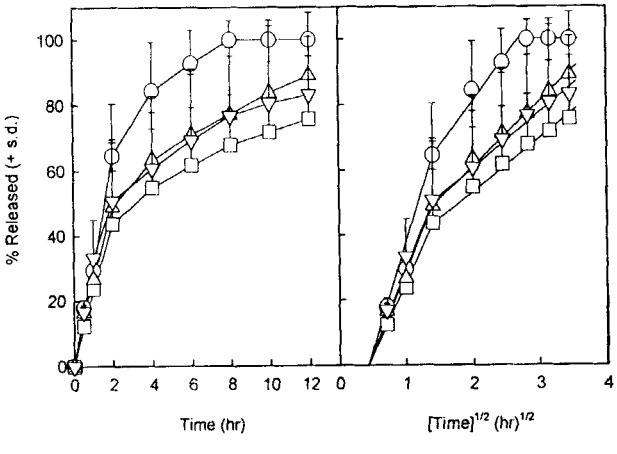

Figure 6. Release profile of the four drugs from sodium carboxymethylcellulose and polyethylene oxide combination tablets and the profile based on polymer matrix-diffusion controlled process. ○ benzocaine, □ hydrocortisone, Δ chlorhexidine, ∇ clotrimazole.

Transmucosal Permeation

The purpose of formulating a mucoadhesive tablet is to deliver drugs in the oral cavity. To ensure that no systemic absorption of released drugs through the mucosae occurs, a transmucosal permeation study across porcine buccal and alveolar mucosae was carried out. These two mucosae were chosen since the tablet would be in close contact with these membranes and the gingival membrane in the upper part of the buccal cavity. The gingival mucosa is keratinized in nature and hence has low permeability to most compounds, while the buccal and alveolar mucosae have higher permeabilities due to their nonkeratinized structure.

The transmucosal permeation experiment was carried out on the 85:15 carboxymethylcellulose:polyethylene oxide combination tablet, containing 5 mg of each active ingredient. Samples were withdrawn at 2 hr intervals for the first 12 hr and a final 24 hr sample taken to determine the effect of prolonged contact on transmucosal permeation.

The results illustrated in Figure 8 indicate that no permeation could be detected for chlorhexidene and

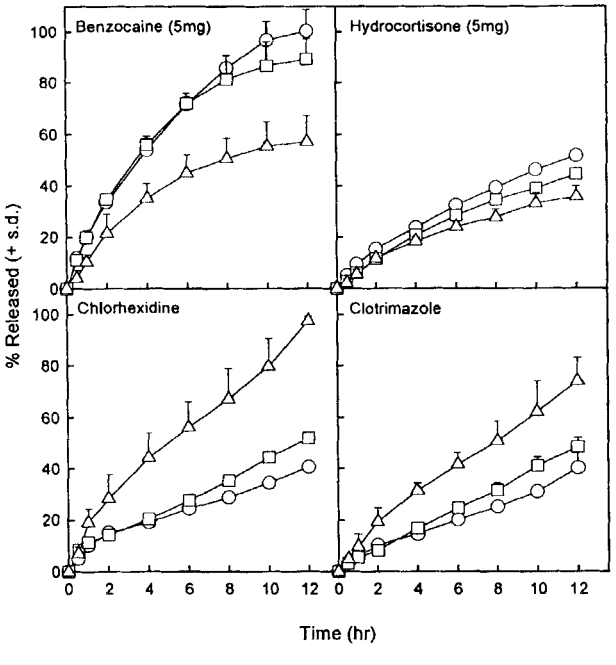

Figure 7. Effect of varying the loading level of antifungal agents, chlorhexidine, and clotrimazole on the release of the four drugs from tablets fabricated using sodium carboxymethylcellulose and polyethylene oxide (80:20). ○ 5 mg, □ 7.5 mg, Δ 10 mg.

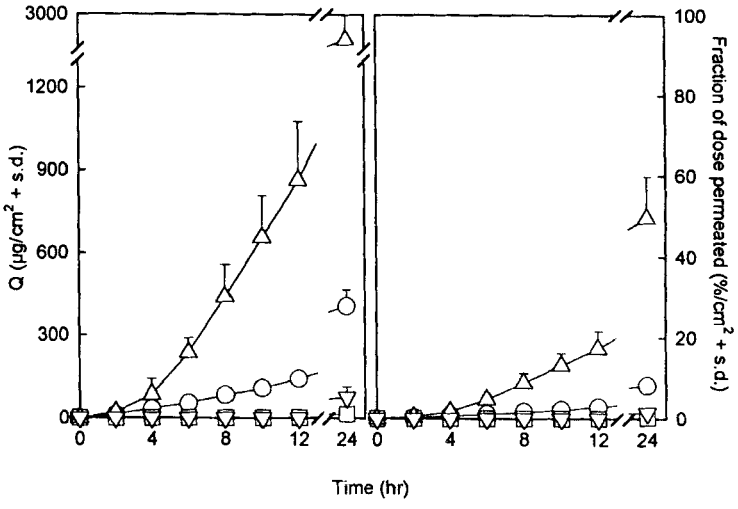

Figure 8. Transmucosal permeation profile of benzocaine and hydrocortisone from tablets fabricated using sodium carboxymethylcellulose and polyethylene oxide (85:15). Δ benzocaine–alveolar, ○ benzocaine–buccal, ∇ hydrocortisone–alveolar, □ hydrocortisone–buccal.

clotrimazole across both the buccal and alveolar membranes, even after 24 hr. Benzocaine and hydrocortisone were found to permeate more readily through the alveolar mucosa than the buccal mucosa. After 12 hr, less than 20% benzocaine and 0% hydrocortisone had permeated through the alveolar mucosa; the fraction of dose permeated increased to almost 50% and 1.5% at 24 hr. On the other hand, less than 3% benzocaine and 0% hydrocortisone permeated across the buccal mucosa in the first 12 hr; the fraction of dose permeated increased to 8% and 0.3% at 24 hr. Thus, permeation of hydrocortisone was negligible, while that of benzocaine through alveolar mucosa was rather significant.

The conditions under which these experiments were conducted—that is, prolonged exposure of the drugs to an isolated section of mucosa—tend to exaggerate the results. It must be borne in mind that under normal in vivo conditions a considerable amount of the drug would be carried away from the application site by salivary flow. Also, the results have been presented as amount/cm^2, while the actual area of the tablet was 0.50 cm^2.

CONCLUSIONS

Although none of the polymers tested resulted in sustained release of all four drugs from mucoadhesive patches, good sustained release for chlorhexidine and clotrimazole was achieved. This was especially seen in the case of polymethylvinylether/maleic anhydride- and sodium carboxymethylcellulose-based patches.

On the other hand, a sustained-release tablet was successfully prepared. Optimum release of 5 mg of each drug within the desired 12 hr period was obtained with tablets formulated from sodium carboxymethylcellulose:polyethylene oxide combination.

ACKNOWLEDGMENTS

The authors would like to acknowledge research support to Dr. M. Nair (currently at Warner-Lambert Company, 170 Tabor Road, Morris Plains, NJ 07950) from Parke-Davis Chair Endowment and Sintong Corporation.

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