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Bioadhesive Polymer Buccal Patches for Buprenorphine Controlled Delivery: Formulation, In-vitro Adhesion and Release Properties

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ABSTRACT

A new bioadhesive polymer patch formulation for buprenorphine controlled delivery and consisting of polyisobutylene, polyisoprene, and Carbopol® 934P was prepared using a two-roll milling method. Carbopol® 934P was the bioadhesive of choice for the current formulation because it demonstrated a higher average peeling strength than hydroxypropyl methylcellulose, chitosan, or acacia as measured during in vitro testing. Other in vitro analyses showed that the milling process did not alter the viscosity or the thermodynamic and rheologic properties of polyisobutylene and polyisoprene. Nearly 75% of the buprenorphine was released from the patches following a 24 hour incubation in phosphate buffer (pH=7). Data obtained from dissolution studies suggested that the major mechanism of buprenorphine release is patch swelling. It was also shown that patch adhesion increased with increasing thickness and up to three months of aging had little effect on adhesive properties. In addition, this formulation maintained the majority of its adhesive strength for at least 24 hours with a linear decline in average peeling load thereafter. In conclusion, buccal patches consisting of a homogeneous mixture of polyisobutylene, polyisoprene, and Carbopol® 934P formed by a two-roll milling process appear to possess

physical properties that are well suited for the transmucosal controlled delivery of buprenorphine.

INTRODUCTION

Absorption of therapeutic agents from the oral mucosa overcomes premature drug degradation within the gastrointestinal tract, as well as active drug loss due to first pass hepatic metabolism that may be associated with other routes of administration (1). The buccal mucosa was investigated as a potential site for drug delivery several decades ago and interest in this area for transmucosal drug administration is still growing
(1-3). This portion of the oral mucosa is an ideal surface for the placement of retentive delivery systems such as patches since it contains a large expanse of smooth, immobile tissue (1). In addition, the buccal site is less permeable than the sublingual site, a difference that makes the former a more suitable choice than the latter if sustained drug delivery is desired.

Buprenorphine is a partial μ agonist opioid analgesic that is well absorbed by both the intramuscular and sublingual routes and is 25-50 times more potent than morphine (4). The drug's onset of action occurs rapidly, with maximum blood drug levels attained within five minutes of intramuscular injection. The duration of action of buprenorphine can be extended from the 4-5 hours obtained with a single intramuscular dose to 5-6 hours with the use of sublingual administration. The latter route is already being developed as an alternative to the injectable formulation (1).

It has been suggested that drugs with biological half-lives in the range of 2-8 hours are good candidates for sustained release formulations (5). The plasma half-life (3 hours), duration of action (4-5 hours), as well as other aspects of its pharmacokinetic profile (ie, liver metabolism) make buprenorphine a suitable candidate for administration via a buccal patch that provides controlled drug delivery and bypasses first-pass hepatic metabolism.

The first step in the development of such a patch is the selection and characterization of an appropriate bioadhesive. Since dissolution of a

bioadhesive occurs naturally during oral administration, it is important to establish the duration of adhesive force provided by the chosen polymer (6). The effects of manufacturing processes on the physical properties of the individual component polymers should also be assessed. Finally, the drug dissolution profile must be evaluated. A variety of in vitro methods have previously been employed to measure these parameters (7-9).

This paper describes the in vitro characterization of a newly developed adhesive patch for the controlled delivery of buprenorphine via the buccal mucosa.

MATERIALS AND METHODS

Bioadhesion testing

The bioadhesion between hydrated polyvinyl pyrrolidone/cellulose acetate hydrogel and patches made from Carbopol® 934P (BF Goodrich, Cleveland, OH), hydroxypropyl methylcellulose (HPMC; DOW Chemical Company, Midland, MI), chitosan (Protan, Inc., Portsmouth, NH), or acacia (Fischer Scientific Company, Fair Lawn, NJ) was assessed using INSTRON (Model 4201, Instron Co., Canton, MA). Adhesion between the patches and the test surface was expressed as the average peeling strength (kg/mm) or load (kg). This methodology was used to compare four bioadhesive polymers, as well as determine bioadhesion duration and effect of thickness or aging on bioadhesion of the final patch preparation.

Buprenorphine patches for buccal controlled delivery.

The development of buccal drug patches included the establishment of suitable ratios of the chosen bioadhesive polymer, Carbopol® 934P, along with buprenorphine (Diosyngy, NJ), polyisobutylene (LMMH grade; EXXON Chemical Co., Houston, TX), and polyisoprene (GoodYear Chemical Co., Akron, OH). These components were homogeneously mixed by a two-roll mill. The polymer mixture was compressed to its desired thickness and patches of appropriate sizes were cut or punched out for in vitro testing.

In vitro testing of patch components

The effects of the milling process on the glass transition temperature, viscosity, and rheological characteristics of the individual patch components, polyisobutylene and polyisoprene, were evaluated as follows: glass transition temperatures were measured with a differential scanning calorimeter (Perkin-Elmer, Chicago, IL); viscosity was evaluated via a digital viscometer (Brookfield, Stoughton, MA); rheological properties were tested by using a rheometer (Bohlin, Cranbury, NJ).

Patch swelling and buprenorphine dissolution

Swelling and dissolution tests were performed in phosphate buffer (pH=7). Buprenorphine patches were affixed to plexiglass sample blocks and placed in flasks containing 100 ml of buffer at 37°C. Aliquots were taken at various times up to 24 hours and assayed for buprenorphine by high-pressure liquid chromatography equipped with a variable-wavelength ultraviolet/visible detector. The gradient system used in this study consisted of mobile phase, CH_3CN/16.6 mM $CH_3(CH_2)_5SO_3Na$ aqueos solution/CH_3COOH, 70%/30%/1%, (v/v/v) at flow rate 1.5 ml/min.

RESULTS

Comparison of bioadhesives

A comparison of the average peeling strength between hydrated polyvinyl pyrrolidone/cellulose acetate hydrogel and the four bioadhesives under consideration revealed that Carbopol® 934P exhibited the strongest bioadhesive strength, followed by HPMC, chitosan, and acacia (Figure 1). The average peeling strength of Carbopol® 934P under the in vitro test conditions used was 0.021 kg/mm, a value which was nearly triple that of HPMC (0.007 kg/mm), the next strongest bioadhesive. Therefore, Carbopol 934 was the polymer included in the current buccal patch formulation.

Effects of milling

The effects of patch processing by a two-roll milling method on the physical properties of polyisobutylene and polyisoprene were studied. The data show that

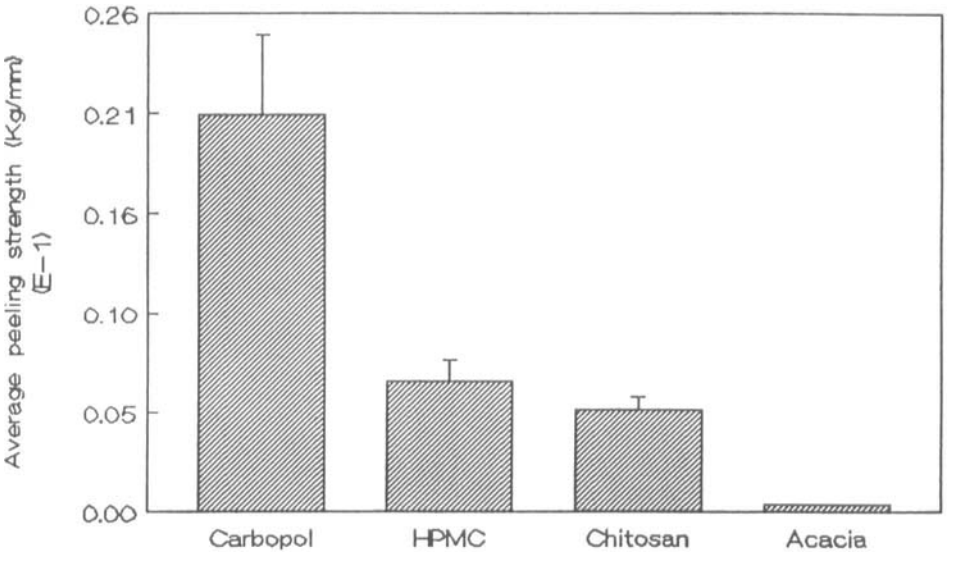


FIGURE 1
The effects of bioadhesives on the bioadhesion of buccal patches.

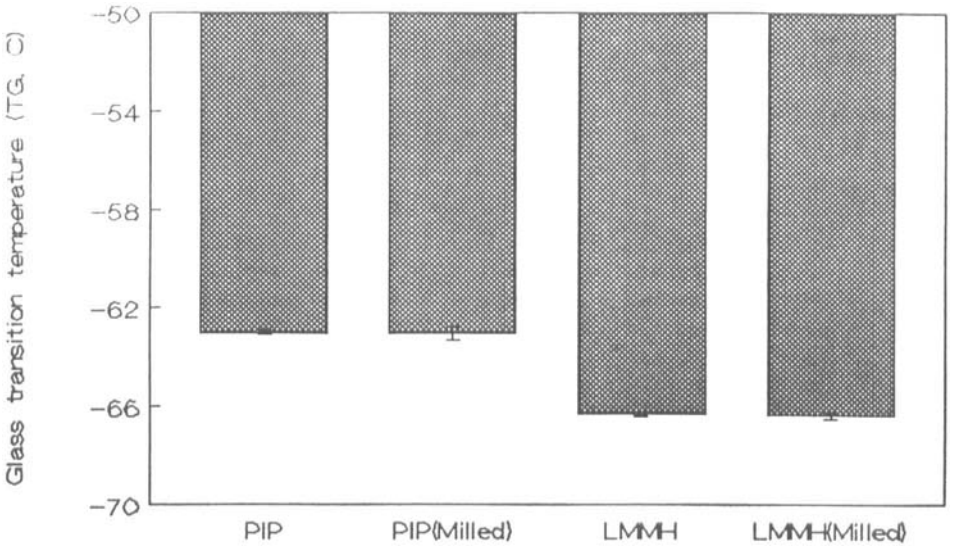


FIGURE 2
The effect of milling process on the glass transiton temperatures of polyisoprene and polyisobutylene.

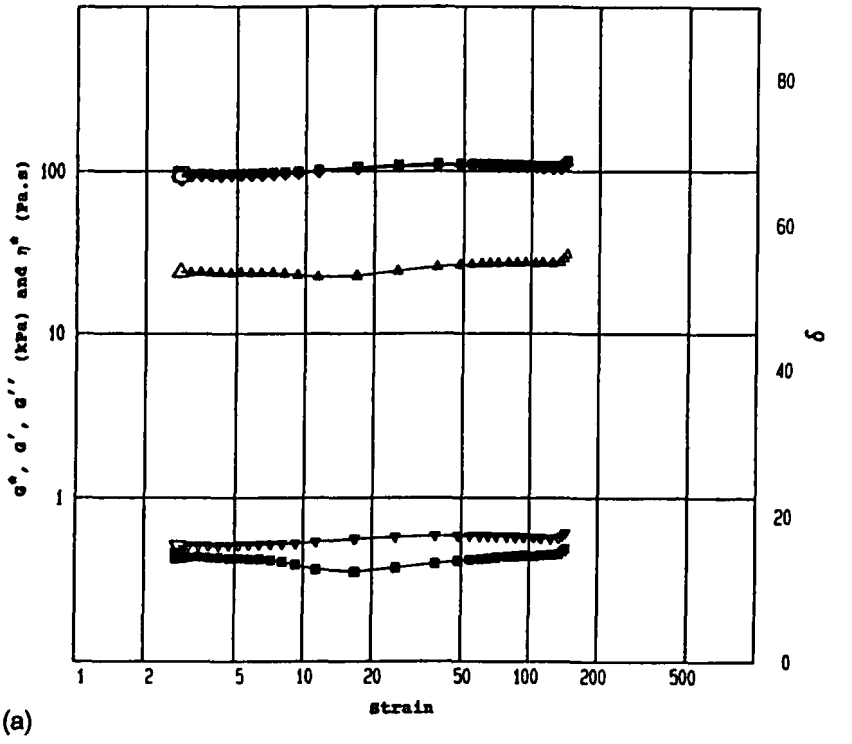
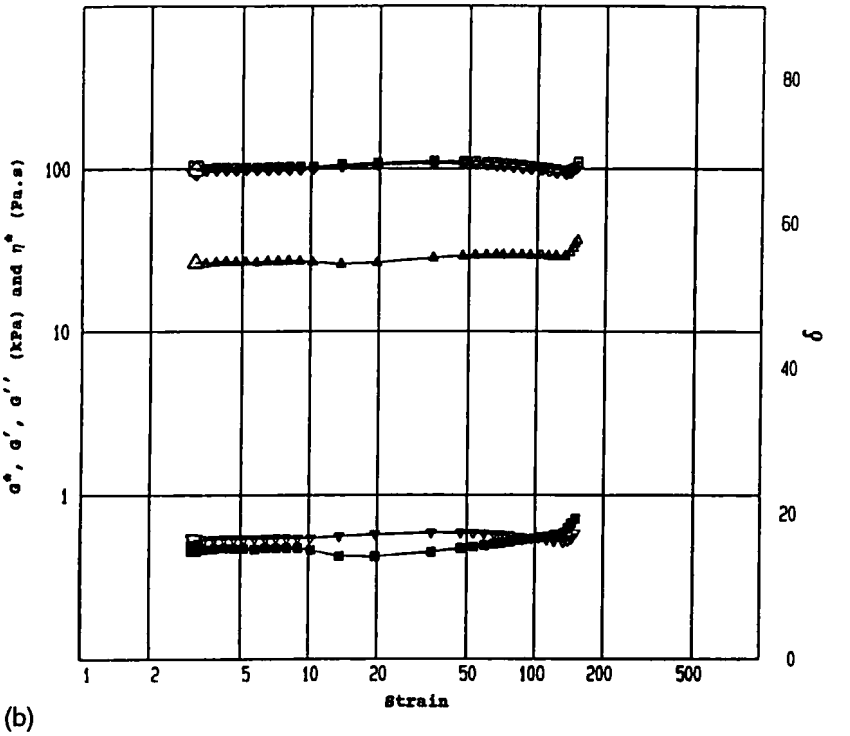


FIGURE 3
The effect of milling process on the rheologicl properties of (a) unmilled and (b) milled polyisoprene. G*(□): complex modulus, G'(◇): storage modulus, G''(△): loss modulus, η^*(▽): complex viscosity, and δ(■): phase angle.

milling did not significantly alter the glass transition temperature of either patch component (Figure 2), the rheological properties of polyisoprene (Figures 3a and 3b), or the viscosity of LMMH grade polyisobutylene (Figure 4).

Buprenorphine dissolution and patch swelling

In vitro dissolution data indicate that buprenorphine was released from the patches in a linear fashion following approximately 10 hours of hydration (Figure 5). By 24 hours, nearly 75% of the drug was released. There was a high degree of correlation between drug dissolution and water uptake. This suggests that



(b)

FIGURE 3. Continued.

swelling is the major mechanism of buprenorphine release from these buccal patches.

Effects of patch thickness and aging on bioadhesion

In vitro testing revealed that the average peeling strength of Carbopol® 934P/polyisobutylene/polyisoprene patches increased with increasing patch thickness and reached a maximum bioadhesion at a thickness of approximately 50 mil (Figure 6). Increases in thickness beyond this point did not alter bioadhesive strength. In adddition, peeling strength was not affected by aging, with 3-month-old patches retaining essentially all of the bioadhesive strength exhibited by 1-day-old patches (Figure 7).

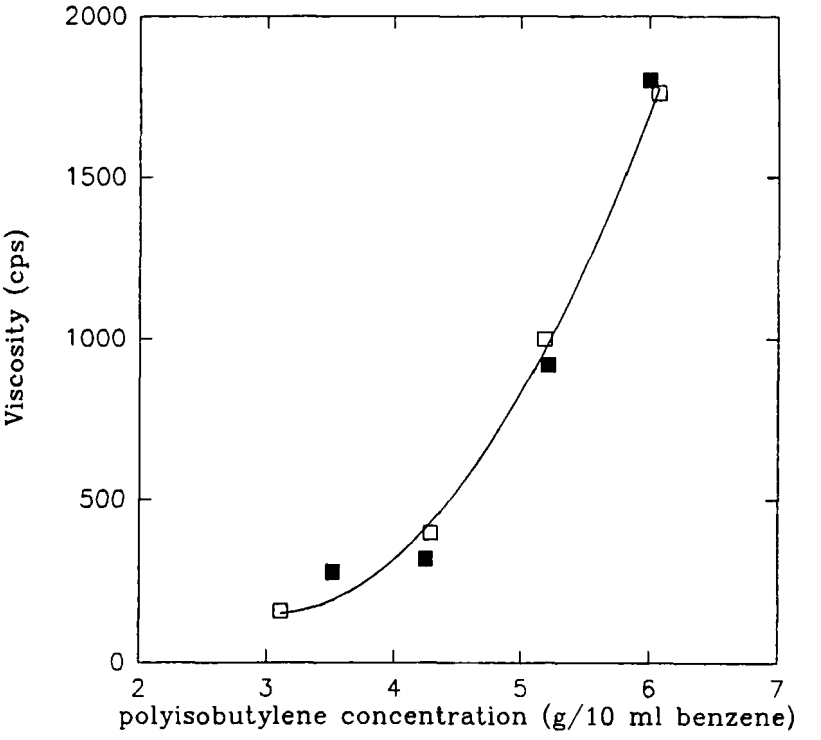


FIGURE 4
The effect of milling process on the viscosity of polyisobutylene benzene solution. (■):milled, (□):unmilled.

Duration of bioadhesion

An initial increase in bioadhesion was found following two hours of patch contact with the test medium, with average peeling strength increasing from 0.21 kg to 0.4 kg (Figure 8). When the duration of bioadhesion provided by buprenorphine buccal patches was further evaluated, it was found that there was no significant change in the average peeling load from the 2-8 hour maximum following 24 hours of contact. In fact, more than 50% of the bioadhesive strength was retained by the patches after 72 hours of contact time.

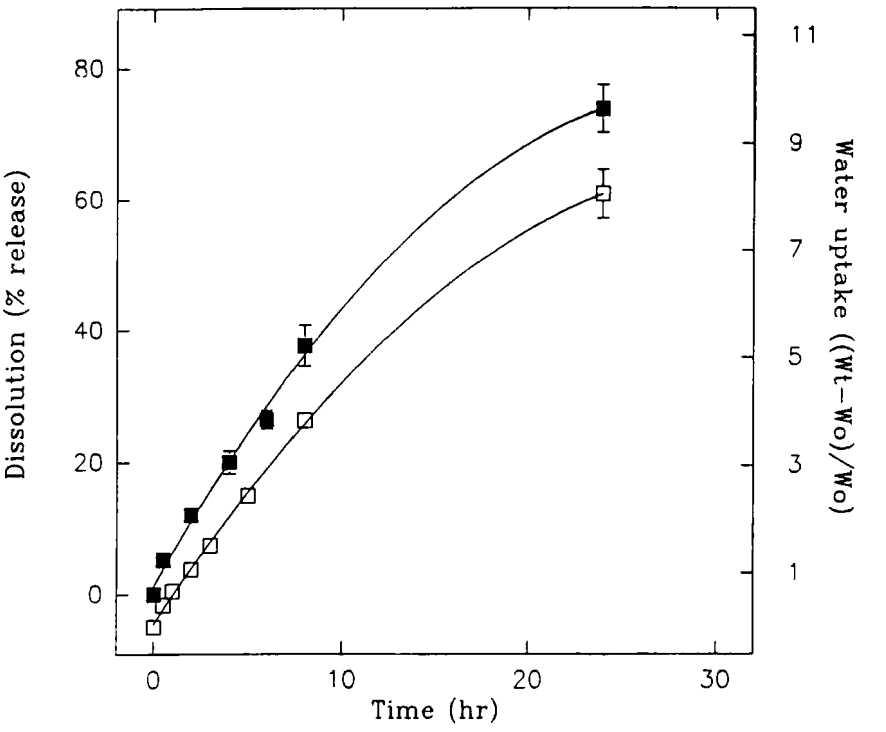


FIGURE 5
The dissolution and swelling profiles of Buprenorphine buccal patches. (■):dissolution, (□):swelling.

DISCUSSION

The in vitro data provided above indicate that the newly developed Carbopol® 934P/polyisobutylene/polyisoprene patches have the desired characteristics for the controlled buccal delivery of buprenorphine. We chose Carbopol® 934P for the current formulation because it was found to be the strongest bioadhesive of the four tested. This is in agreement with Smart et al who reported that Carbopol® 934P was the second strongest bioadhesive of 11 materials tested with a surface tension technique similar to the Wilhelmy plate

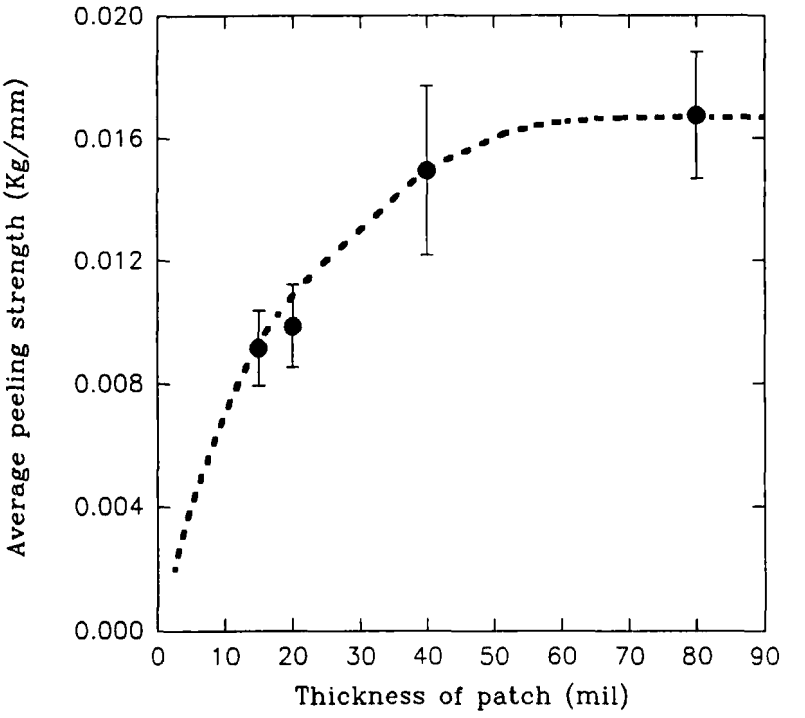


FIGURE 6
The effect of thickness on the bioadhesion of buccal patches.

method (8). Their data showed that Carbopol® 934P provided nearly twice the mucoadhesive force of acacia.

Importantly, our results showed that the milling process did not change the thermal, rheological, or viscous properties of the individual polymers used. In contrast, Anders and Merkle reported declining duration of in vivo mucosal adhesion following freeze drying and convection drying of buccal patches (6). They reasoned that drying may alter the density of the polymeric matrix and thereby affect patch swelling and drug dissolution profiles. We found no evidence that two-roll milling would affect the physical characteristics of the buprenorphine patches.

The buprenorphine dissolution profile found in the present study is similar to that reported by Nagai and Konishi for patches containing 30 mg of a freeze-

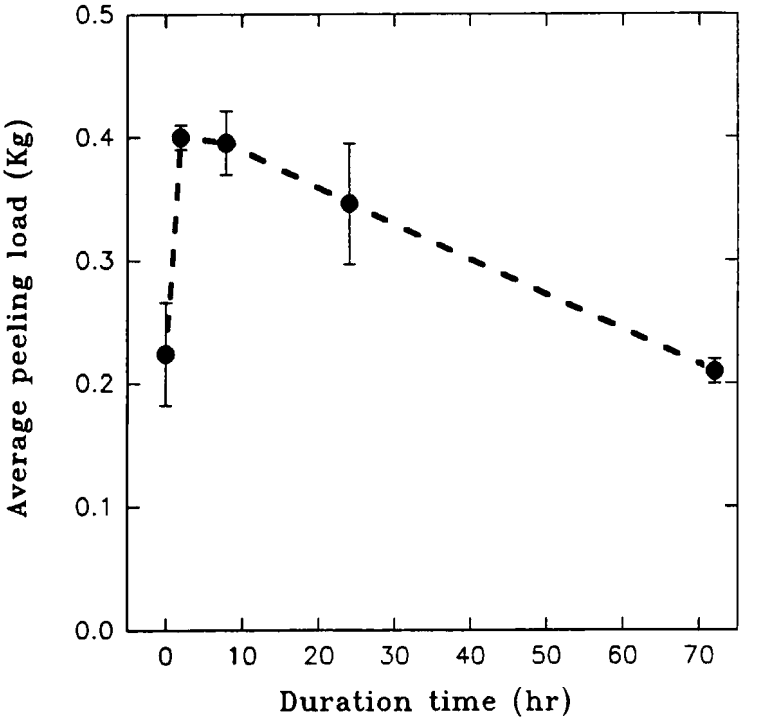


FIGURE 7
The effect of aging on the bioadhesion of bucal pathces.

dried 1:2 mixture of hydroxypropyl cellulose and Carbopol® 934P used for the buccal administration of lidocaine (3). The curve obtained with the current patches suggests a sustained delivery of buprenorphine over a 24-hour period with the ultimate release of nearly 75% of the drug. The correlation between the drug dissolution and water uptake curves also suggests that patch swelling is the major mechanism of buprenorphine release.

The bioadhesive strength of our buccal patches was found to increase with increasing thickness up to a maximum value. This is in agreement with data provided in a review by Gent and Hamed (10). The phenomenon can be explained by an alteration of the dissipation energy of patch polymers of increasing thickness (ie, increasing yield strength) under conditions of viscoelastic and plastic deformation. The bioadhesion of buprenorphine patches

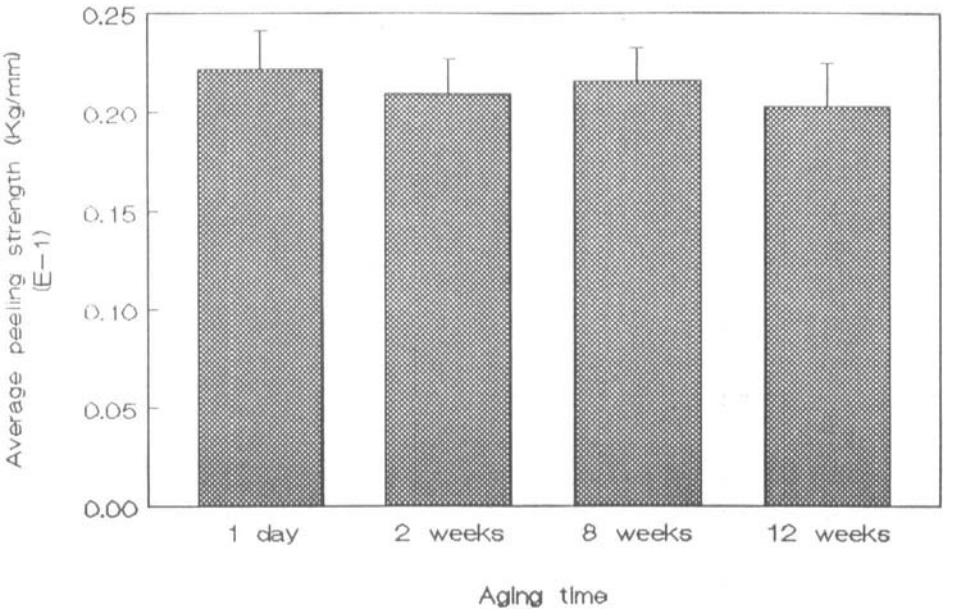


FIGURE 8
The bioadhesion duration of buccal patches.

also increased during the first few hours of contact time. A plausible explanation for this observation (based on the diffusion theory of polymer adhesion) is that the increase is due to the inter-penetration of macromolecular chains at the polymer-polymer interface (11). A majority of this maximal bioadhesive strength was retained by the patches after 24 hours. This indicates that the patches would provide the duration of mucosal adhesion required for a once-daily dosing regimen.

In conclusion, we have developed patches composed of Carbopol® 934P/polyisobutylene/polyisoprene having physical properties that are required for the controlled buccal delivery of buprenorphine.

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