Effect of Hydrophilic Polymers on Buccoadhesive Eudragit Patches of Propranolol Hydrochloride Using Factorial Design

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ABSTRACT

The purpose of this study was to develop formulations and systematically evaluate in vitro performances of buccoadhesive patches of propranolol hydrochloride using the hydrophobic polymer Eudragit L-100 as the base matrix. The hydrophilic polymers Carbopol 934 and polyvinyl pyrrolidone (PVP) K30 were incorporated into the Eudragit patches, to provide the patches with bioadhesive properties and to modify the rate of drug release. The patches, which were prepared by the solvent casting method, were smooth and elegant in appearance; were uniform in thickness, weight, and drug content; showed no visible cracks; and showed good folding endurance. A 3^2 full factorial design was employed to study the effect of independent variables like hydrophilic polymers Carbopol 934 and PVP K30, which significantly influenced characteristics like swelling index, ex vivo mucoadhesive strength, in vitro drug release, and ex vivo residence time. A stability study of optimized Eudragit patches was done in natural human saliva; it was found that both drug and buccal patches were stable in human saliva. It can be concluded that the present buccal formulation can be an ideal system to improve the bioavailability of the drug by avoiding hepatic first-pass metabolism.

KEYWORDS: Eudragit, buccal patch, propranolol hydrochloride, bioadhesion, factorial design.

INTRODUCTION

In recent years, delivery of therapeutic agents through various transmucosal routes has received significant attention owing to the agents' presystemic metabolism or instability in the acidic environment associated with oral administration.[1,2] Oral transmucosal drug delivery can be achieved through 1 of the 3 types of oral mucosa: sublingual, gingival, and buccal. Absorption of therapeutic agents from the oral cavity provides a direct entry for such agents into the systemic circulation, thereby avoiding first-pass hepatic metabolism and gastrointestinal degradation.[3,4] However, the buccal route of drug delivery has received the most attention because of its unique advantages over the other oral transmucosal routes.[5] An ideal buccal film should be flexible, elastic, and soft yet strong enough to withstand breakage due to stress from activities in the mouth. Moreover, it must also possess good mucoadhesive strength so that it is retained in the mouth for the desired duration. To prevent discomfort, swelling of the film should not be too extensive. The mechanical, bioadhesive, and swelling properties of buccal films are critical and must be evaluated. Various mucoadhesive devices, including tablets,[6] films,[7] patches,[8] disks,[9] strips,[10] ointments,[11] and gels,[12] have recently been developed. However, buccal films offer greater flexibility and comfort than adhesive tablets do. In addition, films can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva.[13]

Propranolol hydrochloride, a nonselective beta-adrenergic blocking agent, is widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. Although it is well absorbed in the gastrointestinal tract, its bioavailability is low (15%-23%) because of extensive first-pass metabolism.[14] In addition, initial plasma levels of propranolol (C_{max} between 1 and 2 hours) can vary up to 7-fold after oral administration because of individual variations in hepatic metabolism activity.[15] Since the buccal route bypasses the hepatic first-pass effect, the dose of propranolol hydrochloride could be reduced when it is formulated as a buccal patch. The physicochemical properties of propranolol hydrochloride, such as short half-life (3-5 hours) and low molecular weight (295.81 d), make it a suitable candidate for administration by the buccal route.

The purpose of this study was to develop formulations and systematically evaluate in vitro performances of buccoadhesive patches of propranolol hydrochloride using the hydrophobic polymer Eudragit L-100 as a base matrix. Hydrophilic polymers like Carbopol 934 (CP 934) and polyvinyl pyrrolidone (PVP) K30 were incorporated into Eudragit patches to provide the patches with bioadhesive properties and to modify the rate of drug release. A 3^2 full factorial design was employed to study the effect of the independent variables

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CP 934 and PVP K30 in different ratios on dependent variables like swelling index, $t_{50\%}$, $t_{80\%}$, ex vivo mucoadhesive strength, and ex vivo residence time.

Materials and Methods

Materials

Propranolol hydrochloride (99.96% purity) and CP 934 were gifts from Sarabhai Chemicals Ltd (Baroda, India). Eudragit L-100 was a gift from Helios Pharmaceuticals Ltd (Ahmedabad, India). PVP K30 was obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

Preparation of Mucoadhesive Buccal Patches

The buccal patches were prepared by dissolving the drug in a Eudragit dispersion of ethyl alcohol (95%). To improve drug release and bioadhesive characteristics, the hydrophilic polymers CP 934 and PVP K30 were dissolved separately in ethyl alcohol and then incorporated into the Eudragit dispersion with constant stirring, to obtain a clear solution (50 rpm, 30 minutes). Propylene glycol (5% vol/vol) was added as a plasticizer with constant stirring. The solvent casting technique was used for the preparation of patches.[16] The gel was cast into a glass petri dish and covered with an inverted funnel, the end of which was plugged with cotton wool to allow controlled evaporation of the solvent. These were left undisturbed at room temperature (20°C-30°C) for 24 hours, till a flexible film was formed. Buccal patches were punched out from the film using a specially fabricated punch, packed in aluminum foil, and stored in glass containers.

Folding Endurance

The folding endurance of patches was determined by repeatedly folding 1 patch at the same place till it broke or was folded up to 200 times without breaking.[17] The experiments were performed in triplicate, and average values were reported.

Content Uniformity

Drug content uniformity was determined by dissolving each patch in 10 mL of ethyl alcohol and filtering with Whatman filter paper (0.45 μm). The filtrate was evaporated and drug residue dissolved in 100 mL of phosphate buffer (pH 6.8). The 5-mL solution was diluted with phosphate buffer (pH 6.8) up to 20 mL, filtered through a 0.45-μm Whatman filter paper, and analyzed at 290 nm[18] using a UV spectrophotometer (Shimadzu, SPD-10 A VP, Kyoto, Japan). The experiments were performed in triplicate, and average values were reported.

Swelling Study

Buccal patches were weighed individually (designated as W1) and placed separately in 2% agar gel plates,[19] incubated at 37°C ± 1°C, and examined for any physical changes. At regular 1-hour time intervals until 3 hours, patches were removed from the gel plates and excess surface water was removed carefully using the filter paper. The swollen patches were then reweighed (W2), and the swelling index (SI) was calculated using the following formula[20]:

$$SI = \frac{(W2 - W1)}{W1} \times 100 \quad (1)$$

The experiments were performed in triplicate, and average values were reported.

Ex Vivo Mucoadhesive Strength

Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer (pH 6.8) at 37°C.

The patch's bioadhesive strength was measured on a modified physical balance using the method described by Gupta et al.[21] The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer (pH 6.8). A piece of buccal mucosa was tied in the open mouth of a glass vial, filled with phosphate buffer (pH 6.8). This glass vial was tightly fitted into a glass beaker filled with phosphate buffer (pH 6.8, 37°C ± 1°C) so it just touched the mucosal surface. The patch was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive. Two pans of the balance were balanced with a 5-g weight on the right-hand side pan. The 5-g weight was then removed from the left-hand side pan, which lowered the pan along with the patch over the mucosa. The balance was kept in this position for 5 minutes of contact time. The water was added slowly at 100 drops/min to the right-hand side pan until the patch detached from the mucosal surface. The weight, in grams, required to detach the patch from the mucosal surface provided the measure of mucoadhesive strength. The experiments were performed in triplicate, and average values were reported.

Ex Vivo Residence Time

The ex vivo mucoadhesion time was studied (n = 3) after application of patches on freshly cut sheep buccal mucosa.[22] The fresh sheep buccal mucosa was fixed in the inner side of a beaker, about 2.5 cm from the bottom, with cyanoacrylate glue. One side of each patch was wetted with 1 drop

of phosphate buffer (pH 6.8) and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 200 mL of phosphate buffer (pH 6.8) and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and patch adhesion was monitored for 12 hours. The time required for the patch to detach from the sheep buccal mucosa was recorded as the mucoadhesion time.

Surface pH Study

The method adopted by Bottenberg et al was used to determine the surface pH of patches.[23] A combined glass electrode was used for this purpose. Each patch was allowed to swell by keeping it in contact with 1 mL of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature, and the pH was noted by bringing the electrode into contact with the surface of the patch and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate, and average values were reported.

In Vitro Drug Release

The US Pharmacopeia XXIII rotating paddle method was used to study drug release from the buccal patches; 200 mL of phosphate buffer (pH 6.8) was used as the dissolution medium, at 37.0 ± 0.5°C, and a rotation speed of 50 rpm was used. One side of the buccal patch was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was put in the bottom of the dissolution vessel.[24] Samples (5 mL) were withdrawn at half-hour intervals and replaced with fresh medium. The samples were filtered through 0.45-μm Whatman filter paper and analyzed. The experiments were performed in triplicate, and average values were reported.

In Vitro Buccal Permeation Study

The in vitro buccal permeation study of propranolol hydrochloride through the sheep buccal mucosa was performed using a Keshary-Chien type glass diffusion cell at 37°C ± 0.2°C. Sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. Freshly obtained sheep buccal mucosa was mounted between the donor and receptor compartments. The patch was placed on the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 mL of phosphate buffer (pH 6.8). The receptor compartment (15-mL capacity) was filled with isotonic phosphate buffer (pH 7.4), and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at 50 rpm. At predetermined time intervals, a 1-mL sample was withdrawn and analyzed. The experiments were performed in triplicate, and average values were reported.

Stability Study in Human Saliva

The stability study of patches was performed in natural human saliva.[25] Human saliva was collected from humans (ages 18-50 years) and filtered. Patches were placed in separate petri dishes containing 5 mL of human saliva and put in a temperature-controlled oven (Hicon, Groover Enterprises, Delhi, India) at 37°C ± 0.2°C for 6 hours. At regular time intervals (0, 1, 2, 3, and 6 hours), patches were examined for changes in color and shape, collapse, and drug content. The experiments were performed in triplicate, and average values were reported.

Results and Discussion

The Eudragit patches were evaluated for important parameters like swelling index, ex vivo mucoadhesive strength, in vitro drug release, and general appearance. Patches containing only drug and Eudragit (P1) showed the lowest (0.5 g) ex vivo mucoadhesive strength (0.5 ± 0.1) on sheep buccal mucosa, which indicated that Eudragit has no bioadhesive properties (Table 1). These patches also had the lowest swelling index (0.6 ± 2.31) when patches were kept on 2% agar gel plates, possibly because of Eudragit's hydrophobic nature. Similar results were obtained by Ilango et al,[26] who showed that Eudragit L-100 patches had no swelling property. The addition of the hydrophilic polymer CP 934 significantly improved the bioadhesion of patches but decreased the drug release, as shown in P2 to P12. Also, incorporation of the hydrophilic polymer PVP K30 enhanced the drug release and swelling index but significantly decreased the mucoadhesive strength. Patches containing drug and Eudragit (P1) had good physical appearance, perhaps because of Eudragit's film-forming property. Patches containing a higher concentration of CP 934 had an unsatisfactory physical appearance (P2 and P3), while patches containing a higher concentration of PVP K30 had a good physical appearance because of PVP K30's film-forming property. On the basis of preliminary trials, buccoadhesive patches of propranolol hydrochloride using the hydrophobic polymer Eudragit L-100 as the base matrix were prepared by full factorial design to obtain good physical properties.

3^2 Full Factorial Design

A 3^2 randomized full factorial design was used in this study. Two factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations (Table 2). The amount of CP 934 (X1) and the amount of PVP K30 (X2) were selected as independent variables. The

Table 1. Preliminary Trial of Eudragit Patches Containing Propranolol Hydrochloride*

Batch Code	EL-100 (mg)	CP 934 (mg)	PVP K30 (mg)	SI (%)	MS† (g)	In Vitro Drug Release† (%) at 4 Hours	Patch Appearance
P1	1300	—	—	0.6 ± 2.31	0.5 ± 0.1	36 ± 3.21	Good
P2	1000	275	25	5 ± 1.24	32.0 ± 3.4	45 ± 4.12	NS
P3	1000	250	50	8 ± 3.04	29.0 ± 1.5	51 ± 3.33	NS
P4	1000	225	75	12 ± 2.46	14.0 ± 1.2	77 ± 2.54	Good
P5	1000	200	100	14 ± 3.11	13.0 ± 1.4	78 ± 3.95	Good
P6	1000	175	125	17 ± 2.22	11.0 ± 2.0	82 ± 4.00	Good
P7	1000	150	150	21 ± 3.07	9.0 ± 3.0	84 ± 1.84	Good
P8	1000	125	175	22 ± 3.40	7.0 ± 2.5	92 ± 3.41	Good
P9	1000	100	200	26 ± 1.14	6.0 ± 2.8	99 ± 2.88	Good
P10	1000	75	225	29 ± 3.19	4.0 ± 1.8	100 ± 1.26	Good
P11	1000	50	250	30 ± 2.13	3.0 ± 3.2	100 ± 1.85	Good
P12	1000	25	275	31 ± 2.55	2.0 ± 2.4	100 ± 1.14	Good

*All batches were prepared with 640 mg of propranolol hydrochloride, 0.5 mL of propylene glycol, and 25 mL of ethanol (95%). EL-100 indicates Eudragit L-100; CP 934, Carbopol 934; PVP K30, polyvinyl pyrrolidone K30; SI, swelling index; MS, ex vivo mucoadhesive strength; NS, not satisfactory.
†Statistical significance ($P < .05$) was observed.

time required for 50% and 80% in vitro drug dissolution, ex vivo mucoadhesive strength, ex vivo residence time, and swelling index were selected as dependent variables. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (2)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i is the estimated coefficient for the factor X_i. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The statistical analysis of the factorial design batches was performed by multiple linear regression analysis using Microsoft Excel. The results depicted in Table 3 clearly indicate that all the dependent variables are strongly dependent on the selected independent variables, as shown by the wide variation among the 9 batches (E1-E9). The fitted equations (full model) relating the responses—that is, ex vivo mucoadhesive strength, ex vivo residence time, $t_{50\%}$, $t_{80\%}$, and swelling study—to the transformed factor are shown in Table 3. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (ie, positive or negative). The values of the correlation coefficient were found to be statistically significant at the 5% confidence level.

Table 2. The 3^2 Full Factorial Design Layout of Patches Containing Propranolol Hydrochloride*

	Variable Levels in Coded Form						
Batch Code	X_1	X_2	SI (%)	BS (g)	RT (min)	$t_{50\%}$	$t_{80\%}$
E1	–1	–1	18 ± 2.0	10 ± 0.3	207 ± 8	119 ± 2	211 ± 8
E2	–1	0	23 ± 2.5	7 ± 0.4	178 ± 6	105 ± 3	181 ± 9
E3	–1	1	29 ± 3.0	4 ± 0.2	135 ± 10	86 ± 5	159 ± 7
E4	0	–1	14 ± 1.5	12 ± 0.5	234 ± 12	129 ± 10	225 ± 12
E5	0	0	21 ± 1.0	9 ± 0.6	198 ± 8	120 ± 8	205 ± 8
E6	0	1	26 ± 2.5	7 ± 0.4	180 ± 6	105 ± 6	191 ± 6
E7	1	–1	12 ± 1.0	14 ± 0.5	254 ± 4	147 ± 4	242 ± 4
E8	1	0	18 ± 3.0	12 ± 0.4	236 ± 10	134 ± 3	230 ± 8
E9	1	1	24 ± 3.5	11 ± 0.4	221 ± 11	109 ± 4	199 ± 9
Translation of Coded Levels in Actual Units							
Variable Levels			**Low (–1)**		**Medium (0)**		**High (1)**
Carbopol 934 (mg)			75		150		225
Polyvinyl pyrrolidone K30 (mg)			75		150		225

*SI indicates swelling index; BS, ex vivo bioadhesive strength; RT, ex vivo residence time.

Table 3. Regression Analysis of Patches Containing Propranolol Hydrochloride*

Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
SI (%)	20.44	–2.67	5.83	0.25	0.33	–0.17	0.99
BS (g)	9.11	2.66	–2.33	0.75	0.33	0.33	0.99
RT (min)	203.22	31.83	–26.50	9.75	1.13	1.67	0.99
$t_{50\%}$	122.37	13.87	–15.77	–1.25	–0.88	–5.74	0.99
$t_{80\%}$	206.50	19.91	–21.71	2.30	–3.52	–1.31	0.99

*SI indicates swelling index; BS, ex vivo bioadhesive strength; RT, ex vivo residence time.

Assessment of weight uniformity was done in 10 different randomly selected patches from each batch, and the thickness of patches was measured using a screw gauge at 5 different randomly selected spots from each batch. The means and standard deviations were calculated. Patches showed no visible cracks and showing good folding endurance (Table 4). The drug content in the buccal patches was uniform, indicating that the drug was dispersed uniformly throughout the patches. Patches had a surface pH of 5.82 ± 0.08 to 7.11 ± 0.10. Table 4 shows the important physicochemical parameters of Eudragit buccoadhesive patches of propranolol hydrochloride.

Full Model for Swelling Index

Patches containing hydrophilic polymers CP 934 and PVP K30 showed considerable swelling. The swelling index was found to be proportional to the PVP K30 content and inversely proportional to the CP 934 content. Examination of patches during the dissolution studies revealed that patches showed considerable swelling and gel formation, especially when the hydrophilic polymer PVP K30 was incorporated at higher concentrations. Addition of a certain amount of the hydrophilic polymers increased surface wettability and, consequently, water penetration within the matrix. Patches did not show any appreciable changes in their shape and form during the 3 hours when patches were kept on a 2% agar gel plate. The swelling behavior of patches as a function of time is shown in Figure 1.

The swelling index varied from 12% to 29% (Table 2) and had a good correlation coefficient (Table 3). Thus, it can be concluded that the concentration of CP 934 and PVP K30 had a good effect on the swelling index of the Eudragit patches. The results of the equation indicate that the effect of X_1 (the concentration of CP 934) was greater than the effect of X_2 (the concentration of PVP K30). Moreover, the concentration of CP 934 had a negative effect on percent swelling index; that is, as the concentration of CP 934 increased the percent swelling index decreased.

Full Model for Ex Vivo Mucoadhesive Strength and Ex Vivo Residence Time

Figure 2 shows that the ex vivo mucoadhesive strength was increased linearly with increasing concentration of CP 934 after 5 minutes of contact time with sheep buccal mucosa. The increase in mucoadhesivity may be due to the formation of a strong gel that penetrates deeply into the mucin molecules.[27] The ex vivo mucoadhesive strength after 5 minutes of contact time with sheep buccal mucosa varied from 4 (E3) to 14 g (E7) (Figure 2) and had a good correlation coefficient (Table 3). The results also indicate that the effect of X_1 (concentration of CP 934) was more significant than the effect of X_2 (concentration of PVP K30). Moreover, PVP K30 had a negative effect on ex vivo mucoadhesive strength; that is, as the concentration of PVP K30 increased the ex vivo mucoadhesive strength decreased.

The ex vivo residence time with sheep buccal mucosa in phosphate buffer (pH 6.8) varied from 135 to 254 minutes (Table 2) and had a good correlation coefficient (Table 3). The results also indicate that the effect of X_1 (concentration of CP 934) was more significant than the effect of

Table 4. Important Physicochemical Parameters of Patches Containing Propranolol Hydrochloride

Batch Code	Weight (mg)	Thickness (mm)	Folding Endurance	Drug Content (%)	Surface pH	Ex Vivo Residence Time (min)
E1	68 ± 0.52	0.25 ± 0.05	>200	99.78 ± 0.25	7.11 ± 0.10	207 ± 4
E2	73 ± 0.61	0.30 ± 0.03	>200	99.35 ± 0.21	7.02 ± 0.06	178 ± 6
E3	75 ± 1.00	0.40 ± 0.06	>200	100.58 ± 0.45	6.98 ± 0.10	135 ± 8
E4	73 ± 0.76	0.30 ± 0.07	>200	100.65 ± 0.26	6.75 ± 0.09	234 ± 3
E5	77 ± 0.32	0.38 ± 0.04	>200	94.50 ± 0.35	6.81 ± 0.04	198 ± 5
E6	80 ± 0.76	0.45 ± 0.03	>200	99.35 ± 0.35	6.76 ± 0.07	180 ± 7
E7	79 ± 0.84	0.41 ± 0.05	>200	100.18 ± 0.33	5.82 ± 0.08	254 ± 4
E8	82 ± 0.57	0.48 ± 0.04	>200	99.25 ± 0.43	5.95 ± 0.11	236 ± 5
E9	86 ± 0.51	0.53 ± 0.06	>200	99.68 ± 0.56	5.88 ± 0.14	221 ± 4

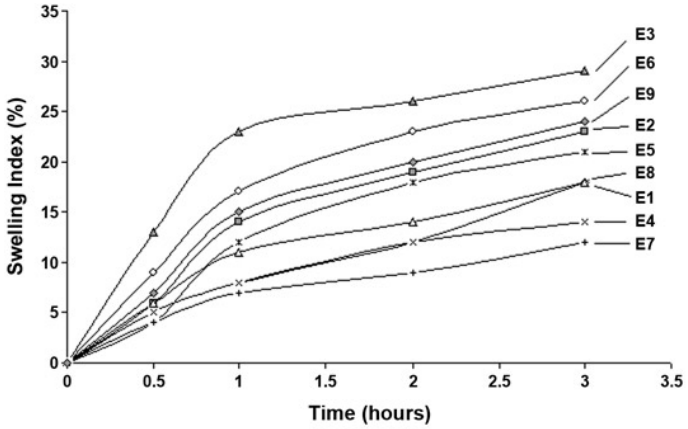

Figure 1. Swelling study of buccal patches.

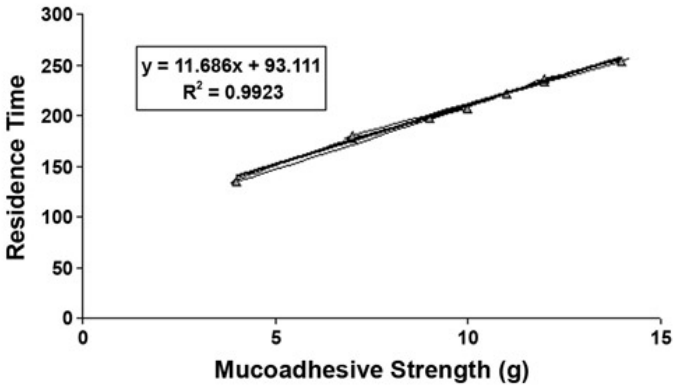

Figure 3. Correlation between ex vivo mucoadhesion and ex vivo residence time.

X_2 (concentration of PVP K30). Moreover, PVP K30 had a negative effect on ex vivo mucoadhesive strength; that is, as the concentration of PVP K30 increased the ex vivo mucoadhesive strength decreased. Good correlation was observed between ex vivo mucoadhesive strength and ex vivo residence time with a correlation coefficient of 0.9923 (Figure 3).

Full Model for Drug Release Profile

Patches containing only drug and Eudragit L-100 showed the minimum in vitro drug release. The drug release rate appeared to increase with an increasing amount of the hydrophilic polymers. The drug release from the Eudragit patches could be modified by addition of the hydrophilic polymers. This observation was in good agreement with the results obtained by Bodmeier and Paeratakul.[28] The increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water-soluble drug. Moreover, the hydrophilic polymers would leach out and, hence, create more pores and channels for the drug to diffuse out of the patches.[28] For patches with CP 934, drug release was sustained even as the CP 934 content increased. This could have been due to the extensive swelling of the polymers, which created a thick gel barrier, making drug diffusion more difficult. In patches containing hydrophilic polymers, the drug release was increased linearly with increasing concentrations of PVP K30 and decreasing concentrations of CP 934. The in vitro release behavior of propranolol hydrochloride from different patches is shown in Figure 4.

The $t_{50\%}$ and $t_{80\%}$ are important variables for assessing the drug release profiles from the dosage forms, thus suggesting how much drug is available at the site of absorption. These parameters are dependent on the formulation variables. The dissolution studies were performed for 240 minutes. The concentration of drug release from the Eudragit patches varied from 77% to 100% (Figure 4) and had a good correlation coefficient (Table 3). The results also indicate that the effect of X_1 (CP 934) was more significant than the effect of X_2 (PVP K30). Also, PVP K30 had a negative effect on $t_{50\%}$ and $t_{80\%}$; that is, as the concentration of PVP K30 increased the $t_{50\%}$ and $t_{80\%}$ decreased.

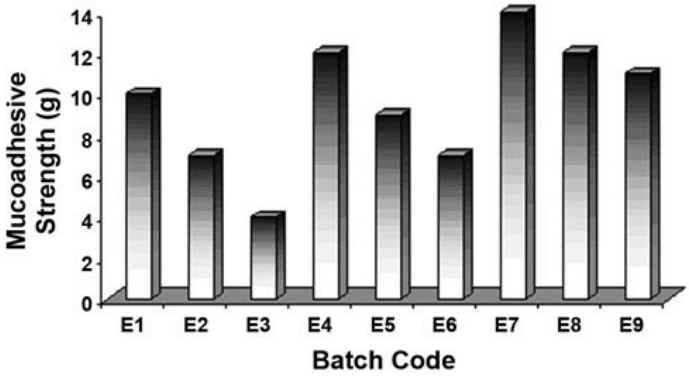

Figure 2. Ex vivo mucoadhesion of patches.

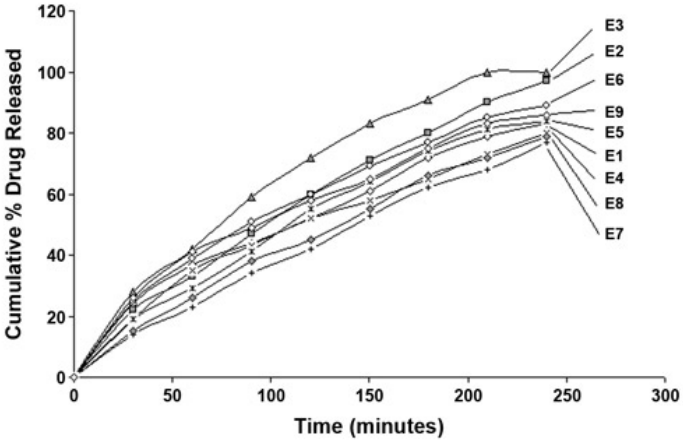

Figure 4. In vitro drug release study of patches.

The release data were analyzed using the well-known semi-empirical Peppas equation:

$$\frac{Mt}{M\infty} = kt^n \quad (3)$$

where Mt/M∞ is the drug fraction released at time t, and k and n are constants incorporating structural and geometric characteristics of the drug/polymer system.[29,30] In particular, the exponent n is related to the release mechanism: its value ranges from 0.5 (Fickian release) to 1.0 (zero-order kinetics), while n values between 0.5 and 1.0 are indicative of non-Fickian, "anomalous" release. The n values used for analysis of the drug release mechanism from patches were determined from log(Mt/Mα) vs log(t) plots, and these values were between 0.5 and 1.0, indicating that the release of propranolol hydrochloride was by non-Fickian diffusion. These obtained values of k (kinetic constant), n (diffusional exponent), and r^2 (correlation coefficient) are presented in Table 5.

Patch E7 was considered to be the optimal patch on the basis of its moderate swelling, convenient ex vivo residence time, ex vivo mucoadhesive strength, and adequate in vitro drug release (Tables 2 and 3). The E7 patch was thus optimized for investigation of in vitro drug permeation through sheep buccal mucosa and a stability study in natural human saliva. The E7 patch had 65% ± 2.72% drug permeation in 240 minutes. The straight line and the high correlation coefficient value (r = 0.9923) proved the good correlation between in vitro drug release and in vitro drug permeation studies.

Usually, stability studies are performed in phosphate buffer solution, whose pH pertains to the buccal cavity. Stability studies performed in natural human saliva would better assess the stability of the drug and the device in the oral cavity in vivo. Therefore, the stability study of the optimized patches (E7) was done in natural human saliva. The E7 patches were evaluated by their appearance characteristics, such as color and shape, and their drug content in natural human saliva. The patches did not exhibit any changes in shape, suggesting the satisfactory stability of the drug and the device in human saliva. The physical properties of the optimized patches, such as thickness and diameter, increased slightly owing to swelling of the system in human saliva.

Table 5. Kinetic Constants (k), Release Exponents (n), and Determination Coefficients (r^2) Following Linear Regression of In Vitro Drug Release of Propranolol

	Peppas Model		
Batch Code	k (%h^{-1})	r^2	n
F1	0.2612	0.9871	0.8338
F2	0.2982	0.9968	0.8508
F3	0.2939	0.9877	0.8831
F4	0.2567	0.9933	0.8200
F5	0.2669	0.9980	0.8270
F6	0.2728	0.9876	0.8528
F7	0.2588	0.9991	0.7864
F8	0.2610	0.9997	0.8003
F9	0.2652	0.9829	0.8487

CONCLUSION

From the above study, one can conclude that Eudragit buccal adhesive patches can be successfully used as a mucoadhesive carrier in buccal drug delivery systems for drugs with high first-pass metabolism.

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