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Formulation, Evaluation, and Comparison of Bilayered and Multilayered Mucoadhesive Buccal Devices of Propranolol Hydrochloride

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ABSTRACT

The purpose of this research work was to establish mucoadhesive buccal devices of propranolol hydrochloride (PRH) in the forms of bilayered and multilayered tablets. The tablets were prepared using sodium carboxymethylcellulose (SCMC) and Carbopol-934 (CP) as bioadhesive polymers to impart mucoadhesion and ethyl cellulose (EC) to act as an impermeable backing layer. Buccal devices were evaluated by different parameters such as weight uniformity, content uniformity, thickness, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, ex vivo mucoadhesion time, in vitro drug release, and in vitro drug permeation. As compared with bilayered tablets, multilayered tablets showed slow release rate of drug with improved ex vivo bioadhesive strength and enhanced ex vivo mucoadhesion time. The mechanism of drug release was found to be non-Fickian diffusion (value of n between 0.5 and 1.0) for both the buccal devices. The stability of drug in both the optimized buccal devices was tested for 6 hours in natural human saliva; both the buccal devices were found to be stable in natural human saliva. The present study concludes that mucoadhesive buccal devices of PRH can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of PRH.

KEYWORDS: Bilayered buccal tablet, multilayered buccal tablet, buccal delivery, mucoadhesion, propranolol hydrochloride.

INTRODUCTION

The interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs impaired by the narrow absorption window in the gastrointestinal tract. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. This route has been used successfully for the systemic delivery of number of drug candidates.[1-5] Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route.[6,7] Moreover, buccal drug delivery offers a safe and easy method of drug utilization, because drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity. It is an alternative route to administer drugs to patients who are unable to be dosed orally. Therefore, adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive tablets,[8,9] adhesive gels,[10,11] and adhesive patches.[1,4]

During the past decade, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery because of their ability to localize the dosage form in specific regions to enhance drug bioavailability.[12] Bioadhesive polymers can not only cause the adhesion effects but can also control the release rate of the drug.[13] From a technological point of view, an ideal buccal dosage form must have 3 properties. It must (1) maintain its position in the mouth for a few hours; (2) release the drug in a controlled fashion, and (3) provide the drug release in a unidirectional way toward the mucosa. In regard to the first requirement, strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can also be achieved. The third objective can be fulfilled by preparing a system having uniform adhesiveness and impermeable backing layer.[14,15]

Propranolol hydrochloride (PRH), 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%) as a result of extensive first-pass metabolism.[16,17] Since the buccal route bypasses the hepatic first-pass effect, the dose of PRH can be reduced. The physicochemical properties of PRH, its suitable half-life (3-5 hours), and its low molecular weight 295.81 make it a suitable candidate for administration by the buccal route.

In the present study, the objective was to prepare mucoadhesive buccal devices of PRH to prolong the residence time

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Table 1. Composition of Bilayered Buccal Tablets of Propranolol Hydrochloride*

Ingredients (mg/tablet)	Batch Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Adhesive layer									
PRH	20	20	20	20	20	20	20	20	20
CP-934	35	30	28	25	23	20	18	14	12
SCMC	35	40	42	45	47	50	53	56	60
PVP-K30	6	6	6	6	6	6	6	6	6
D-mannitol	4	4	4	4	4	4	4	4	4
Polymer ratio	1:1	1.5:2	1:1.5	1:1.8	1:2	1:2.5	1:3	1:4	1:5
Backing layer									
Ethylcellulose	50	50	50	50	50	50	50	50	50

*PRH indicates propranolol hydrochloride; CP, Carbopol-934; SCMC, sodium carboxymethylcellulose; and PVP-K30, polyvinylpyrrolidone K-30.

of the buccal devices, which ensure satisfactory drug release in a unidirectional fashion to the mucosa, and to avoid loss of drug resulting from wash out with saliva. The buccal devices were evaluated by weight uniformity, thickness, friability, hardness, surface pH, swelling index, ex vivo mucoadhesive strength, ex vivo mucoadhesion time, in vitro drug release, and in vitro drug permeation. Both the buccal devices were compared for various in vitro characterizations.

Materials and Methods

Materials

Propranolol hydrochloride (99.96% purity), Carbopol-934 (CP), and ethyl cellulose (EC, 20 cps) were gift samples from Sarabhai Chemicals Ltd, Baroda, India. Sodium carboxymethylcellulose (SCMC, 400 cps), polyvinylpyrrolidone K-30 (PVP-K30), and D-mannitol (S.D. Fine Chemicals, Mumbai, India) were obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

Preparation of Mucoadhesive Buccal Devices

Mucoadhesive bilayered tablets were prepared by a direct compression procedure involving 2 consecutive steps. The mucoadhesive drug/polymer mixture was mixed homogeneously in a glass mortar for 15 minutes. The mixture (100 mg) was then compressed using an 11-mm, round-shaped flat punch in a single-stroke, multistation tablet machine (Dhiman, Jalandhar, India). The upper punch was raised and the backing layer of EC (50 mg) was then added on the above compact and the 2 layers were compressed to form bilayered tablets. The bilayered tablets were prepared using compositions as given in Table 1.

For mucoadhesive multilayered tablets, the mucoadhesive drug/polymer mixture (100 mg) of the core was mixed homogeneously and then compressed in a 9-mm diameter die. The core was then removed and placed in the center of an 11-mm diameter die, and the ingredients of the cap layer (70 mg) were poured over it and recompressed. The upper punch was removed, and the backing layer of EC (50 mg) was added and compressed to form multilayered tablets. The composition of multilayered tablets is shown in Table 2.

Ex Vivo Mucoadhesive Strength

A modified balance method was used for determining the ex vivo mucoadhesive strength.[18] Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C.

The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8, at 37°C ± 1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate

Table 2. Composition of Optimized Multilayered Buccal Tablet of Propranolol Hydrochloride*

Composition	Weight (mg)		
	Core	Cap	Backing Layer
PRH-HCL	20		
CP-934	14	14	
SCMC	56	56	
PVP-K30	6		
D-mannitol	4		
Ethylcellulose			50

*PRH indicates propranolol hydrochloride; CP-934, Carbopol-934; SCMC, sodium carboxymethylcellulose; and PVP-K30, polyvinylpyrrolidone K-30.

Table 3. Physicochemical Properties of Bilayered Buccal Tablets of Propranolol Hydrochloride*

Batch Code	Thickness (mm)	Hardness (kg/cm^2)	% Drug Content	Surface pH	Ex Vivo Muco-adhesion Time (hours)	Muco-adhesive Strength (g)
F1	1.51 ± 0.05	4.11 ± 0.16	100.73 ± 0.4	6.21 ± 0.02	>12	32.46 ± 1.88
F2	1.52 ± 0.04	4.00 ± 0.17	100.26 ± 0.7	6.89 ± 0.09	11 ± 0.8	30.22 ± 1.20
F3	1.54 ± 0.08	4.00 ± 0.24	99.16 ± 0.5	6.96 ± 0.05	10 ± 0.65	29.91 ± 2.57
F4	1.60 ± 0.05	4.12 ± 0.19	100.35 ± 0.6	6.92 ± 0.03	10 ± 1.10	28.69 ± 1.14
F5	1.60 ± 0.03	3.90 ± 0.25	99.28 ± 0.4	6.99 ± 0.05	10 ± 1.20	28.46 ± 2.36
F6	1.58 ± 0.04	3.87 ± 0.30	100.65 ± 0.8	7.02 ± 0.01	9 ± 1.00	26.06 ± 1.23
F7	1.61 ± 0.02	3.82 ± 0.21	100.48 ± 0.5	7.04 ± 0.08	9 ± 0.30	26.11 ± 0.86
F8	1.52 ± 0.04	3.90 ± 0.19	99.54 ± 0.4	7.15 ± 0.04	8 ± 0.50	25.34 ± 1.25
F9	1.50 ± 0.07	3.80 ± 0.23	99.83 ± 0.7	7.20 ± 0.09	8 ± 0.54	23.82 ± 2.10

*Each value represents the mean ± SD of 3 determinations.

adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min) to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

Swelling Study

Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37°C ±1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula[19] given in Equation 1.

$$\text{Swelling Index} = \frac{(W2 - W1)}{W1} \bullet 100 \qquad (1)$$

Surface pH Study

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg et al[20] was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet 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. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

Ex Vivo Mucoadhesion Time

The ex vivo mucoadhesion time was performed (n = 3) after application of the buccal tablet on freshly cut sheep buccal mucosa.[21] The fresh sheep buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet 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 glass slide was then put in the beaker, which was filled with 200 mL of the 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 tablet adhesion was monitored for 12 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time. The results are shown in Table 3.

In Vitro Drug Release

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the bilayered and multilayered tablets. The dissolution medium consisted of 200 mL of phosphate buffer pH 6.8. The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium .The samples were filtered through 0.2-μm Whatman filter paper (Whatman, Brentford, UK) and analyzed after appropriate dilution by UV spectrophotometry (SPD-10 A VP, Shimadzu, Kyoto, Japan) at 290 nm.[22]

In Vitro Drug Permeation

The in vitro buccal drug permeation study of PRH through the sheep buccal mucosa was performed using Keshary-Chien type glass diffusion cell at 37°C ± 0.2°C. Fresh sheep buccal mucosa was mounted between the donor and receptor

compartments. The buccal tablet was placed with the core facing the mucosa and the compartments 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 phosphate buffer pH 7.4, and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm. A 1-mL sample was withdrawn at predetermined time intervals and analyzed for drug content at 290 nm using a UV-spectrophotometer.

Stability Study in Human Saliva

The stability study of optimized bilayered and multilayered tablets was performed in natural human saliva. The human saliva was collected from humans (age 18-50 years). Buccal tablets were placed in separate Petri dishes containing 5 mL of human saliva and placed 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), the tablets were examined for changes in color and shape, collapsing of the tablets, and drug content.

Results and Discussion

The antihypertensive PRH, being highly water soluble, was chosen as model drug for buccal devices in the form of bilayered and multilayered tablets. CP and SCMC were selected as mucoadhesive polymers. EC was chosen as an impermeable backing layer because of its low water permeability and moderate flexibility.[23] D-mannitol and PVP-K30 had been used to improve the release of drug from polymer matrices. The optimum concentration of D-mannitol and PVP-K30 were found to be 4% and 6%, respectively, for both the buccal devices.

Evaluation of Mucoadhesive Bilayered Buccal Tablets

Mucoadhesive bilayered tablets of PRH with CP and SCMC in different ratios were found to be satisfactory, when evaluated for average diameter (11.0 ± 0.05 mm), thickness (1.5 ± 0.08 mm), weight uniformity (150 ± 0.60 mg), hardness (4.0 ± 0.41 kg/cm^2), and drug content (99.79% ± 0.62%) (Table 3).

Appropriate swelling behavior of a buccal adhesive system is an essential property for uniform and prolonged release of drug and effective mucoadhesion.[24] The swelling index study indicated that the rate of swelling was directly proportional to SCMC content and inversely proportional to CP content. Bilayered tablets containing CP and SCMC at the ratio of 1:5 exhibited the highest swelling index (31.4% ± 3.1%). The high amount of water intake by SCMC at a faster rate might have resulted in the higher rate and extent of swelling. The results also indicated that the bilayered tablets did not show any appreciable changes in the shape and form during the 6 hours that they were kept on 2% agar gel plate. The optimized bilayered tablets (F8) had a 30.4% ± 1.9% swelling index after 6 hours. Swelling behavior of mucoadhesive bilayered buccal tablets as a function of time is shown in Figure 1.

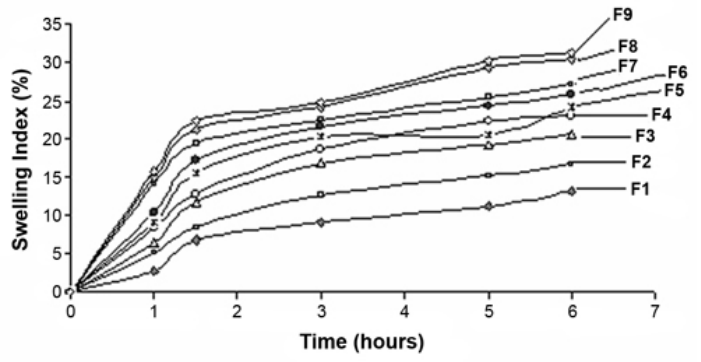

Figure 1. Swelling study of bilayered buccal tablet of propranolol hydrochloride.

Mucoadhesion may be defined as the adhesion between a polymer and mucus. In general, mucoadhesion is considered to occur in 3 major stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors such as molecular weight of polymers, contact time with mucus, swelling rate of the polymer, and biological membrane used in the study.[25] In this study, sheep buccal mucosa was used as biological membrane for mucoadhesion. The bilayered tablets containing a higher proportion of CP showed good mucoadhesive strength for 5 minutes contact time. This high bioadhesive strength of CP may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region, while the other polymers only undergo superficial bioadhesion.[26] Bilayered tablets containing CP and SCMC at the ratio of 1:1 (F1) exhibited the highest bioadhesive strength (32.46 ± 1.88 g), and it was decreased with increasing amount of SCMC and decreasing amount of CP (F2-F9). However, all the bilayered tablets exhibited good mucoadhesive strength with sheep buccal mucosa. The optimized bilayered tablet (F8) showed 25.34 ± 1.25 g mucoadhesive strength (Table 3).

Ex vivo mucoadhesion time for bilayered tablets F1 to F9 varied from 8 to more than 12 hours (Table 3). The optimized bilayered tablets (F8) showed 8 ± 0.5 hours of mucoadhesion time. The difference could be attributed to the combination of various amounts of the polymers, which affected the mucoadhesion. Moreover, SCMC, owing to its solubility in water, resulted in lower mucoadhesion time. In fact, with bilayered tablets containing a higher proportion of CP, mucoadhesion time was found to be increased.

The drug release rate appeared to increase with increasing amount of SCMC and decreasing amount of CP contents

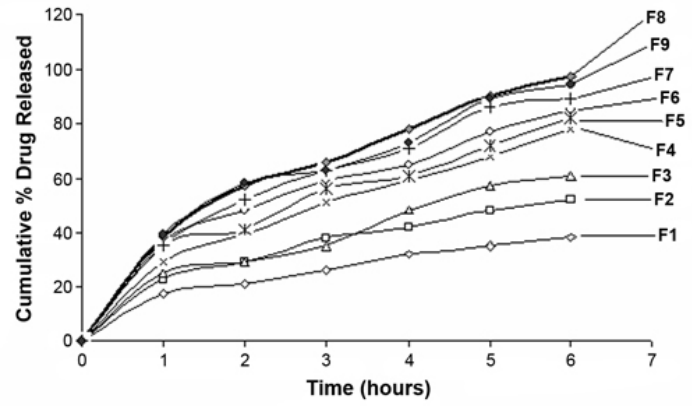

Figure 2. In vitro drug release study of bilayered buccal tables of propranolol hydrochloride.

(Figure 2). The results indicated that bilayered tablets with a higher concentration of SCMC in the batches from F1 to F9 swell faster and, consequently, give rise to more rapid release of drug. The inclusion of higher percentages of CP provides prolonged release of drug through its properties of in situ gelling and slow dissolution. Maximum in vitro drug release of bilayered tablets (F8) was 97.00% ± 1.47% over a period of 6 hours. All bilayered tablets remained intact during the 6-hour period in dissolution study. The release data were analyzed using the well-known semi-empirical equation[27] shown as equation 2:

$$\frac{Mt}{M\infty} = kt^n \qquad (2)$$

where Mt/M_∞ is the fractional releasing of the drug; t denotes the releasing time; k represents a constant, incorporating structural and geometrical characteristics of the buccal devices; and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, $n > 1$. The obtained values of k (kinetic constant), n (diffusional exponent), and r^2 (correlation coefficient) are depicted in Table 4. The values of n were estimated by linear regression of log (Mt/M_∞) versus log t, and these values were between 0.5 and 1.0, indicating that the release of PRH was found to be non-Fickian diffusion.

The surface pH of bilayered tablets was found to be in between 6.21 to 7.15, which was within 7 ± 1.5 units of the neutral pH, and hence these buccal tablets should not cause any irritation in the buccal cavity.

The optimization of the bilayered tablets (F8) was performed on the basis of swelling index, in vitro drug release, ex vivo mucoadhesive strength, and ex vivo mucoadhesion time. The optimized bilayered tablets (F8) subjected to in vitro drug permeation study showed 73.65% ± 1.84% drug permeation in 6 hours through sheep buccal mucosa. The correlation between in vitro drug release and in vitro drug permeation across the sheep buccal mucosa was found to be positive with a correlation coefficient of 0.9855.

Usually the stability studies are performed in phosphate buffer solutions whose pH pertains to buccal cavity. But, the stability studies performed in natural human saliva may be more accurate to mimic the stability of drug and buccal device in the oral cavity in vivo. Therefore, the stability study of optimized bilayered tablets (F8) was examined in natural human saliva. The obtained data are presented in Table 5. The bilayered tablets were evaluated by their appearance characteristics, such as color and shape, and their drug content in natural human saliva. Bilayered tablets did not exhibit change in color or shape, suggesting the satisfactory stability of the drug and buccal device in the human saliva. If the drug is unstable in human saliva, its color will change.[28] Physical properties of the bilayered tablets such as thickness and diameter increased slightly owing to swelling of the system in human saliva. But the bilayered tablets did not collapse in the human saliva until the end of the study, confirming the sufficient strength of the bilayered tablets.

Evaluation of Mucoadhesive Multilayered Buccal Tablets

The composition of optimized bilayered tablets (F8) was selected for preparation of multilayered tablet. In multilayered tablets, the core consisted of the PRH, PVP-K30, and D-mannitol with CP and SCMC in the ratio of 1:4. The cap layer consisted of CP:SCMC (1:4) surrounding the core on 3 sides so as to allow the release of drug to take place only from the side of the core sticking to buccal mucosa. The backing layer consisted of EC to overcome the problem of stickiness. Figure 3 gives a schematic illustration of the multilayered buccal tablet.

Table 4. Kinetic Constants (k), Release Exponents (n), and Determination Coefficients (r^2) Following Linear Regression of In Vitro Drug Release of Bilayered Buccal Adhesive Tablets

Batch Code	k (%h^{-1})	r^2	n
F1	0.12	0.9929	0.6333
F2	0.15	0.9898	0.6930
F3	0.17	0.9902	0.7086
F4	0.20	0.9930	0.7547
F5	0.21	0.9858	0.7687
F6	0.21	0.9841	0.7821
F7	0.22	0.9893	0.7936
F8	0.23	0.9880	0.8076
F9	0.22	0.9844	0.8036

Table 5. Stability Study of Bilayered and Multilayered Buccal Tablets of Propranolol Hydrochloride in Normal Human Saliva

Optimized Formulation	Sampling Time (hours)	Color Change*	Thickness (mm)†	Change in Shape Diameter (mm)†	Collapsing*	Drug Recovered (%)†
Bilayered tablet	0	No	1.55	11.0		99.05
	1	No	1.62	11.5	No	99.12
	2	No	1.70	11.8	No	98.98
	3	No	1.88	12.3	No	99.81
	6	No	1.95	12.6	No	99.35
Multilayered tablet	0	No	1.84	11.0		99.15
	1	No	1.91	11.8	No	99.36
	2	No	2.10	12.1	No	98.98
	3	No	2.25	12.7	No	99.12
	6	No	2.35	12.8	No	99.47

*Visual observation.

†Mean of 3 readings.

The multilayered tablets of PRH were found to be favorable for predicted characteristics when evaluated for average diameter (11.0 ± 0.05 mm), thickness (2.2 ± 0.09 mm), weight uniformity (220 ± 0.80 mg), hardness (4.0 ± 0.32 kg/cm^2), friability (0.72% ± 0.03%), drug content (99.8% ± 0.55%), and surface pH (7.01 ± 0.07).

The swelling index of multilayered tablets was found to be 34.1% ± 1.8% at 6 hours, which does not show any remarkable changes in their shape and form during this period. Multilayered tablets showed 31.5 ± 2.81 g mucoadhesive strength and 11 ± 1.2 hours ex vivo mucoadhesion time with fresh sheep buccal mucosa.

The multilayered tablets exhibited 78% ± 1.54% in vitro drug releases for a period of 6 hours, which followed first-order release kinetics. The release data were analyzed using equation 2,[27] and the values of n were estimated by linear regression of log (Mt/M∞) versus log t, which was found between 0.5 and 1.0 and r^2 value 0.9928 indicating the release of PRH by non-Fickian diffusion.

The multilayered tablets showed 64.71% ± 2.93% in vitro drug permeation during 6 hours through freshly obtained sheep buccal mucosa (Table 6). The correlation between in vitro drug release and in vitro drug permeation through sheep buccal mucosa was found to be positive with a correlation coefficient of 0.9731.

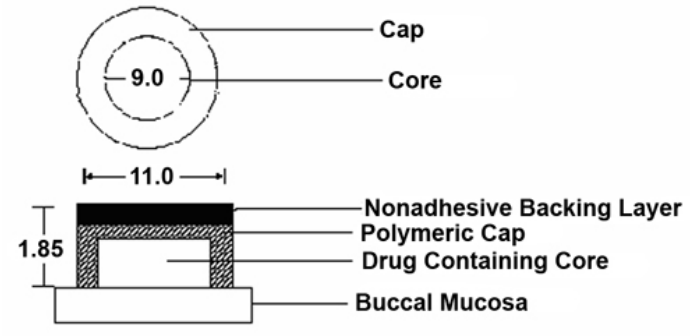

Figure 3. A schematic illustration of multilayered buccal tablet.

The stability of multilayered tablets was examined in natural human saliva. The obtained data are presented in Table 5. Multilayered tablets were evaluated by their appearance characteristics, such as color and shape, and their drug content in natural human saliva. Multilayered tablets did not exhibit any changes in color or shape, suggesting the satisfactory stability of the drug and buccal device in the human saliva. Physical properties of multilayered tablets such as thickness and diameter increased slightly owing to swelling of the system in human saliva, but the tablets remained intact in the human saliva until the end of the study, confirming the sufficient strength of the multilayered tablets.

Table 6. Comparison of Bilayered and Multilayered Buccal Tablets of Optimized Batch F8

Parameters	Bilayered Buccal Tablets*	Multilayered Buccal Tablets
% Swelling index (6 hours)	30.40 (1.90)	34.10 (1.80)
Ex vivo bioadhesive strength (g)	25.34 (1.25)	31.50 (2.81)
Ex vivo mucoadhesion time (hours)	9.00 (0.55)	11.00 (0.75)
In vitro % drug release study (6 hours)	97.00 (1.47)	78.00 (1.54)
In vitro buccal permeation study (6 hours)	73.65 (1.84)	64.71 (2.93)
Release Kinetics (Peppas model)		
n	0.81	0.76
k (%h^{-1})	0.23	0.20
r^2	0.99	0.99

*The ±SD values are given in parentheses.

Comparison of Optimized Mucoadhesive Bilayer Buccal Tablets With Multilayered Buccal Tablets

Mucoadhesive buccal devices of PRH in the forms of bilayered and multilayered tablets were found to be satisfactory when evaluated for average diameter, thickness, weight variation, hardness, friability, and drug content. The multilayered tablets were prepared from the composition of optimized bilayered tablets with additional polymeric coat layer surrounding the core on 3 sides, which increased the thickness of multilayered tablets. Tablet diameter was the same (11-mm punch size) for both the buccal devices.

Swelling study showed that multilayered tablets showed higher swelling index than bilayered tablets (Figure 4). This finding may be owing to the additional pure polymeric coat layer surrounding the core matrix, which swelled fast when kept on 2% agar gel plate.

Ex vivo mucoadhesive strength and ex vivo mucoadhesion time were observed to be significantly higher in multilayered tablets than in bilayered tablets on freshly obtained sheep buccal mucosa (Table 6). Though both buccal devices had the same surface area for mucoadhesion with sheep buccal mucosa, the higher mucoadhesive strength in multilayered tablets might be because of the polymeric layer, which can swell fast and provide higher mucoadhesion. The degree of swelling of bioadhesive polymers is an important issue affecting adhesion.[24] As a result of fast swelling of the polymer, immediate initiation of diffusion occurs, which leads to formation of adhesive bonds resulting in faster initiation of bioadhesion.[29]

In vitro drug release study showed that the drug release rate was found to be slow in multilayered tablets as compared with bilayered tablets (Figure 5). The sustained release of drug in multilayered tablets may be owing to the drug-free polymeric layer surrounding the core on 3 sides, which reduced the drug diffusion (drug loss in saliva) toward the perimetric sides of the tablet and released the drug on only mucosal side. The release data were analyzed using equation 2,[27]

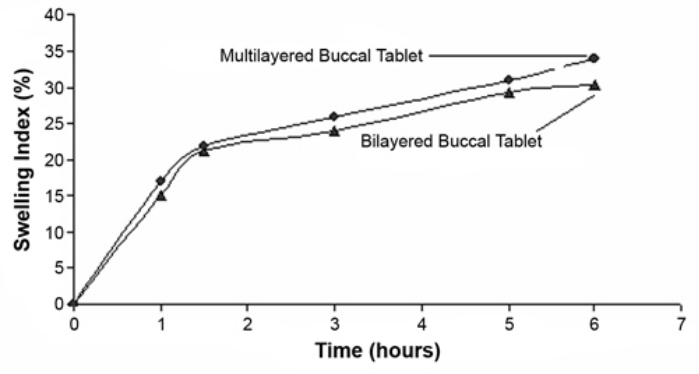

Figure 4. Comparison of swelling index studies of bilayered and multilayered buccal tablets of propranolol hydrochloride.

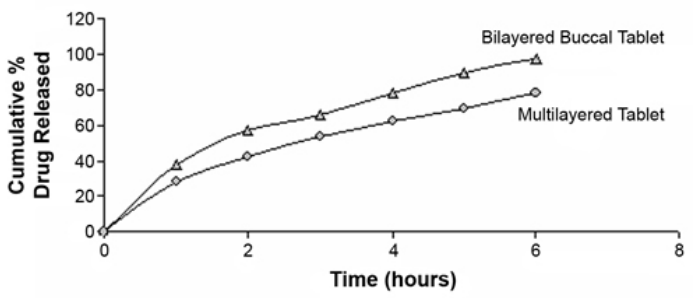

Figure 5. Comparison of in-vitro drug released from bilayered and multilayered buccal tablets of PRH.

which showed non-Fickian diffusion (values of n between 0.5 and 1.0).

In vitro drug permeation study showed that the drug permeation was higher for bilayered tablets than for multilayered tablets (Figure 5). This higher drug permeation might have been due to the greater contact area (11-mm diameter) of drug matrix of bilayered tablets with sheep mucosa than the multilayered tablets (9-mm diameter). Good correlation was obtained between in vitro drug release and in vitro drug permeation study with the correlation coefficient of 0.9855 and 0.9731 for bilayered and multilayered tablets, respectively.

The surface pH of bilayered and multilayered tablets was found to be within 7 ± 1.5 units of the neutral pH, and hence these buccal devices cannot cause any irritation in the buccal cavity.

The stability of bilayered and multilayered tablets was examined in natural human saliva. The obtained data are presented in Table 5. The buccal devices were evaluated by their appearance characteristics, such as color and shape, and their drug content in natural human saliva. Buccal devices did not exhibit change in color or shape, suggesting the satisfactory stability of the drug and buccal devices in the human saliva. Physical properties of the buccal devices such as thickness and diameter increased slightly owing to swelling of the buccal devices in human saliva. But the buccal devices did not collapse in the human saliva until the end of the study, confirming the sufficient strength of the bilayered and multilayered tablets.

CONCLUSION

The mucoadhesive buccal devices of PRH may be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of PRH through buccal mucosa.

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