Mucoadhesive Bilayer Tablets of Propranolol Hydrochloride

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ABSTRACT

The purpose of this research was to study mucoadhesive bilayer buccal tablets of propranolol hydrochloride using the bioadhesive polymers sodium alginate (Na-alginate) and Carbopol 934P (CP) along with ethyl cellulose as an impermeable backing layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, in vitro drug release, ex vivo drug permeation, ex vivo mucoadhesion, and in vivo pharmacodynamics in rabbits. Tablets containing Na-alginate and CP in the ratio of 5:1 (F2) had the maximum percentage of in vitro drug release without disintegration in 12 hours. The swelling index was proportional to Na-alginate content and inversely proportional to CP content. The surface pH of all tablets was found to be satisfactory (7.0 ± 1.5), close to neutral pH; hence, buccal cavity irritation should not occur with these tablets. The mechanism of drug release was found to be non-Fickian diffusion and followed zero-order kinetics. The formulation F4 was optimized based on good bioadhesive strength (28.9 ± 0.99 g) and sustained in vitro drug permeation (68.65% ± 3.69% for 12 hours). The behavior of formulation F4 was examined in human saliva, and both the drug and the buccal tablet were found to be stable. The formulation F4 was applied to rabbit oral mucosa for in vivo studies. The formulation inhibited isoprenaline-induced tachycardia. The studies conducted in rabbits confirmed the sustained release as compared with intravenous administration.

KEYWORDS: Mucoadhesion, bilayer device, buccal drug delivery, propranolol hydrochloride, sodium alginate, Carbopol 934.

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INTRODUCTION

Buccal delivery of drug provides an attractive alternative to the oral route of drug administration. In recent years, delivery of therapeutic agents through various transmucosal routes gained significant attention owing to their presystemic metabolism or instability in the acidic environment associated with oral administration.[1] Buccal delivery provides direct entry into the systemic circulation, thus avoiding the hepatic first-pass effect, ensuring ease of administration, and making it possible to terminate delivery when required.[2] Attempts have been made to formulate various buccal mucoadhesive dosage forms, including tablets,[3] films,[4] patches,[5] disks,[6] and gels.[7] A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a unidirectional way toward the mucosa, in a controlled and predictable manner, to elicit the required therapeutic response. This unidirectional drug release can be achieved using bilayer devices.[6,8]

Propranolol hydrochloride (PRO-HCL), a nonselective beta-adrenergic blocking agent, has been widely used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. PRO-HCL is subjected to an extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability of between 15% and 23%.[9,10] The physicochemical properties of PRO-HCL, its half-life of 3 to 5 hours, and its low molecular weight of 295.81 make it a suitable candidate for administration by the buccal route.

The present study examined mucoadhesive bilayer buccal tablets of PRO-HCL using Carbopol 934P (CP) and sodium alginate (Na-alginate) as the mucoadhesive polymers and ethyl cellulose (EC) as an impermeable backing layer. The buccal tablets were characterized by measuring the ex vivo mucoadhesive strength, swelling, in vitro drug release, in vitro buccal permeation, and in vivo usefulness of the device in suppressing isoprenaline-induced tachycardia in rabbits.

MATERIALS AND METHODS

Materials

PRO-HCL, CP, and EC were gifts from Sarabhai Chemicals Ltd (Baroda, India). Na-alginate (300-400 cps), polyethylene

Table 1. Composition of Bilayer Buccal Tablets of PRO-HCL*

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Adhesive layer									
PRO-HCL	20	20	20	20	20	20	20	20	20
Na-alginate	34.3	33.4	32.0	30.0	26.7	20.0	13.3	10.0	8.0
CP	5.7	6.6	8.0	10.0	13.3	20.0	26.7	30.0	32.0
PVP K-30	30	30	30	30	30	30	30	30	30
D-mannitol	8	8	8	8	8	8	8	8	8
PEG-4000	2	2	2	2	2	2	2	2	2
Backing layer									
Ethyl cellulose	50	50	50	50	50	50	50	50	50
Total	150	150	150	150	150	150	150	150	150

*PRO-HCL indicates propranolol hydrochloride; Na-alginate, sodium alginate; CP, Carbopol 934; PVP, polyvinyl pyrrolidone; PEG, polyethylene glycol.

glycol 4000 (PEG 4000), polyvinyl pyrrolidone K-30 (PVP K-30), and D-mannitol (S.D. Fine Chemicals, Maharashtra, Mumbai, India) were obtained from commercial sources. Isoprenaline sulfate (Unichem Laboratories Limited, Mumbai, India), phenobarbitone sodium (Rhone-poulenc Ltd, Mumbai), and heparin injections (Biological E. Limited, Hyderabad, India) were obtained from commercial sources. All other reagents and chemicals used were of analytical reagent grade.

Preparation of Buccal Tablets

Bilayer buccal tablets were prepared by a direct compression procedure involving 2 steps. Various batches were prepared by varying the ratio of CP and Na-alginate to identify the most effective formulation. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug with CP, Na-alginate, PVP K-30, D-mannitol, and PEG 4000 in a glass mortar for 15 minutes (Table 1). The mixture (100 mg) was then compressed using an 11-mm-diameter die in a single-stroke multistation tablet machine (Dhiman, Jalandhar, India). The upper punch was raised and the backing layer of EC was placed on the above compact; the 2 layers were then compressed into a mucoadhesive bilayer tablet. Each tablet weighed ~150 mg with a thickness of 1.5 to 1.6 mm.

Content Uniformity

Drug content uniformity was determined by dissolving the tablets in ethyl alcohol and filtering with Whatman filter paper (0.45 μm, Whatman, Maidstone, UK). The filtrate was evaporated and the drug residue dissolved in 100 mL of phosphate buffer (pH 6.8). The 5-mL solution was then diluted with phosphate buffer (pH 6.8) up to 20 mL, filtered through 0.45-μm Whatman filter paper, and analyzed at 290 nm using a UV spectrophotometer (Shimadzu, SPD-10 A VP, Kyoto, Japan).[11] The experiments were performed in triplicate, and average values were reported.

Ex Vivo Mucoadhesive Strength

A modified balance method was used for determining the ex vivo mucoadhesive strength.[6,12] 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 fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer pH 6.8, and held on the left side of the balance. The glass vial with rubber stopper was placed and tightly fitted in the center of glass beaker containing phosphate buffer (pH 6.8, 37°C ± 1°C) just touching the mucosal surface. The tablet was stuck to the lower side of the rubber stopper of the glass vial with cyanoacrylate adhesive (instant adhesive). The left and right pans were balanced by adding a 5-g weight on the right-hand pan. When the 5-g weight was removed from the right-hand pan, the left-hand pan along with the tablet was lowered over the mucosa. The balance was kept in this position for 5 minutes. Water (equivalent to weight) was added slowly at 100 drops/min to the right-hand pan until the patch detached from the mucosal surface. The weight (gram force) required to detach the tablet from the mucosal surface gave the measure of mucoadhesive strength. The experiments were performed in triplicate and average values with standard deviation (SD) were reported.

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

using filter paper. The swollen tablet was then reweighed (W2), and the swelling index (SI) was calculated using the following formula[6]:

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

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 irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg et al[13] 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 identified by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1 minute.

Ex Vivo Mucoadhesion Time

The ex vivo mucoadhesion time was examined (n = 3) after application of the buccal tablet on freshly cut sheep buccal mucosa.[12] 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 kept at 37°C ± 1°C. After 2 minutes, a slow 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 (Table 2).

In Vitro Drug Release

The US Pharmacopeia XXIII rotating paddle method was used to study the drug release from the bilayer tablet. The dissolution medium consisted of 200 mL of phosphate buffer pH 6.8. The release study was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of the buccal tablet was attached to the glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.2-μm Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry (Shimadzu, SPD-10 A VP) at 290 nm.[11]

Table 2. In Vitro Mucoadhesive Study of Bilayer Buccal Tablets of PRO-HCL*

Batch Code	Ex Vivo Mucoadhesion Time (hrs)	Mucoadhesive Strength (gram force)
F1	8 ± 0.4	11.7 ± 3.3
F2	10 ± 0.7	13.3 ± 2.1
F3	11 ± 0.8	16.8 ± 2.7
F4	13 ± 0.9	22.3 ± 1.0
F5	14 ± 1.1	23.3 ± 1.3
F6	15 ± 1.2	25.3 ± 1.1
F7	16 ± 0.9	24.6 ± 1.5
F8	18 ± 1.2	27.9 ± 1.7
F9	20 ± 1.1	28.9 ± 2.1

*PRO-HCL indicates propranolol hydrochloride. All values are mean ± SD.

In Vitro Drug Permeation

The in vitro buccal drug permeation study of PRO-HCL through the sheep buccal mucosa was performed using a 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 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 phosphate buffer pH 7.4 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. One-milliliter samples were withdrawn at predetermined time intervals and analyzed for drug content by UV spectrophotometer using a placebo as a blank.

Pharmacodynamic Study

Formulation F4 was evaluated by measuring isoprenaline-induced tachycardia in rabbits.[14,15] Six healthy albino rabbits of either sex (1.75-2.25 kg) were selected for the study and acclimatized to the laboratory environment for 1 week prior to the experiment. Overnight-fasted rabbits were anesthetized by intravenous administration of 50 mg/kg of phenobarbitone in sterile normal saline. A catheter (scalp vein needle gauge 26) was placed in the marginal ear vein for administration of the drug. Anesthesia was maintained by hourly administration of 6 mg/kg of phenobarbitone sodium. Heparinized saline (20 IU/mL) was put into the catheter patent to overcome its dead volume. A front paw of each rabbit was cleaned by removal of hair. The pulse transducer (MP 100) was placed on the paw and connected to the Power Lab 8SP (Multi Channel Data Acquisition System, ADInstruments, Bella Vista, NSW, Australia). Pulses were recorded in the first channel, and heart rate in beats per minute (bpm) was recorded in the second channel.

Table 3. Physicochemical Properties of Bilayer Buccal Tablets of PRO-HCL*

Batch	% Weight Variation	Thickness (mm)	Hardness (kg/cm^2)	% Friability	% Drug Content	Surface pH
F1	0.82 ± 0.15	1.5 ± 0.05	4.41 ± 0.16	0.62 ± 0.05	100.7 ± 0.4	6.41 ± 0.02
F2	0.75 ± 0.21	1.5 ± 0.04	4.22 ± 0.17	0.82 ± 0.05	100.3 ± 0.7	6.29 ± 0.09
F3	0.89 ± 0.17	1.5 ± 0.10	4.00 ± 0.24	0.81 ± 0.06	99.1 ± 0.5	6.36 ± 0.05
F4	0.69 ± 0.11	1.6 ± 0.05	4.12 ± 0.19	0.72 ± 0.03	100.4 ± 0.6	6.13 ± 0.03
F5	0.71 ± 0.09	1.6 ± 0.03	3.90 ± 0.25	0.79 ± 0.02	99.3 ± 0.4	5.89 ± 0.05
F6	0.78 ± 0.20	1.5 ± 0.04	3.77 ± 0.30	0.82 ± 0.05	100.7 ± 0.8	5.82 ± 0.01
F7	0.84 ± 0.13	1.6 ± 0.05	3.60 ± 0.21	0.65 ± 0.04	100.5 ± 0.5	5.79 ± 0.08
F8	0.88 ± 0.16	1.5 ± 0.12	3.50 ± 0.19	0.81 ± 0.03	99.5 ± 0.4	5.65 ± 0.04
F9	0.74 ± 0.14	1.5 ± 0.26	3.40 ± 0.23	0.79 ± 0.07	99.8 ± 0.7	5.70 ± 0.09

*PRO-HCL indicates propranolol hydrochloride. All values are mean ± SD of 3 determinations.

Normal heart rate (250-280 bpm) was recorded for 5 minutes. Isoprenaline (3 μg/kg) was intravenously injected, and heart rate (330-370 bpm) was rerecorded for 15 minutes until it returned to normal. PRO-HCL in sterile normal saline at a dose of 2.5 mg/kg was administered intravenously for 30 seconds through the catheter and flushed with 1 mL of heparinized saline. Isoprenaline (3 μg/kg) was administered at half-hour intervals for 8 hours after PRO-HCL dosing, and heart rate was recorded for 10 minutes before and after isoprenaline administration.

For the pharmacodynamic study, the buccal tablets were wetted with a drop of normal saline and stuck on the upper left oral mucosa of the rabbit after wiping the site with a cotton swab. Isoprenaline (3 μg/kg) was administered at predetermined time intervals, and the heart rate was recorded continuously for 10 minutes. Care was taken to prevent the rabbit from disturbing the buccal tablet. Heart rate was analyzed by PowerLab HRV (heart rate variability) software (ADInstruments).

Results and Discussion

CP and Na-alginate were selected as the bioadhesive polymers because of their excellent bioadhesive properties.[6,16-18] EC has recently been reported to be an excellent backing material, given its low water permeability, hydrophobicity, and moderate flexibility,[19] so it was chosen as an impermeable backing layer. D-mannitol and PVP-K30 were used to improve the release of drug from polymer matrices, and the concentration was optimized during the preliminary trial to find the best formulation of bilayer buccal tablets (Table 1).

Tablets were found to be satisfactory when evaluated for weight variation (0.78% ± 0.15%), thickness (1.5 ± 0.18 mm), hardness (4.005 ± 0.41 kg/cm^2), friability (0.72% ± 0.04%), and drug content (99.79% ± 0.62%). The surface pH of all the tablets was within a range of 5.65 to 6.41 (Table 3), close to neutral pH.

Appropriate swelling behavior of a buccal adhesive system is essential for uniform and prolonged release of the drug and effective mucoadhesion.[20] The swelling study indicated that the rate of swelling was proportional to the Na-alginate content and inversely proportional to the CP content of the tablets (Figure 1) in the initial study up to 1 hour. This finding may have been because of the fast-swelling property of Na-alginate compared with CP. The maximum swelling index was found in batch F1 (33.7 ± 1.7), containing a higher proportion of Na-alginate, and the lowest in F9 (19 ± 0.8). Tablets did not show any appreciable change in their shape and form during the 8 hours they were kept on the 2% agar gel plate.

The ex vivo mucoadhesive strength of the tablets was determined for different contact times, using sheep buccal mucosa. Tablets containing a higher proportion of Na-alginate showed higher mucoadhesion at 1 minute of contact time (Table 2). This finding is owing to the hydrophilic nature of Na-alginate; it is hydrated easily with less contact time and forms a strong gel that entangles tightly with the mucin molecules. A linear increase in mucoadhesion was observed with an increase in contact time to 3 minutes. The tablets containing a higher

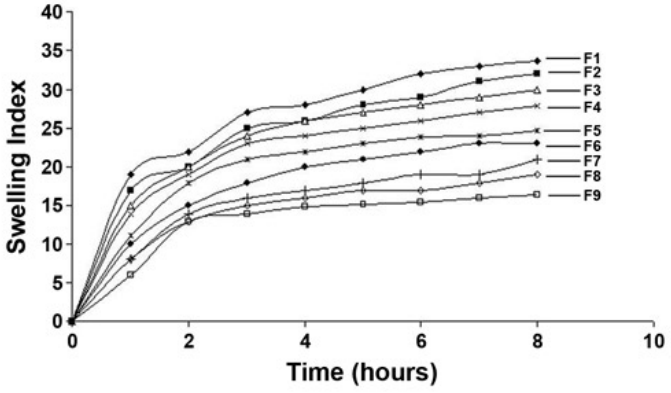

Figure 1. Swelling index of bilayer buccal tablets of batches F1 to F9.

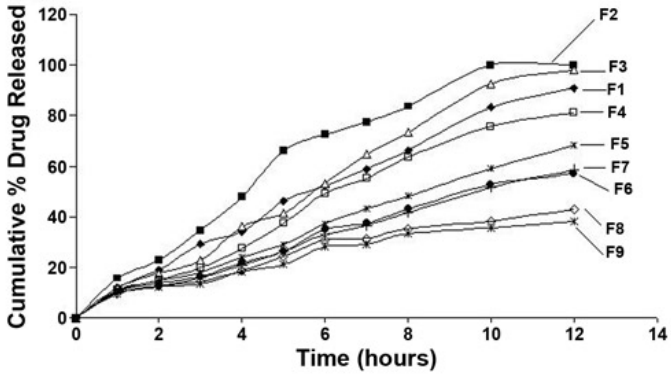

Figure 2. Cumulative percentage of drug released from batches F1 to F9.

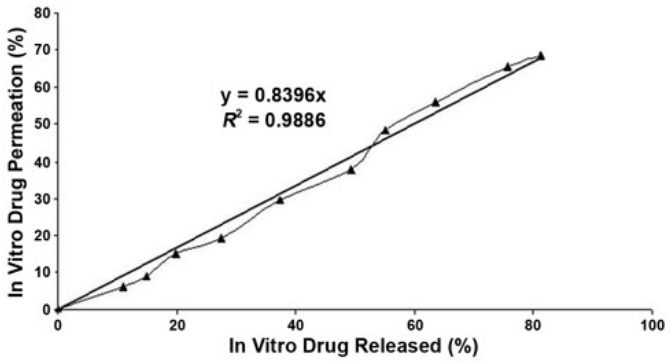

Figure 3. Correlation between in vitro drug release and in vitro drug permeation study.

ratio of CP/Na-alginate showed higher mucoadhesion for 5 minutes of contact time. This high mucoadhesive strength of CP may be due to formation of secondary mucoadhesive bonds with mucin because of rapid swelling and interpenetration of the polymer chains in the interfacial region, while other polymers undergo only superficial bioadhesion.[21] Formulation F4 showed good mucoadhesive strength (22.30 ± 0.99 g) for 5 minutes of contact time. The mucoadhesive time on sheep buccal mucosa ranged from 8 to 20 hours (Table 2). The effect of CP was more significant than the effect of Na-alginate. The increase in concentration of CP in series from formulation F1 to F9, showed a gradual rise in mucoadhesion time, while Na-alginate, which is also a good mucoadhesive polymer, showed a decrease in mucoadhesion time.

In vitro drug release studies indicated that the drug release was proportional to Na-alginate content and inversely proportional to CP content (Figure 2). The higher the uptake of water by the polymer, the greater the amount of drug diffused from the polymer matrix. Thus, this high amount of water uptake by Na-alginate may lead to considerable swelling of the polymer matrix, allowing the drug to diffuse at a faster rate.[22] The progressive decrease in the amount of drug released from batch F1 (90 ± 2.87) to F9 (38.16 ± 1.64) may be attributed to the increase in proportion of CP, which is a water-swellable polymer; at higher concentrations, a decrease in the release rate was obtained, most likely because of CP's higher viscosity on swelling compared with Na-alginate. All tablets (F1-F9) remained intact during the 12-hour period.

The drug release data were analyzed by the following simple power equation[22]:

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

For all the batches, the values of n ranged from 0.5465 to 0.7077 (Table 4), indicating non-Fickian release. Formulation F4 was optimized based on in vitro drug release (81.15 ± 2.08 at 12 hours), swelling index (21.1 ± 2.1 at 8 hours), and ex vivo mucoadhesive strength (22.3 ± 1.0 g at 5 minutes of contact time); it showed good drug release with sufficient mucoadhesion.

Formulation F4 was subjected to an in vitro buccal permeation study using a diffusion cell (Figure 3). The results showed drug permeation of 68.65% ± 3.69% in 12 hours. The correlation between in vitro drug release rate and in vitro

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

Batch Code	Kinetic Constant k (%h^{-1})	Determination Coefficient (r^2)	Release Exponents (n)
F1	0.19	0.9884	0.6655
F2	0.17	0.9914	0.7077
F3	0.18	0.9742	0.6680
F4	0.17	0.9690	0.6395
F5	0.15	0.9797	0.6069
F6	0.13	0.9815	0.5888
F7	0.14	0.9768	0.5840
F8	0.11	0.9867	0.5593
F9	0.10	0.9884	0.5465

Table 5. Stability Study of Optimized Bilayer Buccal Tablet (F4) in Normal Human Saliva

Sampling Time (hrs)	Thickness (mm) *	Change in Diameter (mm) *	Drug Recovered (%) †
0	1.57 ± 0.03	11.03 ± 0.67	99.86 ± 2.21
1	1.62 ± 0.04	11.12 ± 0.72	99.22 ± 1.36
2	1.65 ± 0.01	11.35 ± 0.81	99.20 ± 2.67
3	1.65 ± 0.02	12.20 ± 0.57	99.40 ± 2.82
6	1.71 ± 0.04	12.29 ± 0.78	99.12 ± 1.89

* Visual observation.

† Values are mean ± SD of 3 readings.

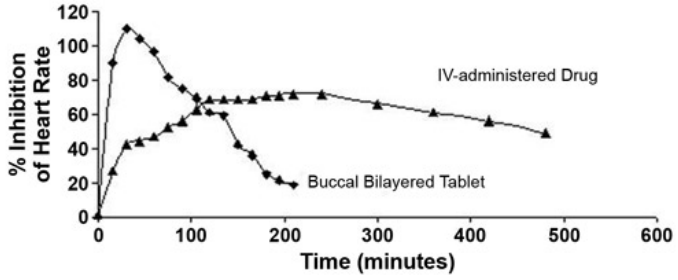

Figure 4. Percentage inhibition of isoprenaline-induced heart rate in rabbits (F4).

drug permeation across the sheep buccal mucosa was found to be positive, with a correlation coefficient (R^2) of 0.9886.

The behavior of formulation F4 in human saliva was examined (Table 5). Tablets did not exhibit changes in shape, suggesting satisfactory stability of both the drug and the device in human saliva. Physical properties of the tablets such as thickness and diameter increased slightly owing to swelling of the system in human saliva, but tablets did not collapse in human saliva until the end of the study, confirming that the device strength was sufficient.

Formulation F4 showed a gradual increase (until 2 hours) in percentage inhibition of heart rate in rabbits and maintained this increase for longer periods (2 hours), then slowly decreased in inhibition, suggesting good sustained release for 7 hours (Figure 4). Tablets showed a maximum inhibitory effect of 71.61% at around 3.75 hours, with a steady state for 2 hours, and then declined in inhibitory effect. The time for 50% inhibition (T50%) of the heart rate for the buccal tablet (F4) and intravenous administered drug was 7.5 and 2.4 hours, respectively, while the time to 70% inhibition (T70%) of the heart rate was 4.15 and 1.7 hours, respectively.

CONCLUSION

The prepared mucoadhesive buccal tablets of PRO-HCL can help bypass extensive hepatic first-pass metabolism and improve bioavailability. The buccal bilayer tablets showed a mucoadhesion time of more than 12 hours. Similarly, in vitro permeation studies showed 68.65% ± 3.69% drug release of the sustained dosage form, which can be used in a twice-a-day tablet.

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