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Research Article

DESIGN DEVELOPMENT AND EVALUATION OF BUCCAL TABLET CONTAINING NICORANDIL AS A MODEL DRUG

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ABSTRACT

Objective: Nicorandil is a vasodilatory drug used to treat angina. Nicorandil has oral bioavailability (70%) and half-life 1 hr. It is administered through the buccal mucosa enters directly in the systemic circulation, thereby minimizing the first pass hepatic metabolism and adverse gastro-intestinal effects. Therefore, the present investigation is concerned with the development of the buccal tablets.

Methods: The present work was performed to develop and evaluate buccal tablet containing anti-diabetic drug (nicorandil). Ethyl cellulose was used as backing membrane and carbopol 934p and hydroxypropyl methyl cellulose K100M was used as bucco adhesive polymer. Aspartame was used as a sweetener. Thickness, hardness, weight variation and drug uniformity were investigated.

Results: The tablet formulations were also subjected to drug release in 250 ml 6.8 phosphate buffer. *Ex vivo* bioadhesion, retention time and permeation through porcine buccal mucosa membrane. F5 formulations showed maximum amounts of drugs release (89.24%) at the end of 10 hrs dissolution study. F5 also showed maximum bioadhesion (0.0791 N) and the resident time of F5 formulation was 9.5 hrs. It shows 49.32% drug release after 10 hrs permeation study through porcine buccal mucosa mounted in Franz cell.

Conclusion: The results of the study suggested that new buccal tablet formulations of combined bucco adhesive polymers can be suitably developed as an alternate to conventional dosage forms.

Keywords: Nicorandil, Buccal tablet, *Ex vivo* bioadhesion, *Ex vivo* permeation.

INTRODUCTION

The mouth is lined with mucous membrane and among the least known of its functions is its capability of serving as a site for the absorption of drugs [1]. In general, drugs penetrate the mucous membrane by simple diffusion and are carried in the blood, which is richly supplied with the salivary glands and their ducts, into the systemic circulation via the jugular vein. Active transport, pinocytosis and passage through aqueous pores usually play only insignificant roles in moving drugs across the oral mucosa [2]. Nicorandil 1-2 is anti-anginals and coronary vasodilators. Angina pectoris possesses little hemodynamic effect on heart rate, blood pressure, or cardiac contractility with clinical doses yielding anti-anginal effect N-[2-(Nitroxy) ethyl]-3-pyridine carboxamide [3]. It has short biological half-life and usual initial dose is 10 mg twice daily (or 5 mg twice daily for patient susceptible for headache), increased as necessary to a maximum of 30 mg twice daily; the usual therapeutic dose is in the range of 10-20 mg twice daily [4].

METHODS

Nicorandil was obtain as a gift sample from Astron Research Lab, hydroxypropyl methyl cellulose (HPMC) K-100M and carbopol 934p from Acurate Pharma, PVP K30, magnesium stearate, ethyl cellulose, mannitol, aspartame from Chemdie Corporation.

Preparation of buccal tablets

Direct compression method has been employed to prepare buccal tablets of nicorandil using carbopol 934p and HPMC K100M as muccoadhesive polymers and the ethyl cellulose act as a backing membrane.

Method

All the ingredients including drug, polymers and excipients were weighed accurately according to the batch formula shown in Table 1. The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then, all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 minutes in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 minutes. The prepared blend (100 mg) of each formulation was pre-compressed [5], on 10-station rotary tablet punching machine at a low compression force to form single layered flat-faced tablet of 9 mm diameter. Then, 50 mg of ethyl cellulose powder was used as a backing layer to prevent the bidirectional flow, and final compression was done at a high compression force.

Compatibility of excipients

Fourier transform infrared (IR) spectroscopy was employed to characterize the possible interactions between the drug and the carriers in the solid state on shimadzu spectrum by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400/cm [6].

Evaluation of buccal tablets

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation, thickness, hardness and friability of the tablets were determined by using Monsanto hardness tester and Roche friabilator respectively [7].

Uniformity of drug content

Accurately weighed quantity of the powder tablet equivalent to 10 mg of the drug was transferred to 100 ml volumetric flask. 50 ml of buffer solution of pH 6.8 was added. Mix with the aid of ultrasonicator for 10 minutes, and then the volume was made up to 100 ml with the same buffer solution, mixed solution was filtered through the membrane filter disc with an average pore diameter not >0.45 µm. A volume of 5 ml of the filtrate was diluted to 100 ml with same buffer solution and examined under ultra violet spectrophotometer at 262 nm [8].

Determination of surface pH

The surface pH of the prepared nicorandil buccal tablets was determined to evaluate the possible irritation effects on the mucosa. The nicorandil buccal tablets were placed in glass tubes and allowed to swell in contact with distilled water (12 ml) and the pH was measured by bringing the pH paper, in contact with the surface of the tablet and allowing it to equilibrate for 1 minute [9].

Moisture absorption study

Agar (5% w/v) was dissolved in hot water, transferred into petri plates and allowed to solidify. Six nicorandil buccal tablets from each batch were placed in a vacuum overnight prior to the study to remove the moisture if any and weighed initially, laminated on one side with cellophane tape (impermeable backing membrane). Then, buccal tablets were placed on the surface of the agar and incubated at 37°C for 1 hr. At the end of the test, buccal tablets were reweighed, and the percentage moisture absorption was calculated using the following formula [10].

$$\% \text{ Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Water absorption ratio and wetting time

A piece of tissue paper folded twice was placed in a petri dish containing 5 ml of water. A pre weighed tablet was placed on the paper, and the time for complete wetting was measured, which is characterized by coloring of tablet. The wetted tablet was then weighed [11]. Water absorption ration R was determined according to the following formula:

$$R = (W_A - W_B / W_B)\ 100$$

Where, W_A=Weight of tablet after absorption of water

W_B=Weight of tablet before absorption of water

Bioadhesive strength

A modified physical balance was used for determining the bioadhesive strength. The left pan was removed. The buccal tablet was then stuck to glass stopper through its backing membrane using an adhesive (Feviquick). To left arm of the balance the glass stopper along with the tablet was hanged. A clean glass mortar was placed below hanging glass stopper. The balance was so adjusted that right hand-side was exactly 5 g heavier than the left. Fresh porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hrs of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues, washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The fresh porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied with the mucosal side upwards using thread over the hollow cylinder, the cylinder was used because it was gave strength to the buccal mucosa and it was not float during the adhesion. The cylinder was then lowered into the glass beaker (250 ml), which was then filled with 200 ml phosphate buffer pH 6.8 kept at 37±0.5°C to keep mucosal membrane moist. This was then kept below the left-hand setup of the balance. The tablet to be tested for bioadhesion was then stuck with a little moisture. The 5 g weight on the right pan was removed. This lowered the tablet over the mucosa, with a force of 5 g. The balance was kept in this position for 3 minutes, and then the weight was added slowly to the right hand pan until the tablet detached from the mucosal surface (Fig. 1). The detachments force gave the bioadhesive strength of the buccal tablet in gram [12,13]. From the bioadhesive strength, force of adhesion and then the averages of three determinations were calculated.

Force of adhesion (F)=(W×g)/1000

Where g is the acceleration due to gravity (9.80665 m/seconds^2)

Residence time

The *ex vivo* residence time was determined using a locally modified USP disintegration apparatus. The disintegration medium was composed of 900 ml (pH 6.8) of phosphate buffer maintained at 37±1°C. The porcine buccal mucosa was tied to the surface of a glass slab, vertically attached to the disintegration apparatus. The buccal tablet was hydrated using phosphate buffer (pH 6.8) and the hydrated surface was brought in contact with the mucosal membrane by keeping the backing membrane outside. The glass slide allowed moving up and down and hence that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point (Fig. 2). The time taken for complete displacement of the tablet from the mucosal surface was noted and repeated thrice [14,15].

***In vitro* drug release study**

This is carried out in USP XXIII tablet dissolution test apparatus-II, employing paddle stirrer at 50 rpm and 250 ml of pH 6.8 phosphate buffer as dissolution medium. The released study is performed at 37±0.5°C. The backing layer of the buccal tablet is attached to glass disk

Table 1: Formulation variables of buccal tablet

Ingredient	Formulation code (quantity mg/tablet)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicorandil	10	10	10	10	10	10	10	10	10
Mannitol	48	33	18	48	33	18	48	33	18
HPMC K 100M	30	45	60	15	22.5	30	-	-	-
Carbopol 934p	-	-	-	15	22.5	30	30	45	60
PVP K30	10	10	10	10	10	10	10	10	10
Aspartame	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1
Backing layer									
Ethyl cellulose	50	50	50	50	50	50	50	50	50
Total weight	150	150	150	150	150	150	150	150	150

PVP: Polyvinylpyrrolidone, HPMC: Hydroxypropyl methyl cellulose

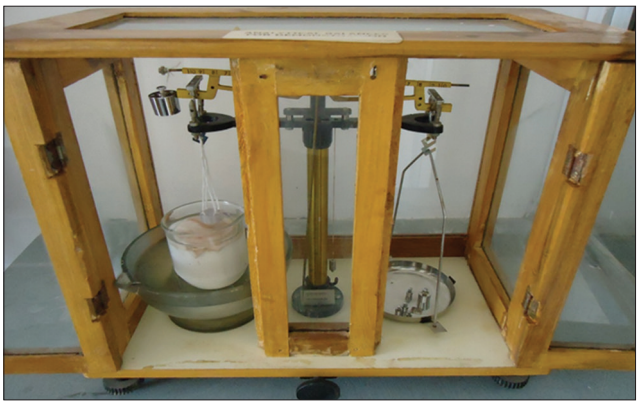

Fig. 1: Determination of bioadhesive strength of nicorandil buccal

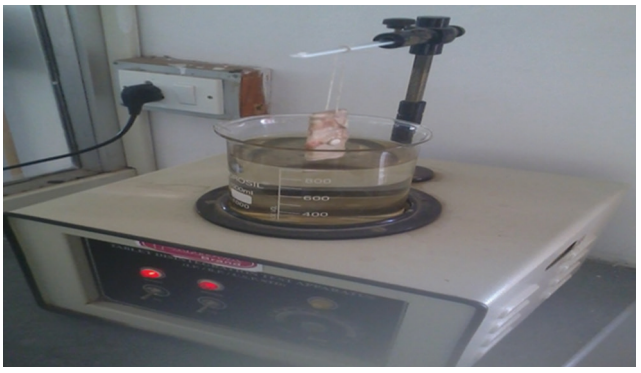

Fig. 2: Determination of residence time of nicorandil buccal tablet

with cyanoacrylate adhesive. The disk is 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 0.45 µm membrane filter disc (Millipore Corporation) and analyzed for nicorandil after appropriate dilution by measuring the absorbance at 262 nm. The experiment was run in triplicate [16].

***Ex vivo* permeation studies**

Ex vivo permeation study of nicorandil buccal tablet was carried out on porcine buccal membrane using modified Franz diffusion cell with a diffusion area of 2.8 cm^2 and the acceptor compartment volume of 30 ml. A semi permeable membrane (porcine buccal mucosa membrane) was clamped between the donor and acceptor compartments. The water in the acceptor compartment was continuously stirred at 100 rpm using a magnetic stirrer and maintained at 37±0.5°C. The buccal tablet was placed into the donor compartment and was wetted with 1 ml of 7.4 phosphate buffer (Fig. 3). The diffusion was carried out for 10 hrs. The amount of nicorandil permeated through the membrane was determined by removing samples periodically and replaced with an equal volume of 7.4 phosphate buffer. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically (Elico, India) at 262 nm [17].

RESULTS AND DISCUSSION

The main goal of this work was to develop new mucoadhesive buccal tablets of nicorandil, is anti-anginals and coronary vasodilators consisting of drug free non-adhesive protective layer. The purity of drug sample was identified by scanning the drug sample on IR spectrophotometer. The peaks of the IR spectra of drug sample were found to be similar with the standard IR spectra of pure nicorandil as reported. Fig. 6 shows the IR spectra of nicorandil. The IR spectra of the mixture of drug and polymer indicated no incompatibility between drug and polymers. Hence carbopol 934p and HPMC K15M were chosen as polymers for further investigations. The spectrum of drug shows absorption bands at 2850/cm C-H aliphatic stretching, 1427/cm C-H bending, 1562/cm N-H amide bending, 3243/cm N-H amide stretching, 1361/cm NO_2 stretching. The double layered structure design was expected to provide drug delivery in an unidirectional fashion to the mucosa and to avoid loss of drug due to wash out by saliva, release drug immediately to produce a prompt pharmacological action and remain in oral cavity and provide a sustained release of enough drug over an extended period of time. A total of nine formulations of mucoadhesive buccal tablets of nicorandil were prepared and evaluated for biological, physical and mechanical parameters. The hardness of prepared buccal tablets of nicorandil was found 4.41-4.61 kg/cm^2. Mean thickness and weights were found to be uniform as indicated by the low values of standard deviation. The thickness and weight of the prepared buccal tablets were found to be in the range of 2.06-2.22 mm and 149-152 mg respectively. Friability values <1% indicate good mechanical strength to withstand the rigors of handling and transportations. Results are given in Table 2. The drug content of buccal tablets was quite uniform as seen in Table 2. The average drug content of the buccal tablets was found to be within the range of 96.35-98.61% and the low values of standard deviation and coefficient of variation (<2) indicate uniform distribution of the drug within the prepared buccal tablets. The surface pH was determined in order to investigate the possibility of any side-effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be almost in neutral pH and ranged between 5.19 and 6.78 and no mucosal irritation was expected. The surface pH of all the formulations is shown in Table 3. The swelling index of mucoadhesive tablets is shown in Table 3. Among all the formulations, F3 showed maximum swelling index of 58% after 8th and followed by F6, F5, F9, F2, F8, F2, F1 and F6. From the swelling index results, as given in Table 3, it was concluded that swelling increases as the time proceeds because the polymer gradually absorb water due to the hydrophilicity of the polymer. The outermost hydrophilic polymer get hydrated, which results in and swelling and a gel barrier is formed at the outer surface. As the gelatinous layer progressively dissolves or disperses. The swelling behavior provides an idea regarding the moisture intake capacities of polymers and the differences in swelling of the hydrophilic polymers may be due

Table 2: Physicochemical property of buccal tablet

Code	Hardness (kg/cm^2) N=10	Thickness (mm) N=10	Friability %	Weight variation N=20	Drug content (%)
F1	4.47±0.0186	2.16±0.0059	0.613	148±1.67	97.13±0.32
F2	4.41±0.0207	2.22±0.0173	0.519	150±1.58	98.16±0.29
F3	4.50±0.0231	2.11±0.0042	0.551	151±1.81	97.42±0.66
F4	4.51±0.0189	2.08±0.0379	0.428	151±1.31	97.91±0.41
F5	4.61±0.0216	2.06±0.0031	0.324	149±1.71	98.61±0.88
F6	4.49±0.0308	2.14±0.0352	0.594	152±1.15	98.01±0.24
F7	4.53±0.0263	2.11±0.0442	0.384	150±1.72	98.31±0.72
F8	4.54±0.0157	2.10±0.0031	0.468	150±1.69	97.01±0.48
F9	4.44±0.0294	2.19±0.0052	0.463	149±1.74	96.35±0.51

The values are expressed as mean±SD, SD: Standard deviation

Table 3: Physicochemical property of buccal tablet

Formulation code	Surface pH N=3	Bioadhesive strength (N)	Residence time (hrs) N=3	Percentage swelling after 8 hrs
F1	5.19±0.04	0.0432	7.5±0.48	37
F2	5.34±0.01	0.0511	7.1±0.31	42
F3	5.18±0.02	0.0697	8.5±0.61	58
F4	6.36±0.30	0.0501	7.1±0.19	39
F5	6.71±0.06	0.0791	9.5±0.33	47
F6	6.52±0.10	0.0713	9.1±0.48	56
F7	5.93±0.05	0.0429	6.2±0.37	31
F8	5.94±0.04	0.0493	6.5±0.18	39
F9	5.98±0.03	0.0551	7.2±0.25	49

The values are expressed as mean±SD, SD: Standard deviation

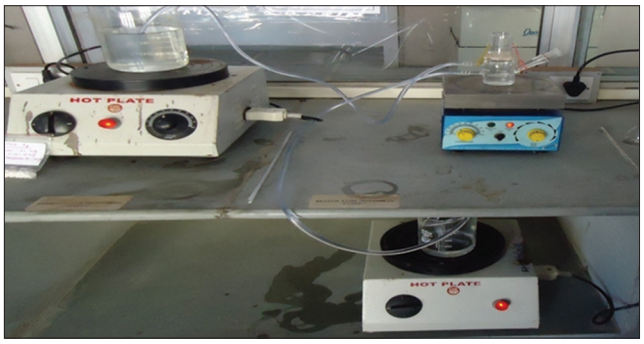

Fig. 3: Determination of permeation studies of nicorandil buccal tablet

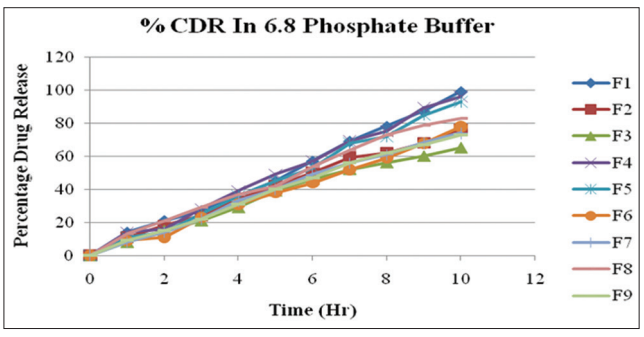

Fig. 4: *In vitro* drug release profile of prototype formulation

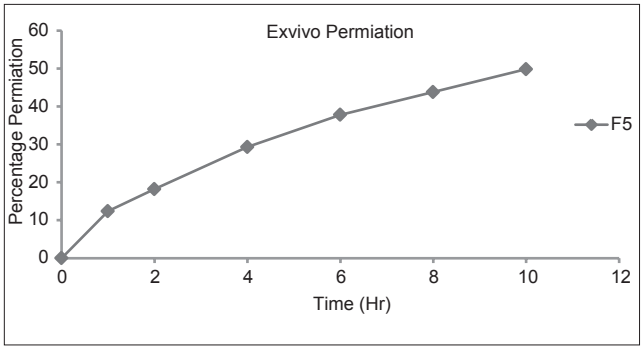

Fig. 5: *Ex vivo* permeation study of formulation F5

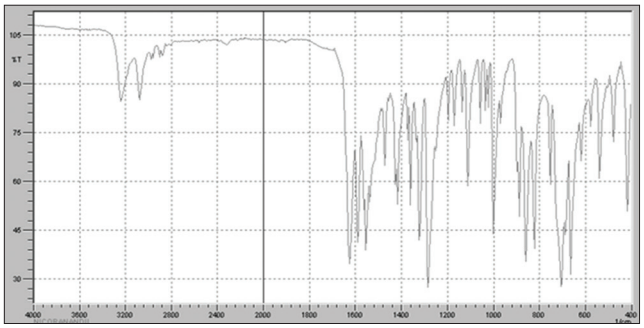

Fig. 6: Fourier transform infrared spectrum of nicorandil pure drug

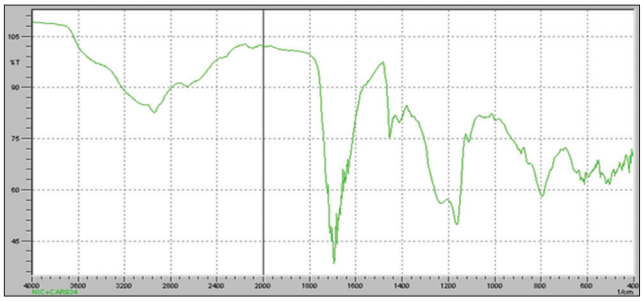

Fig. 7: Fourier transform infrared spectra of nicorandil + carbopol 934p

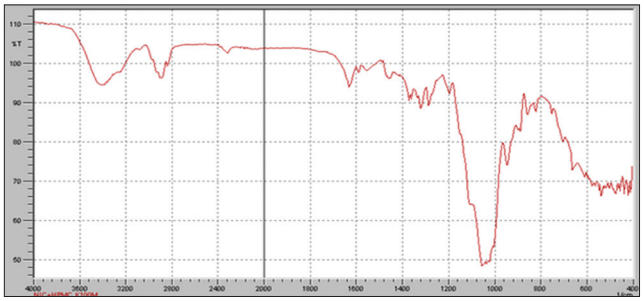

Fig. 8: Fourier transform infrared spectra of nicorandil + hydroxypropyl methyl cellulose K100M

to the difference in resistance of the matrix network structure. The bioadhesion strength and residence time of nicorandil buccal tablets are shown in Table 3. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. The formulation F5 showed maximum mucoadhesion strength and residence time. The mucoadhesive strength of the formulation F5 was found to be maximum of 0.0791 N. The residence time of buccal tablets ranged between 6.2 and 9.5 hrs and noted this much time required for buccal tablets to detach from the buccal mucosa. Among all the nine formulations, F5 was found to be highest percentage drug release. During the study, it was observed that the tablets were initially swell and no erodible over the period of 10 hrs. It was concluded that by increasing the concentration of carbopol 934p and HPMC K100M in the formulation, the drug release rate from the tablets was found to be decreased. This may be due to increased hydration (or) swelling characteristics of polymers with increased concentrations. From the overall data, it was found that the formulation F5 showed the maximum percentage of drug release, i.e. 89.24% at the end of 10 hrs. Based on *ex vivo* mucoadhesion, *ex vivo* residence time and in-*vitro* release studies formulation F5 was selected for *ex vivo* permeation study. Pigs resemble that of humans more closely than any other animal in terms of structure and composition and, therefore, porcine buccal mucosa was selected for nicorandil permeation studies. The results of drug permeation from nicorandil buccal tablets through the porcine buccal mucosa revealed that nicorandil was released from the tablet and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane. The drug permeation was slow and steady, and 49.32% of nicorandil could permeate through the buccal membrane in 10 hrs. The stability studies performed in normal human saliva would be more accurate to mimic the stability of the nicorandil mucoadhesive buccal tablet in the oral cavity *in vivo*. Based on the results of *ex vivo* mucoadhesion, *in-vitro* release studies, *ex vivo* residence, formulation F5 was selected for stability study.

CONCLUSION

The mucoadhesive strength was influenced by the nature and proportions of the mucoadhesive polymers used in the formulations. In all the formulations, as the mucoadhesive polymer mixture concentration increased, the mucoadhesive strength also increased. Buccal tablets formulated (F5) with a mixture of carbopol 934p and HPMC K100M showed comparatively higher bioadhesion than that of all other formulataion. Very strong mucoadhesion could damage the epithelial lining of the buccal mucosa. Mucoadhesive strength exhibited by the formulation F5 tablets can be considered satisfactory for maintaining them in the oral cavity for 12 hrs. The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity. The surface pH of the buccal tablets depends on the nature and composition of mucoadhesive polymers. Surface pH of F5 formulation was found 6.78. This pH is near to the neutral, so the buccal tablet does not cause any irritation on the mucosa. The *ex vivo* residence time was determined by using modified physical balance method. Formulations F5 showed higher bioadhesive time when compared to the other formulations. The residence time also increased. This test reflects the mucoadhesive capacity of polymers used in formulations. The results revealed that the mixture of carbopol 934p and HPMC K100M containing formulations showed better bioadhesion than the mixture of all other muccoadhesive polymer in the formulations. Based on *ex vivo* mucoadhesion, *ex vivo* residence time and *in-vitro* release studies formulation F5 was selected for *ex vivo* permeation study.

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