Original Research Article

Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method

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Abstract

Introduction: In the present study, mucoadhesive buccal bilayer tablets of atenolol were fabricated with the objective of avoiding first pass metabolism and to improve its bioavailability with reduction in dosing frequency. Hence, the aim of this work was to design oral controlled release mucoadhesive tablets of atenolol and to optimize the drug release profile and bioadhesion. **Materials and Methods:** Bilayer buccal tablets of atenolol were prepared by direct compression method using simplex method of optimization to investigate the combined effect of hydroxypropyl methylcellulose 15 cps (X_1), Carbopol (X_2) and mannitol (X_3); the *in vitro* drug release (Y_1) and mucoadhesive strength (Y_2) were taken as responses. The designed tablets were evaluated for various physical and biological parameters like drug content uniformity, *in vitro* drug release, short-term stability, and drug-excipient interactions (FTIR). **Results:** The formulation C containing hydroxypropyl methylcellulose 15 cps (10% w/w of matrix layer), Carbopol 934p (10% w/w of matrix layer) and mannitol (channeling agent, 40% w/w of matrix layer) was found to be promising. This formulation exhibited an *in vitro* drug release of 89.43% in 9 h along with satisfactory bioadhesion strength (7.20 g). Short-term stability studies on the promising formulation indicated that there are no significant changes in drug content and *in vitro* dissolution characteristics ($P<0.05$). IR spectroscopic studies indicated that there are no drug-excipient interactions.

Key words: Atenolol, bioadhesive strength, mucoadhesive buccal tablet, simplex method of optimization, swelling index

INTRODUCTION

The mucosa is considered as a potential site for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vagina, ocular and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages includes possible bypass of the first pass effect, avoidance of presystemic elimination of gastro intestinal tract (GIT).[1]

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism; drug degradation in gastro intestinal environment can be circumvented by administering a drug via buccal route.[2,3] Moreover, buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore, mucoadhesive dosage forms were suggested for oral drug delivery, which includes adhesive tablets, adhesive gels, and adhesive patches.[4]

Atenolol [beta (β) blocker] has been widely used in the management of hypertension. The drug is well absorbed from the GIT but its bioavailability is low (54%) due to extensive first pass metabolism.[5,6] Since the buccal route bypasses first-pass effect, the dose of atenolol could be reduced by 50%. The physicochemical properties of atenolol, its suitable half-life (6-7 h), and low molecular weight (266.34) makes it a suitable candidate for administration by buccal route. The effective permeation of the drug through bovine buccal mucosa has already been reported.[7]

From the technological point of view, an ideal buccal dosage form must have three properties; it must maintain its position in the mouth for a few hours, release the drug in controlled fashion, and provide drug release in a unidirectional way towards mucosa.

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In the present study, the mucoadhesive tablets were developed using hydrophilic polymers (Carbopol 934p, HPMC 15 cps) to get controlled and zero order drug release. The aim of this study was design, development, optimization, and characterization of a buccoadhesive controlled-release tablet of atenolol using some selective polymers like Carbopol 934p (CP) and hydroxypropylmethyl cellulose 15 cps (HPMC). Also, the interaction between polymers, drug-polymers, bioadhesion and *in vitro* release characteristics of atenolol from different buccoadhesive matrix tablets was evaluated to assess the suitability of such formulations.

Optimization using simplex design method[8-10]

A simplex design was adopted to optimize the formulation variables. In this design, three factors were evaluated by changing their concentration simultaneously and keeping their total concentration constant. The simplex design for three component system was represented by an equilateral triangle Figure 1 in two dimensional space. Seven batches (A to ABC) were prepared; one at each vertex (A, B, C), one at half way between vertices (AB, BC, AC), and one at the center point (ABC). Each vertex represents a formulation containing the maximum amount of one component, with the other two components at a minimum level. The half way between the two vertices represents a formulation containing the average of the minimum and maximum amount of the two ingredients represented by two vertices. The center point represents a formulation containing one third of each ingredient. The amount of HPMC 15 cps, Carbopol 934p, and Mannitol were selected as independent variables and *in vitro* drug release and mucoadhesive strength was taken as dependent variables.

MATERIALS AND METHODS

Materials

Atenolol was gifted by Rajat Pharmachem Ltd, Ankaleshwar,

Gujarat. Ethyl cellulose was gifted by Arihant Trading co., Mumbai, India; hydroxypropyl methylcellulose 15 cps and Carbopol 934p were gift samples from Colorcon Asia Pvt. Limited, Verna, India and ShinEtsu Chemical Co. Ltd Japan respectively. All other materials were of analytical or pharmacopoeial grade and used as received.

Methods
Preparation of the buccal tablets[11,12]
Preparation
Direct compression method has been employed to prepare buccal tablets of atenolol using HPMC 15cps and Carbopol 934p as polymers.

Procedure
All the ingredients including drug, polymer, and excipients were weighed accurately according to the batch formula [Tables 1 and 2]. The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricant were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant (sodium stearyl fumarate SSF) was added and again mixed for 2 min. The prepared blend (100 mg) of each formulation was pre-compressed, on a 10-station roatory tablet punching machine (Clit, Ahmedabad) at a pressure of 0.5 ton and turret speed of 2 rpm to form single layered flat-faced tablet of 8 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons and turret speed of 2 rpm to get bilayer tablet.

Design of experiments
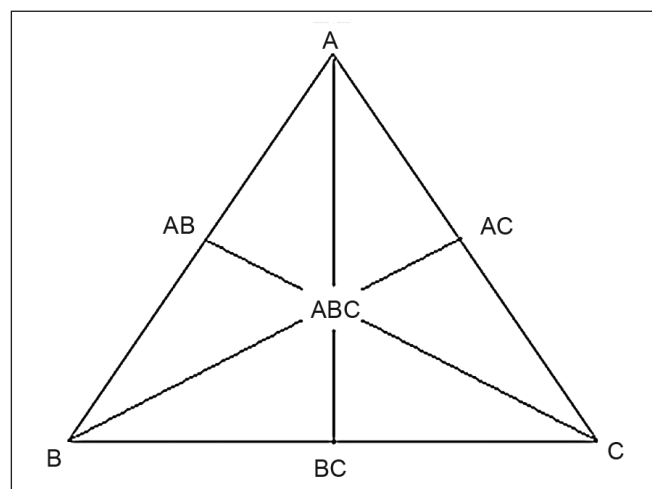Based on the results of preliminary trial formulations obtained

Figure 1: Equilateral triangle representing simplex design method for three components A, B, and C represent maximum amount of component; AB, BC, and AC represents equal amount of components A and B, B and C, A and C, respectively, in formulation; ABC represent equal amount of component A, B and C in formulation

Table 1: Composition of atenolol buccal tablets

Ingredients	Amount (mg)
Atenolol	25
HPMC 15 cps	10-40
Carbopol 934p	10-40
Mannitol	10-40
Aspartame	3
SSF	3
Spray dried flavoring agent	3
Polyvinyl pyrrolidonesK-30	6
Ethyl cellulose	50

Each tablet weight-150 mg, HPMC- hydroxypropyl methylcellulose; PVP- polyvinyl pyrolidone, SSF- Sodium Stearyl Fumarate

Table 2: Combinations as per the chosen experimental design (Simplex design method)

Formulation code	Coded factor levels		
	X_1	X_2	X_3
A	40	10	10
B	10	40	10
C	10	10	40
AB	25	25	10
AC	25	10	25
BC	10	25	25
ABC	20	20	20

Coded level: X_1 - HPMC 15 cps, X_2 - Carbopol 934p, X_3 – Mannitol

from the batches of three mucoadhesive polymers (HPMC 15 cps, HPMC 50 cps, and HPMC K4M), the best mucoadhesive polymer screened was used for the final optimization of direct compression method, we have fixed the constraints for the level of independent variables (X_1, X_2, and X_3) i.e., HPMC 15 cps (X_1), carbopol 934p (X_2), and mannitol (X_3), as shown in Table 2. In this study, a simplex design was adopted to optimize the variables. In this design, two factors were evaluated and experiments were performed on all seven-possible combinations. The amount of HPMC 15 cps (X_1) and Carbopol 934p (X_2) were taken as independent variables since the total concentration of the three variations is constant, variation is the levels of X_1 and X_2 will automatically fix the levels of X_3 and *in vitro* drug release (Y_1) and mucoadhesive strength (Y_2) were taken as dependent variables [Table 3].

Evaluation of buccal tablets

The prepared batches of tablets were evaluated for weight variation, hardness, friability, drug content uniformity, swelling index, surface pH, *ex vivo* mucoadhesive strength, *in vitro* drug release, short-term stability and drug-excipient interaction (IR spectroscopy).

Hardness test

The crushing strength (kg/cm^2) of tablets was determined using Monsanto hardness tester.

Friability test

This was determined by weighing 20 tablets after dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated (% loss in weight).

Uniformity of content

The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation from the mean.

Uniformity of drug content

Five tablets were powdered in a glass mortar and the powder equivalent to 25 mg of drug was placed in a stoppered 100-ml conical flask. The drug was extracted with 25 ml water with

vigorous shaking on a mechanical gyratory shaker (100 rpm) for 2 h and filtered into 50 ml volumetric flask through Whatman No.1 filter paper (mean pore diameter 1.5 μm) and more solvent was passed through the filter to produce 50 ml. Aliquots of the solution were filtered through 0.45-μm membrane filter disc (Millipore Corporation) and analyzed for drug content by measuring the absorbance at 225.6 nm against solvent blank.

Surface pH[13]

For the determination of surface pH of the buccal tablets, a combined glass electrode was used. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.8±0.05) for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min.

Swelling index[14,15]

The swelling index of the buccal tablet was evaluated by using pH. 6.8 phosphate buffer. The initial weight of the tablet was determined (w_1). The tablet was placed in pH. 6.8 phosphate buffer (6 ml) in a petri-dish placed in an incubator at 37±1°C and tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, to 9.0 h), and re-weighed (w_2) [Figure 2]. The swelling index was calculated using the formula:

$$\text{Swelling index} = 100 \ (w_2 - w_1)/w_1.$$

Mucoadhesive strength[16-19]

The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by Gupta *et al*.,[20] using bovine cheek pouch as model mucosal membrane. (The buccal mucosa was collected from the local slaughterhouse).

A double beam physical balance was taken; the left pan was removed. To left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass stopper with uniform surface was tied. A clean glass mortar was placed below hanging glass stopper. In this mortar, a clean 500-ml glass beaker was placed, within which was placed another glass beaker of 50 ml capacity in inverted position and weighted with 50 g to prevent floating. The temperature control system involves placing thermometer in 500-ml beaker and intermittently adding hot water in outer mortar filled with water. The balance was so adjusted that right hand-side was exactly 5 g heavier than the left.

Method

The balance adjusted as described above was used for the study. The bovine cheek pouch was excised, washed, and then tied tightly with mucosal side upward using thread over the base of inverted 50-ml glass beaker. This beaker suitably weighted was lowered into 500-ml beaker, which was then filled with isotonic phosphate buffer (pH 6.8) kept at 37°C such that the buffer reaches the surface of mucosal membrane and keeps it moist. This was then kept below left hand side of balance. The buccal tablet

Table 3: Formulation and evaluation of formulations in simplex design method

Formulation code	Transformed fractions			$t_{25\%}$ (h)	$t_{50\%}$ (h)	Mucoadhesive strength (g)
	X_1	X_2	X_3			
A	1	0	0	0.57	02.20	07.4
B	0	1	0	2.00	10.45	14.63
C	0	0	1	0.39	01.40	07.2
AB	0.5	0.5	0	1.14	03.70	108.27
AC	0	0.5	0.5	0.61	03.08	105.33
BC	0.5	0	0.5	0.78	03.08	54.53
ABC	0.33	0.33	0.33	-1.10	03.90	85.61

X_1 = HPMC 15 cps, X_2= Carbopol 934p, X_3= mannitol, $t_{25\%}$= time required to release 25% drug, $t_{50\%}$= time required to release 50% drug
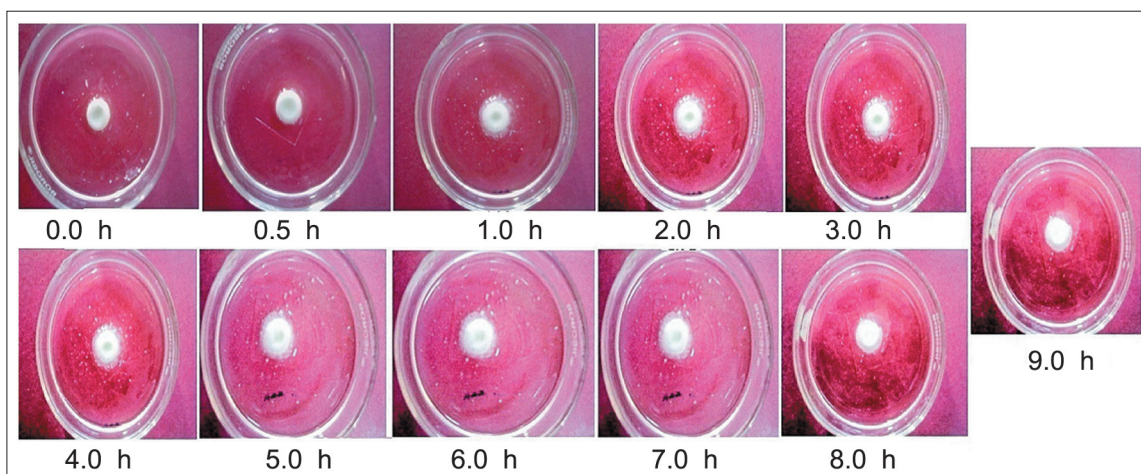
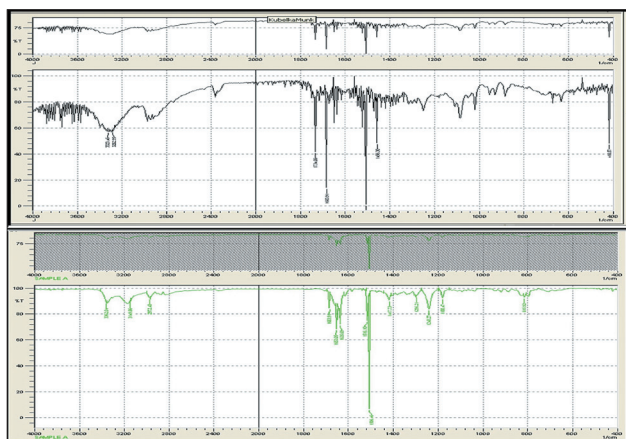**Figure 2:** Swelling index study of formulation C

Figure 3: FTIR spectra of atenolol pure drug and promising formulation C

was then stuck to glass stopper through its backing membrane using an cyanoacrylete adhesive (Feviquick). The 5 g on right hand side is removed; this causes application of 5 g of pressure on buccal tablet overlying moist mucosa. The balance was kept in this position for 3 min and then slowly weights were increased on the right pan, till tablet separates from mucosal membrane. The total weight on right pan minus 5 g gives the force required to separate tablet from mucosa. This gives bioadhesive strength in grams. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 min before reading a new tablet of same formulation to get reproducible multiple results for the formulation.

In vitro drug release study[21-23]
This was carried out in USP XXIII tablet dissolution test apparatus-II (Electrolab TDT-06N Mumbai, India), employing paddle stirrer at 50 rpm and 200 ml of p. 6.8 phosphate buffer as dissolution medium. The release study was performed at 37 ± 0.5° C. The backing layer of the buccal tablet was attached to 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 were replaced with fresh medium. The samples were filtered through 0.45 μm Whatman filter paper and analyzed for atenolol after appropriate dilution by measuring the absorbance at 226.7 nm. The experiment was run in triplicate.

Stability studies
Accelerated stability studies were performed at a temperature of 40±2°C/75±5% RH over a period of three months (90 days) on the promising buccal tablets of atenolol (formulation C) Sufficient number of tablets (15) were packed in amber colored rubber stoppered vial and kept in a stability chamber maintained at 40±2°C/75±5% RH. Samples were taken at one month interval for drug content estimation. At the end of three months period, dissolution test was also performed to determine the drug release profiles.

Drug-excipient interaction studies
The IR spectra of atenolol, Carbopol 934p, HPMC 15cps, PVP K-30, SSF, and formulation (C) were obtained by KBr pellet method. (Perkin-Elmer series 1615 FTIR Spectrometer) [Figure 3].

RESULTS AND DISCUSSION

It has been proposed that mucoadhesion occurs in three stages. The first stage involves the formation of an intimate contact between the mucoadhesive and mucous. Second, the mucoadhesive macromolecules swell and interpenetrate the mucous macromolecules, becoming physically entangled. Third, these molecules interact with each other via secondary, non-covalent bonds such as hydrogen bonds.

The main goal of this work was to develop new buccoadhesive bilayer tablets of atenolol, an antihypertensive drug (beta blocker), consisting of drug free non-adhesive protective layer. The double layered structure design was expected to provide drug delivery in unidirectional fashion to the mucosa and to avoid loss of drug due to washout 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 seven formulations of buccoadhesive bilayer tablets of atenolol were prepared and evaluated for biological, physical, and mechanical parameters. The blends were also evaluated for various pre compression parameters. These blends displayed angle of repose values of about 35°; bulk density, tapped density and Carr's index values were found to be approximately 0.35 g/cc, 0.41 g/cc, and 14.63%, respectively. According to work plan, the tablets were evaluated for their thickness, hardness, friability, weight variation, swelling index, surface pH, drug content, and mucoadhesive strength.

The appearance of buccoadhesive tablets was smooth and uniform on physical examination. The hardness of prepared tablets of atenolol was found to be 3.53 to 5.77 kg/cm²; hardness increases with an increase in Carbopol 934p proportion in the formulation. The thickness and weight variation were found to be uniform as indicated by the low values of standard deviation and were found to be in the range of 2.97 to 3.03 mm and 148.7 to 150.8 mg, respectively. Friability values less than 1% indicate good mechanical strength to withstand the rigors of handling and transportation. Results are given in Table 4. The drug content of the tablets was quite uniform as seen in the above mentioned table. The average drug content of the tablets was found to be within the range of 95.35% to 102.61% and the low values of standard deviation and coefficient of variation (<1, not shown in the table) indicate uniform distribution of the drug within the prepared buccoadhesive tablets. The surface pH of all the tablets was within a range of 5.85 to 6.79 [Table 4], which was close to neutral pH. Hence, it is assumed that these formulations cause no irritation in the oral cavity. The swelling profile of different batches of the tablets is shown in Table 4. The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. 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. Results indicate that as the concentration of Carbopol 934p increases the swelling index increases. The mucoadhesive strength of the tablets was found to be maximum in case of

formulation B, i.e., 14.63 g. This may be due to fact that positive charges on surface of Carbopol 934p could give rise to strong electrostatic interaction with mucous or negatively charged mucous membrane.

The amounts of HPMC 15 cps (X_1), Carbopol 934p (X_2), and mannitol (X_3) were selected as independent variables in a simplex lattice design. The time required for 25% (t_{25}), 50% drug dissolution (t_{50}), and mucoadhesive strength were taken as responses. A statistical model incorporating seven interactive terms was used to evaluate the responses.[10]

$$Y = b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3 \quad (1)$$

Where, Y is the dependent variable (response); X_1, X2, X_3 represent transformed percentage concentrations of A, B and C respectively and b_1 = response at 100% A; b_2 = response at 100% B; b_3 = response at 100% C; b_{12} = response at 50-50 AB; b_{13} = response at 50-50 AC; b_{23} = response at 50-50 BC; b_{123} = response at 1/3 A, 1/3 B and 1/3 C. The main effects (X_1X_2 and X_3) represent the average result of changing 1 factor at a time from its different concentration. The interaction terms (X_1X_2, X_2X_3, X_1X_3 and $X_1X_2X_3$) show how the response changes when two or more factors are simultaneously changed. The statistical analysis of simplex design method batches was performed by linear regression analysis using Microsoft Excel. The values [Table 2] for t_{25}%, t_{50}% and mucoadhesive strength for all the 7 batches (A to ABC) showed a wide variation (i.e., 0.39 to 1.45, 1.40 to 10.45 and 7.20 to 14.63 g, respectively). The data clearly indicate that the values of $t_{25\%}$, $t_{50\%}$, and mucoadhesive strength are strongly dependent on the selected independent variables. The fitted equations relating the responses mucoadhesive strength, t_{25} and t_{50} to the transformed factor are shown in Equation 2, Equation 3, and Equation 4, respectively.

Mucoadhesive strength =
$$7.40X_1 + 14.63X_2 + 7.20X_3 + 388.99X_1X_2 + 183.92X_1X_3 + 377.70X_2X_3 + 17931.34X_1X_2X_3$$
$$(R^2 = 0.3942) \dots\dots(2)$$

$$t_{25\%} = 0.57X_1 + 2.0X_2 + 0.39X_3 + 0.58X_1X_2 + 0.52X_1X_3 - 1.66X_2X_3 - 14.76X_1X_2X_3 (R^2 = 0.4955) \dots\dots(3)$$

Table 4: Evaluation of buccal tablets

Formulation code	Mean hardness* (kg/cm²)	Mean thickness* (mm)	Weight variation* (mg)	Friability (%)	Mean% drug content*	Mean surface PH*	Mean swelling index* (after 9 h)	Mucoadhesive strength* (g)
A	4.40±0.10	3.00±0.10	148.7±0.90	0.46±0.0	100.40±1.31	6.73±0.11	73.43±3.37	7.40±0.10
B	5.77±0.15	3.03±0.15	150.3±1.10	0.47±0.0	96.45±2.06	6.15±0.06	119.24±1.48	14.63±0.35
C	3.53±0.06	0.00±0.10	150.8±0.98	0.27±0.0	100.67±2.85	6.74±0.06	50.03±4.14	7.20±0.20
AB	4.97±0.06	2.97±0.06	149.5±1.02	0.46±0.00	99.77±2.03	5.89±0.04	103.95±4.96	10.80±0.30
AC	4.27±0.12	3.00±0.00	149.7±0.90	0.34±0.0	95.35±2.22	5.96±0.03	54.65±4.19	8.33±0.25
BC	4.77±0.06	3.03±0.12	150.2±0.79	0.39±0.0	99.84±0.36	6.68±0.11	93.02±2.33	11.83±0.21
ABC	4.63±0.06	3.03±0.12	149.5±1.36	0.47±0.03	97.95±1.22	5.85±0.05	89.85±0.05	8.20±0.10

*Average of three determinations, values shown in parenthesis are standard deviations. Formulation C was selected as the best and used for further studies

$$t_{50\%} = 2.20X_1 + 10.45X_2 + 1.40X_3 + 66.66X_1X_2 + 5.12X_1X_3 + 34.82X_2X_3 + 422.88X_1X_2X \ (R^2 = 0.4334) \quad (4)$$

The relatively higher values (≥ 0.4) of correlation coefficients for t_{25}, t_{50} and mucoadhesive strength indicates a good fit, i.e., good agreement between the dependent and independent variables. The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). The equation for mucoadhesive strength suggests that the factor X_2 has more significant effect on mucoadhesive strength followed

by factor X_1 and X_3. From the equations 3 and 4, it can be concluded that, factor X_1 and X_2 have more important role in prolonging both, t_{25} and t_{50}. The magnitude of coefficients indicates that factor X_1 and X_2 have more favorable effect on both the dependent variables than factor X_3 also the high value of X_1X_2 suggests that the interaction between X_1 and X_2 has a significant effect on t_{25} and t_{50}. From the results of linear regression analysis, it can be concluded that the drug release pattern can be changed by appropriate selection of the X_1, X_2 and X_3 levels. The promising formulation was selected on the basis of the acceptance criteria for mucoadhesive strength, t_{25} and t_{50} as mentioned earlier. Results were as shown in Figure 4.
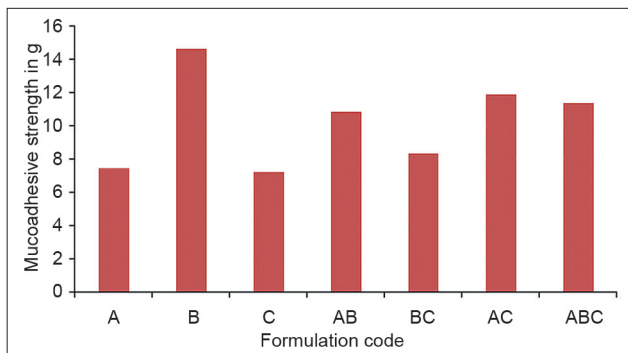
In vitro drug release

From dissolution data it is evident that the designed formulations have displayed more than 41.38% drug release in 9 h. The formulation C containing hydroxypropyl methylcellulose 15 cps (10% w/w of matrix layer), Carbopol 934p (10% w/w of matrix layer), and mannitol (channeling agent, 40% w/w of matrix layer) was found to be promising, which showed $t_{25\%}$, $t_{50\%}$, $t_{60\%}$, and $t_{70\%}$ values of 0.39, 1.40, 3.00, and 6.36 h, respectively, and released 89.43% drug within 9 h. Results are shown in Table 5 and the drug release profiles depicted in Figure 5. A comparison of the release parameters is shown in Figure 6.
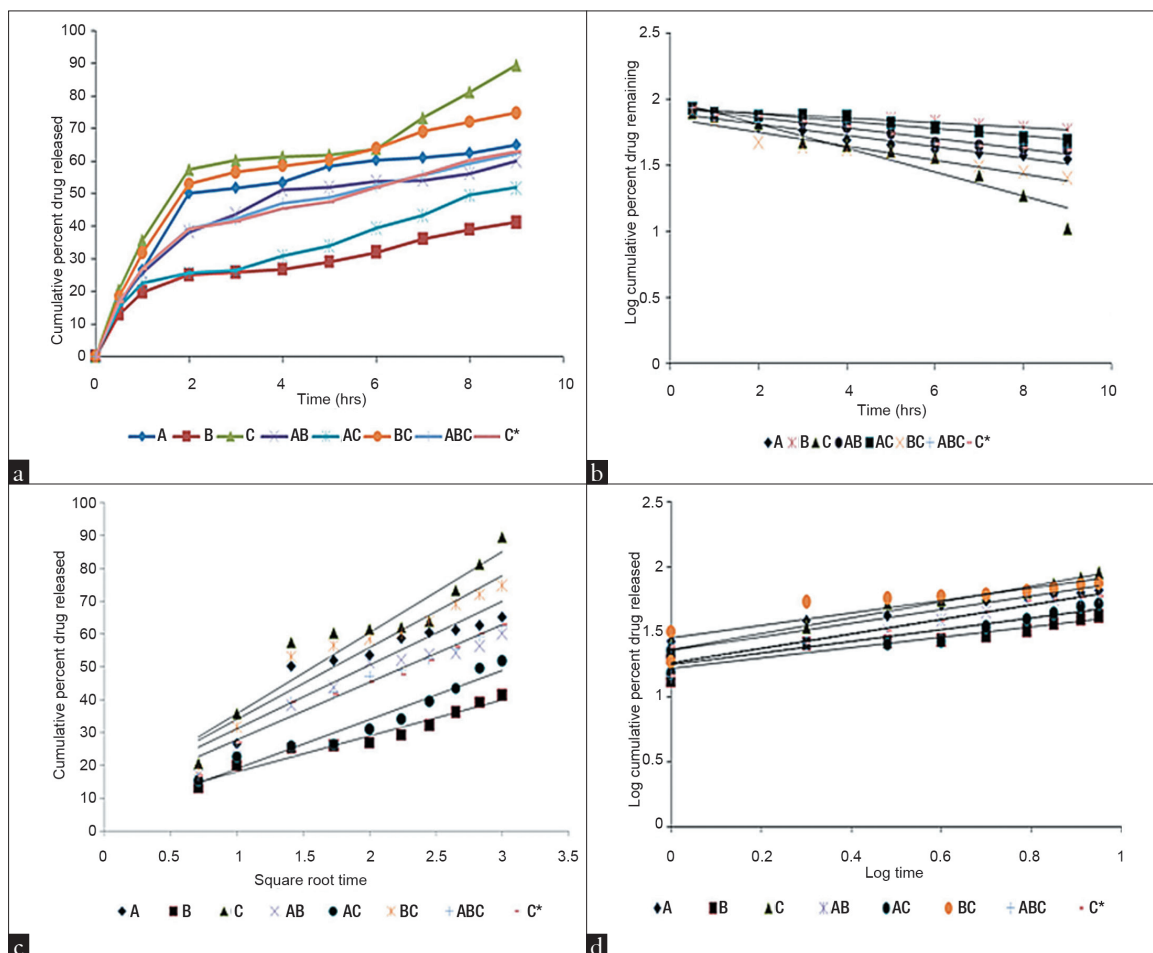

Figure 4: Mucoadhesive strength of formulations

Figure 5: Release rate profile of formulations: (a) Zero order; (b) First order; (c) Higuchi plots; (d) Peppas plots

Table 5: Dissolution parameters for the formulations

Formulation Code	$t_{25\%}$ (h)	$t_{50\%}$ (h)	$t_{60\%}$ (h)	$t_{70\%}$ (h)	Cumulative% drug release in 9 h
A	0.57	2.20	5.35	---	65.01
B	2.00	10.45	---	---	41.38
C	0.39	1.40	3.00	6.36	89.43
AB	0.57	3.45	8.54	---	60.15
AC	1.45	8.06	---	---	51.85
BC	0.42	1.51	4.42	7.18	74.84
ABC	1.09	3.27	8.30	---	61.99
C*	0.51	1.59	5.24	---	66.39

$t_{25\%}$, $t_{50\%}$, $t_{50\%}$ and $t_{70\%}$ are time for 25%, 50%, 6o% and 7o% drug release respectively

Drug release kinetics

In vitro drug release data of all the buccoadhesive tablet formulations of atenolol was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetics, and according to Higuchi's and Peppas models to ascertain mechanism of drug release. It was evident that all the formulations displayed zero-order release kinetics (after an initial burst release of 13-21% drug, with 'r' values from 0.847 to 0.943). Higuchi and Peppas data reveals that the drug is released by non-Fickian diffusion mechanism ('r' values from 0.469 to 0.999 and 'n' values from 0.803 to 0.981). The IR spectrum of the pure drug atenolol displayed characteristic peaks at 3362.04 cm^{-1} and 1636.69 cm^{-1} due to N-H and C=O amide groups, respectively. The peaks of 1240.27 cm^{-1} and 2972.40 cm^{-1} are due to alkyl aryl ether linkage and alcoholic –OH groups respectively. All the above characteristic peaks were also found in the IR spectrum of the formulation BT$_1$ (peaks at 3356.12 cm^{-1} and 1647.26 cm^{-1}due to -NH and C=O stretching, respectively, and peaks at 1244.11 cm^{-1} and 2972.40 cm^{-1} are due to alkyl aryl ether linkage and alcoholic –OH groups, respectively) as shown in Figure 3. The presence of above peaks confirms undisturbed structure of drug in the above formulation. Hence, there are no drug-excipient interactions. The stability studies data indicates that the drug content of formulation BT$_1$ was not significantly affected at 40±2°C/75±5% RH after storage for three months. The 't' value was found to be 1.03 against the table value of 4.3 ($P<0.05$).

CONCLUSIONS

The results of the present study indicate that buccoadhesive bilayer tablets of atenolol with controlled drug release can be successfully prepared by direct compression method using HPMC 15 cps and Carbopol 934p as mucoadhesive polymers and ethyl cellulose as backing layer. It exhibited well controlled and delayed release pattern. This study concludes that the addition of Carbopol 934p increases the viscosity and swelling of tablets there by controls the release of drug and improves the mucoadhesive properties.

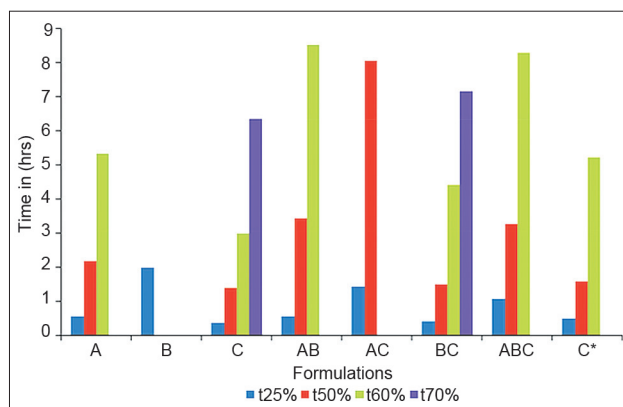The formulation C containing hydroxypropyl methylcellulose 15 cps (10% w/w of matrix layer), Carbopol 934p (10% w/w

Figure 6: Comparison of dissolution parameters ($t_{25}\%$, $t_{50}\%$, $t_{70}\%$, $t_{90}\%$) of buccal tablets of atenolol

of matrix layer), and mannitol (channeling agent, 40% w/w of matrix layer) was found to be promising, which shows an *in vitro* drug release of 89.43% in 9 h along with satisfactory bioadhesion strength (7.20 g).

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