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Design and Evaluation of Buccoadhesive Compacts of Selective Antihypertensive Agents

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Abstract

The purpose of this research was to design, develop and evaluate BC's of enalapeil maleate using Carbopol 934P, HPMC 4KM, HPMC 15KM, and HPMC 100KM in various ratios such as 1:0, 1:1 & 0:1 by direct compression method. Effect of polymer type, proportion and combination was studied on the drug release rate, release mechanism and bioadhesive strength of the prepared formulations. The mixed blend was evaluated for preformulation parameters. The BC's were evaluated for physical parameters, surface pH, Swelling studies, bioadhesive strength, content uniformity study, *in vitro* dissolution studies, *ex vivo* permeation studies and stability studies. The physical parameters and content uniformity of BC's were found within specified limits. Swelling index studies and surface pH study results were found in the range of 131.19 to 378.33% after 6 hours and 5.73 to 5.95 after 4 hours. FTIR studies showed no evidence on interactions between drug, polymers, and excipients. *In vitro* drug release & ex vivo permeation for the formulation F2 was found 90.92 % & 85.23% at the end of 8 hr. Drug release and mucoadhesive strength were found to depend upon polymer type, proportion and viscosity. The release mechanism of was found to be of anomalous non-Fickian type. The stability studies revealed that there is no decrease in the drug content of F2 for the period of 3 months. This may be concluded that the stable formulation could be developed by incorporating carbopol and HPMC 4KM in the ratio of 1:1 controlling the release of enalapril maleate from BC's.

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Enalapril maleate; Buccoadhesive compacts, Carbopol 934P; Bioadhesive strength; *Ex-vivo* residence time.

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INTRODUCTION:

The buccal route has long been advocated as possible route of delivery of drugs having poor oral bioavailability because of high first pass metabolism

or degradation in the gastrointestinal tract. This route is well vascularised, with venous blood draining the buccal mucosa reaching the heart directly via the internal jugular vein. Although, the drug fluxes via this route are less than that obtained with sublingual mucosa due to permeability barrier [1], the relative immobility of buccal musculature, as compared to that of sublingual route, makes this site ideally suited for sustained delivery of drugs [2]. Thus, adhesive delivery systems like tablets [3], gels [4], and patches [5], have been recommended for buccal drug delivery.

Mucoadhesive polymers are able to interact with mucus which is secreted by the underlying tissue. More specifically, it is predicted that such polymers interact with mucus glycoprotein, called mucins, which are responsible for gel-type characteristics of the mucus. Mucoadhesive polymers can increase the contact time with the mucosal tissue and moreover, also increase directly drug permeability across epithelial barriers. [6, 7]

From the technical point of view, an ideal buccal dosage form must have three properties. It must maintain its position in mouth for few hours, release the drug in a controlled fashion and provide the drug release in a unidirectional way towards the mucosa. The daily salivary volume secreted in humans in between 0.5 to 2 l, which is sufficient to hydrate oral mucosal dosage forms. This water rich environment of the oral cavity is the main reason behind the selection of hydrophilic polymeric matrices as vehicles for this study [8].

The angiotensin converting enzyme inhibitors have become the first line therapy in treating hypertensive patients. The advantage of ACE inhibitors over other antihypertensive medication includes preventing coronary heart failure, renal failure of type-2diabetic patients and etc. Most ACE inhibitors are bipeptides that are too hydrophilic to dissolve and penetrate through the lipid layers. Enalapril maleate was selected among the ACE inhibitors due to molecular size, therapeutic dosage, and the overall lipophilicity of the drug molecules. Prodrug of enalapril is also exhibited a significantly higher buccal penetration rate [9].

The aim of this current study is to design, develop and characterize a buccoadhesive compact of enalapril maleate. The buccal route was chosen because of its good accessibility, robustness of the epithelium, facile removal of the dosage form, relatively low enzymatic activity, and natural clearance -mechanisms for elimination of the drug from buccal area, satisfactory patient acceptance and avoiding the hepatic first pass metabolism [10]. Apart from the overall increased bioavailability, because of bypassing the first pass effect and sufficient time to produce therapeutic effect [11], an important advantage of buccal delivery for enalapril maleate is also potentially better control of plasma levels, typically lower variation in bioavailability, reduced costs of the drug because of application of much lower doses than necessary for oral products. An attempt was made to develop BC's of enalapril maleate by direct compression, which would increase the bioavailability of enalapril maleate. The prepared BC's were evaluated for physical properties (thickness, weight variation, friability and hardness), swelling index, bioadhesion test, *in vitro* drug release and accelerated stability studies.

MATERIALS:

Enalapril maleate Gift sample from Kemwell Pvt. Ltd-Bangalore, HPMC 4KM(Gift sample from Apotex Labs Pvt Ltd-Bangalore and Colorcon Pvt. Ltd. Madgoa, Goa), HPMC 15KM(Gift sample from Apotex Labs Pvt Ltd-Bangalore and Colorcon Pvt. Ltd. Madgoa, Goa), HPMC 100KM(Gift sample from Apotex Labs Pvt Ltd-Bangalore and Colorcon Pvt. Ltd. Madgoa, Goa), Carbopol 934P(Gift sample from Remedex Pharma Pvt. Ltd. Bangalore), Ethyl Cellulose(Gift sample from Colorcon Pvt Ltd. Goa), Lactose, Mannitol, Microcrystaline cellulose pH 102(Microlabs Pvt. Ltd-Hosur, TN), coloring agents

Gift sample from Colorcon Pvt. Ltd. Madgoa, Goa), and Magnisium stearate (Loba chemicals Ltd).

METHOD:

The buccoadhesive compact(BC) contains two layers i.e. core layer and backing layer. Core layer was prepared by transferring specified quantity of lactose, microcrystalline cellulose pH 102, mannitol, carbopol 934P and HPMC to the mortar and pestle and mixed well. Enalapril maleate was added to the above mixture and mixed well. Then specified quantity of Magnesium stearate was added to the above mixture and mixed well. From the above directly compressible mixture specified of powder was transferred to 8 mm die cavity of compression machine and compressed. Then add specified quantity of the backing layer powder containing Ethyl cellulose, Magnesium stearate and color to the above the core layer compact and compressed (Table 1.).

Table 1: Formulation of buccoadhesive compacts of enalapril maleate (F_1- F_9)

Sl. No.	Ingredients	Formulations								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Core layer										
1.	Enalapril Maleate	5	5	5	5	5	5	5	5	5
2.	HPMC 4KM	0	15	30	-	-	-	-	-	-
3.	HPMC 15KM	-	-	-	0	15	30	-	-	-
4.	HPMC 100KM	-	-	-	-	-	-	0	15	30
5.	Carbopol 934P	30	15	0	30	15	0	30	15	0
6.	Microcrystaline cellulose	44	44	44	44	44	44	44	44	44
7.	Mannitol	25	25	25	25	25	25	25	25	25
8.	Lactose	44.5	44.5	44.5	44.5	44.5	44.5	44.5	44.5	44.5
9.	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Backing layer										
1.	Ethyl cellulose	48.5	48.5	48.5	48.5	48.5	48.5	48.5	48.5	48.5
2.	Colouring agent	1	1	1	1	1	1	1	1	1
3.	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

EVALUTION

1. Precompressional parameters buccoadhesive compacts of enalapril maleate:

a. Moisture content:

Accurately weighed 3 gm of granules were poured on the plate in the IR moisture analyzer until the red mark needle in the reading displayer coincide with the '0' reading. Switch on the instrument reading was recorded when granules starts charring.

b. Bulk Density (BD):

It was measured by pouring the weighed granules (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted and initial volume is called as the bulk volume. Bulk density was calculated according to the formula mentioned below. It was expressed in gm/cc and was given by

BD = M/ Vb

Where, M and Vb are mass of granules and bulk volume of the granules respectively.

c. Tapped Density (TD):

Blend was tapped for a fixed number of taps. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (TD) was calculated using following formula.

TD = M/ Vt

Where, M and Vt are mass of granules and tapped volume of the granules respectively.

d. Carr's index (or) % compressibility (I):

It indicates granules flow properties. It was expressed in percentage and given by

I = TD – BD/TD X 100

Where, TD and BD are tapped density and bulk density respectively.

e. Hausner's ratio:

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by the following formula.

Hausner's ratio = TD / BD

Where, TD and BD are tapped density and bulk density respectively.

f. Angle of Repose (θ):

The granules blend was allowed to flow through the funnel freely on to the surface. The diameter and height of the granules cone were measured and angle of repose was calculated using the following equation.

tan θ = h/r

Where, h and r are the height and radius of the powder cone.

g. Drug-Excipient compatibility studies by using FT-IR spectroscopy:

The FT-IR study of pure drug-enalapril maleate, polymers-HPMC 4KM, HPMC 15KM, HPMC 1004KM, carbopol 934P & all formulations (**F_1- F_9**) were carried out by using Bruker FT-IR spectroscopy instrument. The FT-IR spectra were recorded in the range of 1000 to 3600 cm^{-1}. [12, 13, 14]

2. Characterization of buccoadhesive compacts of enalapril maleate.

a. Weight variation test:

20 BC's were randomly selected from each formulation and weighed using electronic balance to determine the average weight and compared with the individual weight of the compact. The percentage of weight variation was calculated.

b. Hardness test:

In this test, 5 BC's were taken from each formulation randomly and measured for hardness by using Pfizer hardness tester. From this average and standard deviation was calculated.

c. Thickness and Diameter test:

The thickness and diameter of the BC's were determined by selecting 5 compacts randomly from each formulation and measured for thickness by using digital vernier calipers. From this average and standard deviation was calculated.

e. Friability test:

Accurately weighed 10 dedusted BC's were randomly taken. The weight of compacts was noted as "W_1". Then compacts were subjected to rotating drum of Electrolab friability apparatus. and operated at a speed of 25rpm for 4 minutes. After completion of 100 revolutions, the compacts were removed, dedusted and reweighed. The weights of compacts were noted as "W_2". Percentage friability was calculated by the following formula. [15, 16, 17]

Percentage friability = (W_1-W_2) X 100/W_1

f. Swelling studies:

The swelling rates of BC's were evaluated using 1% W/W agar gel plate. For each formulation, 3 BC's were weighed and the weight was noted as (W_1). The BC's were placed with core layer facing the gel surface in 3 separate Petri dishes containing 5 ml of 1% W/W agar gel. Which were placed in an incubator at 37 ± 1°C. Three BC's were removed at regular intervals of 0.5, 1, 2, 4 and 6 hour, excess water on the surface was carefully removed using filter paper and swollen compacts were weighed and noted as (W_2). Swelling index was calculated by using the formula. [16, 17]

% Swelling index = (W_2-W_1) x 100 / W_1

g. Surface pH studies:

The BC's were allowed to swell by keeping it in contact with1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature in separate three Petri dishes for each formulation. The pH was measured.[18, 19]

h. Content uniformity test:

10 BC's of enalapril maleate were taken randomly and crushed as powder. Weigh 5 mg equivalent weight of powder and dissolve in phosphate buffer 6.8. The samples were analyzed at 206.5nm using Shimadzu UV-Visible spectrophotometer 1601[20].

i. *In vitro* bioadhesion studies

The apparatus used for *in vitro* bioadhesion studies is shown in Figure 1. *In vitro* bioadhesion studies were carried out using sheep buccal mucosa and modified two armed balance. The beaker on one side of the balance was counter balanced by using suitable weights on the other side. The BC was fixed to the tissue holder with cyanoacrylate adhesive. A circular piece of sheep buccal mucosa was fixed to the tissue holder with cyanoacrylate adhesive and was immersed in tyrode solution and the temperature was maintained at 37±1˚C. Then the BC was placed on the buccal mucosa by using a preload of 50gms and kept it aside for 5 min to facilitate adhesion bonding. After preloading time, the preload was removed and the water was allowed to flow into the beaker kept on the other side of the balance at the flow rate of 1 drop/sec until the BC detaches from the buccal mucosa. The weight required to detach the BC from the buccal mucosa was noted. The force of adhesion is calculated by using the following formula [21, 22].

Force of adhesion (N) = **(**Mucoadhesive strength X 9.81)/100

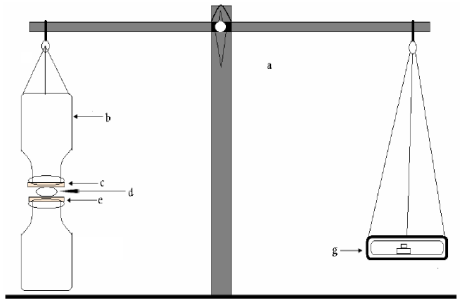


Figure 1. Measurement of bioadhesive strength.

j. *In vitro* release studies:

In vitro release study of BC's of enalapril maleate for all the formulations were carried out using USP XXIV dissolution apparatus with rotating basket method at 37 ± 0.5˚C and 50 rpm. Study was conducted in triplicate. Dissolution medium used for the dissolution studies was 900ml of phosphate buffer pH 6.8. The dissolution studies were carried out for 8 hours. Aliquot samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper number 42. The samples were analyzed using Shimadzu UV-Visible spectrophotometer 1601 at 206.5nm. [20, 23]

k. *In vitro* permeation studies

In vitro studies were carried out using verticle diffusion cell. The dissolution medium used for i*n vitro* permeation studies is phosphate buffer pH 6.8. The vertical diffusion cell with rabbit buccal mucosa containing magnetic bead was kept on the magnetic stirrer and stirred at 50rpm. The temperature maintained during the studies was 37 ± 0.5˚C. Aliquot samples (1ml) were withdrawn at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper number 42 and suitably diluted. The samples were analyzed using Shimadzu UV-Visible spectrophotometer 1601 at 206.5nm [24, 25].

l. Stability studies

The optimized formulation was subjected to stability testing at 40 ± 2˚C(75 ± 5% RH) for three months. Tablets were evaluated periodically for physical

parameters, bioadhesive strength and *in vitro* drug release [26, 27].

RESULTS AND DISCUSSION

In the present study, BC's of enalaprill maleate were prepared by using using Carbopol 934P, HPMC 4KM, HPMC 15KM, and HPMC 100KM in various ratios such as 1:0, 1:1 & 0:1 by direct compression method was studied for bulk density, tapped density, angle of repose, carr's index, hausners's ratio and moisture content. The results were shown in Table 2. The blend of all the batches were evaluated for parameters like angle of repose was found to be between 27.74 ± 0.29 and 29.80 ± 0.26, Bulk density was found to be between 0.36 ± 0.01 and 0.43 ± 0.01 g/cm^3 and tapped density between 0.38 ± 0.01 and 0.50 ± 0.01 g/cm^3. Carr's index was found to be between 10.01 ± 0.16 and 14.64 ± 1.58 %. Hausner's ratio was found to be between 1.11 ± 0.00 and 1.17 ± 0.02 %. Moisture content was found to be between 1.60 ± 0.00 and 2.10 ± 0.00. All the formulations showed good blend properties for direct compression and hence tablets were prepared by direct compression technology.

Table 2: Precompressional parameters buccoadhesive compacts of enalapril maleate

Formulation Code	Angle of repose* (°) Mean ± S.D.	Bulk density* (gm/cc) Mean ± S.D.	Tapped density* (gm/cc) Mean ± S.D.	Carr's index* (%) Mean ± S.D.	Hausner's ratio* (%) Mean ± S.D.	Moisture content*(%) Mean ± S.D.
F_1	28.39 ± 0.00	0.42 ± 0.01	0.47 ± 0.01	12.31 ± 0.96	1.14 ± 0.00	2.00 ± 0.00
F_2	28.39 ± 0.00	0.42 ± 0.01	0.48 ± 0.01	12.31 ± 0.96	1.14 ± 0.01	1.85 ± 0.04
F_3	29.80 ± 0.26	0.43 ± 0.01	0.50 ± 0.01	14.07 ± 1.47	1.16 ± 0.02	2.00 ± 0.00
F_4	27.74 ± 0.29	0.40 ± 0.01	0.46 ± 0.01	13.15 ± 1.22	1.15 ± 0.02	1.70 ± 0.03
F_5	28.93 ± 0.00	0.39 ± 0.01	0.43 ± 0.00	10.35 ± 0.17	1.12 ± 0.00	1.90 ± 0.00
F_6	29.58 ± 0.00	0.36 ± 0.01	0.38 ± 0.01	14.64 ± 1.58	1.17 ± 0.02	2.00 ± 0.00
F_7	27.97 ± 0.25	0.38 ± 0.01	0.42 ± 0.01	10.01 ± 0.16	1.11 ± 0.00	1.60 ± 0.00
F_8	28.73 ± 0.28	0.40 ± 0.01	0.46 ± 0.01	13.06 ± 0.84	1.15 ± 0.01	1.90 ± 0.00
F_9	29.20± 0.00	0.38 ± 0.00	0.44 ± 0.01	14.44 ± 1.35	1.17 ± 0.02	2.10 ± 0.00

Compatibility studies using FTIR showed no evidence on interactions between drug, polymers, and excipients. From the post compression parameters observations it was concluded weight variation, hardness, thickness, diameter, friability and content uniformity of BC's were lying within IP limit (Table 3.)

Table 3. Post compression Parameters, Content uniformity of buccoadhesive compacts of enalapril Maleate

Formulation code	Weight variation (mg) Mean ± S.D.	Hardness (Kg/cm^2) Mean ± S.D.	Thickness (mm) Mean ± S.D.	Diameter (mm) Mean ± S.D.	Friability (%)	Content uniformity(%) Mean ± S.D.
F_1	200.00 ±0.64	6.00 ± 0.06	3.40±0.03	8.00 ±0.00	0.49	100.24 ± 0.060
F_2	200.30 ± 0.93	6.00 ±0.03	3.36 ±0.03	8.00 ±0.00	0.20	99.68 ± 0.021
F_3	200.10 ± 0.73	6.12 ±0.05	3.40± 0.06	8.00 ± 0.00	0.30	99.72 ± 0.058
F_4	200.05 ± 0.61	5.98 ± 0.07	3.36 ±0.08	8.00 ± 0.00	0.40	99.80 ± 0.070
F_5	200.10 ± 0.79	6.06 ±0.05	3.38 ± 0.05	8.00 ± 0.00	0.25	99.56 ± 0.065
F_6	200.15 ± 0.88	6.12 ±0.05	3.34 ±0.03	8.00 ± 0.00	0.20	99.38 ± 0.090
F_7	200.05± 0.68	6.14 ± 0.04	3.44 ±0.03	8.00 ± 0.00	0.35	99.92 ± 0.068
F_8	200.15 ± 0.75	6.14 ±0.03	3.44 ±0.03	8.00 ± 0.00	0.19	99.10 ± 0.082
F_9	200.40 ± 0.78	6.04 ± 0.03	3.44 ± 0.03	8.00 ± 0.00	0.20	98.32 ± 0.042

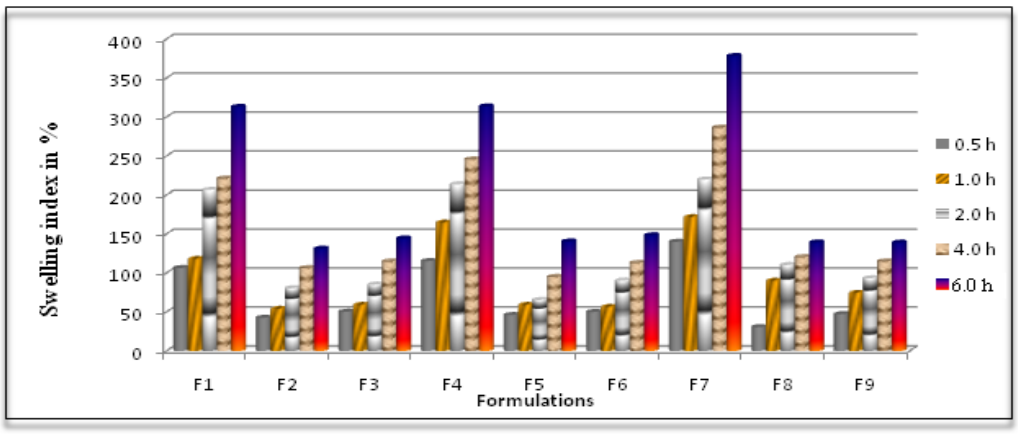
The bioadhesion and drug release profile are dependent on swelling behaviour of BC's. Swelling index was calculated with respect to time. Swelling index was increased as the weight gain by the BC's increased proportionally with the rate of hydration as shown in Table 4 and Figure 2. Swelling indices of

BC's with CP and HPMC increased with increasing concentrations of CP. **F_2** showed minimum swelling index whereas **F_7** showed maximum swelling index. It is evident from the above data, that the BC's containing CP alone showed higher swelling index than compared to BC's containing HPMC. However there is no significant difference in the swelling index, when the individual polymers are compared.

Table 4: Swelling index of BC's of enalapril Maleate

Formulation	Swelling Index*(%)Mean ± S.D.				
	Time(h)				
	0.5	1	2	4	6
F_1	106.51 ± 5.49	118.02 ± 4.96	206.59 ± 12.85	221.35 ± 1.57	313.17 ± 1.15
F_2	42.54 ± 4.05	54.05 ± 3.15	80.56 ± 7.58	106.51 ± 2.99	131.19 ± 0.03
F_3	50.29 ± 4.24	59.13± 2.99	85.24 ± 8.36	114.92 ± 4.57	144.29 ± 0.07
F_4	115.44 ± 4.89	164.65 ± 6.14	213.77 ± 5.39	245.88 ± 2.99	313.77 ± 5.39
F_5	46.11 ± 5.49	59.13 ± 2.99	65.63 ± 3.09	95.16 ± 3.38	140.51 ± 2.50
F_6	50.08 ± 3.72	56.51 ± 2.49	90.40 ± 3.23	113.02 ± 4.98	148.41 ± 2.39
F_7	140.00 ± 2.30	171.67 ± 1.50	220.00 ± 2.32	286.67 ± 3.63	378.33 ± 4.25
F_8	30.61 ± 2.79	90.09 ± 7.03	110.44 ± 7.30	120.53 ± 5.04	139.30 ± 8.05
F_9	47.37 ± 4.14	74.39 ± 14.84	93.33 ± 16.49	115.07 ± 4.22	139.04 ± 2.83

Figure 2. Swelling index of BC's of enalapril maleate



The surface pH of BC's were found to be in between 5.73 to 5.95 as shown in Table 5, which was within 7 ± 1.5 units of the neutral pH, indicating no risk of mucosal damage or irritation in the buccal cavity, more over there is no significant difference in the pH among the formulations[28].

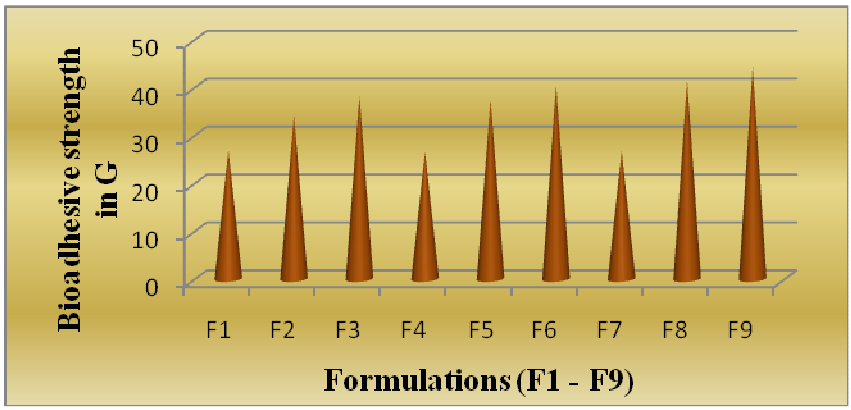
The bioadhesive characters were found to be affected by the nature and proportions of the bioadhesive polymers used in the formulations. Bioadhisive strength data was reported in Table 5 and Figure 3. The highest adhesion force i.e. Highest strength of the biooadhesive bond was observed with the formulation F_9 containing only HPMC 100KM. This was followed with F_8, F_6, F_5, F_3, F_2 & F_1. The reason for such finding might be the ionization of HPMC at salivary pH which leads to attachment of the device to mucosal surface. Adhesive force is decreased with the addition of another polymer carbopol. Formulations containing carbopol alone showed least adhesion force than the BC's of all other formulations. This might be due to low viscosity of the carbopol. These observations indicate that bioadhesive force of HPMC is much more than Carbopol. It is evident from the above data, that the

BC's containing a mixture of carbopol & HPMC 100KM comparatively higher bioadhesion than that of carbopol & HPMC 15KM and carbopol & HPMC 4KM respectively. In all the formulations, as the HPMC concentration increased, the bioadhesion was increased. The order of bioadhesion of polymers used in the preparation can be given as HPMC 4KM > carbopol & HPMC 4KM. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa. Bioadhesive strength exhibited by the formulation F_2 tablets can be considered satisfactory for maintaining them in the oral cavity for 12hrs.

Table 5. Bioadhisive strength & Surface pH of BC's of enalapril maleate(F_1-F_9)

Formulation Code	Bioadhesive strength (G)* Mean ± S.D.	Bioadhesion Force*(N) Mean ± S.D.	Surface pH* Mean ± S.D.
F_1	26.8 ± 0.24	2.62908	5.73 ±0.48
F_2	34.03 ± 0.32	3.338343	5.92 ± 0.02
F_3	38.23 ± 0.13	3.750363	5.85 ± 0.00
F_4	26.5 ± 0.28	2.59965	5.81±0.01
F_5	37.36 ± 0.19	3.665016	5.95± 0.00
F_6	40.36± 0.06	3.959316	5.85± 0.00
F_7	26.7 ± 0.10	2.61927	5.73± 0.02
F_8	41.27 ± 0.12	4.048587	5.87± 0.02
F_9	44.27 ± 0.12	4.342887	5.92± 0.05

Figure 3. Bioadhisive strength of BC's of enalapril maleate(F_1-F_9)



In vitro release profile for all formulations is shown in Table 6 and Figure 4. Out of all the three formulations F_1 exhibited the maximum release, i.e. 98.12%, but the surface pH of this compact was in the acidic range, formulation F_2 was selected as optimized formulation. Cumulative % of drug release from F_2 was found 90.92%. Cumulative % of drug release from F_3, F_4 & F_5 was found 86.58%, 98.08% & 85.48%. Cumulative % of drug release from F_6, F_7, F_8 & F_9 was found 81.52%, 97.94%, 82.86% & 76.84. No statistically significant difference was obtained between cumulative % drug releases from F_1 & F_2.

Carbopol 934P is more hydrophilic than HPMC, it can swell rapidly, therefore decrease of carbopol content delays the release from formulation F_2 and F_3. The maximum cumulative % drug release of enalapril maleate from formulation F1 could be attributed due to the presence of higher amount of carbopol. The release rate of enalapril maleate decreased with increasing concentration of HPMC 4KM< HPMC 15KM <HPMC 100KM of F_2 to F_3, F_5 to F_6 and F_8 to F_9 respectively. These findings are in compliance with the ability of HPMC to form complex network which leads to delay in release of

drug from the device. carbopol is more hydrophilic than HPMC, hence it can swell rapidly therefore decrease of carbopol content decreases the drug release in F_2, F_5 and F_8. Drug release rate was increased with increasing amount of hydrophilic polymer. The maximum cumulative % release of enalapril maleate from formulation F_1 could be attributed to ionization of carbopol at pH environment of the dissolution medium. The continued swelling of the polymer matrix causes the drug to diffuse out from the formulation at a faster rate. Formulation F_1, F_4 and F_7 showed relatively high rate of release of enalapril maleate which is due to rapid swelling and erosion of carbopol. Moreover hydrophilic polymers would leach out and hence create more pores and channels for the drug to diffuse out of device. Formulations F_1, F_4 and F_7 get eroded during dissolution study before stipulated study period.

In kinetic studies, observed that n (diffusion exponent) lies between 0.5 to 1.0 in all the formulations exhibiting a non-fickian release behaviour controlled by a combination of both diffusion and chain relaxation mechanism. Results of kinetic data (Table 7) revealed that the release rate from all formulations well fitted in square root 't' kinetics.

Table 6: *In vitro* release profile of BC's of enalapril maleate(F_1-F_9)

Formulation Number→ Time in hours↓	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	15.62 ± 0.14	13.42 ± 0.08	12.16 ± 0.11	15.36 ± 0.09	10.29 ± 0.07	9.88 ± 0.08	15.55 ± 0.05	9.52 ± 0.05	9.02 ± 0.09
2	28.46 ± 0.13	22.26 ± 0.23	20.24 ± 0.09	28.32 ± 0.03	20.86 ± 0.04	19.05 ± 0.06	28.38 ± 0.02	17.86 ± 0.07	16.22 ± 0.04
3	42.23 ± 0.09	36.80 ± 0.13	34.57 ± 0.15	42.20 ± 0.10	33.43 ± 0.07	31.52 ± 0.11	42.44 ± 0.04	31.20 ± 0.06	27.86 ± 0.07
4	66.56 ± 0.15	51.20 ± 0.11	48.62 ± 0.12	66.44 ± 0.14	49.40 ± 0.09	44.63 ± 0.06	65.69 ± 0.08	47.54 ± 0.07	41.59 ± 0.08
5	80.22± 0.12	66.80 ± 0.14	64.92 ± 0.12	80.04 ± 0.11	64.78 ± 0.08	61.86 ± 0.07	80.48 ± 0.07	63.15 ± 0.05	57.42 ± 0.04
6	98.12 ± 0.09	74.82 ± 0.08	72.18 ± 0.13	98.08 ± 0.12	71.25 ± 0.08	70.02 ± 0.07	97.94 ± 0.06	68.44 ± 0.07	65.40 ± 0.08
7	-	83.92 ± 0.08	80.34 ± 0.09	-	80.56 ± 0.09	78.26 ± 0.04	-	78.18 ± 0.05	71.22 ± 0.09
8	-	90.92 ± 0.14	86.58 ± 0.13	-	85.48 ± 0.06	81.52 ± 0.07	-	82.86 ± 0.09	76.84 ± 0.08

Figure 4. *In vitro* release profile of BC's of enalapril maleate(F_1-F_9)

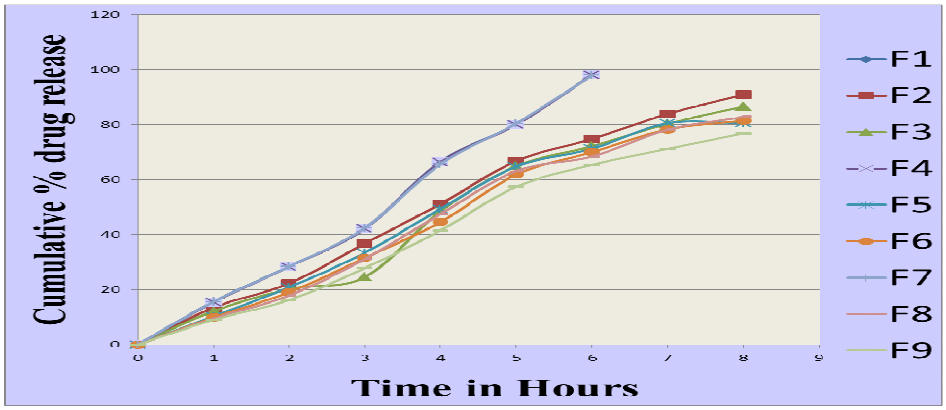


Table 7: Kinetic release parameters of BC's of enalapril maleate(F_1-F_9)

Formulation Code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Peppas	
				slope(n)	(r^2)
F_1	0.992	0.799	0.883	0.621	0.992
F_2	0.989	0.949	0.926	0.717	0.989
F_3	0.986	0.968	0.92	0.718	0.988
F_4	0.992	0.752	0.882	0.621	0.992
F_5	0.985	0.973	0.918	0.717	0.991
F_6	0.984	0.972	0.91	0.673	0.99
F_7	0.993	0.759	0.883	0.621	0.992
F_8	0.982	0.864	0.941	0.718	0.988
F_9	0.983	0.981	0.902	0.718	0.988

The release found after 8 hours was 85.23% and was shown in Table 8. It showed that there is no significant change in the release rate.

Table 8. *In vitro* permeation profile of BC's of enalapril Maleate

Formulation Number→ Time in hours↓	F2 Mean ± S.D.
1	11.58 ± 0.03
2	20.87 ± 0.10
3	33.87 ± 0.04
4	47.36 ± 0.07
5	63.44 ± 0.11
6	72.22 ± 0.04
7	8071 ± 0.07
8	85.23 ± 0.09

From the accelerated stability studies, it was observed that there is no significance change in physical parameters, bioadhesive strength and *in vitro* release studies.

Table 9: Accelerated Stability studies of BC's of enalapril Maleate

Formulation code	Hardness* (Kg/cm^2) Mean ± S.D.	Bioadhesive strength (G)* Mean ± S.D.	Drug content (%)* Mean ± S.D.	*In vitro* drug release (%)* Mean ± S.D.
F_2	6.30 ± 0.08	34.72 ± 0.10	99.63 ± 0.07	80.82 ± 0.08

CONCLUSION:

From the entire study it was concluded that the stable formulation could be developed by incorporating carbopol 934P and HPMC 4KM in the ratio of 1:1 controlling the release of enalapril maleate from BC's with adequate adhesiveness, retension time and swelling properties.

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