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FORMULATION AND EVALUATION OF BIOADHESIVE BUCCAL TABLETS OF ENALAPRIL MALEATE

Joan Vijetha R. [1, 2], S. N. Santha [2] and K. Balamurugan [* 1]

Annamalai University [1], Annamalai Nagar, Chidambaram - 608002, Tamil Nadu, India.
Department of Pharmaceutics [2], Mohamed Sathak A. J. College of Pharmacy, Chennai - 600119, Tamil Nadu, India.

Keywords:

Enalapril Maleate, Carbopol, Chitosan, HPMC K-100M, *In-vitro* and *ex-vivo* drug release

Correspondence to Author:
Dr. K. Balamurugan

Department of Pharmacy, FEAT, Annamalai University, Annamalai Nagar, Chidambaram - 608002, Tamil Nadu, India.

E-mail: placementbala@yahoo.co.in

ABSTRACT: Enalapril maleate competitively inhibits the ACE to hinder the production of angiotensin II, a key component of the rennin angiotensin aldosterone system that promotes vasoconstriction and reabsorption of sodium ion in the kidney, overall decrease in blood pressure. The study's main objective was to formulate and evaluate bioadhesive buccal tablets to avoid the first-pass metabolism in the liver and patient acceptance. Bioadhesive buccal tablets were prepared by direct compression method using bioadhesive polymers like Chitosan, Carbopol 934, and HPMC K100M in different ratios to a drug. The physicochemical compatibility of drugs and polymers was studied by FT-IR spectroscopy. Prepared tablets were evaluated for permeation study through the porcine buccal mucosa, *in-vitro* drug release, swelling index, moisture absorbance, surface pH; among the prepared formulation containing F6 Shows maximum drug release 88.5 % in 8 h the optimized formulation F6 showed surface pH 6.9 and swelling index 82.2%. The formulation followed Peppas order release kinetic non Fickian kinetics.

INTRODUCTION: The present aim of the work is to develop buccal tablets for the treatment of hypertension and congestive heart failure; an oral route of drug administration has been one of the most convenient routes and novel drug delivery. This concept of mucoadhesion was introduced into sustained drug delivery. Which becomes a major part of the novel drug delivery system in the recent era. Some of the potential sites for attachment of any mucoadhesive system are included in the buccal cavity, nasal cavity, eyes, vagina, rectal, sublingual route, and gastrointestinal area. Mucoadhesive polymers are able to interact with mucus which is secreted by the underlying tissue.

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The concept of the mucoadhesive polymer has been accepted as a promising strategy to prolong the residence time and to improve localization of drug delivery systems on various membranes. Buccal delivery of drugs is an alternative to oral route of drug administration; this buccal route has numerous advantages like good convenience, the toughness of epithelium, sudden removal of dosage form in case of need, relatively low enzymatic activity, prevent drug degradation in gastro intestinal tract by avoiding hepatic first pass metabolism. Enalapril maleate to a class of angiotensin receptor antagonist which acts by binding selectively and non-competitively to angiotensin II receptor type 1, thus preventing actions of angiotensin II.

MATERIALS AND METHODS:

Materials: Enalapril Maleate and Aspartame were obtained as a gift sample from Dr. Reddy's Laboratories. Ltd. Hyderabad. India. PVP-K30, (Polyvinyl pyrrolidone), Chitosan are gift samples from HETERO laboratories, Hyderabad. HPMC

K100M (Hydroxy Propyl Methyl Cellulose) and Ethylcellulose (EC) were procured from SD Fine Chemicals. Pvt. Ltd. Mumbai. India. Mannitol was purchased from Finar chemicals. Ltd. Mumbai. Magnesium stearate was obtained from Himedia Laboratories; the entire chemical used is of Analytical grade.

Methods:

Spectrum Scanning: 10 µg/ml concentration of a drug is taken for spectrum scanning, scanning was done with 400 to 200 nm, maximum absorbance was found at 212 nm, in 6.8 pH Phosphate buffer as shown in **Table 1**.

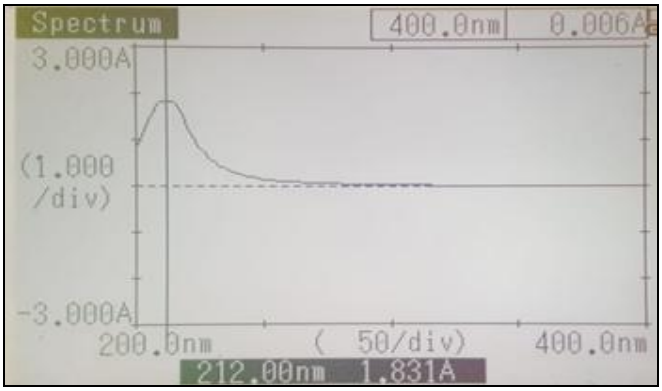

FIG. 1: SPECTRUM SCANNING OF ENALAPRIL MALEATE

Standard graph of Enalapril Maleate: Standard graph of Enalapril maleate was done in 6.8 pH phosphate buffer where drawn linearity was found to be from 0 to 10 µg/Ml with R^2= 0.9858 with an intercept of y = 0.0933 × + 0.0611 at 212 nm.

TABLE 1: STANDARD GRAPH OF ENALAPRIL MALEATE (6.8 PH PHOSPHATE BUFFER)

Concentration (µg/mL)	Absorbance (nm)
0	0
2	0.313
4	0.456
6	0.612
8	0.805
10	0.980

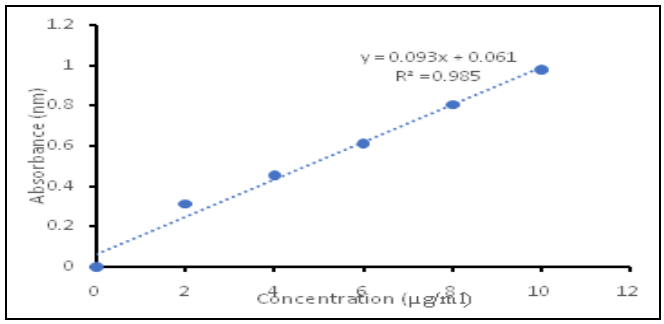

FIG. 2: STANDARD GRAPH OF ENALAPRIL MALEATE

Preparation of Double Layered Buccal Tablets: The formulations were prepared as shown in **Table 2;** each tablet contains 20 mg of Enalapril maleate before direct compression, all the ingredients were screened through sieve no 100.

The backing layer (EC) was compressed using an 8.0 mm flat-faced punch on a tablet compression machine. Enalapril Maleate was mixed manually with different ratios of Carbopol, PVP K-30, HPMC K-100M, and Chitosan as mucoadhesive polymers and mannitol as a diluent for 10 min.

TABLE 2: COMPOSITION OF BUCCAL TABLETS OF ENALAPRIL MALEATE

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Enalapril maleate	20	20	20	20	20	20	20	20
Carbopol 934	5	10			5	10	10	5
HPMC K100M	20	20	20	20	20	20	20	20
Chitosan	---	---	7.5	15	7.5	15	7.5	15
PVP K-30	30	30	30	30	30	30	30	30
Mg stearate	1	1	1	1	1	1	1	1
Mannitol	33	28	30.5	23	25.5	13	20.5	18
Aspartame	1	1	1	1	1	1	1	1
Backing membrane (EC)	50	50	50	50	50	50	50	50
Total	160	160	160	160	160	160	160	160

The blend was mixed with magnesium stearate for 3-5 min and then compressed into tablets by the direct compression method using 8 mm flat-faced punches. The tablets were compressed using a sixteen station CEMACH rotary tablet punching machine. The composition of the prepared bioadhesive buccal tablet formulations of Enalapril Maleate was given in **Table 2.**

Evaluation of Enalapril Maleate Buccal Tablets: The Buccal tablets were evaluated for various tests.

Compatibility Studies: The drug excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra-red spectra of pure drug and optimized formulation were recorded.

Weight Variation Test: A weight variation test was performed for ten tablets from each batch using an electronic balance (Shimadzu, Model: AUW220D); an average value with standard deviation was calculated, as given in **Table 4.**

Thickness: The thickness of the buccal tablet was determined by using a screw gauge. Five individual tables from each batch were taken, and an average with standard deviation was calculated, as given in **Table 4.**

Hardness: A hardness test was conducted for five tablets from each batch using Monsanto tester, and the average with standard deviation was calculated as given in **Tablet 4.**

Friability: The friability of the tablets was determined using a rotating drum-like apparatus (Roche friabilator) sample size of 10 tablets from each tablet was initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min (100 times); after 100 revolutions the tablets were reweighted again. The friability was then calculated using the formula.

Friability % = Initial weight - Final weight / Initial weight × 100

Assay: The tablet was performed for buccal tablet without backing membrane, 6 tablets were selected at random and were powdered in a mortar by using a pestle, calculated amount of powder is taken, which is equivalent to single-dose was dissolved in 6.8 phosphate buffer by sonication for 30 min and filtered through Whatman filter paper. The drug content was analyzed spectrophotometrically at 212 nm using a UV-spectrophotometer.

Surface pH Study: The buccal tablets were made in contact with 1 ml of water and kept aside to swell for 2 h at room temperature. The pH was measured by bringing the pH meter electrode in contact with the surface of the tablet, periodically at 1, 2, 3, 4, 5, 6, 7, and 8 h. Values were recorded, as shown in **Table 4**.

Measurement of Bioadhesive Strength: Bio-adhesive strength of the tablet was measured the using sheep buccal mucus membrane, procured from the slaughter house. The tissue was washed thoroughly with 6.8 pH Phosphate buffer. The membrane was adhered to the base of the equipment and hydrated using 6.8 pH Phosphate buffer. One side of the tablet was sticked onto the plastic vial cap and the cap was tied to the nylon thread. Other end of the thread was tied to a plastic cup containing counter weight. Thus, the thread was allowed to pass through two pulleys. Now the tablet was placed over the membrane and 50 g weight was placed over the tablet for 15 minutes to induce mucoadhesion. After 15 minutes, an increment of 0.1 g of weight was added to the cup and the counter weight at which the tablet detaches from the membrane was determined.

Swelling Study: The swelling studies of buccal tablets. The test was performed for buccal tablets with backing membrane, buccal tablets were weighed individually initial weight was (W_1) and placed in petri dish containing 5 ml of phosphate buffer (pH 6.8) solution tablet is placed in petri dish which shows backing membrane being viewed from top. Tablet were soaked in such a way that a tablet completely immersed in the buffer solution at regular intervals (1, 2, 3,4, 5,6, 7 and 8 h) the buccal tablets were removed from the petri dish by using forceps and excess of water around the tablet is removed by using Whatman's filter paper. The swollen tablet was reweighed (W_2) the degree of swelling was calculated according to the following equation.

$$\text{Degree of Swelling} = W_2 - W_1 / W_1$$

W_1 = Initial weight of tablet
W_2 = Final weight of tablet

Disintegration Test: Disintegration test of tablets without backing membrane is performed by using water as a media. The disintegration time of each batch was determined by using the USP disintegration apparatus (Electrolab) to estimate the average disintegration time. 1000 ml of water was placed in the vessel, from each formulation batch, 6 tablets are selected randomly were placed on the sieve, above the tablets disc were placed Average time of disintegration was noted for all the six tablets, where the tablet particles passed through the sieve.

***In-vitro* Drug Release Studies:** The USP II apparatus rotating paddle method was used to study the release of drug from buccal tablets, the dissolution medium consists of 500 ml of

phosphate buffer pH 6.8 with constant maintains of temperature at 37 ± 0.2 °C and 50 rpm rotational speed of paddle. The backing layer of the tablet was attached to a glass slide with adhesive. The slide was placed at the bottom of the vessel for unidirectional release of drug from the buccal tablet; at regular predetermined time intervals, samples of 2 ml were withdrawn, and an equal amount of buffer is replaced. The sample is filtered with Whatman filter paper and analyzed by appropriate dilution by UV spectrophotometer at 212 nm.

Release Kinetics of the Optimized Formulation: The *optimized batch's in-vitro release data* was fitted to various kinetic models (Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models). The best fit was found out to describe the kinetics of drug release.

RESULTS AND DISCUSSION: Compatibility study: From the FT-IR study, the drug was found to be compatible with all the excipients, as shown in **Fig. 3** & **4** and **Table 4.**

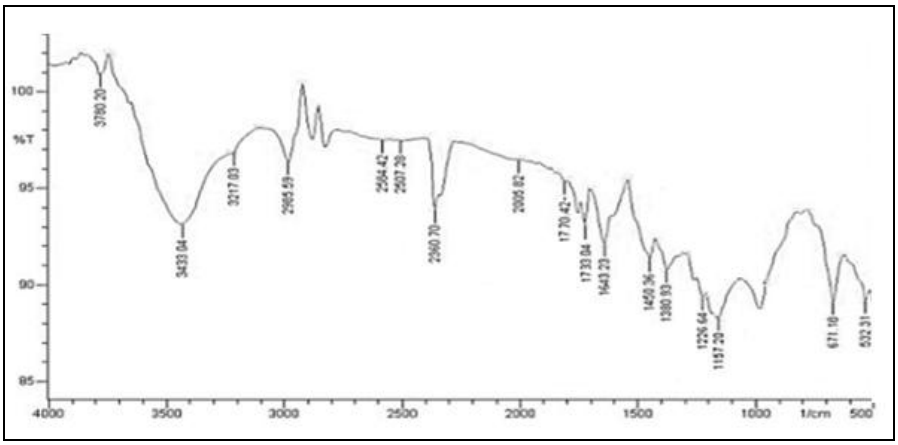

FIG. 3: FTIR OF PURE DRUG (ENALAPRIL MALEATE)

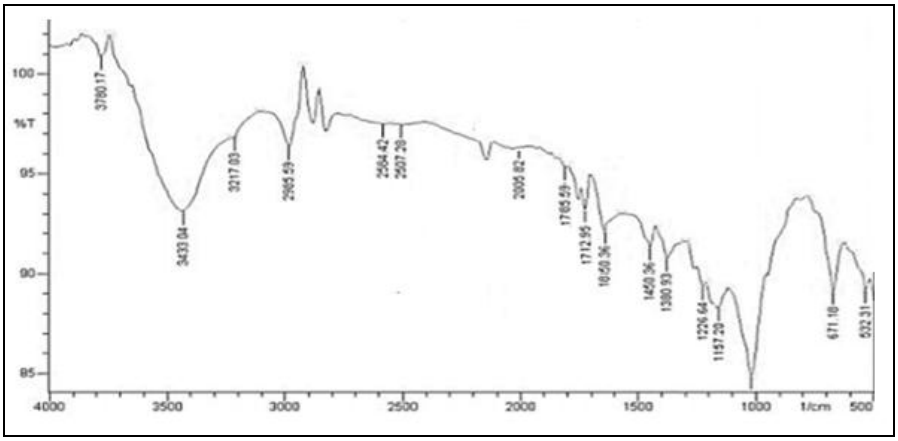

FIG. 4: FTIR OF OPTIMIZED FORMULATION (F6)

TABLE 3: FTIR VALUES OF PURE DRUG AND OPTIMIZED FORMULATION

S. no.	Characteristic Peak	Pure Drug	Optimized Formulation (F6)
1	C=O Stretching (ester)	1733.05	17.12.95
2	C=O Stretching (amide)	1643.23	1650.36
3	C=O Stretching (carboxylic acid)	1770.42	1785.59
4	N-H stretching (amide)	3780.20	3780.17

Evaluation of Buccal Tablets: All 8 formulations were tested for physical parameters like weight variation, thickness, hardness, friability and found to be within pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were acceptable. The results of the physical tests of the formulations were within limits and complied with the standards.

The weight of the tablets ranged from as per USP standards, the weights being within 169.2 ± 5.01-160.6 ± 4.77 (mg). The thickness was found to be in the range of 2.12 to 2.54 mm. The hardness of the tablets was in the range of 4.2-4.9 kg/cm², and the friability was in the range of 0.54 to 0.70. All these parameters were within acceptable limits. The drug content of all formulated found to be an average of 17.1 ± 0.92 to 19.2 ± 0.92 mg.

Surface pH Study: The surface pH of the buccal tablets was determined to investigate any possible irritation due to pH to the buccal mucosa; it was determined to keep the surface pH as close to neutral as possible.

The surface pH of the selected formulations was found to be 6.6 to 6.9, and the pH was found to be near to the neutral.

These results recommended that the formulation is suitable for oral application and they were not irritant to the buccal mucosa. Surface pH values for all the formulations are shown in **Table 4.**

TABLE 4: PROCESS PARAMETERS OF VARIOUS FORMULATIONS:

F. Code	Weight Variation(mg) Avg ± SD n= 10	Thickness (mm) Avg±SD n= 5	Hardness (kg/cm^2) Avg ± SD n= 5	Friability (%)	Assay Avg ± SD n= 3	pH	Disintegration time (min)
F1	169.2 ± 5.01	2.12 ± 0.02	4.5 ± 0.25	0.63	18.5 ± 0.93	6.8	164.16 ± 2.48
F2	160.6 ± 4.77	2.43 ± 0.05	4.2 ± 0.40	0.70	18.9± 0.57	6.7	182.33 ± 19.6
F3	161.6 ± 4.34	2.33 ± 0.01	4.7 ± 0.27	0.54	18.4 ± 0.92	6.8	171.50 ± 1.04
F4	169.0 ± 3.30	2.54 ± 0.02	4.3 ± 0.31	0.60	18.5 ± 1.00	6.9	198.17 ± 0.75
F5	162.8 ± 4.34	2.35 ± 0.02	4.8 ± 0.81	0.58	17.2 ± 0.72	6.6	210.50 ± 0.83
F6	169.2 ± 5.01	2.24 ± 0.02	4.9 ± 0.68	0.54	19.2 ± 0.92	6.9	226.67 ± 1.21
F7	162.4 ± 4.02	2.38 ± 0.03	4.3 ± 0.91	0.70	17.5 ± 0.75	6.7	217.17 ± 0.98
F8	169.2 ± 3.54	2.34 ± 0.04	4.4 ± 0.45	0.62	17.1 ± 0.92	6.8	221.34 ± 1.21

Disintegration Time: According to the USP, buccal tablet should disintegrate within 4 h. All though all the formulations disintegrated within a given time. The disintegration time was found to be in the range of 226.67 ± 1.21 to 164.16 ± 2.48 min for F1-F8 are close to 4 h.

The least disintegration time was observed with F1 containing a lower concentration of carbopol causes fast disintegration of tablet due lack of gel-forming ability in the water and highest disintegration time was observed in F6 containing a higher concentration of carbopol and chitosan in combination has ability to seal the pores during compression, resulting from higher hardness and higher disintegration time.

***In-vitro* Drug Release Profile:** *In-vitro* drug release studies were conducted in phosphate buffer pH 6.8, and the studies revealed that the release of Enalapril Maleate from different formulations varies with characteristics and composition of polymers, as shown in **Table 5** and **Graph 5**.

TABLE 5: *IN-VITRO* CUMULATIVE PERCENTAGE DRUG RELEASE PROFILE OF ENALAPRIL MALEATE FORMULATIONS

Time (h)	Cumulative Percentage Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
0	0	0	0	0	0	0	0	0
1	20.35±0.76	15.95±0.30	19.60±0.24	17.35±0.19	15.85±0.19	13.08±0.19	14.34±0.19	12.07±0.19
2	36.75±0.38	20.10±0.20	32.88±0.38	27.36±0.18	28.74±0.36	22.32±0.36	26.45±0.36	21.34±0.36
3	56.35±0.19	38.75±0.21	47.85±0.16	32.55±0.32	39.85±0.24	40.75±0.24	45.05±0.24	38.12±0.24
4	74.22±0.12	55.35±0.37	69.96±0.23	45.58±0.17	59.05±0.25	50.45±0.25	58.85±0.25	46.42±0.25
5	88.75±0.38	69.25±0.15	79.95±0.21	58.25±0.29	62.35±0.26	61.51±0.26	60.65±0.26	54.90±0.26
6	98.00±0.29	78.25±0.24	89.64±0.41	79.97±0.30	87.21±0.30	85.14±0.30	85.75±0.30	80.51±0.30
7		98.42±0.12	99.05±0.39	98.59±0.18	97.25±0.35	92.65±0.35	92.94±0.35	89.00±0.35
8						99.50±0.18	96.54±0.22	92.54±0.10

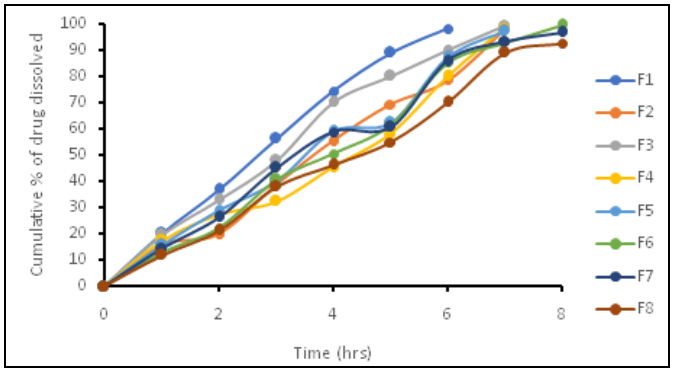

FIG. 5: CUMULATIVE % OF DRUG DISSOLVED F1-F8

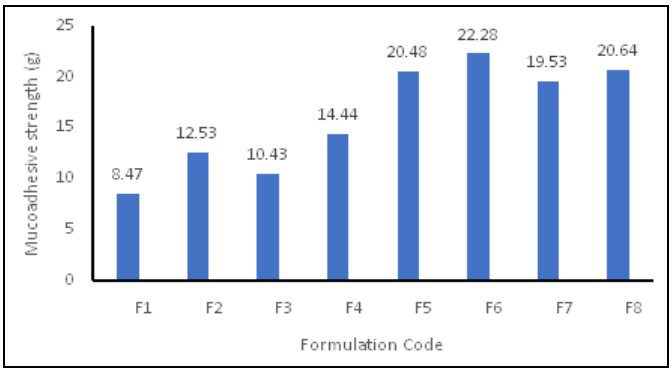

FIG. 6: MUCOADHESIVE STRENGTH OF F1-F8

TABLE 6: MEASUREMENT OF BIOADHESIVE STRENGTH

F. Code	Mucoadhesive Strength (g) Avg ± SD n= 6
	F6
F1	08.47 ± 0.212
F2	12.53 ± 0.448
F3	10.43 ±0.336
F4	14.44 ± 0.222
F5	20.48± 0.309
F6	22.28± 0.216
F7	19.53± 0.230
F8	20.64± 0.529

Swelling Studies of Buccal Tablets: Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drugs and proper bioadhesion. The polymeric tablet formulations displayed an increase in weight due to water uptake. The mucoadhesive polymers (Carbopol, and Chitosan with HPMCK 100M) used in the study were hydrogels that swelled upon contact with water and retained a large amount of water. Chitosan hydrophobic nature. So, it did not absorb a sufficient amount of water and showed a lesser swelling index. The viscosity of the polymer affects the swelling index. The higher swelling index may lead to reduced bioadhesive strength, and too low a swelling index may not be producing sufficient bioadhesive strength. So, the optimum swelling index was produced by the formulation containing Chitosan with a combination of Carbopol.

TABLE 7: SWELLING STUDIES OF BUCCAL TABLET

Time (h)	% Swelling Index
	F6
0	0
1	22.7
2	35.5
3	40.4
4	55.7
5	67.9
6	77.6
7	80.1
8	86.4

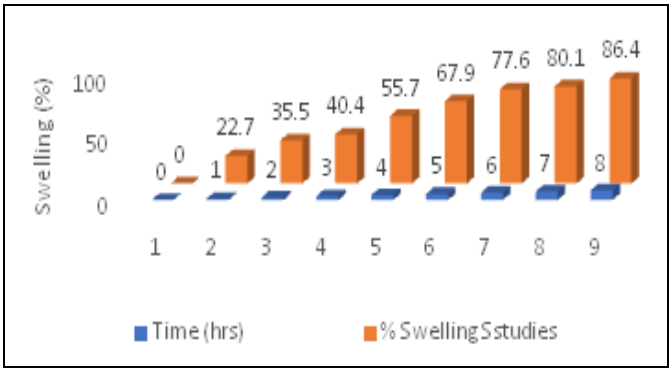

FIG. 7: SWELLING STUDIES OF ENALAPRIL MALEATE SELECTED BUCCAL TABLETS (F6)

The % swelling index was found to be in the range of 86.4 at 8th hr for the formulation containing Chitosan, Carbopol, and HPMCK 100M (F6) swelling index values of the formulation were given in **Table 6.** The swelling behavior of buccal tablets of all formulations as a function of time is shown in **Fig. 7.**

Mathematical Release Kinetics: The formulations F6 followed Korsmeyer-Peppas order release kinetics governed by anomalous or non-Fickian mechanism, *i.e.*, the drug release proceeded by both diffusion as well as erosion of the polymer. Therefore, the release of the drug from the prepared tablets is controlled by the initial swelling of the polymer, followed by drug diffusion through the swollen polymer and slow erosion of the polymer. The drug release is depending upon the swelling behavior of the polymers, which is produced by the slow dissolution of the systems.

It was concluded that the release of the drug from the tablets followed the diffusion-controlled mechanisms in all the formulations. The release kinetics and correlation coefficients were calculated for all the formulations, and values were presented in the.

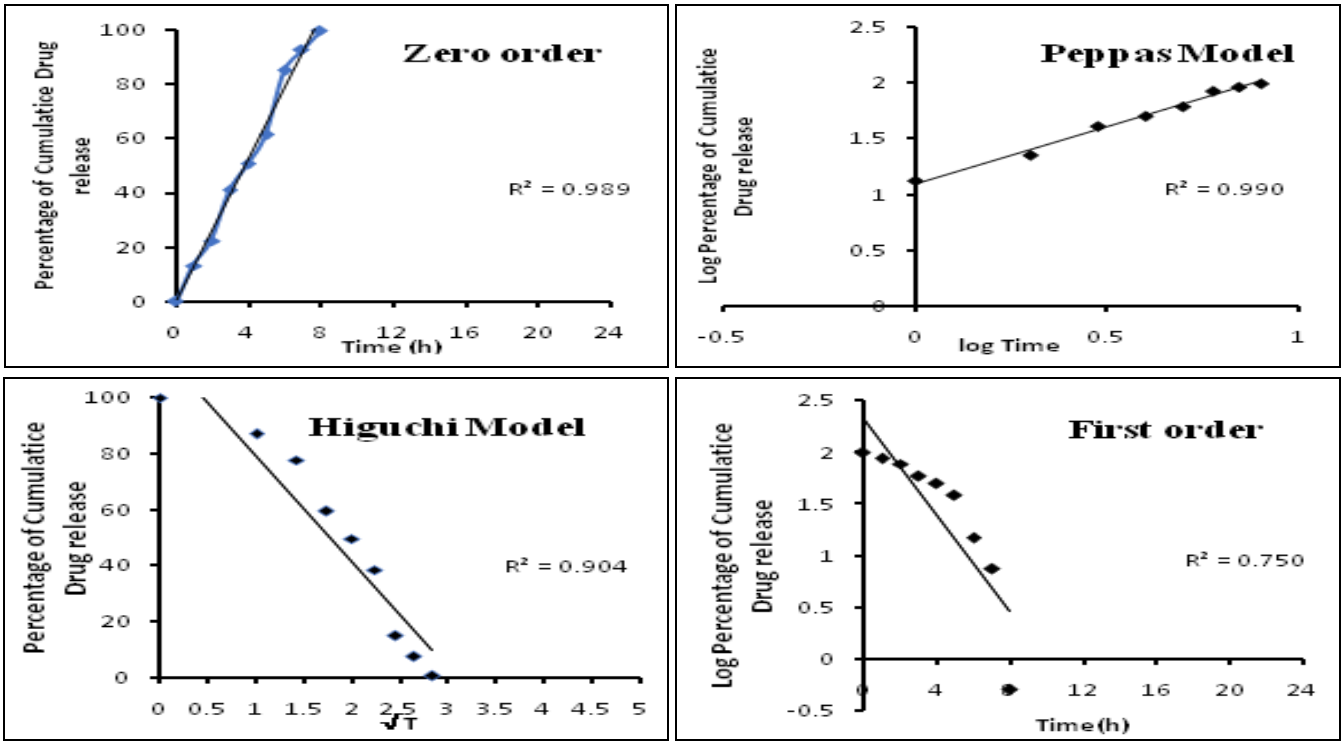

FIG. 8: VARIOUS RELEASE KINETICS OF F6

TABLE 8: RELEASE KINETICS AND CORRELATION COEFFICIENTS

	Mathematical Release Kinetics					
F. Code	**Zero order**		**First order**	**Higuchi**	**Peppas**	
	R^2	**K**	**R^2**	**R^2**	**R^2**	**n**
F1	0.9911	16.72	0.8596	0.9405	0.9966	0.9049
F2	0.9904	13.86	0.7085	0.8862	0.9589	0.9932
F3	0.9876	14.63	0.8040	0.9446	0.9918	0.8662
F4	0.9726	13.20	0.6561	0.8558	0.9508	0.8759
F5	0.9895	13.78	0.7948	0.9040	0.9902	0.9364
F6	0.9899	13.05	0.7505	0.9045	0.9903	1.02
F7	0.9798	12.60	0.8970	0.9279	0.9872	0.9467
F8	0.9843	12.26	0.9022	0.8958	0.9889	1.025

CONCLUSION: Bioadhesive buccal tablets of Enalapril Maleate were prepared to avoid the first-pass metabolism and to improve bioavailability. These are prepared by the direct compression method. Various physicochemical parameters tested for all the formulations showed good results.

From the results, it was concluded that the *in-vitro* drug release showed maximum drug release in formulation F6; further, studies like moisture absorption studies, swelling studies, and *ex-vivo* permeation studies of the optimized formulations are suitable for buccal delivery.

The optimized formulation is F6 containing chitosan with carbopol followed by Korsemeyer-Peppas order of release kinetics governed by Super case II diffusion mechanism.

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CONFLICTS OF INTEREST: There are no conflicts of interest to publish this article in this journal.

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