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FORMULATION AND *IN-VITRO* EVALUATION OF BUCCAL MUCOADHESIVE TABLETS OF CATOPRIL BY USING NATURAL AND SYNTHETIC POLYMERS

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ABSTRACT

Captopril is widely used for the treatment of arterial hypertension, myocardial infarction and in diabetic nephropathy. The drawback of this drug is that, is taken three times daily, which may give poor patients compliance. In the present study, an attempt was made to decrease dosing frequency and increase bioavailability by preparing a buccal mucoadhesive tablets. Various polymers such as carbopol 934P, HPMC K4M, chitosan, and sodium alginate are used as a mucoadhesive polymers. Formulations are subjected to friability, drug content, surface pH, swelling index, moisture absorption, wash off test, mucoadhesive strength and dissolution study. All the results for all the formulations are within the official limit and acceptable. F5 Formulation containing combination of natural and synthetic polymers (carbopol 934p and chitosan) shows better mucoadhesive strength as well as drug release.

KEYWORDS: Mucoadhesive Tablet, Buccal Mucoadesive Tablet, Captopril.

1. INTRODUCTION

Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended period of time by interfacial forces. Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Other advantages such as low enzymatic activity, suitability for drugs or

excipients that mildly and reversibly damages or irritates the mucosa, painless administration, easy drug withdrawal, etc. It prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability, serves as an alternative to oral route, whereby the drug is protected from degradation in the acidic environment of the GIT. Hence, buccal mucoadhesive drug delivery systems is promising option for continued research.

The short half-life and sever first pass metabolism of captopril makes it suitable for administration via a buccal delivery system. Mucosal-adhesive polymers are hydrophilic macromolecules containgroups. Bioadhesive polymers not only cause the adhesion effects, but also control the release rate of drug. Also, different blends of two or more adhesive polymers may be used as mucoadhesive systems. Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to "dose dumping phenomenon".

Attempts have been made to regulate their release process by using of mucoadhesive polymers in order to achieve a once-a-day dose treatment.

2. EXPERIMENTAL

2.1 Materials: Captopril was perchased from Wockhardt pharma Ltd. Aurangabad, carbopol 934p and spray dried lactose were perchased from S.D. Fine Chem Pvt. Ltd. Mumbai, HPMC K4M and chitosan were perchased from Ozone internationals, Mumbai, sodium alginate was perchased from Merck specialities Pvt. Ltd. Mumbai, mannitol and magnesium stearate were perchased from LOBA chemic Pvt. Ltd. Mumbai. All other chemicals and solvents were of laboratory grade.

2.2 Apparatus

Digital weigh balance, Jasco UV spectrophotometer, FTIR(8400 S) Shimadzu, DSC (Lab: METTLER STAR SW 12.10), Lab press tablet compression machine, Monsanto hardness tester, Roche friabilator, dissolution test apparatus, incubator shaker, stability chamber.

2.3 Method

2.3.1 Preformulation Studies

1. ***Infrared absorption spectrum***

The Fourier Transform Infrared (FTIR) spectral measurements were recorded at ambient temperature using IR spectrophotometer. The spectrum of pure drug (Captopril) was analyzed

for the purity of the drug. FTIR was also used as a parameter to determine for any drug-polymer incompatibility.

2. Differential scanning calorimetry

Thermogram of Captopril was recorded as shown. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 10°C/min over temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min.

3. Compatibility Studies

The compatibility of drug and polymers under experimental condition is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymer and excipients under experimental condition and affect the shelf life of product. This is confirmed by Infrared light absorption scanning spectroscopy. It is most powerful technique for chemical identification of drug.

4. Standard calibration curve

a. Scanning of drug solution

Accurately weighed 10mg of Captopril was dissolved in 100 ml of methanol (Conc. 100 µg/ml). From this solution 10ml was pipetted out in to 100 ml volumetric flask and volume was made up to 100 ml with methanol (Conc. 10 µg/ml). The solution containing 10 µg/ml of Captopril in methanol was scanned over the range of 200 to 400 nm against ethanol as blank using double beam UV spectrophotometer. The maximum absorbance obtained in the graph was considered as λ_{max} for the pure drug.

b. Preparation of standard calibration curve of Captopril

Accurately weighed 10 mg Captopril was dissolved in 100 ml of methanol. Aliquots of 2, 4, 6, 8, 10, and 12 ml were transferred to series of 100ml volumetric flask and volume was made up to the mark with methanol to get serial dilution containing 2-12 µg/ml of drug. The absorbance values at 205 nm corresponding to each concentration were then evaluated.

2.3.2 Formulation of Buccal Mucoadhesive Tablet

Direct compression method: Captopril bioadhesive tablets (160 mg) were prepared by mixing the drug (50 mg) with 100 mg of each of the selected polymers or their mixtures as mentioned in Table 7.3. Each tablet contains 1% magnesium stearate, 1% mannitol and spray dried lactose and then compressed directly using the single punch tablet press. Compression was performed on a 8 station Lab press tablet compression machine using 6-mm punches.

Table No. 1: Formulation composition of tablet (160mg).

Sr. No.	Ingredients (mg)	Formulations							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Captopril	50	50	50	50	50	50	50	50
2	Carbopol 934	100	-	-	-	50	50	-	-
3	HPMC K4M	-	100	-	-	-	-	50	50
4	Chitosan	-	-	100	-	50	-	50	-
5	Sodium Alginate	-	-	-	100	-	50	-	50
6	Magnesium Stearate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
7	Spray Dried Lactose	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8
8	Mannitol	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
	Total weight (mg)	160	160	160	160	160	160	160	160

2.3.3 Evaluation of Buccal Mucoadhesive Tablet

A. **Precompression parameters**

Angle of repose, tapped density, bulk density, compressibility index and hausner's ratio of powder blend were evaluated.

B. Post-compression parameters

I. Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in light.

II. Uniformity of thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using venire-caliper.

III. Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and analyzed for hardness. The mean and standard deviation values were calculated

IV. Friability test

Friability is the test for a tablet to see whether the tablet is stable to abrasion or not, it is tested by using Roche friabilator. This is made up of a plastic drum fixed with a machine which rotated at 25 rpm for 100 revolutions. And then the twenty tablets which were weighed prior to the test are taken out of the drum and cleaned with a cloth and weighed once again, the weight variation must not be less than 0.5 to 1.0% for a conventional tablet.

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

V. Weight variation

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

VI. %Drug content uniformity

Tablet containing 10 mg of drug is dissolved in 100ml of Phosphate buffer pH 6.6. The drug is allowed to dissolve in the solvent, the solution was filtered and 1ml of filtrate was taken in 10 ml of volumetric flask and diluted up to the mark with phosphate buffer pH 6.6 and analyzed spectrophotometrically at 205nm. The amount of Captopril was estimated by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each batch of formulation.

VII. Swelling index

For conducting the swelling study, the tablet was weighed (Wo) and placed in a petri dish containing 5 mL of phosphate buffer (pH 6.8) for 8 hours. After that, the tablets were taken out from the petri dish and excess water was removed carefully by using filter paper and weighed again (Wt). The swelling index was calculated using the following formula:

SI = (Wt-Wo) / Wo × 100

Where SI = Swelling index.
Wt = Weight of tablets after time (t)
Wo = Weight of tablet before placing in the Petri dish

VIII. *In vitro* dissolution studies

The release rate of Captopril buccal tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of Phosphate buffer pH 6.6, at 37 ± 0.5°C and speed of 50 rpm. . Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. Aliquot (5 ml) of the solution was collected from the dissolution apparatus for every 1 hr upto 8 hrs and were

replaced with fresh dissolution medium. The aliquots were filtered through whatmann filter paper no. 41. Absorbance of these solutions was recorded at 205 nm (Captopril) in photometric mode for single drug and in multi component mode analysis for combined drugs.

IX. Surface pH study: The Bottenberg method was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1ml of distilled water (pH 6.5±0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

X. Mucoadhesive Strength test: Mucoadhesive strength of the tablets was measured on the modified physical balance. The apparatus consist of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. Goat intestinal mucosa was used as a model membrane and phosphate buffer pH 6.6 was used as moistening fluid. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in glass beaker. The beaker was filled with phosphate buffer pH 6.6 up to the upper surface of the goat intestinal mucosa to maintain intestinal mucosa viability during the experiments. The one side of the tablet was attached to the glass slide of the right arm of the balance and then the beaker was raised slowly until contact between goat intestinal mucosa and mucoadhesive tablet was established. A preload of 10 mg was placed on the slide for 15 mins (preload time) to established adhesion bonding between mucoadhesive tablet and sheep stomach mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in left side arm by peristaltic pump at a constant rate. The addition of water was stopped when mucoadhesive tablet was detached from the sheep stomach mucosa. The weight of water required to detach mucoadhesive tablet from stomach mucosa was noted as mucoadhesive strength in grams. Force of adhesion was calculated from this test by using the following formula.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

Fig. No. 1:- Mucoadhesion test apparatus

XI. *In-vitro* residence time (Wash off test): The mucoadhesive properties of the tablets were evaluated by an *in-vitro* adhesion testing method known as wash-off method. Pieces of intestinal mucosa were mounted on to glass slides were connected with suitable support. Tablet attached on to the slide and the support was hung on to the arm of a USP tablet disintegrating test machine. By operating the disintegrating test machine was given a slow regular up and down movement in the test fluid (phosphate buffer pH 6.6) at 37° C temperatures. At the time of detachment of tablet was noted down.

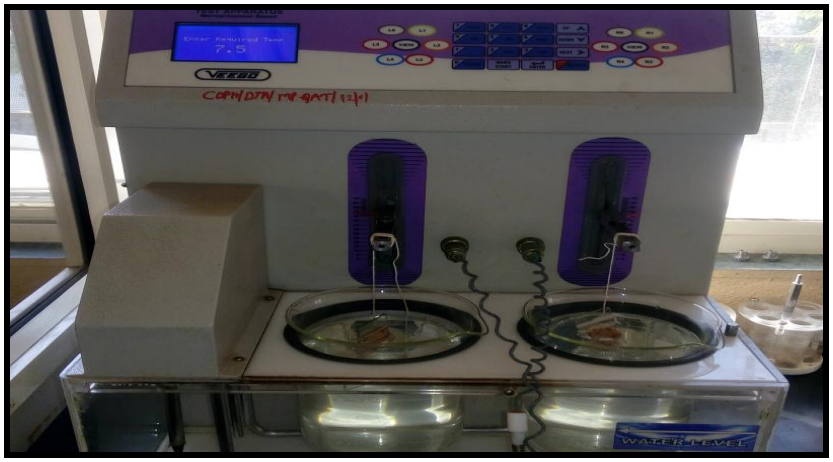

Fig. No. 2:- Modified USP tablet disintegration apparatus

XII. Moisture absorption study: This study was performed in a solidified agar. Agar (5%, w/v) was dissolved in hot water and transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any and one side of the tablet was laminated with a impermeable backing membrane. They were then weighed and placed on the surface of the solidified agar

and incubated at 37 °C for one hour. Then the tablets were removed and reweighed and the percentage of moisture absorption was calculated by using the following formula:

% moisture absorption = (final weight – initial weight x 100) / initial weight

XIII. *In-vitro* drug permeation study

The test was carried out in the standard Franz diffusion cell with a diffusion area of 6.16 cm^2 and the acceptor compartment volume of 16 ml. A porcine buccal mucosa was clamped between the donor and acceptor compartments. The phosphate buffer of pH 6.6 (37^0C) in the acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer. The tablet was placed into the donor compartment and was wetted with 1ml of phosphate buffer. The amount of drug that permeated through the membrane was determined by removing aliquots from the receptor compartment and replacing the same volume of buffer. Then the samples were analyzed by using UV-Visible spectrophotometer at λmax of 205 nm.

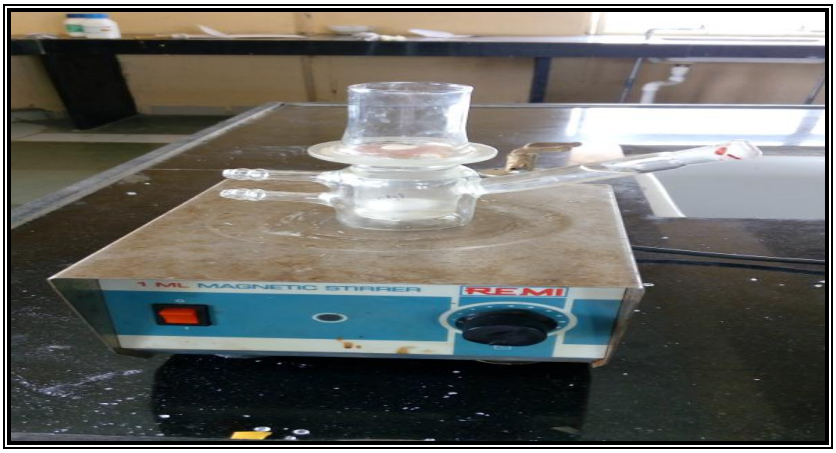

Fig. No. 3: Franz diffusion cell

XIV. Stability studies: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established.

Table No. 2: ICH Q1A (R2) stability guidelines.

	Study conditions specification	Time period
Long Term	25^0C ± 2^0C /60% RH ± 5% RH or 30^0C ± 2^0C /65% RH ± 5% RH	12 months
Intermediate	30^0C ± 2^0C /65% RH ± 5% RH	6 months
Accelerated	40^0C ± 2^0C /75% RH ± 5% RH	6 months

3. RESULT AND DISCUSSION

3.1 Preformulation studies

1. Infrared absorption spectrum: The IR spectrum of pure drug (Fig. No.4) was found to be similar to the standard spectrum of Captopril.

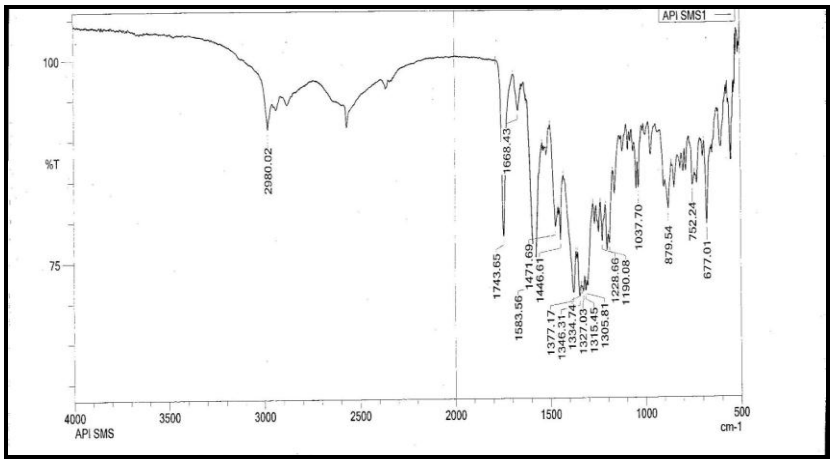

Fig. No. 4: IR spectrum of Pure Captopril.

2. Differential scanning calorimetry: Differential Scanning Calorimetry (DSC) is a thermo analytical technique used for analyzing thermal transitions involving thermal energy with a great sensitivity.

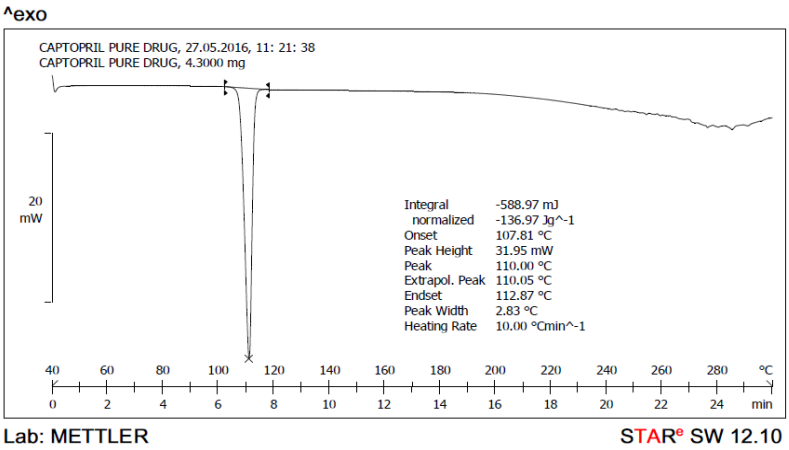

Fig. No. 5: DSC data of Pure Captopril.

3. Compatibility studies: From the spectra of pure drug Captopril, physical mixture of all polymers, and formulations, it was observed that all the characteristic peaks of Captopril were present in the combination spectrum, thus indicating compatibility of the drug and polymer and other excipients. IR spectra of the pure drug Captopril, physical mixture of all polymers, and formulations F5 and F6 are shown in Figure No. 6, 7.

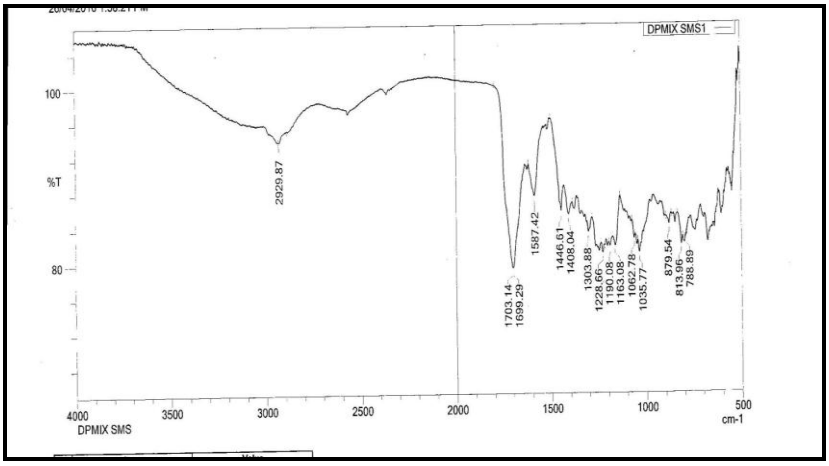

Fig. No. 6: IR Spectrum of physical mixture of all polymers

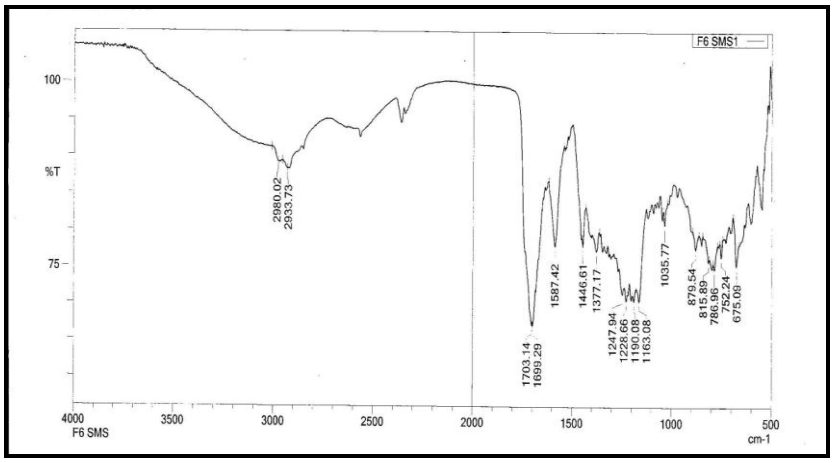

Fig. No. 7: IR Spectrum of formulation F5

4. Standard calibration curve

a. Scanning of drug: The pure drug Captopril was scanned over a range 200-400 nm to determine its λmax. The peak was observed at the 205 nm for Captopril (Fig. No. 8).

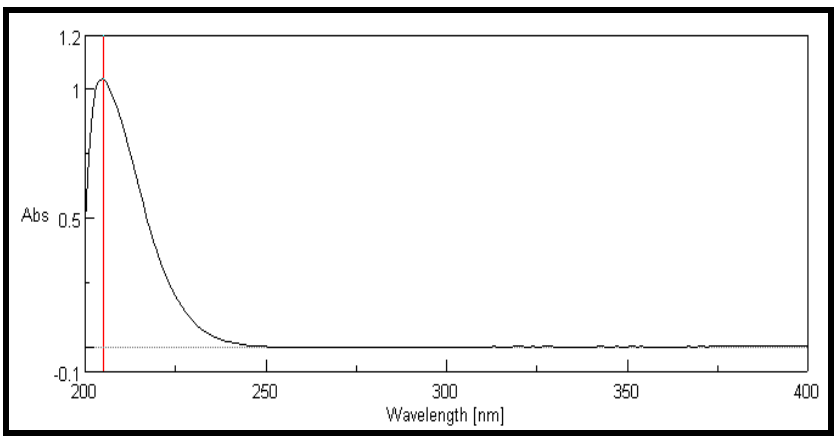

Fig. No. 8: Standard calibration curve of Captopril.

b. Preparation of standard calibration curve of Captopril: The standard calibration curve of Captopril was obtained by plotting Absorbance V/s. Concentration.

Table No. 3: Standard calibration curve of Captopril.

Sr. No.	Concentration (mcg/ml)	Absorbance at 205 nm
1	0	0.0564
2	5	0.4512
3	10	0.7825
4	15	1.1152
5	20	1.3654
6	25	1.6258

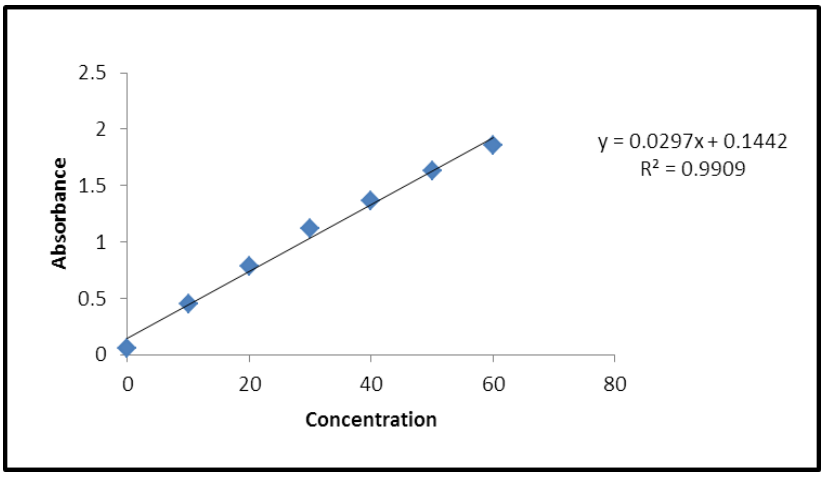

Fig. No. 9: Linearity of Captopril.

3.2 Evaluation of buccal mucoadhesive tablet

A. Precompression parameters

Table No. 4: Evaluation of pre-compression parameter of tablet.

Formulation code	Angle of repose (θ)	Bulk density (gm/ml)	Tap density (gm/ml)	% Compressi-bility	Hausner's Ratio
F1	21.17±1.1507	0.30±0.041	0.28±0.068	7.14±0.881	1.13±0.03
F2	21.11±1.017	0.34±0.034	0.33±0.073	4.03±1.831	1.18±0.05
F3	22.14±1.8615	0.32±0.037	0.30±0.040	6.66±0.479	1.16±0.06
F4	21.25±1.1663	0.34±0.110	0.32±0.073	6.25±0.881	1.20±0.05
F5	22.18±1.766	0.30±0.072	0.29±0.095	4.44±1.766	1.24±0.10
F6	22.82±1.1254	0.31±0.014	0.30±0.052	5.61±1.054	1.15±0.03
F7	21.16±1.0254	0.33±0.045	0.29±0.082	6.25±0.951	1.54±0.03
F8	21.52±1.4241	0.32±0.120	0.31±0.074	6.44±0.452	1.23±0.05

B. Post- compression parameters

I. Shape and color of tablets: Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for color. All tablets of all the batches showed flat, circular in shape and white in color.

II. Uniformity of thickness: The thickness of the tablets was measured by using vernier caliper by picking the tablets randomly. The mean values are shown in Table No.5. The values are almost uniform in all formulations.

III. Hardness test: Table No.5 Shows results obtained for of all the formulation of hardness. Hardness test was performed by Monsanto hardness tester. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness.

IV. Friability test: The study results are tabulated in Table No.5, was found well within the approved range (<1%) in all the formulations. Formulation F1 to F8 possesses good mechanical strength.

V. Weight variation test: The percentage weight variation for all the formulation is tabulated in Table No.5. All the tablets passed weight variation test as the % weight variation was within the Indian pharmacopoeias limits of not more than 7.5%. It was found to be from 154 to 161mg. The weight of all the tablets was found to be uniform.

VI. % Drug content uniformity: The content uniformity was performed for all the five formulations and results are shown in Table No.5. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The results indicated that in all the formulations the drug content was uniform.

Table no.5: Evaluation of post compression parameter of tablet.

Formulation Code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug Content (%)
F1	2.1±0.001	8.0±0.4	0.48±0.01	159±2.001	96.35
F2	2.2±0.001	6.2±0.33	0.23±0.05	159.7±1.52	98.25
F3	2.1±0.002	7.5±0.4	0.35±0.01	161.1±1.20	99.84
F4	2.2±0.001	6.7±0.4	0.61±0.03	160.5±1.53	95.67
F5	2.1±0.001	8.2±0.31	0.52±0.02	158±2.31	99.53
F6	2.1±0.001	8.0±0.42	0.71±0.01	159±2.15	98.21
F7	2.2±0.002	6.8±0.3	0.54±0.03	155±4.28	94.52
F8	2.2±0.001	6.6±0.4	0.24±0.02	154±5.34	97.95

(n=3)

VII. Swelling index: Wetting time is closely related to the inner structure of tablets. The result of the swelling index is shown in Table No.6 and Fig. No. 10, 11.

Table no. 5: % Swelling Index

Time (hr)	Swelling Index (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	40.25	42.36	35.21	15.2	23.1	40.63	27.66	27.42
2	65.23	50.02	49.61	28.61	52.84	53.28	39.24	39.22
3	82.66	62.21	55.26	46.53	70.72	76.23	50.02	67.52
4	95.36	79.66	68.68	54.81	104.15	104.23	62.58	84.15
5	106.32	99	72.05	75.44	121.6	107.53	87.44	98.26
6	123.96	113.25	88.43	82.52	123.08	104.53	98.51	96
8	109.52	105.01	96	92.65	119.11	113.22	102.06	97.88

(n=3)

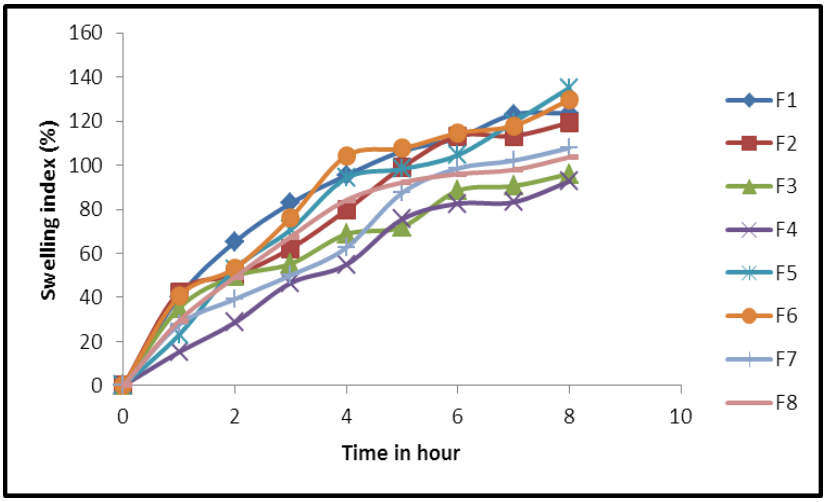

Fig. No. 10: swelling index (%) plot of all formulations

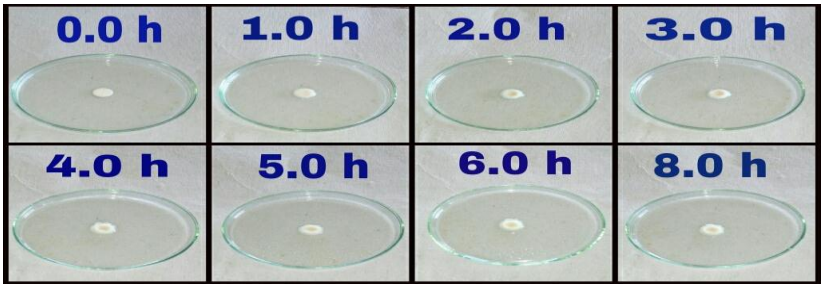

Fig. No. 11: swelling index of formulation F5

VIII. *In-vitro* dissolution studies: The results obtained in the in vitro drug release for the formulations F1 to F8 are tabulated in Table No. 6 and 7 and Figure No.12.

Formulation F1 to F8 prepared by direct compression method was found to be drug release in the range of 85.175% to 99.995%. Here in all batch of F1 to F8 the dissolution rate was found to increase linearly with time. It's showed in Table No.7 and 8. In all formulation the drug

release was zero order and nearer to 100% within 8 hours. F5 prepared by direct compression method showed good drug release (99.995%) than other formulation.

Table No. 7: *In-vitro* % drug release of formulation F1 to F4.

Time in hr	Formulation Code			
	F1	F2	F3	F4
0	0	0	0	0
1	15.009	13.575	22.347	12.133
2	24.801	30.351	39.958	20.593
3	35.496	39.216	45.972	38.609
4	51.033	51.547	52.635	50.172
5	55.818	58.531	65.27	53.47
6	73.536	63.338	73.561	72.709
7	81.034	70.39	80.46	82.147
8	97.042	85.175	97.085	88.035

Table No. 8: *In-vitro* % drug release of formulation F5 to F8.

Time in hr	Formulation Code			
	F5	F6	F7	F8
0	0	0	0	0
1	11.66	11.323	15.523	11.981
2	19.892	30.79	25.745	19.715
3	37.748	42.505	35.749	34.062
4	56.11	59.788	44.707	42.497
5	61.913	69.504	56.692	49.826
6	70.339	82.791	66.054	66.729
7	78.2	85.791	76.851	78.782
8	99.995	97.085	93.525	89.038

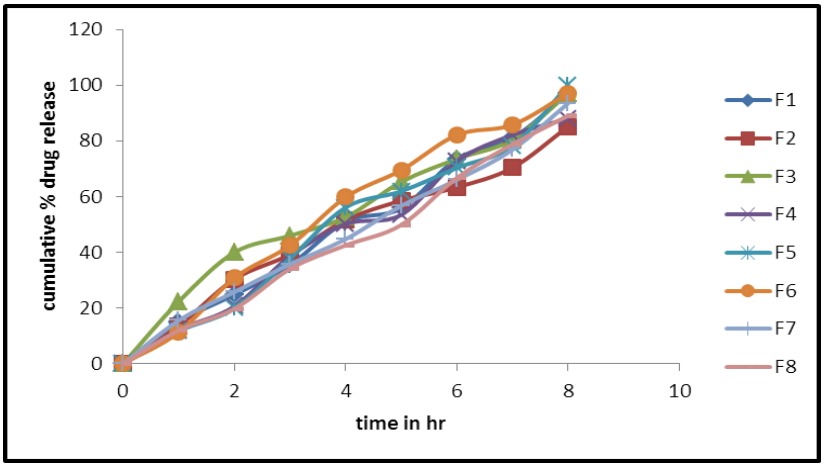

Fig. No. 12: *In-vitro* % drug release of all formulation.

Release kinetics and mechanism: To know the release mechanism and kinetics of Captopril optimized formulations (F5) was attempted to fit into mathematical models and n, r^2 values

for zero order, first order, matrix Korsmeyer- Peppas and Hixon-Crowel models were represented in Table No.9.

Observation of all the R^2 values indicated that the highest R^2 value was found for Zero order release which are shows in Table No.8 and fig. no. 11.

Table No. 9: In-vitro Drug Release Kinetics of F5 formulation.

Models	R^2 value	K value
Zero order	0.9921	12.0985
1st order	0.6273	-.05239
Matrix	0.9288	28.2738
Korsmeyer- Peppas	0.9914	11.3240
Hixon- Crowel	0.8507	-0.0757

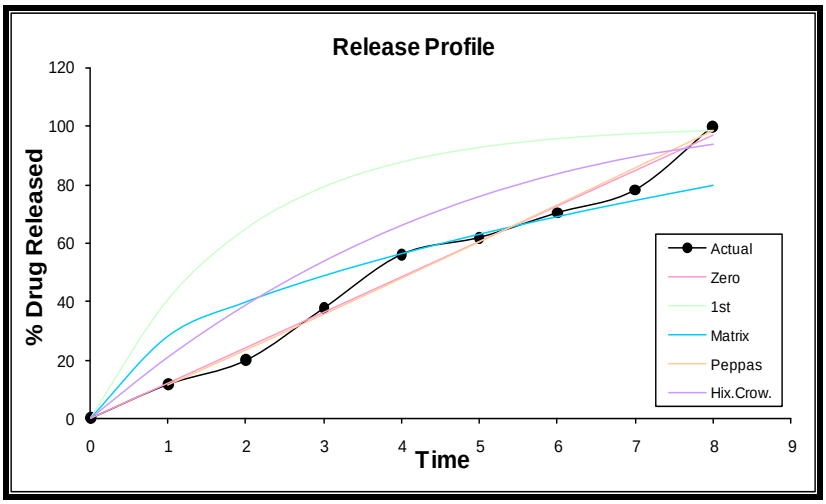

Figure No. 13: *In-vitro* Drug Release Kinetics of F4 formulation.

IX. Surface pH

The surface of buccal tablets is determined in order to investigate the possibility of any side effects *in-vivo*Surface pH of all formulation was found to be 6.3±0.1075 to 6.4±0.9968 except F1. The pH is near to the neutral, so the formulation does not cause any irritation on the mucosa. Surface pH values for all the formulations shown in Table No. 10.

X. Mucoadhesive strength

The values for mucoadhesive strength and the force of adhesion of all formulations are tabulated in Table no. 10. From all the values shown in table, it was clear that the mucoadhesive strength of tablets containing combination of natural and synthetic polymers is greater than that of the single polymer. Formulation F5 shows maximum mucoadhesive strength (51.75±0.531) and the force of adhesion (0.509±0.025) that provide the strong

interaction between mucus and the mucoadhesive tablet which is suitable for the prolong release.

Table No. 10: surface pH, mucoadhesive strength and force of adesion of all formulations.

Formulation Code	Surface pH	Mucoadhesive Strength (mg)	Force of adhesion (N)
F1	3.5±0.04	49.25±0.445	0.485±0.025
F2	6.6±0.08	43.5±0.535	0.428±0.036
F3	6.4±0.06	40.55±0.452	0.399±0.041
F4	6.4±0.05	31.5±0.614	0.309±0.058
F5	6.6±0.07	51.75±0.531	0.509±0.025
F6	6.6±0.02	49.25±0.521	0.485±0.014
F7	6.5±0.04	49±0.123	0.48±0.086
F8	6.6±0.03	43.75±0.152	0.443±0.095

(n=3)

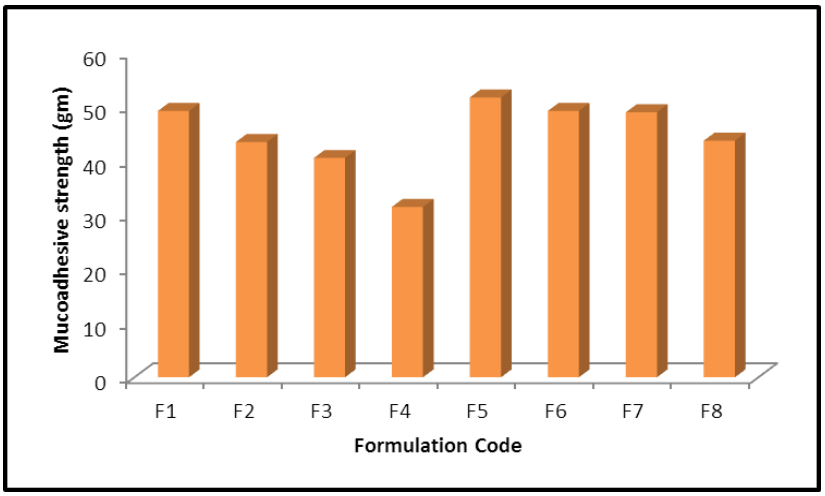

Fig. No. 14: Comparative mucoadhesive strength of all formulations

XI. In-Vitro residence time: The residence time for all formulations varied from 6 to 8 hrs. The optimized formulation (F5) showed 8 hrs. The difference in the resident time could be due to the different ratios of polymers, which may affect the muco-adhesion. Residence time values were given in Table No.11. The maximum residence time (8 hrs) was found for formulations F5 and low residence time (6 hrs) was found for formulations F4. As the polymer concentration in formulation increased, residence time increased.

XII. Moisture absorption: The moisture absorption (Table No.11) was more in formulations containing Carbopol 934p when compared to formulations containing HPMC K4M. This may be due to the more hydrophilic nature of Carbopol 934p.

Table No. 11: In-Vitro residence time and moisture absorption of all formulations

Formulation Code	In-Vitro residence time (hr)	Moisture absorption (%)
F1	7±0.04	18.37±0.445
F2	7±0.08	15.87±0.535
F3	6.5±0.06	6.25±0.452
F4	6±0.05	10.85±0.614
F5	8±0.07	19.21±0.531
F6	8±0.02	17.85±0.521
F7	7±0.04	15.58±0.123
F8	7±0.03	14.53±0.152

(n=3)

XIII. *In-vitro* drug permeation study

Based on the *in vitro* drug release, mucoadhesion strength, moisture absorption and *in vitro* retention time of all formulations, the F5 formulation was selected as optimized best formulation and *in vitro* permeation studies were conducted for this formulation.

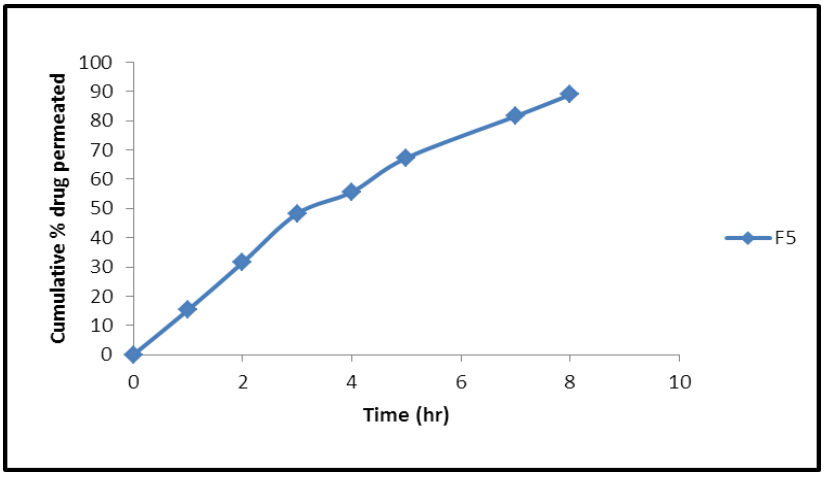

Fig. No. 15: *In-vitro* drug permeation of Captopril

XIV. Stability study: From the stability study, it was proved that the evaluated formulation (F5) showed there was no influence of variety of environmental factors such as temperature, humidity and light, and during storage conditions or shelf life of drug.

Table No. 12: Stability Parameters after 0, 30, 60 and 90 days.

Days	Study conditions specification	% Drug Content F5
Initial	4-8˚C	98.20±0.27
	Room Temperature	98.21±0.53
	40^0C ± 2^0C/75% ± 5% RH	98.19±0.64
After 30 day	4-8˚C	98.20±0.31

	Room Temperature	98.21±0.83
	$40^0C \pm 2^0C$/75% RH ± 5% RH	98.20±0.18
After 60 day	4-8˚C	98.19±0.54
	Room Temperature	98.21±0.46
	$40^0C \pm 2^0C$/75% RH ± 5% RH	98.20±0.85
After 90 days	4-8˚C	98.20±0.38
	Room Temperature	98.21±0.88
	$40^0C \pm 2^0C$/75% RH ± 5% RH	98.20±0.63

(n=3)

4. CONCLUSION

An attempt to develop buccal mucoadhesive tablets of Captopril was achieved within view to improve bioavailability and by pass the first pass metabolism problems. DSC data and IR spectra revealed that, polymers and excipients used were compatible with drug. In-Vitro mucoadhesive strength, force of adhesion and in-vitro residence time showed good results in formulations containing combination of natural and synthetic polymers than single polymer. Formulation F5 showed better mucoadhesive strength and in-vitro drug release in comparison to other formulations, the F5 formulation was selected as optimized best formulation and *in vitro* permeation studies and stability studies were conducted for this formulation. The results of drug permeation from buccal tablets through the porcine buccal mucosa, revealed that Captopril was released from the formulation and permeated through the porcine buccal membrane and could possibly permeate through the human buccal membrane and not much variation in any parameter even after 90 days. From these results it was conclude that, F5 Formulation was found to be stable and superior with respect to mucoadhesion and release kinetic.

5. ACKNOWLEDGEMENT

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