Research Article

Formulation and Evaluation of Mucoadhesive Buccal Tablets of Captopril

Y. Chaitanya Kumar

Sri Vani School of Pharmacy, Chevuturu, G. Konduru-521229,

Andhra Pradesh, India.

ABSTRACT

The objective of this study was to develop effective mucoadhesive buccal tablets of Captopril. Tablets of Captopril were prepared by direct compression method using bioadhesive polymers like Acritamer 940, Manugel, Hypromellose K100. Buccal tablets were prepared by taking polymers in different ratios. Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, swelling index, surface pH, *in-vitro* drug release, *ex vivo* drug permeation, *in-vivo* mucoadhesive performance studies. I*n vitro* assembly was used to measure the bioadhesive strength of tablets with fresh porcine buccal mucosa as model tissue. The tablets were evaluated for *in vitro* release in pH 6.8 phosphate buffer for 8 hr in standard dissolution apparatus. In order to determine the mode of release, the data was subjected to Zero order, first order, Higuchi, Korsmeyer and Peppas diffusion model. The formulation F2 showed maximum drug release (98.56%) in 8 hrs. The optimised formulation F2 showed a surface pH of 6.18 and swelling index 89.90%. This formulation was following First order mechanism with regression value of 0.991. FT-IR studies revealed the absence of any chemical interaction between drug and polymers used. Captopril mucoadhesive tablets for buccal delivery could be prepared with required *in-vitro* release properties.

Keywords: Captopril, Buccal tablets, Acritamer 940, Manugel, Hypromellose K100, *in-vitro* drug release.

INTRODUCTION

The aim of present work is to formulate and evaluate bioadhesive buccal tablets of Captopril to release the drug unidirectionally in the buccal cavity.

METHOD AND DISCUSSION

PREFORMULATION STUDIES

1.1. Drug-excipient compatibility studies [83,84]

Fourier Transform Infrared spectroscopic studies

A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipient (binary mixture of drug: excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4000 cm^{-1}. Pure drug of Captopril, Captopril with physical mixture (excipients) compatibility studies were performed.

Analytical Method Used in the Determination of Captopril

Preparation of 0.2M Potassium Dihydrogen Orthophosphate Solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2M potassium dihydrogen ortho phosphate and 112.5 mL of 0.2M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Preparation of standard graph in phosphate buffer pH 6.8

100 mg of Pure Drug was dissolved in small amount of Methanol (5-10 ml), allowed to shake for few minutes and then the volume was made up to 100ml with phosphate buffer pH 6.8, from this primary stock (1mg/ml), 10 ml solution was transferred to another volumetric flask made up to 100 ml with phosphate buffer pH 6.8. From this secondary stock 0.5, 1.0, 1.5, 2.0, 2.5, ml was taken separately and made up to 10 ml with phosphate buffer pH 6.8 to produce 5, 10, 15, 20, 25 µg/ml respectively. The absorbance was measured at 221 nm using a UV spectrophotometer.

Solubility Studies [1,11]

The solubility of Captopril in phosphate buffer solution pH 6.8 was determined by phase equilibrium method. An excess amount of drug was taken into 20 ml vials containing 10 ml of phosphate buffers (pH 6.8). Vials were closed with rubber caps and constantly agitated at room temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm Whatman's filter paper. The amount of drug solubilized was then estimated by measuring the absorbance at 221 nm using a UV spectrophotometer.

The standard curves for Captopril were established in phosphate buffers (pH 6.8) and from the slope of the straight line the solubility of Captopril was calculated. The studies were repeated in triplicate (n = 3), and mean was calculated.

1.2. *Ex-vivo* permeation studies through porcine buccal mucosa [1]

The aim of this study was to investigate the permeability of buccal mucosa to Captopril. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the buccal absorption.

1.2. a. Tissue permeation

Buccal tissue was taken from Pigs slaughter-house. It was collected within 10 minutes after slaughter of pig and tissue was kept in Krebs buffer solution. It was transported immediately to the laboratory and was mounted within 2hrs of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffer saline to remove the adherent material. The buccal membrane from the tissue was isolated using surgical procedure. Buccal membrane was isolated and buccal epithelium was carefully separated from underlying connective tissue. Sufficient care was taken to prevent any damage to the epithelium.

Table 1: Composition of Tyrode solution (Krebs buffer)

Ingredients	Quantity(gm)
Sodium chloride	8.0
Potassium chloride	0.2
Calcium chloride dehydrate	0.134
Sodium bicarbonate	1.0
Sodium dihydrogen orthophosphate	0.05
Glucose monohydrate	1.0
Magnesium chloride	0.1
Distilled water up to	1.0Litre

1.2.b. *Ex-vivo* permeation of drug solution [14,15]

Ex-vivo permeation study of Captopril through the porcine buccal mucosa was performed using Franz diffusion cell and membrane assembly, at 37°C ± 0.2°C and 50 rpm. This temperature and rpm was maintained by magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2hr of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection. After the buccal membrane was equilibrated for 30 min with the buffer solution between both the chambers, the receiver chamber was filled with fresh buffer solution (pH 7.4), and the donor chamber was charged with 5mL (1mg/mL) of drug solution. Aliquots (5mL) were collected at predetermined time inter wells up to 6hr and the amount of drug permeated through the buccal mucosa was then determined by measuring the

absorbance at 221 nm using a UV spectrophotometer. The medium of the same volume (5mL), which was pre-warmed at 37°C, was then replaced into the receiver chamber.

1.3 Formulation development of tablets

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Acritamer 940, Manugel and Hypromellose K100M are the mucoadhesive and biodegradable polymers used in this preparation of buccal mucoadhesive drug delivery systems.

Captopril was mixed manually with different ratios of Acritamer 940, Manugel and Hypromellose K100M and Microcrystalline Cellulose as diluent for 10 min. The blend was mixed with talc and magnesium stearate for 3-5 min.

1.4. Evaluation of Pre-Compression Blend: [82,85]

The quality of tablet, once formulated, by rule is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characterization of blends produced. Prior to compression, granules were evaluated for their characteristic parameter such as Tapped density, Bulk density, Carr's index, Angle of repose, Hausner's ratio. Compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus. The various characteristics of blends tested are as given below:

a) Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan\theta = h/r$$

Where, θ = angle of repose
h = height of the cone
r = radius of the cone base

The relationship between the angle of repose and flowability is as follows:

Table: Angle of repose values

S. No	Angle of Repose	Flowability
1.	<25	Excellent
2.	25-30	Good
3.	30-40	Passable
4.	>40	Poor flow

b) Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping and storage of raw material and blend. It is also important in size blending equipment. 30 gm of powder blend introduced into a dry 100 mL cylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume V_0, was read. The bulk density was calculated using the formula:

$$\rho b = M/V_0$$

Where, ρb= Apparent bulk density.
M=Weight of the sample.
V=Apparent volume of powder.

c) Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides a fixed drop of 14±2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2% and then tapped volume, $V_{f\ was}$ measured, to the nearest graduated unit. The tapped density was calculated, in gm per mL, using the formula:

$$\rho_{tap} = M/V_f$$

Where, ρ_{tap}= Tapped density.
M = Weight of the sample.
V_f = tapped volume of the powder.

d) Carr's index

The compressibility index (Carr's index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measure of the relative importance of interparticle interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility index which is calculated using the following formula:

$$\text{Carr's index} = [(\rho_{tap}-\rho b)]/\rho_{tap}]\times 100$$

Where, ρb= bulk density
ρ_{tab}= tapped density

S. No.	Carr's Index	Flowability
1.	5-12	Free Flowing
2.	13-16	Good
3.	18-21	Fair to Passable
4.	23-35	Poor
5.	33-38	Very Poor
6.	>40	Extremely Poor

e) Hausner's ratio:

It is the ratio of tapped density to the bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally, a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

$$\text{Hausner's Ratio} = \rho_{tap}/\ \rho b$$

Where, ρ_{tap} = Tapped density.
ρb = Bulk density.

Table: Hausner's ratio values

S. No.	Hausner's Ratio	Flowability
1.	0-1.2	Free flowing
2.	1.2-1.6	Cohesive powder

Preparation of Tablets

Then the powder blend was compressed into tablets by the direct compression method using 6mm flat faced punches. The tablets were compressed using a sixteen station LAB PRESS rotary tablet-punching machine. The weights of the tablets were determined using a digital balance and thickness with digital screw gauge. Composition of the prepared bio adhesive buccal tablet formulations of Captopril were given in Table10.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Acritamer 940	12.5	25	50	-	-	-	-	-	-
Manugel	-	-	-	12.5	25	50	-	-	-
Hypromellose K100M	-	-	-	-	-	-	12.5	25	50
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
MCC pH 102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total Weight (mg)	200	200	200	200	200	200	200	200	200

EVALUATION OF BUCCAL TABLETS: [82,85]

1.5.1. Physicochemical characterization of tablets

The prepared Captopril buccal tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

A. Weight variation:

The weight variation test is done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage. The weight variation test would be a satisfactory method of determining the drug content uniformity.
The percent deviation was calculated using the following formula:

% Deviation = (Individual weight – Average weight / Average weight) X 100

The average weight of tablets in each formulation was calculated and presented with standard deviation.

Pharmacopoeia specifications for tablet weight variation

Average weight of tablets (mg)	Maximum % of difference allowed
80 or less	10
More than 80 but less than 250	7.5
250 or more	5

B. Tablet Thickness

The Thickness and diameter of the tablets from production run is carefully controlled. Thickness can vary with no change in weight due to difference in the density of granulation and the pressure applied to the tablets, as well as the speed of the tablet compression machine. Hence this parameter is essential for consumer acceptance, tablet uniformity and packaging. The thickness and diameter of the tablets was determined using a Digital Vernier calliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablets is calculated and presented with standard deviation.

C.Tablet Hardness

Tablet hardness is defined as the force required to breaking a tablet in a diametric compression test. Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Six tablets were taken from each formulation and hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm^2.

D. Friability

Tablet hardness is not an absolute indicator of the strength because some formulations when compressed into very hard tablets lose their crown positions. Therefore, another measure of the tablet strength, its friability, is often measured. Tablet strength is measured by using Roche friabilator. Test subjects to number of tablets to the combined effect of shock, abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

A sample of pre-weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as

$$\text{Friability (\%)} = \frac{\text{Initial weight of 10 tablets – final weight of 10 tablets}}{\text{Initial weight of 10 tablets}} X\ 100$$

$$F\ (\%) = [Wo\text{-}W/W_O]\ X100$$

E. Drug content

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 221 nm using pH6.8 phosphate buffer.

1.5.2. *In vitro* release studies

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. 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. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 221nm.

1.6 Kinetic Analysis of Dissolution Data: [87,88,89]

To analyse the in vitro release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsmeyer equation / Peppa's model – Log cumulative % drug released versus log time.

Zero order kinetics

Zero order release would be predicted by the following equation:-

$$A_t = A_0 – K_0t$$

Where, A_t = Drug release at time't'.

A_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K_0.

First Order Kinetics

First – order release would be predicted by the following equation:-

$$\text{Log } C = \log C_0 - K_t / 2.303$$

Where, C = Amount of drug remained at time't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

Higuchi's model

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D\varepsilon / \tau (2A - \varepsilon Cs) Cst]^{1/2}$$

Where, Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes:

$$Q = Kt^{1/2}$$

Korsmeyer equation / Peppa's model

To study the mechanism of drug release from the buccal tablets of Captopril, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$M_t / M_a = Kt^n$$

Where, M_t / M_a = the fraction of drug released at time't'.

Above equation can be simplified by applying log on both sides,

And we get:

$$\text{Log } M_t / M_a = \text{LogK} + n \text{ Logt}$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for anomalous transport 'n' ranges between 0.5 and 1.0.

Mechanism of Drug Release as per Korsmeyer Equation / Peppa's Model

S.No	n value	Drug Release
1.	n <0.5	Fickian release
2.	0.5<n<1	Non-Fickian release
3.	n>1	Case II transport

1.6.1 Swelling Studies

Buccal tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.8) solution. At regular intervals (0.5, 1, 2, 3, 4, 5 and 6hr), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2) (Ritthidej et al., 2002). This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Eq.

$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} X\ 100$$

1.6.2 *In vitro* bio adhesion strength

Bio adhesion strength of tablets were evaluated using a microprocessor based on advanced force gauge equipped with a motorized test stand (Ultra Test Tensile strength tester, Mecmesin, West Sussex, UK) according to method describe as it is fitted with 25kg load cell, in this test porcine membrane was secured tightly to a circular stainless steel adaptor and the buccal tablet to be tested was adhered to another cylindrical stainless steel adaptor similar in diameter using a cyanoacrylate bio adhesive. Mucin 100 µl of 1 % w/v solution was spread over the surface of the buccal mucosa and the tablet immediately brought in contact with the mucosa. At the end of the contact time, upper support was withdrawn at 0.5mm/sec until the tablet was completely detached from the mucosa. The work of adhesion was determined from the area under the force distance curve.

The peak detachment force was maximum force to detach the tablet from the mucosa.

$$\text{Force of adhesion} = \frac{\text{Bioadhesion strength x } 9.8}{1000}$$

$$\text{Bond strength} = \frac{\text{Force of adhesion}}{\text{surface area}}$$

1.6.3. Surface pH

Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.8 phosphate buffers (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3).

1.6.4. Moisture absorption

Agar (5% m/V) was dissolved in hot water. It was 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 laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\%\ \text{Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} x\ 100$$

1.6.5. *Ex vivo* residence time

The *Ex vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised pig mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 500 ml of phosphate buffer, pH 6.8, at 37^0C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (figure 10). The time for complete erosion or detachment from the mucosa was recorded.

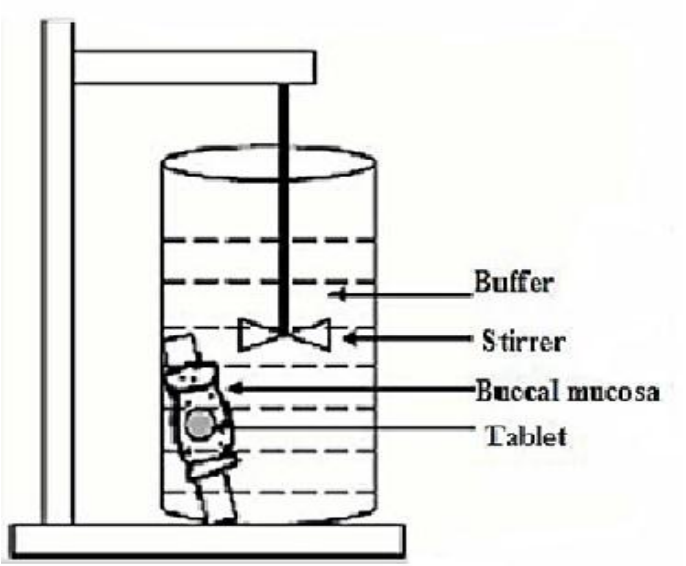


Fig. 4: Schematic representation of *Ex vivo residence* time study

1.7 PREFORMULATION STUDIES

1.7.1 Drug – excipient compatibility studies by physical observation

Captopril was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions.

FTIR

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra of pure Captopril drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Captopril are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

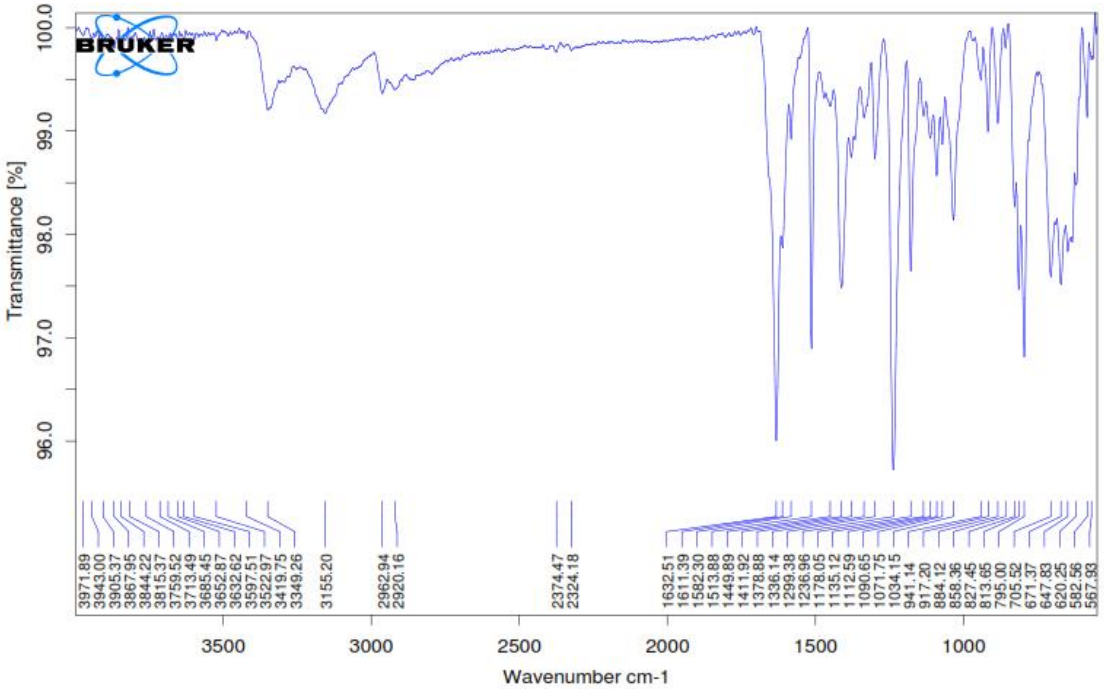
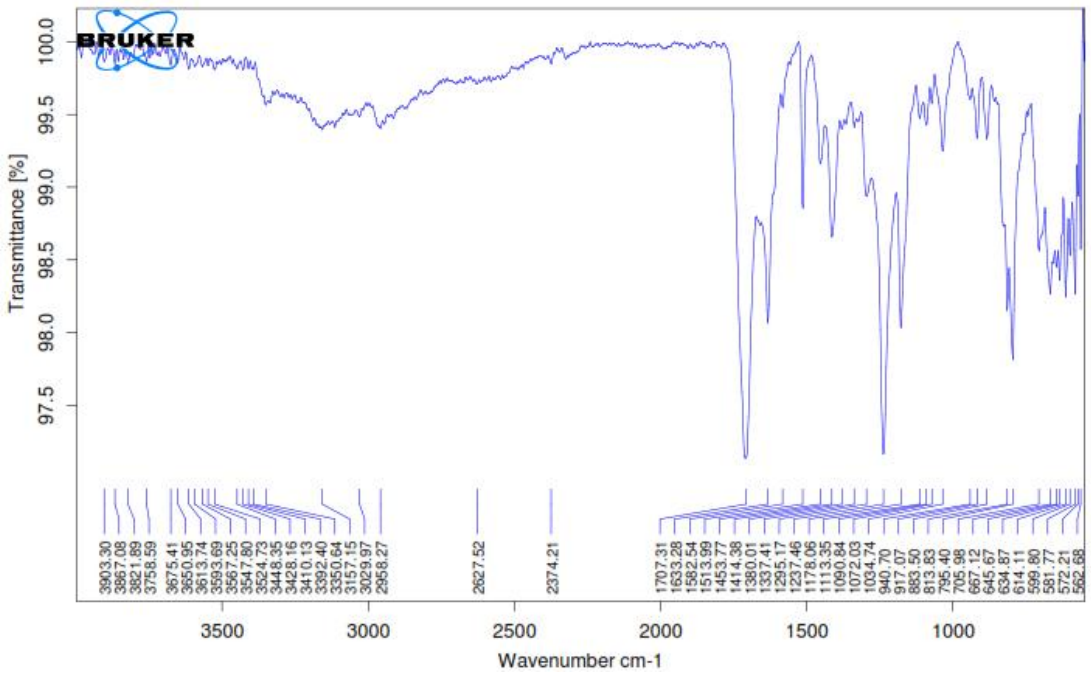


Fig.: FTIR Peak of Pure drug Captopril



FTIR Peak of Optimised formulation

Solubility Studies

S. No	Medium	Amount present (µg/mL)
1	Phosphate pH6.8 buffer	86
2	Phosphate pH 7.4 buffer	94

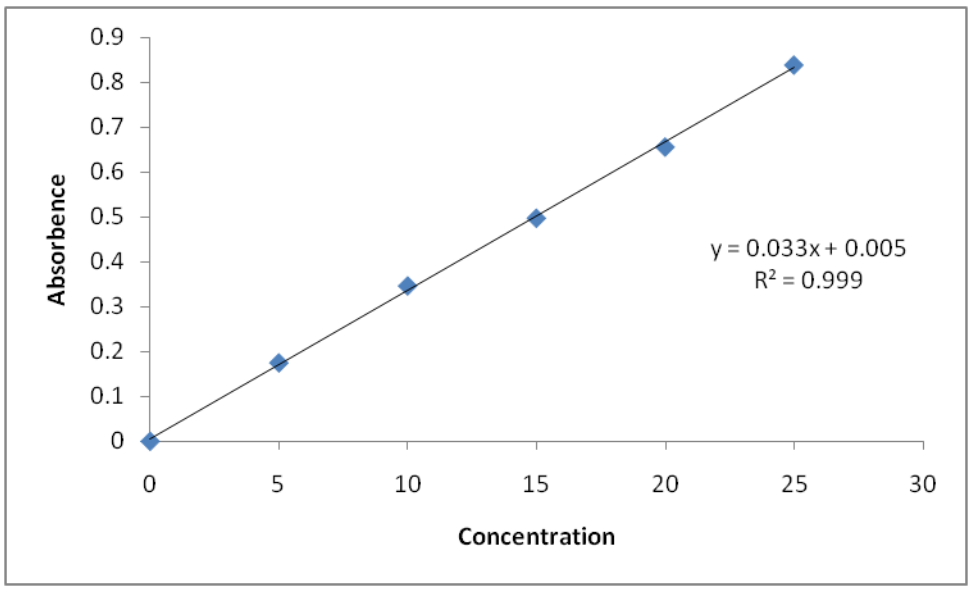
Saturation solubility of Captopril in various buffers were studied and shown in the Table. The results revealed that the solubility of the Captopril was increased from pH 6.8 to 7.4. The solubility of the Captopril in phosphate buffer pH 6.8 is 86 µg/mL and it was selected as the suitable media for the release studies because the pH of the phosphate buffer pH 6.8 is nearer to that of buccal mucosa pH.

Standard graph in phosphate buffer pH 6.8 (λ_{max} 221 nm)

Standard graph of Captopril was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig**.** The standard graph of Captopril showed good linearity with R^2 of 0.999, which indicates that it obeys “Beer- Lamberts” law.

Standard graph values of Captopril in pH 6.8 phosphate buffer

S.No	Concentration (µg/mL)	Absorbance
0	0	0
1	5	0.176
2	10	0.348
3	15	0.497
4	20	0.658
5	25	0.841



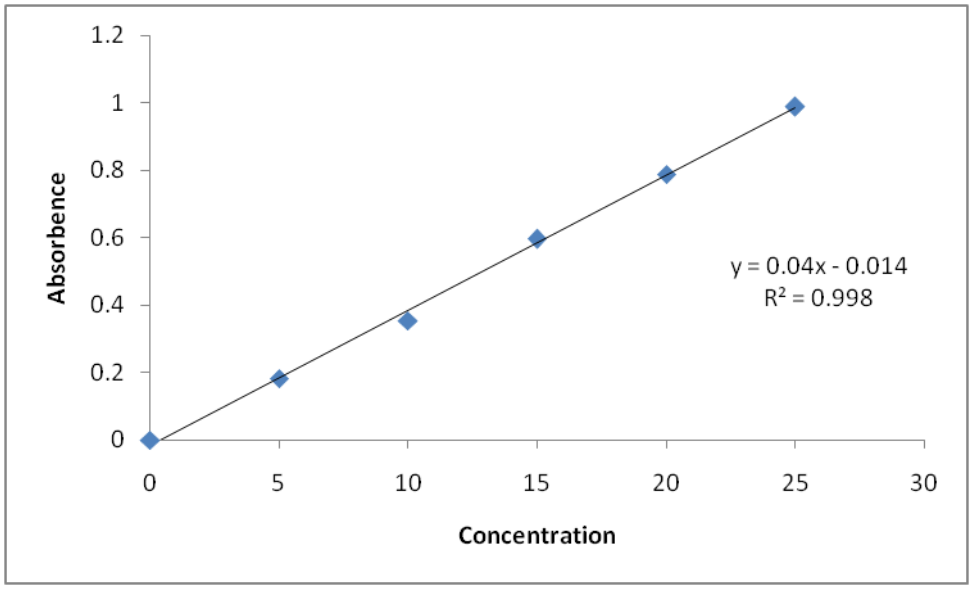
Standard graph of Captopril in pH 6.8 phosphate buffer

Standard graph in phosphate buffer pH 7.4 (λ_{max} 221 nm)

Standard graph of Captopril was plotted as per the procedure in experimental method and its linearity is shown in Table and Fig. The standard graph of Captopril showed good linearity with R^2 of 0.997, which indicates that it obeys "Beer- Lamberts" law.

Standard graph values of Captopril in pH 7.4 phosphate buffer

S.No	Concentration (µg/mL)	Absorbance
0	0	0
1	5	0.183
2	10	0.355
3	15	0.597
4	20	0.789
5	25	0.989



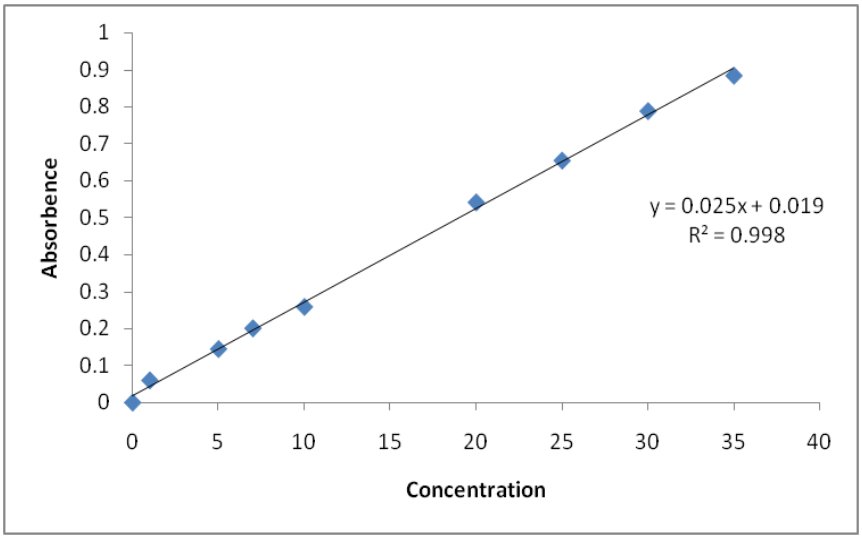
Standard graph of Captopril in pH 7.4 phosphate buffer

***Ex vivo* permeation of drug solution through the porcine buccal mucosa**

Ex vivo permeation study of Captopril drug solution through the porcine buccal mucosa was performed using franz diffusion cell. The membrane assembly was kept at 37±0.2°C and 450 rpm. This rpm was maintained by magnetic stirrer. Phenol red was used as marker compound and not to permeate through porcine membrane. Absence of phenol red in the receiver compartment indicates the intactness of the buccal membrane.

Standard graph of Phenol red

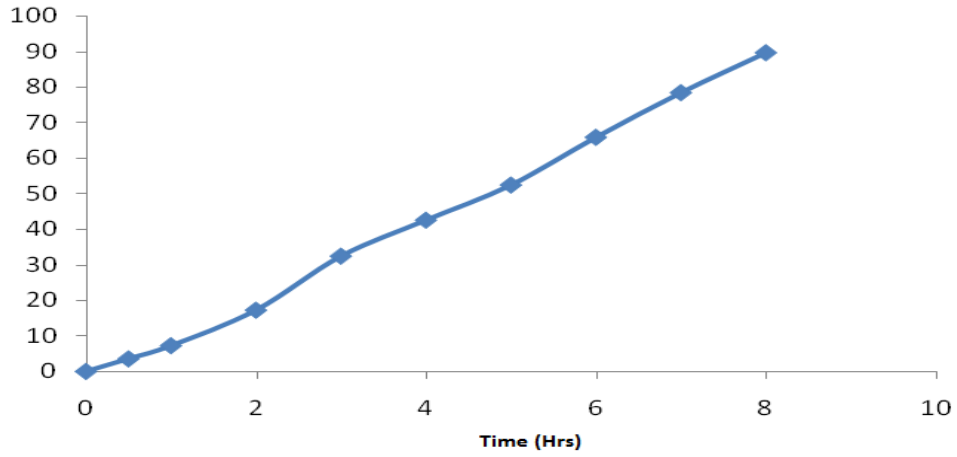
S. No.	Concentration (µg/mL)	Absorbance
1	0	0
2	1	0.10
3	5	0.145
4	7	0.201
5	10	0.259
6	20	0.542
7	25	0.655
8	30	0.789
9	35	0.885



Standard graph of Phenol red

***Ex vivo* permeation of Captopril drug solution through the porcine buccal mucosa**

Time (hrs)	Cumulative amount of Captopril permeated (%)
0	0
0.5	3.54
1	7.25
2	17.24
3	32.45
4	42.91
5	52.55
6	65.38
7	78.39
8	89.23
Flux	424.735 µg.hr^{-1}cm^{-2}



***Ex vivo* permeation of drug solution through the porcine buccal mucosa**

The tissue could be isolated successfully because no detectable level of phenol red (Marker compound) was observed in the receiver compartment. Hence it did not show any penetration and shows the intactness of the porcine buccal mucosa. The flux, permeability coefficient was found to be 424.735 µg.hr^{-1}cm^{-2}, 0.418 cm/hr respectively.

Evaluation

Characterization of pre-compression blend: The pre-compression blend of Captopril buckle tablets were characterized with respect to angle of repose, bulk density, tapped density, carr's index and hausner's ratio**.** Angle of repose was less than 28^{o}, carr's index values were less than 11 for the pre-compression blend of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow property

Physical properties of pre-compression blend

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25.10°±0.10	0.52±0.01	0.60±0.01	13.33±0.2	1.15±0.22
F2	25.43°±0.12	0.52±0.03	0.62±0.03	16.12±0.3	1.19±0.26
F3	25.41°±0.15	0.50±0.06	0.59±0.04	15.25±0.2	1.18±0.24
F4	26.40°±0.17	0.53±0.05	0.62±0.06	14.51±0.3	1.16±0.33
F5	27.12°±0.16	0.56±0.08	0.64±0.07	12.50±0.1	1.14±0.32
F6	25.31°±0.20	0.58±0.07	0.68±0.09	14.70±0.5	1.17±0.31
F7	26.11°±0.14	0.55±0.04	0.64±0.02	14.06±0.6	1.16±0.34
F8	26.15°±0.21	0.52±0.06	0.59±0.04	11.86±0.7	1.13±0.21
F9	26.10°±0.15	0.53±0.04	0.62±0.03	14.51±0.9	1.16±0.26

Evaluation of buccal tablets

Physical evaluation of Captopril buccal tablets: The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 22. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 3.6 to 5 kg/cm^2 and the friability values were less than 0.561% indicating that the buccal tablets were compact and hard. The thickness of the tablets ranged from 2.71 - 2.91 mm. All the formulations satisfied the content of the drug as they contained 98-100% of Captopril. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Physical evaluation of Captopril buccal tablets

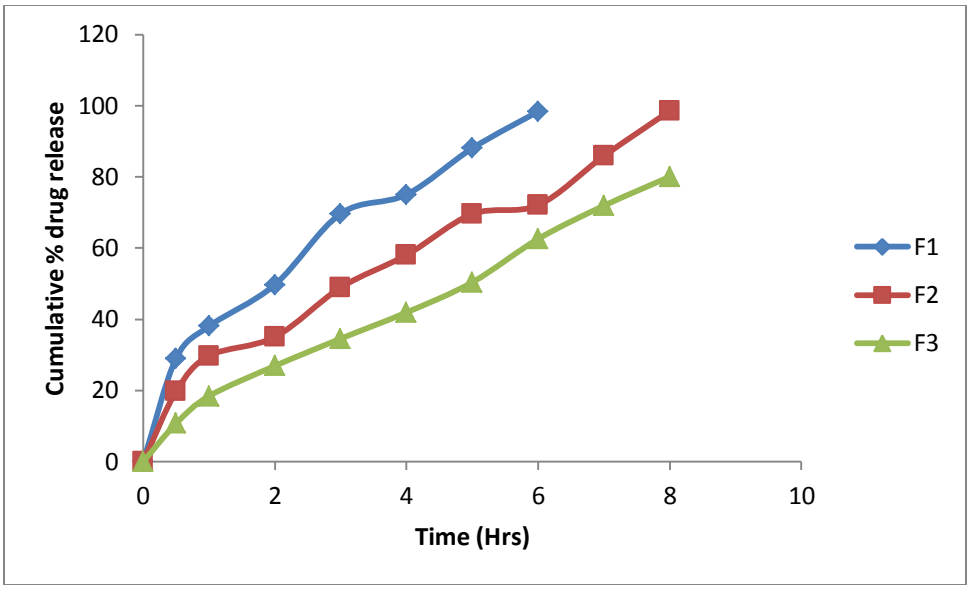
Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity(%)
F1	202±0.1	4.76±0.1	4.6±0.11	0.430±0.01	99±0.1
F2	203±0.3	4.74±0.1	4.3±0.12	0.391±0.03	101±0.1
F3	201±0.2	4.71±0.2	4.0±0.11	0.383±0.05	103±0.1
F4	197±0.5	4.80±0.3	4.6±0.15	0.491±0.08	108±0.1
F5	198±0.3	4.81±0.2	3.9±0.16	0.522±0.09	98±0.2
F6	197±0.4	4.74±0.2	4.2±0.14	0.563±0.05	97±0.3
F7	198±0.6	4.76±0.3	5.1±0.15	0.532±0.06	99±0.2
F8	200±0.7	4.71±0.1	4.7±0.13	0.492±0.04	98±0.2
F9	199±0.9	4.73±0.2	4.2±0.17	0.482±0.07	100±0.1

***In vitro* release studies**

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Captopril from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs.

***In vitro* dissolution data for formulations F1 – F3 by using Acritamer 940**

Time(hrs)	% Cumulative drug release		
	F1	F2	F3
0	0	0	0
0.5	29.04	19.73	10.73
1	38.06	29.73	18.42
2	49.72	35.04	26.9
3	69.68	48.92	34.56
4	75.06	58.06	41.93
5	88.06	69.57	50.4
6	98.36	72.08	62.58
7		85.9	71.92
8		98.56	80.06

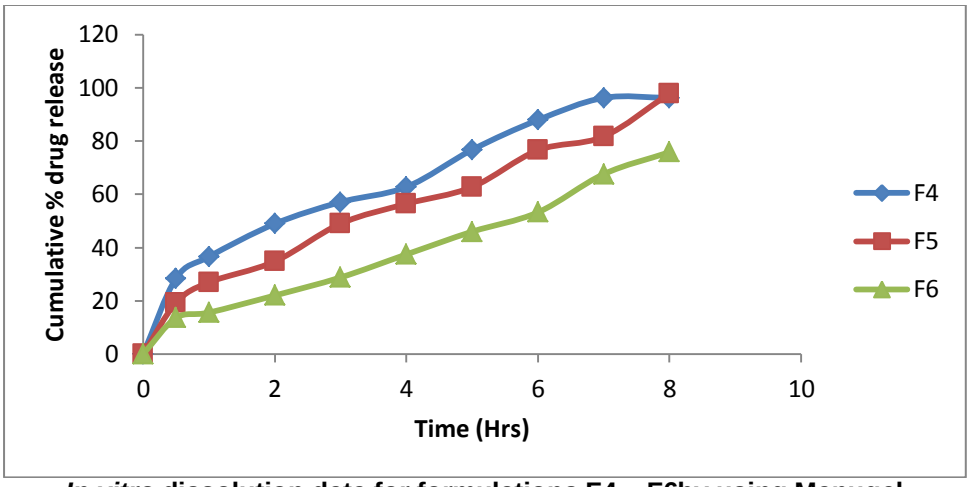


***In vitro* dissolution data for formulations F1 – F3 by using Acritamer 940**

From the above graphs it was evident that Acritamer 940 in the concentration of 25% of polymer of the total tablet weight (F2) drug with other two ratios 12.5%, 50%. In case of F1 formulation the polymer quantity was insufficient to produce the required retarding nature up to 8 hrs, maximum drug release was occured in 6 hrs only and where as in F3 formulation the quantity of polymer was high hence it showed more drug retardation with less drug release that is 80.06% in 8 hrs.

***In vitro* dissolution data for formulations F4 – F6 by using Manugel**

Time(hrs)	% Cumulative drug release		
	F4	F5	F6
0	0	0	0
0.5	28.42	19.28	13.56
1	36.57	26.93	15.58
2	48.91	34.78	21.99
3	57.07	48.97	28.77
4	62.74	56.43	37.42
5	76.72	62.74	45.97
6	87.91	76.56	53.23
7	96.23	81.73	67.58
8	96.23	97.9	75.83

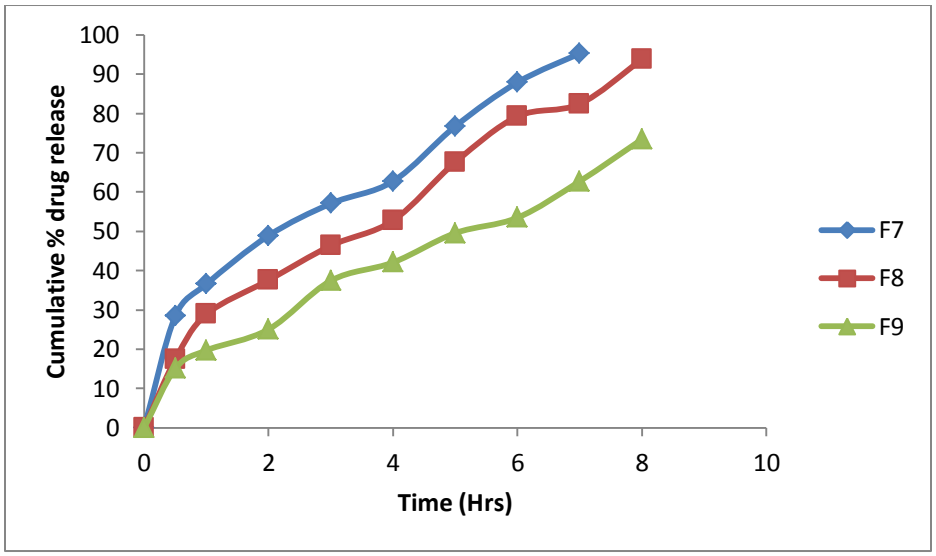


***In vitro* dissolution data for formulations F4 – F6by using Manugel**

From the above graphs it was evident that Manugel in the Polymer concentration of 25% of the total tablet (F5), is showing better result 97.90% drug release when compared with other two ratios F4 and F6. As the concentration of polymer increases the retarding of drug release also increased. Hence they were not considered.

***In vitro* dissolution data for formulations F7 – F9 by using Hypromellose K100M**

Time(hrs)	% Cumulative drug release		
	F7	F8	F9
0	0	0	0
0.5	28.42	17.42	15.06
1	36.57	28.89	19.73
2	48.91	37.59	25.07
3	57.07	46.35	37.45
4	62.74	52.75	42.09
5	76.72	67.58	49.56
6	87.91	79.23	53.48
7	95.23	82.42	62.74
8		93.73	73.42



***In vitro* dissolution data for formulations F7- F9 by using Hypromellose K100M**

From the above graphs it was evident that Hypromellose K100M in the Polymer concentration 25% of the total tablet weight (F8), is showing better result 93.73 % drug release when compared with other two formulations.

***Ex vivo* residence time, moisture absorption, surface pH, bio adhesion strength values of selected formulations**

Formulation Code	*Ex vivo* residence time (hrs)	Moisture absorption	Surface pH	Bio adhesion strength	
				Peak detachment force (N)	Work of adhesion (mJ)
F2	7hr 51min	62	6.18	4.5	16.43
F5	7hr 34min	53	6.11	4.5	15.24
F8	6hr 33min	49	6.14	4.9	13.43

Swelling studies

Swelling index of selected formulations

Time (hrs)	% Swelling Index		
	F2	F5	F8
0	0	0	0
0.5	13.4	11.3	13.6
1	21.5	17.4	22.1
2	26.3	20.1	23.3
3	30.1	23.1	28.3
4	34.3	30.3	33.2
5	43.2	38.1	39.4
6	56.3	44.3	46.4
7	69.4	53.3	51.3
8	81.3	58.2	61.4

Swelling studies of captopril selected buccal tablets

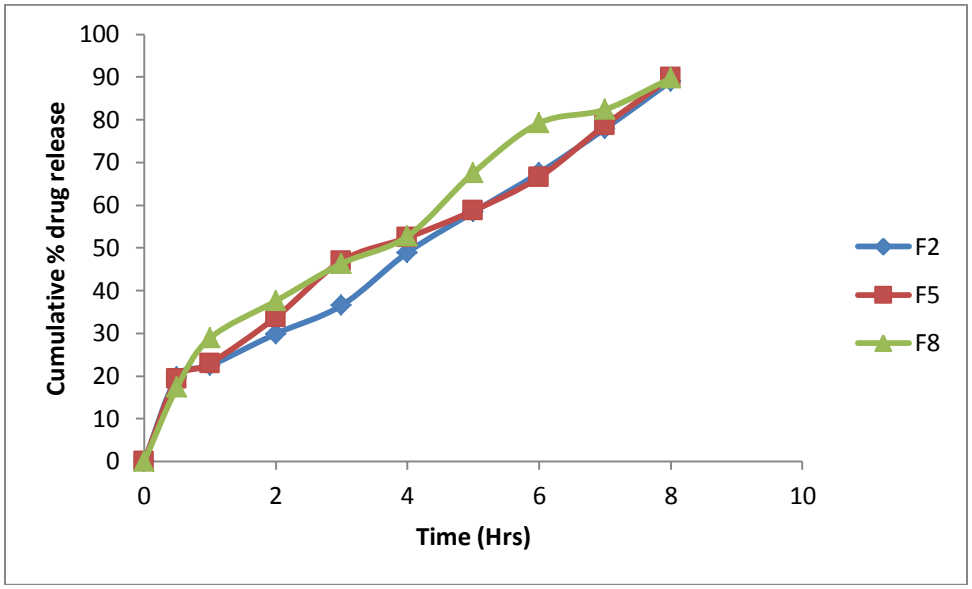
The swelling studies were performed for the formulations which were shown desired drug release. Swelling behavior of a buccal system was essential for uniform and prolonged release of drug and proper bioadhesion. The swelling index values for the formulations F2, F5, F8 were reported.

***Ex vivo* permeation studies through porcine buccal mucosa**

The aim of this study was to investigate the permeability of buccal mucosa to Captopril . It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the buccal absorption was shown in table & fig.

***Ex vivo* permeation studies of selected formulations through porcine buccal mucosa**

Time (hrs)	F2	F5	F8
0	0	0	0
0.5	19.73	19.28	17.42
1	22.42	22.93	28.89
2	29.90	33.78	37.59
3	36.56	46.97	46.35
4	48.93	52.43	52.75
5	58.40	58.74	67.58
6	67.58	66.56	79.23
7	77.92	78.73	82.42
8	89.06	89.90	89.73
Flux ($\mu g.hrs^{-1}cm^{-2}$)	499.43	469.32	434.38
Permeability coefficient (cm/hr)	0.4994	0.2218	0.1525



***Ex vivo* permeation studies graph of selected formulations through porcine buccal mucosa**

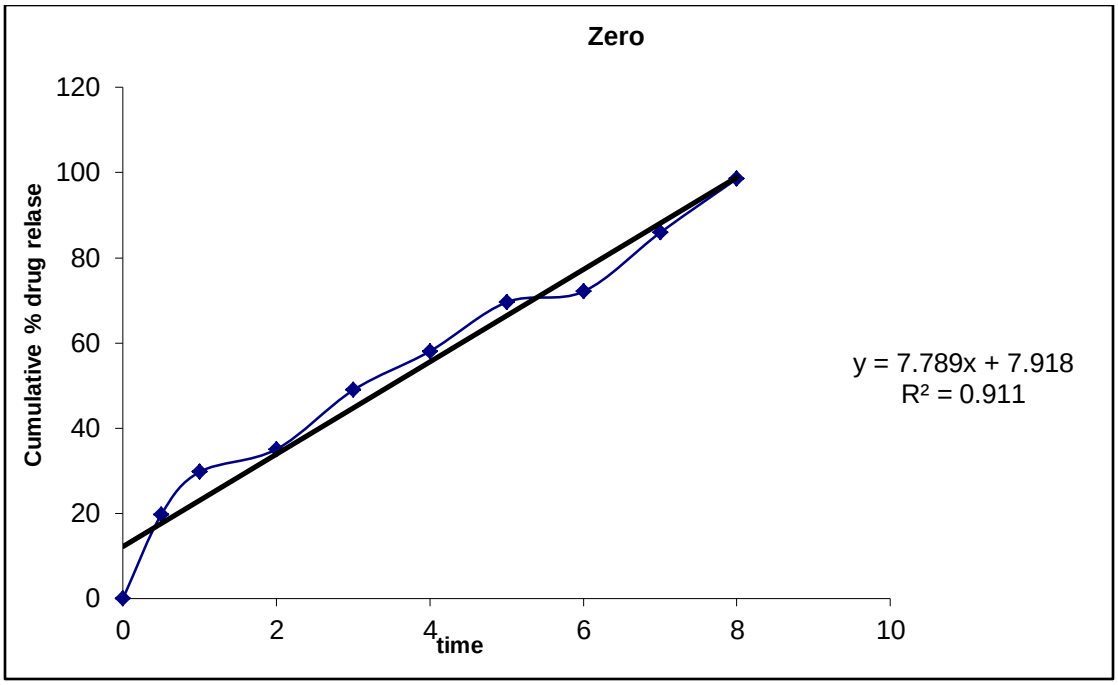
From the Table it was evident that selected formulations were showing good flux and permeability coefficient values. Among the selected formulations F2 formulation was showing maximum flux value of 499.43 ($\mu g.hrs^{-1}cm^{-2}$) and permeability coefficient value was 0.4994 (cm/hrs).

8. Release kinetics

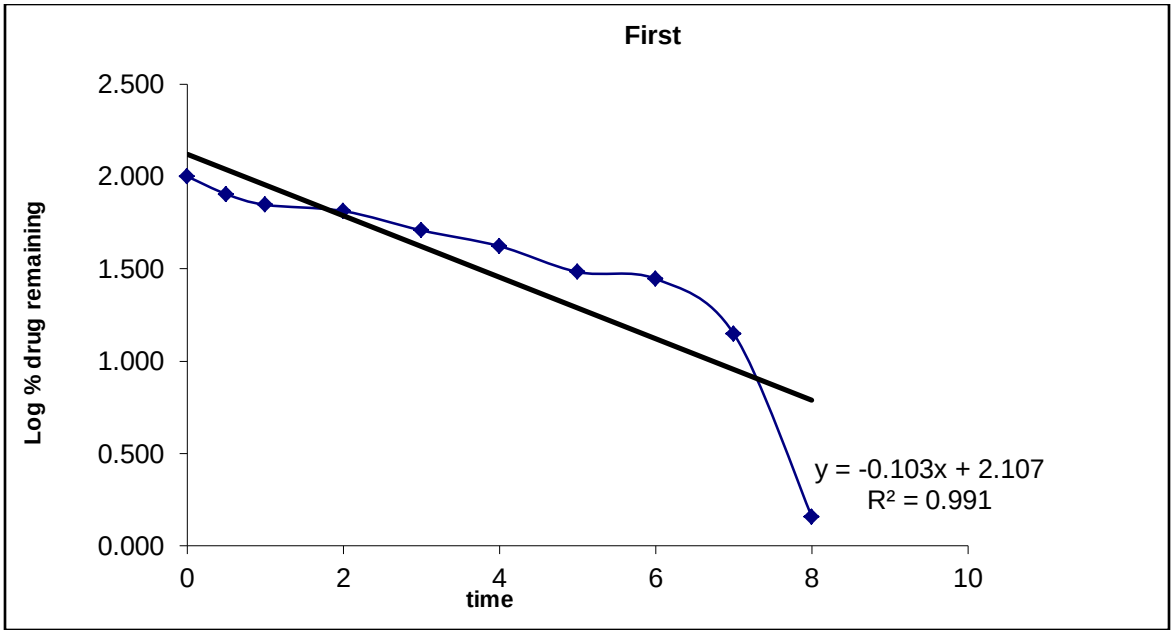
Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Captopril release from buccal tablets. The data was fitted into various kinetic models such as zero, first order kinetics, higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Release kinetics and correlation coefficients (R^2)

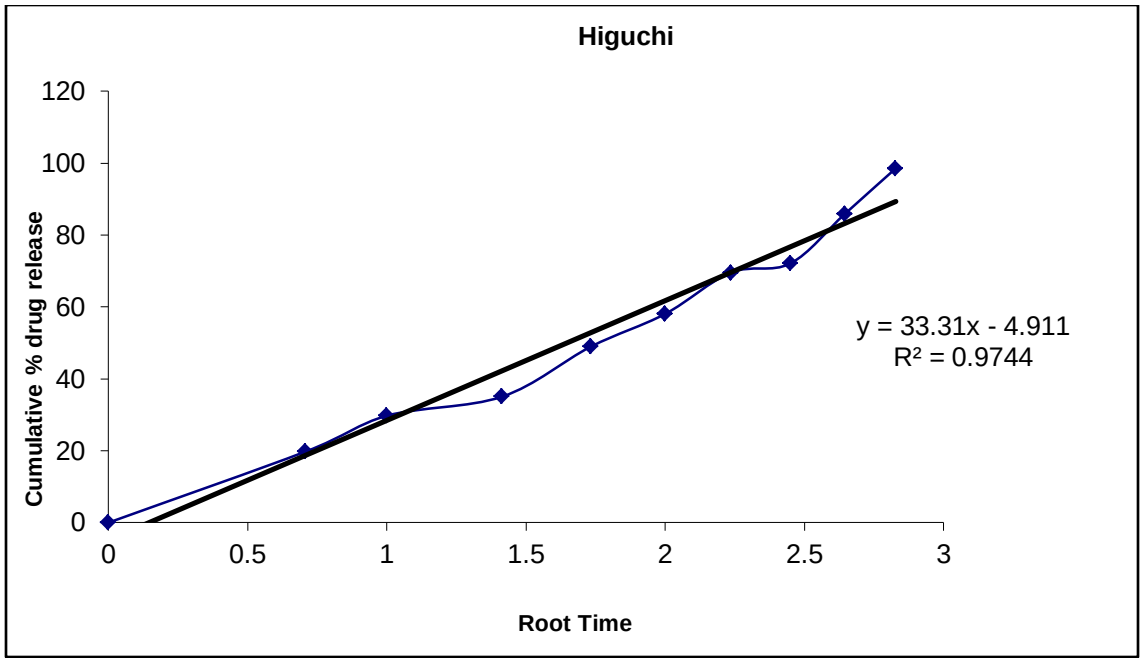
CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
19.73	0.5	0.707	1.295	-0.301	1.905
29.73	1	1.000	1.473	0.000	1.847
35.04	2	1.414	1.545	0.301	1.813
48.92	3	1.732	1.689	0.477	1.708
58.06	4	2.000	1.764	0.602	1.623
69.57	5	2.236	1.842	0.699	1.483
72.08	6	2.449	1.858	0.778	1.446
85.9	7	2.646	1.934	0.845	1.149
98.56	8	2.828	1.994	0.903	0.158



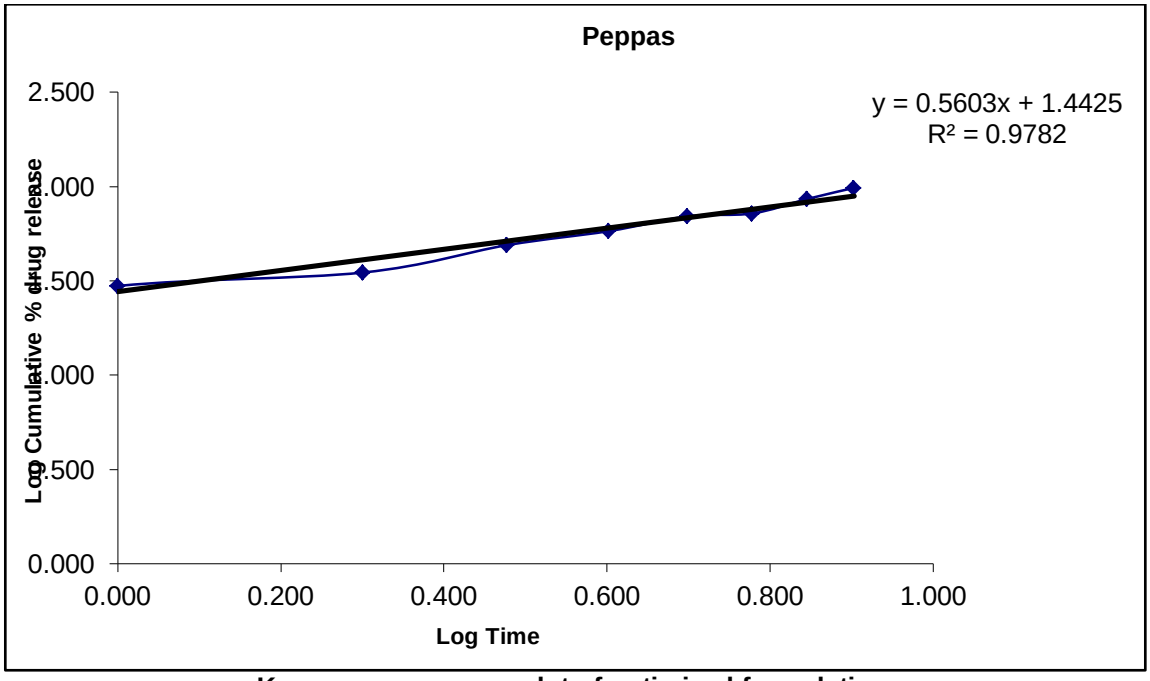
Zero order plot of optimized formulation



First order plot of optimized formulation



Higuchi plot of optimized formulation



Koresmeyer-peppas plot of optimized formulation

Based on the all studies F2 formulation was found to be better when compared with all other formulations. F2 formulation has shown more residence time when compared with other formulations. F2 formulation has shown good moisture absorption. The surface pH of the F2 formulations was found to be 6.18 and the pH was near to the neutral. These results suggested that the polymeric blend identified was suitable

for oral application and formulations were not irritant to the buccal mucosa. Peak detachment force (N) and work of adhesion were calculated and they were found to be good for the formulation F2. Swelling index value was also found to be good for this formualion. F2 formulation was showing maximum flux value, permeability coefficient value i.e.,499.43 ($\mu g.hrs^{-1}cm^{-2}$), 0.494 (cm/hrs) respectively. This formulation was following First order mechanism with regression value of 0.991.

CONCLUSION

Development of bio adhesive buccal drug delivery of Captopril tablets is one of the alternative routes of administration to avoid first pass hepatic metabolism effect and provide prolonged sustained release of drug.

Buccal tablets of Captopril were prepared by direct compression method using various bio adhesive polymers like Acritamer 940, Manugel, Hypromellose K100M in different ratios.

The formulated buccal tablets were evaluated for different parameters such as drug excipient compatibility studies, weight variation, thickness, hardness, content uniformity, *In vitro* drug release, surface pH, swelling index, *ex vivo* residence time, moisture absorbtion studies, *ex vivo* drug solution and tablets permeation through porcine buccal mucosa. *In vitro* drug release studies performed in phosphate buffer pH 6.8 for 8 hrs in standard dissolution apparatus the data was subjected to zero order, first order, Zero and First diffusion models.

The following conclusions could be drawn from the results of various experiments

- The feasibility of delivering Captopril was investigated by conducting *ex vivo* permeation studies using freshly prepared porcine buccal mucosal membrane.
- FTIR studies concluded that there was no interaction between drug and excipients.
- The physio-chemical properties of all the formulations prepared with different polymers like Acritamer 940, Manugel, Hypromellose K100M were shown to be within limits.
- Properties and from the results, it was concluded that the *in vitro* drug release, moisture absorption studies, surface pH, *ex vivo* residence time, swelling studies and *ex vivo* permeation studies of the optimized formulations is suitable for buccal delivery.
- *In-vitro* drug release studies demonstrated the suitability of developed formulations for the release of Captopril.

- Finally, suitably formulations were selected and *ex-vivo* permeation studies were conducted by using freshly prepared porcine buccal mucosal membrane. Satisfactory drug release rates and final percentage of drug release could be obtained from the selected formulation.

- The present study concludes that buccal delivery of Captopril tablets can be a good way to bypass the first metabolism and to prolong duration of action of drug by reducing the frequency of dosing of Captopril. Present study concludes that buccal drug delivery system may be a suitable method for Captopril administration. The optimized formulation was found to be F2 formulation.

REFERENCES

1. K.Naga Raju, S.Velmurugan, B.Deepika, Sundar Vinushitha, Formulation and In-vitro Evaluation of Buccal Tablets of Metoprolol Tartrate,International Journal of Pharmacy and Pharmaceutical Sciences.3(2);239-246:2011.
2. M.S.El-Samaligy, S.A.Yahia, E.B.Basalious, Formulation and Evaluation of Diclofenac sodium buccoadhesive discs, International Journal of Pharmaceutics.286;27-39:2004.
3. Silvia Rossi, Givseppina Sandri, Carla M.Caramella,Buccal drug delivery Today: Technologies, Drug Delivery or formulation and nanotechnology.2(1);59-65:2005.
4. Prasad B Kadam, Remeth J Dias, Kailas K Mali, Vijay D Havaldar, Niranjan S Mahajan, Formulation and Evaluation of buccoadhesive tablets of Atenolol, J Pharm Res.1(2);193-199:2008.
5. Noha Adel Nafee, Fatma Ahmed Ismail, Nabila A Boraie, Mucoadhesive Delivery Systems I, Evaluation of Mucoadhesive Polymers for Buccal Tablet Formulation, Drug Dev Ind Pharm.30(9);985-993:2004.

6. M.S.El Samaligy, N.N.Afifi, E.A. Mahmoud, Increasing Bioavailability of silymarin using a buccal liposomal delivery system: Preparation and Experimental design investigation, International Journal of Pharmaceutics.308;140-148:2006.
7. Choy Fun Wong, Kah Hey Yuen, Kok Khiang Peh., Formulation and Evaluation of controlled release Eudragit buccal patches, International Journal of pharmaceutics.178;11-22:1999.
8. G.Ikinci, S.Senel, C.G.Wilson, Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation, International Journal of Pharmaceutics.27;173-198:2004.
9. N Lagoth, H Kahibacher, G Scoffmann,I Schmerold, M Schuh, Sonja franz, Peter Kurka, Andreas Bernkop-Schnurch, Thiolated Chitosans: Design and In-vivo Evaluation of a Mucoadhesive Buccal Peptide Drug Delivery Systems,Pharmaceutical Research. 23(3);573-579:2006.
10. Calum R Park, Dale L.Munday, Development and Evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy, International Journal of Pharmaceutics.237;215-226:2002.
11. Yajaman Sudhakar, Ketousetuo kuotsu, A.K.Bandyopadhyay,Buccal bioadhesive drug delivery-A promising option for orally less efficient drugs, Journal of Controlled Release.114;15-40:2006.
12. Han-Gon Choi, Chong-Kook Kim, Development of omeprazole buccal adhesive tablet with stability enhancement in human saliva. Journal of Controlled Release.68;397-404:2006.
13. Gazzi Shaker, Chegonda K.Kumar, Chandra Sekhara Rao Gonugunta,Formulation and Evaluation of Bioadhesive Buccal Drug Delivery of Tizanidine Hydrochloride Tablets, AAPS PharmSci Tech.10(2);530-539:2009.
14. Noha A Nafee, Fatma A Ismail, Mucoadhesive buccal patches of miconazole nitrate: in-vitro/ in-vivo performance and effect of aging,International Journal of Pharmaceutics.264;1-14:2003.
15. Vamshi Vishnu Yamsani,Ramesh Gannu, Chandrasekhar Kolli,M.E.Bhanoji Rao and Madhusudhan Rao Y.Development and in-vitro evaluation of buccoadhesive carvedilol tablets,Acta Pharm.57;185-197:2007.
16. Nishan N. Bobade, Sandeep C. Atram, Vikrant P. Wankhade, Dr. S.D. Pande, Dr. K.K. Tapar.A Review on Buccal Drug Delivery System. International Journal of Pharmacy and Pharmaceutical Science Research.3(1);35-40:2012.
17. D.M. Brahmankar, S.B. Jaiswal, Biopharmaceutics and Pharmacokinetics- A Treatise., Vallabh Prakashan, New Delhi,1995: 2; 64-65.
18. D. Harris, J.R. Robinson, Drug delivery via mucous membrane of the oral cavity, J. Pharm. Sci,1992: 81(1); 1-10.
19. T.M.Pramodkumar, K.G. Desai, H.G. Shivakumar, Mechanism of buccal permeation enhancers, Ind. J. Pharm. Edu.,2002:36 (3) ;147-152.
20. V.H.K. Li, J.R. Robinson, V.H.L. Lee, Influence of drug properties and routes of drug administration on the design of sustained and controlled release system. In: Robinson J R and Lee VHL (Eds.), Controlled drug delivery: fundamental and applications, Marcel Dekker, Inc. New York, 2:1987; 42-43.
21. C. Vijayraghavan, T.K. Ravi, Buccal delivery of Nifedepine using novel natural mucoadhesive polymer as an excipients in buccal tablets, Indian Drugs, 2004 :41(3) ;143-148.
22. A. Gupta, S. Garg, R.K. Khar, Mucoadhesive buccal drug delivery system-A Review, Indian Drugs, 29 (13) : 586-593; 1992.
23. R. Khanna, S.P. Agarwal, A. Ahuja, Mucoadhesive buccal drug delivery -A potential to conventional therapy, Ind. J. Pharm. Sci., 60 (1):1-11;1998.
24. A.H. Shojaei, Buccal mucosa as a route for systemic drug delivery: a review. J. Pharm. Pharmaceut. Sci.1(1); 15-30:1998.
25. N. Verma, P. Chattopadhay, Polymeric platform for mucoadhesive buccal drug delivery system: a review, IJCPR, 3(3); 3-8:2011.
26. Hao J, Heng P W S, Buccal delivery systems, Drug development and industrial pharmacy.29(8);821-832:2003.
27. Duchene D,Touchard F and Peppas NA, Pharmaceutical and medical aspects of bioadhesive systems for drug administration. Drug Dev Ind Pharm.14;283- 318:2012
28. Gurny R, Meyer JM and Peppas NA. Bioadhesive intraoral release systems: design testing and analysis. Biomaterials, 5 ; 336-340:1984.

29. Barrer RM, Barrie JA and Wong PSL. The diffusion and solution of gases in highly cross linked copolymers. Polymer,9;609-627:1968.
30. Chen JL, Cyr G. Composition Producing adhesion through hydration, Adhesion in biological system, Academic Press, New York,1988:1;163-181.
31. Gurny R, Peppas NA. Semisolid dosage forms as buccal bioadhesives, Bioadhesive Drug Delivery System. Boca Ritan,CRC:1990;133-163.
32. Govind S.Asane, Yamsani Madhusudan Rao,A.V.Jithan Advances in Drug delivery, Vijayprakashan,2010:2;185-266.
33. Lehr cm, Poelme FCG, Junginger HE, Tukker JJ , An estimate of turnover time of intestinal mucus gel layer in the rats, In-situ loop. Int J Pharm.70;235-240:1991.
34. Allen A, Pain RH ,Robson TR. Model for the structure of the gastric mucus gel,Nature.264;88-89:1976.
35. Ahuja RP and Khar JA.Mucoadhesive drug delivery system, Drug Dev. Ind Pharma.23;489-515:1997.
36. Singh B, Ahuja N. Response surface optimization of drug delivery system. In: Jain NK, Progress in Controlled and Novel Drug Delivery Systems.CBS Publishers and Distributors; New Delhi, India: 2004:20;240.
37. N.R.Jimenez-Castellanos, H. Zia and C.T.Rhodes, Mucoadhesive drug Delivery Systems, Drug Dev. Ind. Pharm.19;143:1993.
38. Nagai.T, Machida.Y, Mucosal Adhesive Dosage Forms,Pharm.,Int.196-200:1985.
39. Devarajan, P.V. and Adani, M.H., In; Jain, N.K., Eds , Controlled and Novel Drug Delivery, CBS Publishers and Distributors;New Delhi,India:2004, 52-81.
40. Gandhi, R.B., Robinson, J.R, Oral cavity as a Site for Bioadhesive Drug Delivery, Adv. Drug Del. Rev.,13;43-74:1994.
41. Bodde, H.E., De Vries, M.E.and Junginger, H.E., Mucoadhesive Polymers for the Buccal Delivery of Peptides, Structure-Adhesiveness Relationships, J. Control. Rel.,13;225-231:1990.
42. Mikos AG and Peppas NA. Scaling concepts and molecular theories of adhesion of synthetic polymers to glycoprotenic networks, In Bioadhesive drug delivery systems,CRC Press,1990;25.
43. Mortazavi SA, Carpenter BG and Smart JD, Factors influencing gel strengthening at the mucoadhesive-mucous interface. J Pharm Pharmacol.46;86-91:1994.
44. Amit Gupta, RS Gaud ,S Ganga, Buccal adhesive dosage forms: Research to market, The Pharma student ,25:1-12;2012.
45. George Y WU, The pharmacology of prokinetic agents and their role in treatment of gastro intestinal disorders, IJGE .1(4) ;6-13 : 2003.
46. P. Naresh, S.Sujatha, Formulation and evaluation of buccal tablets of Tapentadol HCl, World Journal Of Pharmacy And Pharmaceutical Sciences, Volume 3, Issue 10, 1228-1243.
47. Neha Sharma, Saroj Jain, Satish Sardana, Buccoadhesive Drug Delivery System: A Review. Journal of advanced Pharmacy Education and Research.3(1);1-15:2013.
48. M.Muthukumaran, D.Dhachinamoorthi, K.B.Chandra shekhar, Mucoadhesive buccal drug delivery system -A Promising alternative for orally poor efficient drugs. American journal of pharmaTech research.3(3);1-22:2013.
49. Jasvir Singh and Pawan Deep, A Review Article On Mucoadhesive Buccal Drug Delivery System. International journal of pharmaceutical sciences and research.4(3);916-927:2013.
50. Shrisand SB, sarasija suresh, GG Keshashetti, PV Swamy, P Vijay prakash reddy. Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method. International journal of pharmaceutical investigation.2(1);34-41:2012.
51. Gowthamrajan, N Jawahar et al.,Development of buccal tablets of Curcumin using Anacardium occidentale gum carbohydrate polymers. 2012; 88(4): 1177-1183.
52. Gururaj s. Kulkarni , n.g raghavendra rao, Design development and evaluation of mucoadhesive buccal tablets of salbutamol with natural polymer. World Journal Of Pharmacy And Pharmaceutical Sciences.1(2);704-716:2012.
53. Dr. N.G Raghavendra Rao, Gururaj S. Kulkarni, Formulation and Evaluation of Mucoadhesive Buccal Bilayered Tablets of Salbutamol. International Journal of Drug Development & Research.4(4);375-384:2012.

54. Borgaonkar Pa, Virsen Tg, Hariprasanna Rc And Najmuddin M, Formulation And *In Vitro* Evaluation Of Buccal Tablets Of Loratadine For Effective Treatment Of Allergy. International Journal Of Research In Pharmacy And Chemistry.1(3);551-559:2011.
55. Chinna Reddy Palem, Ramesh Gannu, Shravan Kumar Yamsani, Vamshi Vishnu Yamsani, and Madhusudan Rao Yamsani.Development of bioadhesive buccal tablets for felodipine and pioglitazone in combined dosage form: in-vitro, ex-vivo and in-vivo characterization. Drug delivery .18(5);344-352:2011.
56. Saikat pande,Marina Koland,Jolly R Parikh,Ajay B.Solanki,Gaurav Negi,Rahul Trivedi. Buccoadhesive tablets of Losartan potassium: design and characterization. International journal of pharmaceutical & Biological archieves.1(2);150-154:2010.
57. Nisreen Hassan, R. K. Khar, Mushir Ali and Javed Ali. Development and Evaluation of Buccal Bioadhesive Tablet of an Anti-emetic Agent Ondansetron. AAPS PharmSci Tech.10(4);1085-1092:2009.
58. V.DeCaro,G.Giandalia,M.G.Siragusa,G.Campisi,L.I.Giannola.Galantamine delivery on buccal mucosa: Permeation enhancement and design of matrix tablets. Journal of bioequivalence & bioavailability.1(4);127-134:2009.
59. R.Manivannan,Balasubramaniam,DCPremanand,G.Sandeep,N.Rajkumar.Form--ulation and in-vitro characterization of mucoadhesive buccal tablets of Diltiazam hydrochloride.Research J.Pharm.and Tech.1(4);478-480:2008.
60. Emami J,Varshosaz J ,Saljoughian N. Development and evaluation of controlled release buccoadhesive verapamil hydrochloride tablets.DARU.16(2);60-69:2008.
61. Prasad b kadam, Ramesh j dias, kailas k mali, Vijay d havaldar, niranjan s mahajan.Formulation and evaluation of buccoadhesive tablets of atenolol. Journal Of Pharmacy Research.1(2);193-199:2008.
62. Launa Perioli, Valeria Ambrogi, Stefacno Giovagnoli, Paolo Blasi, Alessandra Manicini, Maurizio ricci, Carlo Rossi. Influence of Compression force on the behaviour of mucoadhesive buccal tablets. AAPS Pharmasci tech,9(1);274-281:2008.
63. Shrikant Charde ,Madri Mudgal,lajwinder Kumar,Ranendra saha.Development and evaluation of buccoadhesive controlled release tablets of Lercanidipine. AAPS Pharma Sci Tech.9(1);182-190:2008.
64. VamshivishnuY,RameshGannu,ChandrashekarKolli,M.E.Bhanojirao,Madhusudhan rao.Y.Development and invitro evaluation of buccoadhesive carvedilol tablets.Acta pharm.57;185-197:2007.
65. Nakhat PD, Kondawar AA, Babla IB.Studies on buccoadhesive tablets of Terbutaline sulphate. Indian J Pharm Sci.69;505-510:2007.
66. Y.Takahashi,C.Takeda,I.Seto,G.Kawano,Y.Machida. Formulation and evaluation of Lactoferrin bioadhesive tablets. International journal of Pharmaceutics.1(2);220-227:2007.
67. VishnuM.Patel,BhupendraG,Prajapati,MadhabhaiMPatel.Formulation,evaluation and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride.AAPS Pharma Sci Tech.8(1);147-154:2007.
68. C.Narendra, Srinath MS, Prakash rao B. Development of three layered buccal compact containing metaprolol tartarate by statistical optimization technique. Int J Pharm.304;102-114:2005.
69. Kashappa Goud H Desai, Pramod kumar TM. Preparation an devaluation of novel buccal adhesive system. AAPS Pharma Sci Tech 5(3);Article35:2004.
70. Jug.M, Becirevic-Lacan M. Influence of hydroxy propyl- β-cyclodextrin complex action on piroxicam release from buccoadhesive tablets. Eur.J.Pharm Sci.21;251-260:2004.
71. Ramboli B,Verreck G, Baert L, Massart D.L. Itraconazole formulation studies of the melt extrusion process with mixture design. Drug Dev.Ind.Pharm.29;641-652:2003.
72. J.Varshosaz ,Z.Dehghan. Development and characterization of buccoadhesive nifedipinetablets.EuropeanJournalofPharmaceuticsandBiopharmaceutics.54(2);135-141:2002.
73. Choi Han - Gon, Jung Jac -Hee, Yong Soon Chul, Rhee Chong- Dal, Lee Mi-Kyung, Han Jeon-hee, Park Kyung-Mi, Kim Chong -Kook. Formulation and in-vivo evaluation of omeprazole buccal adhesive tablets. Journal of Controlled Release.68(3);405-412:2000.
74. Dortune B,Ozer L, Uyanik N. Development and in-vitro evaluation of buccoadhesive pindolol tablet formulations. Drug Dev Ind Pharm.24;281-288:1998.

75. Senthil kumaran K, Mnajunath SY, Wamorkar VV. Development of a floating multiple unit controlled release system for mosapride. Asian J Pharm.4;163-167:2010.
76. https://en.wikipedia.org/wiki/Captopril
77. http://www.drugbank.ca/drugs/DB01197
78. Rang, Dale, J.M.Ritter & R.J.Flower ,Pharmacology. Elesevier Ltd,2007;6:394.
79. Good R.J, Polymer profile; 8(1): 1976.
80. Raymend, Hand Book of Excipients ,4; 111-115 & 346-349.
81. United States Pharmacopoeia, NF 23 several individual carbomer monographs: section 4 and 9.
82. Leon Lachmann, Herbret A. Liberman ,The Theory and Practice of Industrial Pharmacy , 3 ;430-456.
83. Nihar Ranjan Pani, Lila Kanta Nath, Sujata Acharya, Compatibility studies of nateglinide with excipients in immediate release tablets. Acta Pharm. 61;237–247: 2011.
84. Santanu Mallik,Mahendra D. Kshirsagar,Vipin Saini, Studies on physical /chemical compatibility between synthetic and herbal drugs with various pharmaceutical excipients. Der Pharmacia Lettre.3 (5);173-178:2011.
85. The Indian Pharmacopoeia, Controller of Publications, Ministry of Health and Family Welfare, 1996, Vol. 1, 381-82.
86. Abolghasem Jouyban , Mohammad A.A. Fakhree , Ali Shayanfar. Solubility Prediction Methods for Drug/Drug Like Molecules. Recent Patents on Chemical Engineering, 1;220-231:2008.
87. Peppas NA. Analysis Of Fickian And Non-Fickian Drug Release From Polymers. Pharm.Acta.Helv. 60(4);110-111:1985.
88. Korsmeyer RW, Gurny R, Doelker E, Peppas NA. Mechanism Of Solute Release FromPorous Hydrophilic Polymers. Int. J. Pharm. 15;25-35:1983.
89. Hixon AW, Crowell JH. Dependence Of Reaction Velocity Upon Surface And Agitation,I-Theoretical Consideration. Ind. Eng. Chem. 23;923-931:1931.