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FORMULATION AND INVITRO EVALUATION OF BIOADHESIVE BILAYERED BUCCAL TABLETS OF ENALAPRIL MALEATE

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ABSTRACT

In the present study bilayer buccal tablets were formulated by using ethyl cellulose as backing membrane. From the foregoing investigation it may be conclude that the release rate of drug from the buccal tablets can be governed by the polymer and concentration of the polymer employed in the preparation of tablets. Regulated drug release in first order manner attained in the current study indicates that the hydrophilic matrix tablets of enalapril maleate was prepared using carbopol 934 and HPMC K100 can successfully be employed as a buccoadhesive controlled released during delivery system. The pre compression blend for all formulations was subjected to various evaluation parameters and the results were found to be within limits. The post compression parameters for all the formulations also found to be within limits. Slow, controlled and complete release of enalapril maleate over a period of 9 hours was obtained from matrix tablets formulated employing HPMC K 100 (F5 Formulation) with 93.45 % drug release.

KEYWORDS: Bilayer buccal tablet, Enalapril maleate, HPMC, Carbopol.

INTRODUCTION

MUCOADHESIVE DOSAGE FORMS: The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration

and hence can be used for targeting a drug to a particular region of the body including the buccal mucosa, gastrointestinal tract, the urogential tract, the airways, the ear, nose and eye. These represent potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system may includes

- Buccal delivery system
- Gastrointestinal delivery system
- Nasal delivery system
- Ocular delivery system
- Vaginal delivery system
- Rectal delivery system

Buccal Delivery System

The unique environment of the oral cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect).

Delivery through Buccal Mucosa

Administration of a drug via the buccal mucosa (the lining of the cheek) to the systemic circulation is defined as buccal delivery. Despite, the buccal mucosa is significantly less permeable than the sublingual mucosa and usually not able to provide rapid drug absorption or good bioavailability; it is relatively more permeable than the skin and also offers other advantage over alternative delivery routes. The fact that the buccal mucosa is less permeable than sublingual floor makes it more desirable site for sustained drug delivery. Apart from avoiding enzymatic degradation and first pass metabolism, the non acidic conditions and lipophilic nature of the buccal tissue provide potential and promises for successful delivery of peptide and proteins. The various strategies Employed for Buccal Delivery.

- Bio adhesive buccal tablets
- Bio adhesive buccal gels
- Bio adhesive buccal patches

Bio adhesive Buccal Tablets

Bio adhesive tablets are immobilized drug delivery systems. They can be formulated into monolithic, partially coated or multi-layered matrices. Monolithic tablets are easy to manufacture by conventional techniques and provide for the possibility of loading large

amount of drug. In case of bi-layered tablets, drug can be incorporated in the adhesive layer, which comes in contact with the mucosal surface. This drug containing mucoadhesive layer is then protected from the oral cavity environment by a super upper inert layer (backing layer), which faces into the oral cavity.

Bio adhesive Buccal Patches

Adhesive patches can be designed either for unidirectional release into the oral mucosa or for bi-directional release into the oral cavity as well as into the oral mucosa. The adhesive part of the system can be used as drug carrier or as an adhesive for the retention of a drug loaded non-adhesive layer. In this respect, a peripheral adhesive ring could be casted. The use of an impermeable backing layer will maximize the drug concentration gradient and prolong adhesion because the system is protected from saliva.

Bio adhesive buccal Gels

Viscous adhesive gels have been designed for local therapy using polyacrylic acid and polymethacrylate as gel forming polymers. Gels are reported to prolong residence time on the oral mucosa to a significant level. This not only improves absorption but also allows for sustained release of the active principle.

BUCCOADHESIVE DRUG DELIVERY

The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption.

Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect).

Buccal route of administration: The medicament is placed between the cheek and the gum. The barrier to drug absorption from this route is the epithelium of oral mucosa. Passive diffusion is the major mechanism for absorption of drugs. Drugs with short biological half-lives, requiring a sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via bio adhesive buccal delivery systems.

Advantages of Buccal route

1. Rapid absorption and higher blood levels due to high vascularisation of the region and therefore particularly useful for administration of antinational drugs.
2. No first-pass hepatic metabolism.
3. No degradation of drugs such as that encountered in the GIT.
4. Presence of saliva facilitates both drug dissolution and its subsequent permeation by keeping the oral mucosa moist.
5. It is a safer method of drug administration, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity.

Disadvantages of buccal route

1. Accidental swallowing of the formulation by the patient.
2. Difficulty in speaking and drinking.

Limitations

1. Only limited amount of drug can be used in these systems (25-50 mg).
2. Drug must be non-irritant to the buccal mucosa.

Factors affecting systemic absorption of drugs through the buccal mucosa:

There are several factors affecting the absorption of drugs through the buccal mucosa.

a) Biological factors

- ❖ Mucosal surface area
- ❖ Thickness of oral epithelium
- ❖ Structure of oral mucosa
- ❖ pH of environment
- ❖ Salivary secretion

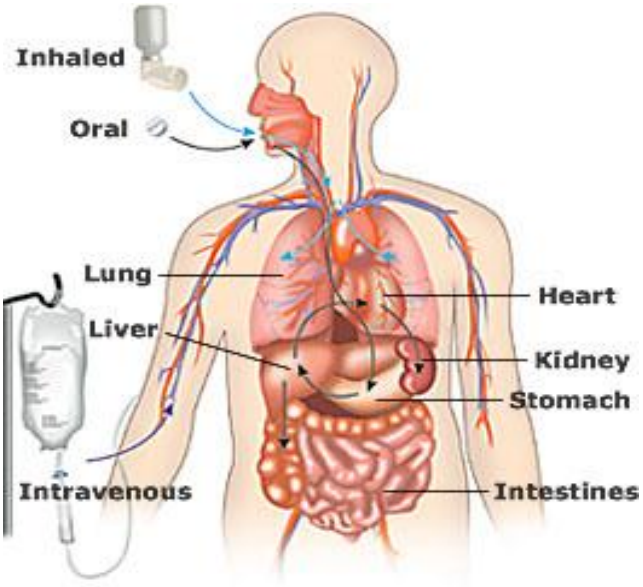
b) Drug factors

- ❖ Solubility
- ❖ Biological half life
- ❖ Drug stability
- ❖ Rate of absorption

c) Formulation factors

- ❖ Size and shape

- Texture
- Properties of excepients
- Release characteristics
- Mobility of backing layer



A drug's life in the body

Medicines taken by mouth (oral) pass through the liver before they are absorbed into the bloodstream. Other forms of drug administration (buccal, sublingual) bypass the liver, entering the blood directly.

Mechanism of Bio adhesion

Adhesion of a polymer to a tissue involves contribution from three main regions. The surface of the bio adhesive material, the first layer of the natural tissue and the interfacial regions between the two layers. Adhesion between a polymer and a tissue is primarily due to three types of interactions

1. Physical or mechanical bonds
2. Secondary chemical bonds
3. Primary bonds

Physical or Mechanical bond

It is formed when the polymer material is deposited on and include in the crevices of the tissue. This inclusion is necessary for the establishment intimate contact between the polymer and tissue, which is critical to the occurrence of a good bio adhesive bond.

Secondary chemical bonds

Including hydrogen bonding and Vander Waals forces can contribute to bio adhesion some functional groups that forms hydrogen bonds contributing to adhesion include hydroxyl, carboxyl, sulphate and amino groups on both the bio adhesive material and on the glycoprotein of the mucus.

Primary bonds

These are formed by chemically reacting the polymer and the substrate. This type of bonding is only desirable when the connection between the substrate and adhesive is to be permanent, such as in dental or orthopaedic applications.

ADVANTAGES OF BUCCOADHESIVE DRUG DELIVERY SYSTEM

1. It is robust and comparatively much less sensitive to irreversible irritation even on long-term treatment.
2. Its close resemblance to oral route seems well acceptable to the patients.
3. Improved patient compliance is anticipated due to the easy accessibility and administration as dosage forms.
4. It can be attached and removed without any pain or discomfort.
5. Absence of drug degradation in GIT and avoid hepatic first pass metabolism.
6. A prolonged residence time at the site of action or absorption.
7. Buccoadhesive also increases the intimacy and duration of contact between a drug-containing polymer and a buccal mucosa. The combined effects of the direct drug prolonged residence time allow for an increased bioavailability of the drug with smaller dosage and less frequent administration. Drugs that are absorbed through the buccal mucosal lining of the tissues can enter directly into the blood stream and prevent from enzymatic degradation in the GIT and avoids the first pass metabolism in the liver.

Bio adhesive polymers

Bio adhesive polymers are classified into two main categories.

1. Hydrophilic polymers that are water soluble
2. Water insoluble polymers that are swellable networks joined by cross-linking agents.

In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties. Poly vinyl pyrrolidine (PVP), methyl cellulose (MC), sodium carboxy methyl cellulose (SCMC), hydroxyl propyl cellulose (HPC) and other cellulose

derivatives. Hydrogels are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia i.e.

- Anionic group --- Carbopol, Polyacrylates and their cross linked modifications.
- Cationic group --- Chitosan and its derivatives
- Neutral group --- Eudragit-NE30D etc.

USE OF MUCOSAL ADHESIVE PREPARATIONS

- The extent of drug absorption is limited by the residence time of the drug at the absorption site.
- In ocular drug delivery, less than 2 min are available for drug absorption after instillation of a drug solution into the eye, since it is removed rapidly by solution drainage and hence the ability to extend contact time improves drug bioavailability.
- In oral drug delivery, the drug absorption is limited by the GI transit time of the dosage form.
- In most of the roots of drug administration ocular, nasal, buccal, respiratory, gastrointestinal, rectal and vaginal are coated with mucus layer; mucoadhesives are expected to increase the residence time.
- Mucoadhesives provide intimate contact between a dosage form and the absorbing tissue which may result in high drug concentration in local area.
- Mucoadhesion has high drug flux through the absorbing tissue; further the intimate contact may increase the total permeability of high molecular weight drugs such as peptides and proteins.
- Many drugs are absorbed only from the upper small intestine, localizing oral drug delivery systems in the stomach or in the duodenum would significantly improve the extent of drug absorption.

MATERIALS AND METHODS

NAME OF THE MATERIAL	SOURCE
Enalapril maleate	SURA LABS
Microcrystalline cellulose	Signet Chemical Corporation, Mumbai, India
Magnesium Stearate	Merck Specialties Pvt Ltd, Mumbai, India
Talc	Merck Specialties Pvt Ltd, Mumbai, India
Ethyl cellulose	Merck Specialties Pvt Ltd, Mumbai, India
Carbopol	Merck Specialties Pvt Ltd, Mumbai, India
HPMC K15M	Merck Specialties Pvt Ltd, Mumbai, India
HPMC K100M	Merck Specialties Pvt Ltd, Mumbai, India

List of Materials Used

NAME OF THE EQUIPMENT	MANUFACTURER
Weighing Balance	Sartourious
Tablet Compression Machine (Multistation)	Cemach Limited, India.
Hardness tester	Sisco, Mumbai, India.
Vernier callipers	Mitutoyo, Japan.
Roche Friabilator	Lab India, Mumbai, India
Dissolution Apparatus	Lab India, Mumbai, India
UV-Visible Spectrophotometer	Lab India, Mumbai, India
pH meter	Lab India, Mumbai, India
FT-IR Spectrophotometer	Per kin Elmer, United States of America.

List of Equipment's used

METHODOLOGY

Pre-formulation studies

The goals of the pre-formulation study are

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excepients.

Hence, pre-formulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

Estimation of Enalapril Maleate

A) Determination of λmax of Enalapril Maleate in phosphate buffer pH 6.8 solution.

Weighed amount of enalapril is dissolved in phosphate buffer pH 6.8 to obtain a 1000 mcg/ml solution. This solution was subjected to scanning between 200-400 nm and absorption maximum was determined. The effect of dilution on absorption maxima was studied by diluting the above solution to10 mcg/ml and scanned from 200-400 nm. From the spectra of drug max of Enalapril Maleate 216 nm was selected for the analysis. The calibration curve was prepared in the concentration range of 2-12 µg/ml at 216 nm. By using the calibration curve, the concentration of the sample solution can be determined.

B) Standard calibration curve of Enalapril Maleate in phosphate buffer pH 6.8 solution.

Standard Stock Solution

A stock solution containing 1mg/ml of pure drug was prepared by dissolving 100 mg of Enalapril in sufficient phosphate buffer pH 6.8 to produce 100 ml solution in a volumetric

flask.

Stock solution

From the standard stock solution, 5 ml of the stock solution was further diluted to 50 ml with phosphate buffer pH 6.8 into a 50 ml volumetric flask and diluted up to the mark with phosphate buffer pH 6.8. Aliquots of 0.2, 0.4, 0.6, 0.8, 1 and 1.2 ml of stock solution were pipette out into 10ml volumetric flasks. The volume was made up to the mark with phosphate buffer pH 6.8. These dilutions give 2, 4, 6, 8, 10 and 12 mcg/ml concentration of Enalapril Maleate respectively. The absorbance was measured in the UV-Visible spectrophotometer at 216 nm using distilled water as blank and graph of concentration versus absorbance was plotted. The absorbance data for standard calibration curves are given.

Drug – Excepients compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Pre-formulation parameters

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 characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

The angle of repose was calculated using the following formula.

Tan θ = h / r Tan θ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Angle of Repose values (as per USP)

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/cm3. 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. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully levelled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula.

Bulk Density = M / V_o

Where, M = weight of sample, V_o = apparent volume of powder

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 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula.

Tap = M / V

Where,

Tap= Tapped Density, M = Weight of sample, V= Tapped volume of powder

Measures of powder compressibility

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 measures of the relative importance of interparticulate 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 formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk density, Tap = Tapped density

CARR'S INDEX	PROPERTIES
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Carr's index value (as per USP)

METHOD OF PREPARATION OF MUCOADHESIVE TABLETS

Buccoadhesive bi-layered Tablets

Preparation

Direct compression method has been employed to prepare buccal tablets of enalapril maleate using HPMC K15, HPMC K100 and CARBOPOL 934 as polymers.

Procedure

All the ingredients including drug, polymer and excepients were weighed accurately according to the batch formula. All the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (230 mg) of each formulation was pre-compressed, on multi stationed tablet punching machine at a pressure of 0.5 ton for 30 s to form single layered flat-faced tablet of 9 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done

at a pressure of 3.5 tons for 30 s to get bilayer tablet. Compositions of the designed bi-layer tablets are given.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
ENALAPRIL MALEATE	20	20	20	20	20	20	20	20	20
HPMC K15	20	30	40	-	-	-	-	-	-
HPMC K100	-	-	-	20	30	40	-	-	-
CARBOPOL 934				-	-	-	20	30	40
Talc	3	3	3	3	3	3	3	3	3
MAGNESIUM STEARATE	3	3	3	3	3	3	3	3	3
MCC pH 102	QS	QS	QS	QS	QS	QS	QS	QS	QS
ETHYL CELLULOSE	50	50	50	50	50	50	50	50	50
TOTAL	280	280	280	280	280	280	280	280	280

Composition of enalapril maleate bi-layer buccal tablets

CHARACTERIZATION OF BUCCAL TABLETS OF ENALAPRIL MALEATE

Evaluation of muco adhesive buccal tablets of Enalapril Maleate

1) Hardness test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

2) Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge.

3) Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablet was determined by using Roche Friabilator as per IP procedure of friability. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$F = (W_{inital} – W_{final}) * 100 / W_{initial}$

% Friability of tablets less than 1% is considered acceptable.

4) Uniformity of weight

The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

5) Uniformity of drug content

Five tablets were powdered in a glass mortar and the powder equivalent to 50 mg of drug was placed in a stoppered 100 ml conical flask. The drug was extracted with 40 ml distilled water with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 1 hour. Then heated on water bath with occasional shaking for 30 minutes and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more distilled water through filter, further appropriate dilution were made and absorbance was measured at 220 nm against blank (distilled water).

6) Swelling Index

The swelling index of the buccal tablet was evaluated in phosphate buffer pH 6.8 The initial weight of the tablet was determined($W_{1)}$and then tablet was placed in 6 ml phosphate buffer pH 6.8 in a petridish and then was incubated at 37 ^{o} C. The tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h) blotted with filter paper and reweighed (W_2). The swelling index is calculated by the formula:

Swelling index = 100 (W_2-W_1) / W_1

Where, W1 = Initial weight of the tablet, W2 = Final weight of tablet.

7) In vitro drug release study

The study was carried out in USP XXIII tablet dissolution test apparatus-II Labindia, Mumbai, India, employing paddle stirrer at 50 rpm and 900 ml of phosphate buffer pH 6.8 as dissolution medium maintained at 37 0.5^{0}C. The tablet was supposed to release drug from one side only hence a one side of tablet was fixed to glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. At different time interval 5 ml of sample was withdrawn and replaced with fresh medium. The samples were filtered through 0.25 μm

membrane filter paper and analyzed for enalapril maleate after appropriate dilution at 216 nm using Lab India, Mumbai, India UV-Visible spectrophotometer.

8) Release Kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsemeyer equation.

Zero Order Release Kinetics.

It defines a linear relationship between the fraction of drug released versus time.

$Q = k_o t$

(Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant)

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is.

$In (1-Q) = - K_1 t$

(Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant)

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi's equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time**.**

$Q=K_2t^{½}$

Where, K2 is the release rate constant.

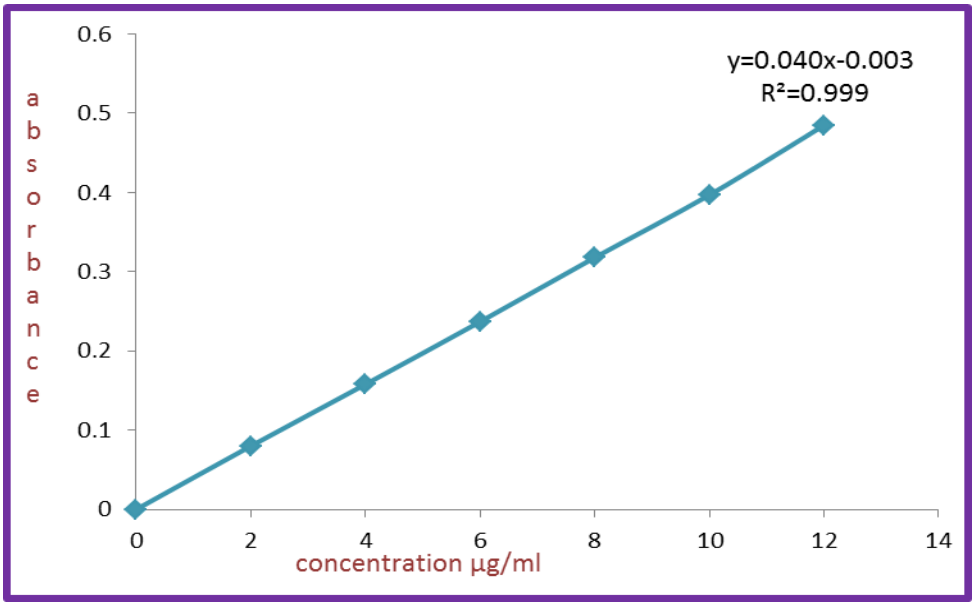
A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent

RESULTS AND DISCUSSION

The main aim of this work was to develop buccoadhesive bilayered tablets to release the drug at buccal mucosal site in unidirectional pattern for extended period of time without wash out of drug by saliva. Carbopol 934, HPMC K15, HPMC K 100 was selected as buccoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness, while ethyl cellulose, being hydrophobic, used as a backing material. Ethyl cellulose has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility.

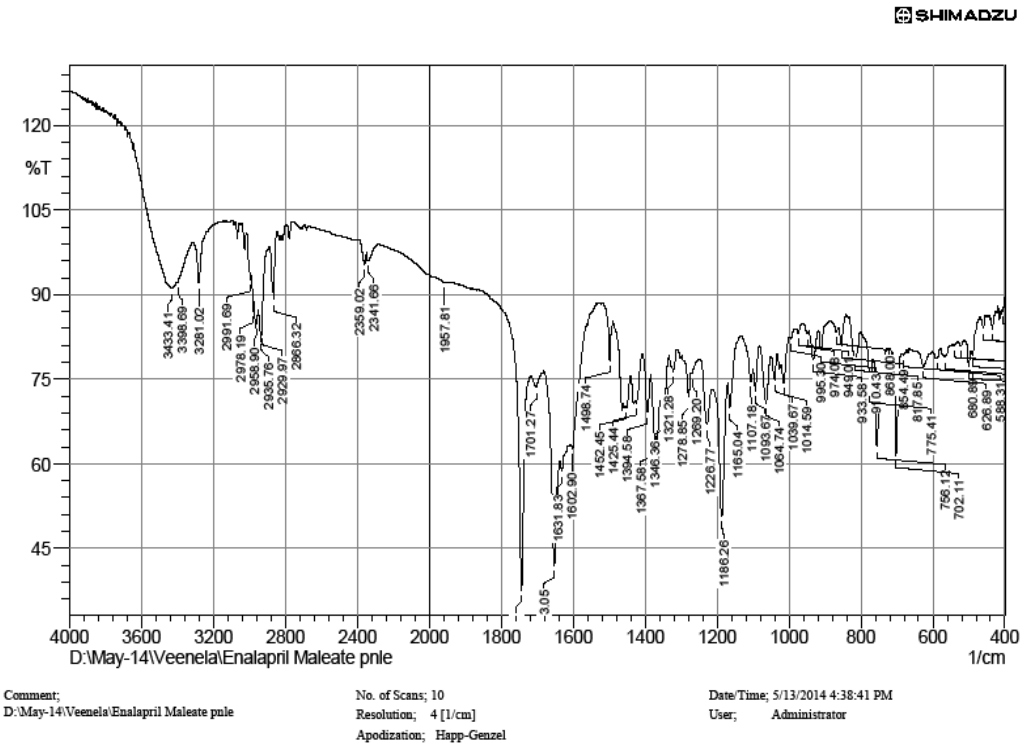
STANDARD CALIBRATION GRAPH OF ENALAPRIL MALEATE

Concentration (mcg/ml)	Absorbance* (mean ± SD)
2	0.08
4	0.158
6	0.237
8	0.318
10	0.397
12	0.485

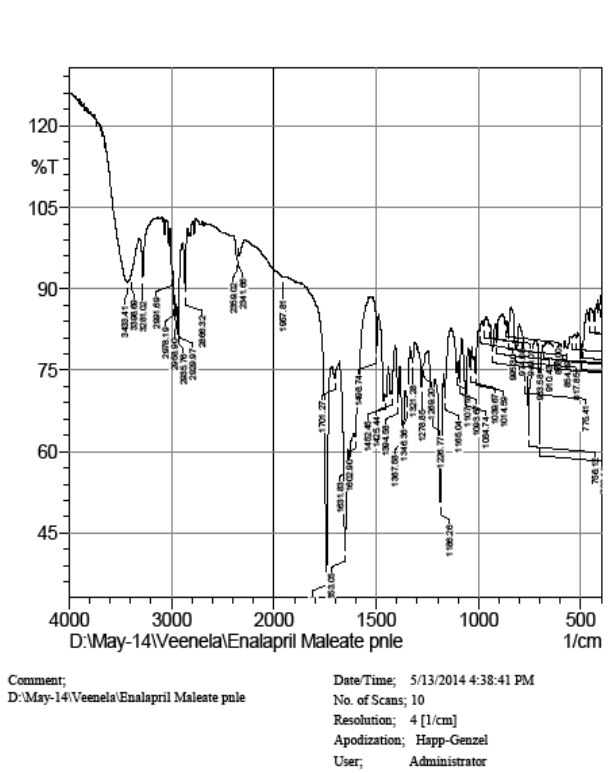


Calibration curve of Enalapril maleate

DRUG-EXCIPIENT COMPATIBILITY STUDIES



FTIR spectrum of pur drug



	Peak	Intensity	Corr. Inte	Base (H)	Base (L)	Area	Corr. Are
1	405.06	86.616	1.467	408.92	399.28	0.516	0.022
2	434	83.955	2.314	437.86	426.28	0.788	0.064
3	459.07	84.029	2.242	468.72	455.22	0.934	0.064
4	489.94	79.35	1.584	493.79	470.65	1.87	0.05
5	499.58	77.215	3.222	509.22	495.72	1.353	0.097
6	522.73	80.938	0.786	528.51	516.94	1.043	0.029
7	540.09	80.97	0.394	545.87	530.44	1.387	0.012
8	567.09	78.952	1.758	578.66	553.59	2.47	0.142
9	588.31	78.823	1.435	601.81	580.59	2.129	0.097
10	626.89	77.377	2.343	642.32	609.53	3.427	0.197
11	680.89	79.351	0.389	684.75	673.18	1.142	0.014
12	702.11	61.426	18.462	717.54	686.68	3.939	0.925
13	756.12	63.087	14.93	761.91	727.19	4.548	1.002
14	775.41	72.943	6.208	800.49	769.62	3.07	0.217
15	817.85	76.706	6.063	831.35	802.41	2.642	0.54
16	854.49	80.952	4.056	862.21	842.92	1.49	0.164
17	868	83.358	0.924	883.43	864.14	1.435	0.033
18	910.43	80.161	3.604	916.22	885.36	2.39	0.129
19	933.58	78.516	4.941	943.22	918.15	2.293	0.329
20	949.01	83.098	0.761	960.58	945.15	1.186	0.027
21	974.08	83.171	1.055	979.87	962.51	1.304	0.03
22	995.3	82.187	0.408	997.23	981.8	1.226	0.008
23	1014.59	74.406	4.792	1022.31	999.16	2.448	0.234
24	1039.67	74.981	4.311	1049.31	1033.88	1.739	0.183
25	1064.74	70.683	9.207	1082.1	1051.24	3.741	0.74
26	1093.67	72.885	5.353	1099.46	1084.03	1.794	0.211
27	1107.18	74.638	2.966	1134.18	1101.39	3.323	0.108
28	1165.04	69.923	5.742	1170.83	1136.11	3.87	0.311
29	1186.26	50.701	22.868	1211.34	1172.76	7.446	2.293
30	1226.77	66.996	8.317	1247.99	1213.27	4.934	0.742
31	1269.2	75.957	0.442	1271.13	1249.91	2.337	0.008
32	1278.85	71.941	4.927	1290.42	1273.06	2.167	0.206
33	1321.28	76.42	3.301	1332.86	1309.71	2.472	0.2
34	1346.36	68.334	6.93	1357.93	1334.78	3.223	0.397
35	1367.58	63.629	8.525	1383.01	1359.86	4.006	0.791
36	1394.58	69.148	8.322	1406.15	1384.94	2.833	0.478
37	1425.44	70.726	1.157	1427.37	1408.08	2.399	0.079
38	1452.45	70.03	2.089	1458.23	1440.87	2.474	0.13
39	1498.74	78.366	7.952	1518.03	1489.1	2.085	0.3
40	1602.9	62.758	2.049	1606.76	1537.32	7.352	0.092
41	1631.83	58.717	2.018	1635.69	1614.47	4.522	0.092

FTIR Spectrum of optimised formulation (F5)

PRECOMPRESSION EVALUATION PARAMETERS OF TABLETS

Formulation Code	Bulk density	Tapped density	Compressibility Index	Hausner's ratio	Angle of Repose
F1	0.49±0.07	0.57±0.01	16.21±0.06111	0.86±0.06	20
F2	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05	…..25
F3	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03	…..22
F4	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04	21
F5	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08	23
F6	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09	30
F7	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03	29
F8	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09	28
F9	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02	27

Micromeritic properties of powder blend

Formulations blend of all the formulations were passed the pre compression parameters like angle of repose, bulk density, tapped density and Hausners ratio.

Formulation code	Hardness (kg/cc)	Thickness (mm)	Weight variation(mg)	Friability (%)	Drug content (%)
F1	4.8±0.02	2.80±0.00	279.6±0.99	0.79±0.01	100.09±0.56
F2	4.3±0.05	2.83±0.06	278.8±0.99	0.67±0.01	102.73±0.46
F3	4.3±0.05	2.87±0.06	279.8±0.38	0.57±0.01	98.75±0.88
F4	5.7±0.06	2.86±0.06	280.7±0.99	0.55±0.00	99.70±0.34
F5	5.4±0.03	2.87±0.06	279.8±0.38	0.51±0.01	97.95±0.38
F6	5.0±0.02	2.90±0.00	280.1±0.99	0.87±0.03	98.75±0.88
F7	5.6±0.07	2.97±0.06	279.6±0.17	0.46±0.01	103.36±0.83
F8	5.3±0.05	3.01±0.01	281.0±0.40	0.72±0.01	101.09±4.00
F9	5.1±0.02	2.95±0.00	280.0±0.20	0.56±0.02	99.75±0.38

Evaluation Data of Enalapril Maleate Buccoadhesivetablets

The assayed drug content in various formulations varied between 98.64% and 100.26% (mean 99.68%). The average weight of the tablet was found to be between 281.4 mg and 283.2 mg (mean 280.2 mg), % friability range between 0.46 and 0.76(mean 0.43%) and thickness of the tablets for all the formulations was found to be between 2.80 mm and 3.00 mm with average of 2.90 mm.

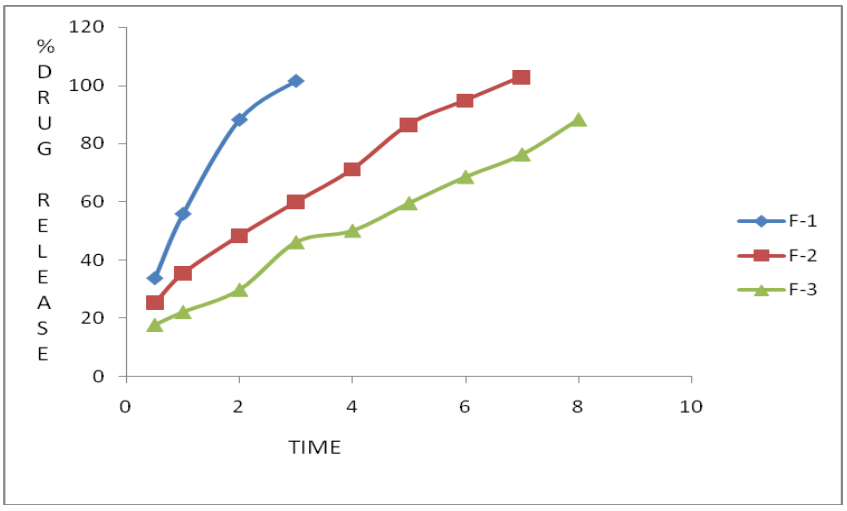
Buccoadhesive tablets containing Carbopol showed hardness in the range of 5.00 to 5.60 kg/cm^2 and it increased when used in combination with HPMC k100. The hardness of the tablets containing HPMC K15 was much lower, ranging from 4.30 to 4.8 kg/cm^2 and increased with increasing amounts of HPMC or Carbopol. The difference in the tablet strengths are reported not to affect the release of the drug from hydrophilic matrices. Drug is

released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet.

IN-VITRO DRUG RELEASE STUDIES

Time (h)	F-1	F-2	F-3
0.5	33.91±0.25	25.46±0.54	17.89±0.91
1	55.97±1.56	35.56±1.19	22.28±0.27
2	88.24±0.74	48.51±0.49	29.96±0.47
3	101.52±0.58	60.03±1.21	46.20±0.21
4		71.23±1.77	50.15±0.65
5		86.59±0.62	59.59±0.25
6		94.82±1.17	68.59±1.54
7		102.95±1.54	76.28±0.53
8		---------	88.24±0.11

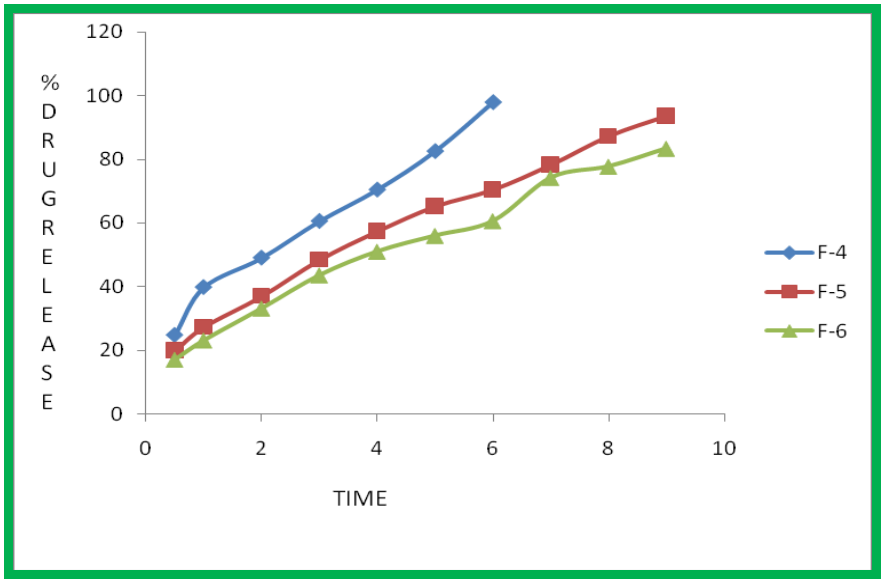
In vitro *release data of Enalapril Maleate mucoadhesive tablets (F1, F2 & F3)*



Invitro *dissolution graph of formulations F1-F3*

Time (h)	F-4	F-5	F-6
0.5	24.69±0.35	19.86±0.99	17.11±0.08
1	39.73±1.35	27.32±0.25	23.14±1.18
2	48.95±2.36	36.98±1.77	33.20±1.13
3	60.47±2.02	48.40±1.31	43.60±1.10
4	70.35±2.65	57.40±1.95	51.06±0.21
5	82.42±1.95	65.19±0.79	56.02±0.47
6	97.79±0.34	70.46±1.34	60.64±1.65
7	------	78.25±0.38	74.24±1.09
8	------	87.25±0.79	77.75±0.38
9	------	93.62±1.95	83.41±1.31

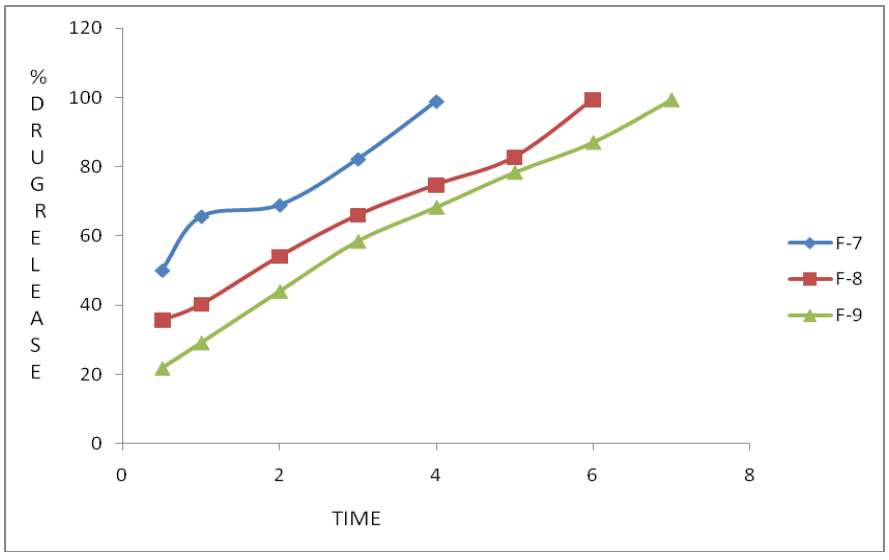
In vitro *release data of Enalapril Maleate mucoadhesive tablets containing HPMC K100 (F4, F5 & F6)*



Invitro *dissolution graph of formulations F4-F6*

Time (h)	**F-7**	**F-8**	**F-9**
0.5	50.04±0.26	35.56±0.32	21.84±0.44
1	65.63±0.29	40.17±0.18	29.19±0.38
2	68.92±0.72	54.00±0.16	44.02±0.24
3	82.20±2.38	65.96±2.22	58.51±1.59
4	98.89±3.45	74.74±0.33	68.37±0.55
5	------	82.75±0.18	78.36±0.48
6	------	99.43±1.98	87.03±0.82
7	------	------	99.32±1.98

In vitro *release data of Enalapril Maleate containing Carbopol 934 (F7, F8 & F9)*



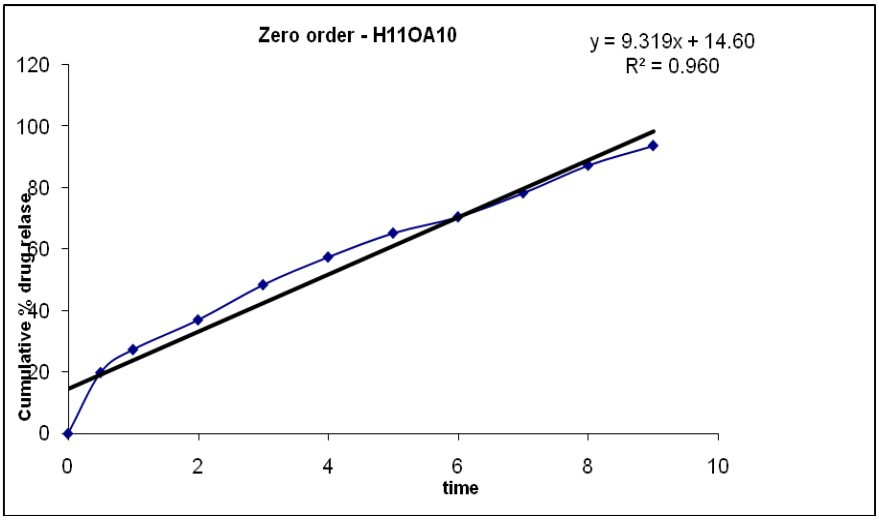
In Vitro *dissolution graphs of formulation (F7, F8 & F9)*

In vitro drug release studies revealed that the release of Enalapril Maleate from different formulations varies with characteristics and composition of matrix forming polymers. The release rate of Enalapril Maleate decreased with increasing concentrations of the polymers. The Release rate of the tablets decreased from F1 to F3 when tablets are prepared with HPMC K15 in 1:1, 1:1.5 and 1:2 ratios respectively.

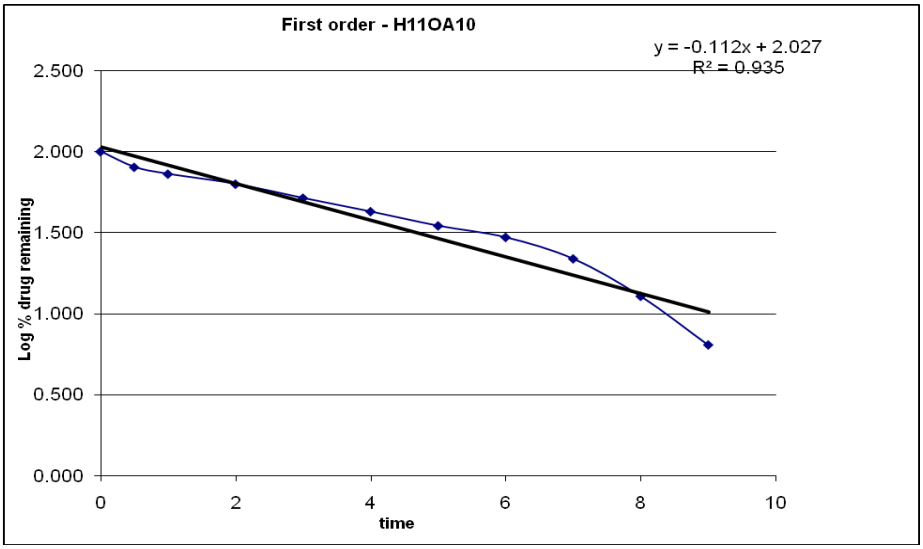
The release rates were similarly studied with increasing concentrations of HPMC K100 and the release rate decreased with increasing concentrations from F4 to F6 respectively. Similarly release rates were studied with Carbopol 934 in increasing concentrations i.e. 1:1, 1:1.5, and 1:2 and release rate was found to be decreased with all the three polymers when used in the ratio 1:2.

Among all the formulations Formulation F5 containing HPMC K100 M in the concentration of 1:1.5 was found to be good with better drug release i.e., 93.62% in 9 hours.

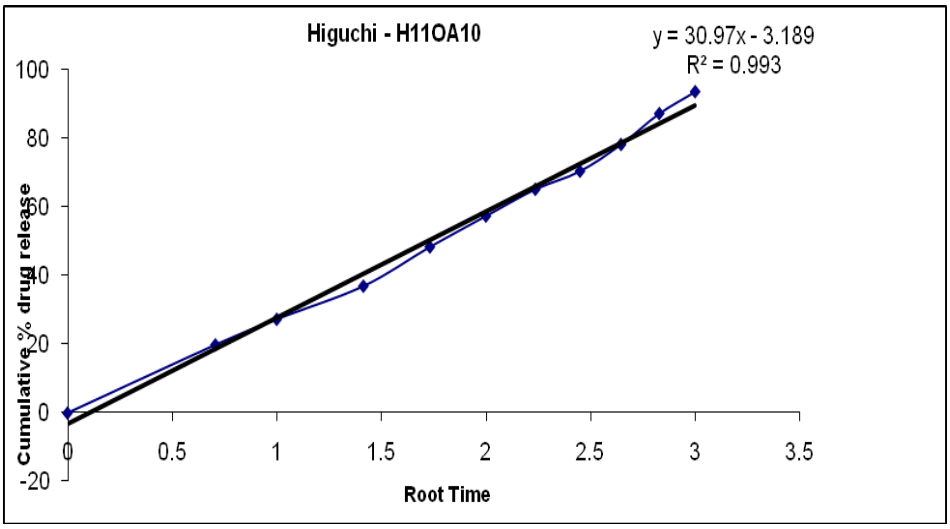
Several kinetic models describing drug release from immediate and modified released dosage forms. The model that best fits the release data was evaluated by correlation coefficient (r). The correlation coefficient (r) value was used as criteria to choose the best model to describe the drug release from the buccoadhesive tablets. The 'r' values obtained for fitting the drug release data to first order, indicating that the drug release mechanism follows first order kinetics. From higuchi's equation, the high values of correlation coefficient 'r' indicating that the drug release mechanism from these tablets was diffusion controlled. The values of **'n'** in Peppas model indicated the drug release follows non-Fickian diffusion.



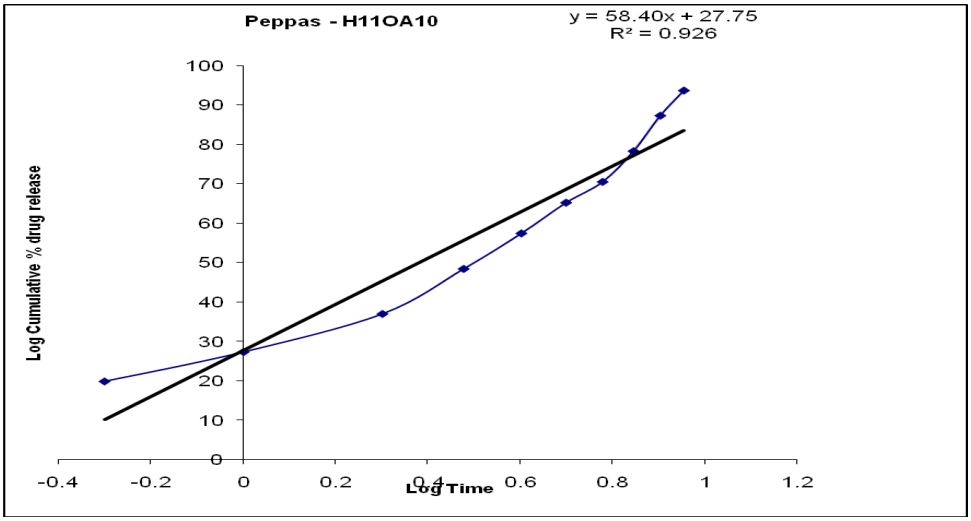
Zero order release kinetics graph for F5 formulation



First order release kinetics graph for F5 formulation



Higuchi release kinetics graph for F5 formulation



Korsmayer peppas release kinetics graph for F5 formulation

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F5	0.960	0.935	0.993	0.926

Regression analysis of the in vitro release data according to various release kinetic models

From the above results it is concluded that the drug release from the formulated bucco adhesive tablets of enalapril maleate followed Higuchi release kinetics and was diffusion controlled.

CONCLUSION

The present concludes that preparation of buccoadhesivebilayered tablets to release the drug at buccal mucosal site in unidirectional pattern for extended period of time without wash out of drug by saliva. Carbopol 934, HPMC K15, HPMC K 100 was selected as buccoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness, while ethyl cellulose, being hydrophobic, used as a backing material. Ethyl cellulose has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility slow, controlled and complete release of enalapril maleate over a period of 9 hours was obtained from matrix tablets formulated employing HPMC K 100 (F5 Formulation) with 93.45% drug release.

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