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Research Article

**DESIGN AND INVITRO EVALUATION OF ESOMEPRAZOLE
BUCCOADHESIVE TABLETS****V. Jayasankar Reddy*¹, K.Ramesh Reddy¹ and G.Sindhu**¹Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati, Andhra Pradesh, India.²Academic consultant, Division of Pharmacy, SV University, Tirupati, Andhra Pradesh.**Abstract:**

The present research was formulation and evaluation of Esomeprazole buccoadhesive tablets, Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract and depending on the particular drug, a better enzymatic flora for drug absorption. . Tablets were evaluated their compatibility studies by using FT-IR, micrometrics properties, post formulation characters such as hardness, thickness, friability, content uniformity, Ex vivo mucoadhesive strength and in-vitro dissolution studies.

Key Words: Esomeprazole, Trans mucosal, Buccoadhesive, Mucoadhesion.

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INTRODUCTION:

The sites of drug administration in the oral cavity include the floor of the mouth (sublingual), the inside of the cheeks (buccal) and the gums (gingival). In view of the systemic transmucosal drug delivery, the buccal mucosa is the preferred region as compared to the sublingual mucosa. One of the reasons is that buccal mucosa is less permeable and is thus not able to elicit a rapid onset of absorption and hence better suited for formulations that are intended for sustained release action. Further, the buccal mucosa being relatively immobile mucosa and readily accessible, it makes it more advantageous for retentive systems used for oral transmucosal drug delivery. Bioadhesion may be defined as the state in which two materials, at least one of which is biological in nature, are held together for extended periods of time by interfacial forces. In the pharmaceutical sciences, when the adhesive attachment is to mucus or a mucous membrane, the phenomenon is referred to as mucoadhesion. Over the years, mucoadhesive polymers were shown to be able to adhere to various other mucosal membranes. The capability to adhere to the mucus gel layer which covers epithelial tissues makes such polymers very useful excipients in drug delivery. Mucoadhesion is known to increase the intimacy and duration of contact between drug-containing polymer and a mucous surface. It is believed that the mucoadhesive nature of the device can increase the residence time of the drug in the body. The bioavailability of the drug is improved because of the combined effects of the direct drug absorption and the decrease in excretion rate. Increased residence time and adhesion may lead to lower API concentrations and lower administration frequency to achieve the desired therapeutic outcome.

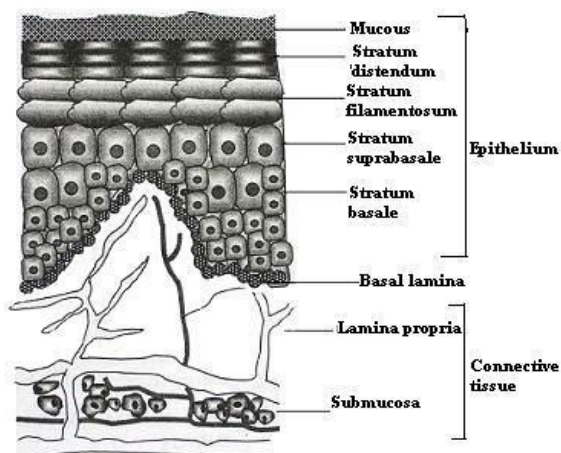


Fig1: Cross section view of buccal mucosa

MATERIALS AND METHOD:

The present investigation was carried out by using following materials Esomeprazole (Gift sample from Reddy's lab, Hyderabad), Carbopol 934 (Indian drugs, Hyderabad), Hydroxyl Propyl Methyl Cellulose (Indian drugs, Hyderabad), Sodium Carboxy Methyl Cellulose (Indian drugs, Hyderabad), Micro Crystalline Cellulose (Indian drugs, Hyderabad), Ethyl Cellulose (Indian drugs, Hyderabad), Magnesium stearate (Sd fine Chem.Ltd. Mumbai), Potassium di hydrogen phosphate (Sd fine Chem.Ltd. Mumbai), Di sodium hydrogen phosphate (Sd fine Chem.Ltd. Mumbai), Sodium hydroxide (Sd fine Chem.Ltd. Mumbai).

Drug – polymer compatibility studies by FTIR:

Drug polymer compatibility studies were performed by FTIR (Fourier Transform Infrared Spectroscopy). Infrared (IR) spectra were obtained using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1} . FTIR absorption spectra of pure drug and all the polymers used like HPMC, SCMC, CP, MCC and EC the combination of drug and polymers shows no significant interaction between drug and polymers.

Flow Properties

Before formulation of drug substances into a dosage form, it is essential that drug polymer should be chemically and physically characterized. Preformulation studies gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the manufacture of a dosage form.

Derived properties

Bulk Density

It was determined by pouring pre-sieved drug excipients blend into a graduated cylinder and measuring the volume and weight "as it is". It is generally expressed in g/mL and is given by,

$$D_b = M / V_o$$

Where, M is the mass of powder and V_o is the Bulk volume of the powder.

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipients blend, on mechanical tapping apparatus.

$$D_T = M / V_T$$

Where, M is the mass of powder and V_T is the tapped volume of the powder.

The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL.

Powder flow properties

Angle of repose

This is the maximum angle possible between the surface of the pile or powder and horizontal plane. Angle of repose was determined by using funnel method. The frictional forces in the loose powder can be measured by Angle of repose. The tangent of Angle of repose is equal to the coefficient friction between the particles.

$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose, h is the height in cm and r is the radius in cm.

Compressibility index

It is an important measure that can be obtained from the bulk and tapped densities. A material having values less than 20 to 30% is defined as the free flowing material. Based on the apparent bulk density and tapped density, the percentage compressibility of

the bulk drug was determined by using the following formula.

$$I = D_T - D_b / D_T \times 100$$

Where, I is the Compressibility index,

D_t is the tapped density of the powder, D_b is the bulk density of the powder.

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density

$$H = D_t / D_b$$

Where, H is the Hausner's ratio D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Construction of Calibration Curve:

The calibration curve of Esomeprazole was prepared by using phosphate buffer pH 6.8 and phosphate buffer pH 7.4 at 279 nm. The selection of two buffers (pH 6.8 and pH 7.4) is to mimic the buccal cavity pH and systemic pH respectively.

Table 1: Calibration curve data for Esomeprazole in phosphate buffer (pH 6.8)

Concentration ($\mu\text{g/ml}$)	Absorbance (279 nm)
4	0.11
8	0.223
12	0.314
16	0.447
20	0.507
24	0.593
28	0.697
32	0.799
36	0.874
40	0.989

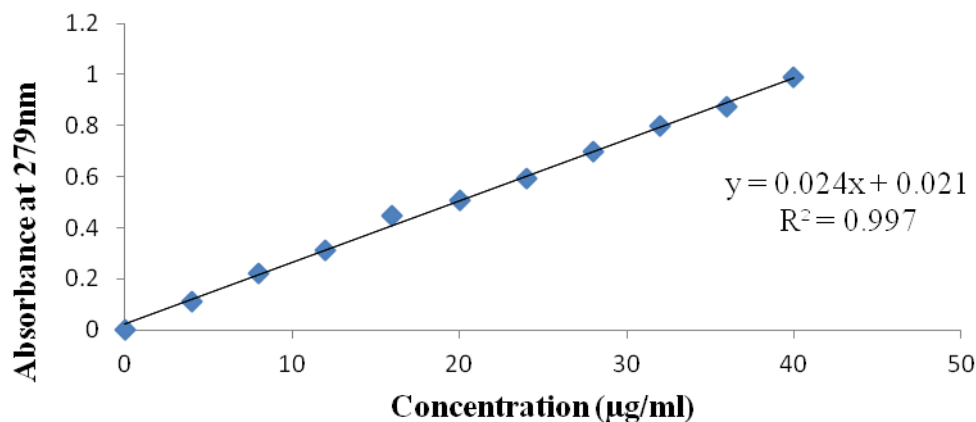
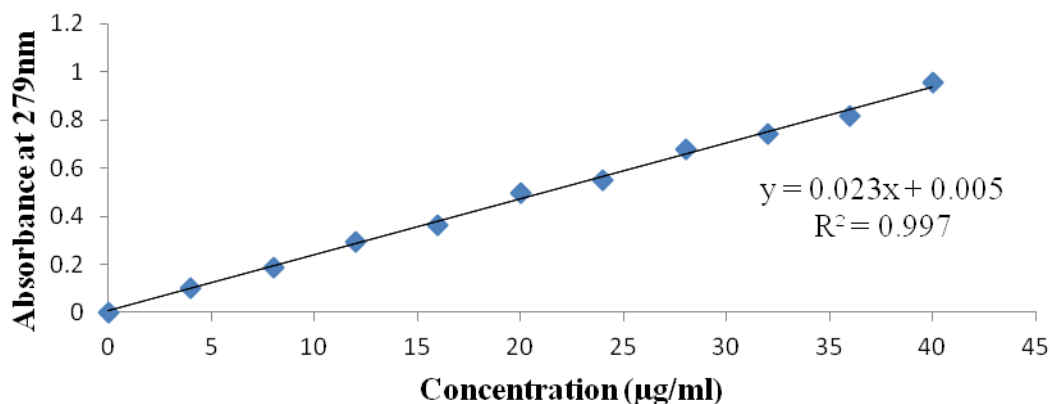


Fig 2: Calibration Curve of Esomeprazole in Phosphate Buffer pH 6.8

Table 2: Calibration curve data for Esomeprazole in phosphate buffer (pH 7.4)

Concentration ($\mu\text{g/ml}$)	Absorbance (279 nm)
4	0.101
8	0.189
12	0.291
16	0.365
20	0.497
24	0.549
28	0.676
32	0.741
36	0.815
40	0.955

**Fig 3: Calibration curve of Esomeprazole in phosphate buffer pH 7.4**

Preparation of Buccoadhesive Tablets of Esomeprazole

Buccal tablets containing Esomeprazole were prepared by direct compression method⁵⁶⁻⁵⁹. Various batches were prepared by changing the ratio of HPMC K 100, SCMC and Carbopol-934 to identify the most effective formulation. The drug and polymer mixture was prepared by homogeneously mixing the drug with HPMC K 100, SCMC, CP-934 (mucoadhesive polymers) and micro crystalline cellulose (binder) in a glass mortar for 15 minutes. Before direct compression, the powder were screened

through a 60 μm sieve and thoroughly blended. The blend was lubricated with magnesium stearate for 3-5 min. The mixture (150 mg) was then compressed using an 8 mm diameter die in a 9-station rotary punching machine (Chamunda pharma pvt Ltd, Ahmedabad, India). The upper punch was raised and the backing layer of EC (50mg) was placed on the above compact. The two layers were then compressed into a mucoadhesive tablet. Each tablet weighed 200 mg and the composition of each formulation was given in Table 3.

Table 3: Composition of Buccoadhesive Tablets of Esomeprazole

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	
Ingredients (mg)	Esomeprazole	25	25	25	25	25	25	25	25	25	25	25	
	HPMC K 100	85	-	-	25	45	65	-	-	-	25	45	65
	Carbopol 934	-	85	-	65	45	25	25	45	65	-	-	-
	SCMC	-	-	85	-	-	-	65	45	25	65	45	25
	MCC	48	48	48	48	48	48	48	48	48	48	48	48
	Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
	EC	50	50	50	50	50	50	50	50	50	50	50	50

Physico-Chemical Evaluation of Buccoadhesive Tablets

Thickness

The thickness of the each Tablet was measured by using vernier calliper and the average thickness was calculated.

Weight variation

$$\% \text{ Weight Variation} = \frac{\text{Average Weight} - \text{Individual Weight}}{\text{Average Weight}} \times 100$$

Hardness

The hardness of Tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm².

Friability

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

Drug Content

Drug content uniformity was determined as triplicate by dissolving the tablets in methanol and filtering with Whatman filter paper (0.45 μm, Whatman, Maidstone, UK). The filtrate was evaporated and the drug residue dissolved in 100 ml of phosphate buffer (pH 6.8). The 5 ml solution was then diluted with phosphate buffer up to 20 ml, filtered through Whatman filter paper and analyzed at 279 nm using a UV spectrophotometer.

Surface pH study

The surface pH of the buccal Tablets was determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The tablet was allowed to swell by keeping it in contact with 5 ml of phosphate buffer containing agar medium (pH 6.8±0.01) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the Tablet and allowing it to equilibrate for 1 min.

Swelling index

Tablets were weighed individually (designated as W1) and placed separately in petridish containing phosphate buffer pH 6.8. At regular intervals (0.5, 1, 2, 3, 4 h), samples were removed from the petridish and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (W2). The swelling index of each system was calculated using the following formula:

$$\text{Swelling Index (S.I)} = [(W2-W1)/W1] \times 100$$

Where, W1- initial weight of Tablet, W2- weight of disks at time t

Measurement of Bioadhesive Force

$$\text{Force of adhesion (N)} = (\text{Bioadhesive strength (g)} \times 9.8) / 1000$$

$$\text{Bond strength (N m}^{-2}\text{)} = \text{Force of adhesion} / \text{surface area.}$$

In-Vitro Drug Release Studies

The USP type II rotating paddle apparatus was used to study the drug release from the bilayer tablet. The dissolution medium consisted of 500 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5° C, with a rotation speed of 50 rpm. The backing layer of the buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, with appropriate dilutions with phosphate buffer pH 6.8 and were analyzed spectrophotometrically at 279 nm.

RESULTS AND DISCUSSION:

Drug –polymer compatibility studies by FTIR

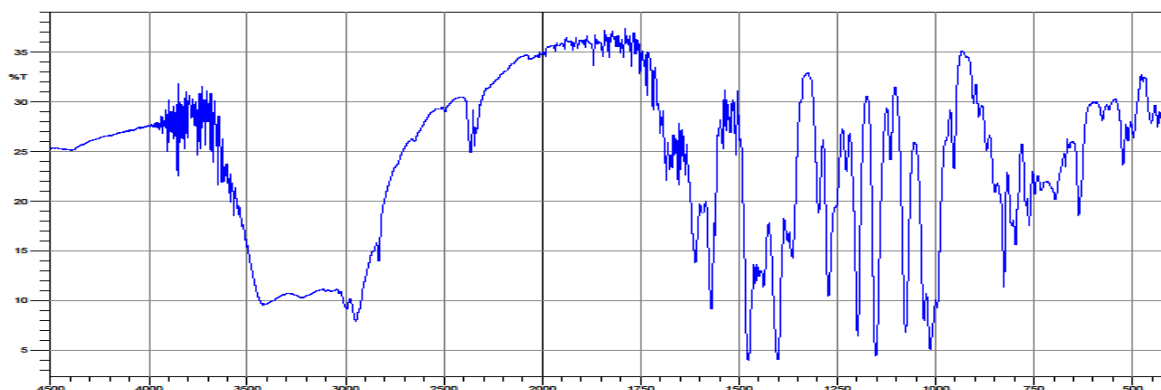


Fig 4: FTIR spectra for pure drug Esomeprazole

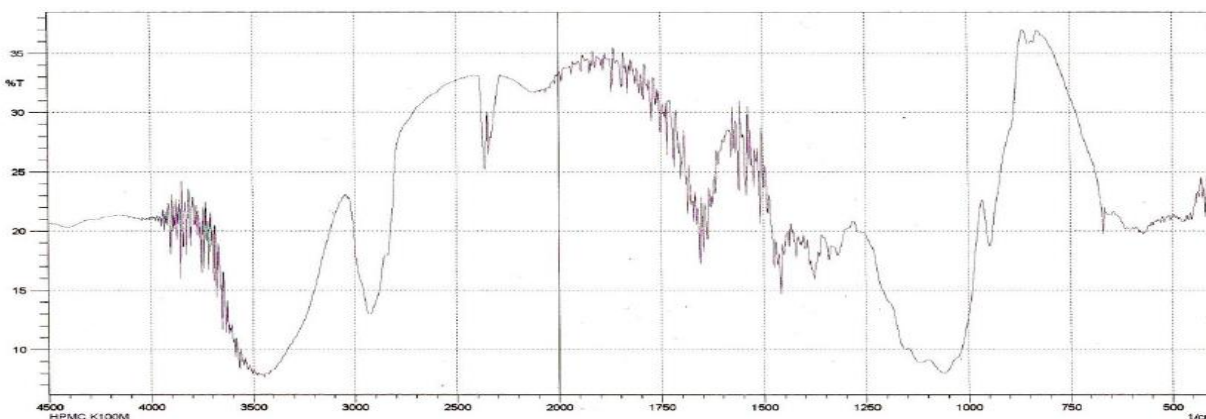


Fig 5: FTIR spectra for Hydroxy Propyl Methyl Cellulose

Table 4: Results for Derived and Flow properties

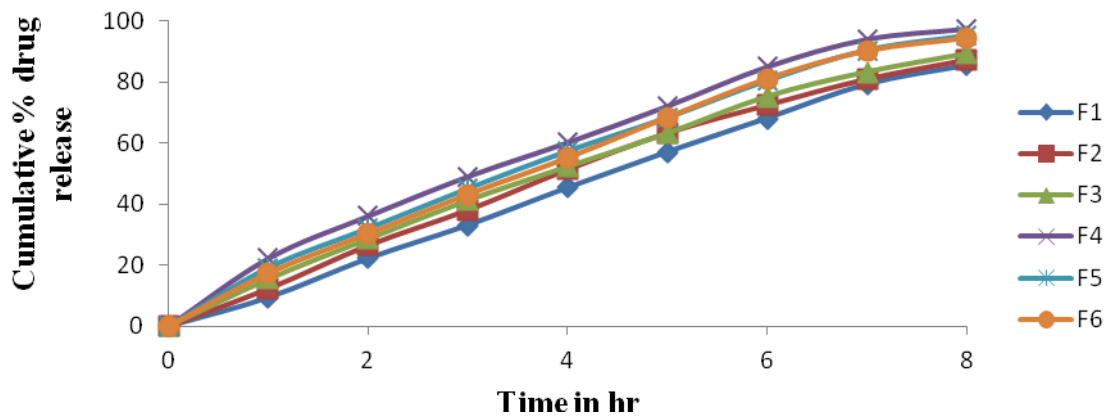
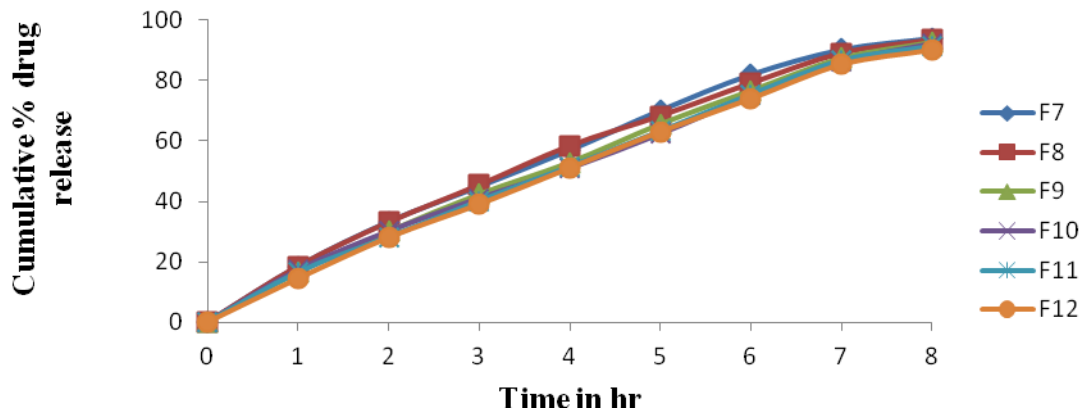
Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.426±0.01	0.483±0.015	31.45±0.30	11.44±1.97	1.129±0.02
F2	0.433±0.015	0.513±0.02	35.21±0.39	11.22±1.96	1.126±0.03
F3	0.442±0.015	0.524±0.01	33.97±0.68	11.86±3.97	1.135±0.05
F4	0.463±0.015	0.536±0.015	30.21±0.96	14.48±1.81	1.105±0.02
F5	0.423±0.02	0.487±0.03	27.94±0.73	12.65±2.25	1.145±0.03
F6	0.410±0.01	0.463±0.006	23.25±0.36	12.2±3.16	1.103±0.04
F7	0.444±0.025	0.526±0.025	28.21±0.29	15.54±1.19	1.184±0.02
F8	0.435±0.01	0.521±0.017	27.87±0.40	11.69±3.61	1.136±0.05
F9	0.413±0.01	0.447±0.025	25.17±0.34	12.87±2.84	1.113±0.04
F10	0.433±0.015	0.537±0.032	26.78±0.63	14.21±1.11	1.165±0.01
F11	0.404±0.02	0.417±0.01	29.93±0.46	13.47±2.48	1.156±0.03
F12	0.423±0.02	0.473±0.015	28.21±0.27	14.23±3.22	1.144±0.05

Table 5: Physicochemical evaluation of buccal Tablets of Esomeprazole

Formulation Code	Thickness (mm± SD)	Weight variation (mg ± SD)	Hardness (Kg/cm ² ± SD)	Friability (% ± SD)	Drug content(% ± SD)	Surface pH ± SD
F1	3.11±0.39	195±1.55	4.36±0.05	0.43±0.025	98.96±0.3	6.41±0.061
F2	3.21±0.23	191±0.94	4.1±0.5	0.54±0.03	99.16±0.45	6.73±0.03
F3	3.16±0.36	192±0.81	4.3±0.05	0.60±0.042	98.49±0.29	6.62±0.026
F4	3.37±0.21	197±0.72	4.56±0.05	0.48±0.036	99.43±0.32	6.79±0.040
F5	3.39±0.30	199±0.19	4.27±0.2	0.48±0.01	99.11±0.17	6.56±0.065
F6	3.19±0.25	196±0.84	4.12±0.03	0.51±0.02	99.1±0.11	6.77±0.066
F7	3.28±0.23	194±0.38	4.33±0.05	0.61±0.038	98.23±0.5	6.77±0.061
F8	3.44±0.19	198±0.52	4.42±0.07	0.54±0.025	98.13±0.59	6.56±0.066
F9	3.45±0.22	195±0.76	4.67±0.05	0.44±0.01	97.73±0.62	6.76±0.045
F10	3.25±0.12	198±0.41	4.13±0.1	0.44±0.026	98.73±0.4	6.72±0.04
F11	3.13±0.28	192±0.82	4.22±0.05	0.48±0.03	98.41±0.39	6.67±0.045
F12	3.11±0.19	195±0.48	4.35±0.04	0.69±0.025	97.73±0.64	6.64±0.077

Table No.6 Bioadhesive Force values for Formulations F1-F12

Formulation Code	Bio adhesive Force (N)
F1	0.189±0.001
F2	0.283±0.004
F3	0.147±0.002
F4	0.279±0.002
F5	0.299±0.002
F6	0.269±0.002
F7	0.226±0.004
F8	0.231±0.002
F9	0.221±0.003
F10	0.182±0.001
F11	0.185±0.001
F12	0.191±0.002

Fig 6: Comparative *in-vitro* drug release plot for F1-F6Fig 7: Comparative *in-vitro* drug release plot for F7-F12

CONCLUSION:

Esomeprazole buccoadhesive tablets were prepared by direct compression method using different buccoadhesive polymers such as Hydroxy Propyl Methyl Cellulose (HPMC), Sodium Carboxy Methyl Cellulose (SCMC) and Carbopol 934P along with Ethyl Cellulose (EC) as an impermeable backing layer. Drug-polymer compatibility studies by FTIR indicates there is no possible interactions between the drug and polymer and prepared tablets were characterized for their physico-chemical characteristics, surface pH, swelling index and results were within the limits of pharmacopoeia in all formulations(F1-F12). Among all, formulations F4 consists of Esomeprazole (20mg), carbopol (60mg), HPMC (20mg), microcrystalline cellulose (48mg), ethyl cellulose (50mg), magnesium stearate (2mg) was selected as best formulation. Various physicochemical parameters tested for this formulation showed good results. Good correlation was observed between in-vitro and in- vivo drug release profiles. Formulation F4 was stable and non-significant from P value obtained by one way ANOVA. Thus Esomeprazole is suitable candidate for oral controlled drug delivery via buccoadhesive tablets. Further work is recommended to support its efficacy claims by long term pharmacokinetic and pharmacodynamic studies in human beings.

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