International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

IJAMSCR |Volume 4 | Issue 4 | Oct - Dec - 2016
www.ijamscr.com

Research article *Medical research*

Formulation and *invitro* evaluation of bucco adhesive bi layer tablets of Eprosartan

G. Anuhya Goud, Kolikapogu Suvarna roja, G. Venkataih, Dr.A. Yasodha*[1], A.Sivakumar[2]

[1]*Dhanvanthri College of Pharmaceutical Sciences, Mahabubnagar- 509002, Telanagana, India.*
[2]*AurobindoPharma Limited, Unit –VII, Jadcherla, Hyderabad.*

***Corresponding Author**: **Dr.A.Yasodha**
Email id: **yyasodhasivakumar@gmail.com**

ABSTRACT

Eprosartan buccoadhesive bilayered tablets containing bioadhesive layer and drug free backing layer were formulated to release the drug for extended periods of time with reduction in dosing frequency. The tablets were prepared by direct compression method using bioadhesive polymers like Carbopol 934p, Magnesium stearate and Hydroxy propyl cellulose alone or in combination, Ethyl cellulose has incorporated as an impermeable backing layer. Tablets were evaluated for weight and content uniformity, thickness, hardness, surface pH, swelling index, *invitro* drug release and *invitro* drug permeation. The modified *invitro* assembly was used to determine and compare the bioadhesive strength of tablets all characteristics of formulated tablets were shown to be dependent on composition of bioadhesive materials used. Maximum bioadhesion strength was observed for tablets formulated with Carbopol 934P.

Keywords: Eprosartan Buccoadhesive, Carbopol 934p, Hydroxy Propyl Cellulose.

INTRODUCTION

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 [1-3]. 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 [4-8]. 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). The aim of the present study was to design buccoadhesive bilayered tablets to release the drug unidirectionally in buccal cavity for extended period of time in order to avoid first-pass metabolism for improvement in bioavailability, to reduce the dosing frequency and to improve patient compliance. The objective behind this work is to prepare and evaluate Eprosartan tablets, prolongation of residence time of drug in buccal

mucosa, and targeting and localization of the dosage form at a specific site [9-10].

MATERIALS AND METHODS

Preparation of Buccoadhesive bilayered Tablets

The buccoadhesive bilayered tablets were prepared using different polymers either alone or in combinations with varying ratios. Bilayered tablets were prepared by direct compression procedure involving two consecutive steps [11-13]. The buccoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 min. Magnesium sterate (MS) was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 8 mm flat faced punch using single punch tablet compression machine (Cadmach), the upper punch was then removed and backing layer material ethyl cellulose was added over it and finally compressed at a constant compression force [14-15].

Composition of Eprosartan Tablets

Formulation	Drug	Carbopol	HPMC K4m	HPMC K15m	Sodium CMC	Mg Stearate	Ethyl cellulose
F_1	50 mg	150 mg	-------	-------	-------	5 mg	50 mg
F_2	50 mg	75 mg	75 mg	-------	-------	5 mg	50 mg
F_3	50 mg	50 mg	100 mg	-------	-------	5 mg	50 mg
F_4	50 mg	100 mg	50 mg	-------	-------	5 mg	50 mg
F_5	50 mg	75 mg	-------	75 mg	-------	5 mg	50 mg
F_6	50 mg	50 mg	-------	100 mg	-------	5 mg	50 mg
F_7	50 mg	100 mg	-------	50 mg	-------	5 mg	50 mg
F_8	50 mg	-------	150 mg	-------	-------	5 mg	50 mg
F_9	50 mg	-------	-------	150 mg	-------	5 mg	50 mg
F_{10}	50 mg	-------	-------	75 mg	75 mg	5 mg	50 mg
F_{1S1}	50 mg	-------	-------	50 mg	100 mg	5 mg	50 mg
F_{12}	50 mg	-------	-------	100 mg	50 mg	5 mg	50 mg

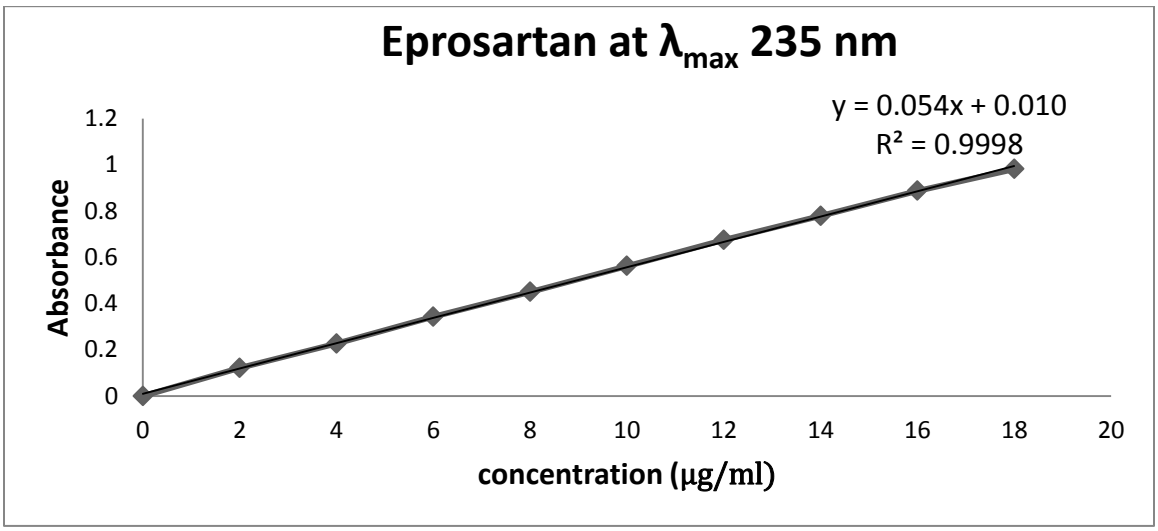
Construction of Calibration curve of Eprosartan

Accurately weighed 100 mg of Eprosartan and transferred into 100 ml of volumetric flask and dissolved in small quantity of methanol and diluted with 6.8 phosphate buffer up to the mark to give stock solution 1 mg/ml. 1 ml was taken from stock solution in another volumetric flask and diluted up to 100 ml to give a stock solution 10 µg/ml. Further dilutions were made from 2-40 µg/ml with 6.8 phosphate buffer and absorbance was measured at 235 nm.

Calibration curve of Eprosartan in pH 6.8 phosphate buffer at 235 nm

S.No.	Concentration	Absorbance
1	2 µg/ml	0.122
2	4 µg/ml	0.227
3	6 µg/ml	0.343
4	8 µg/ml	0.450
5	10 µg/ml	0.562
6	12 µg/ml	0.670

7	14 µg/ml	0.779
8	16 µg/ml	0.887
9	18 µg/ml	0.981
10	20 µg/ml	1.074

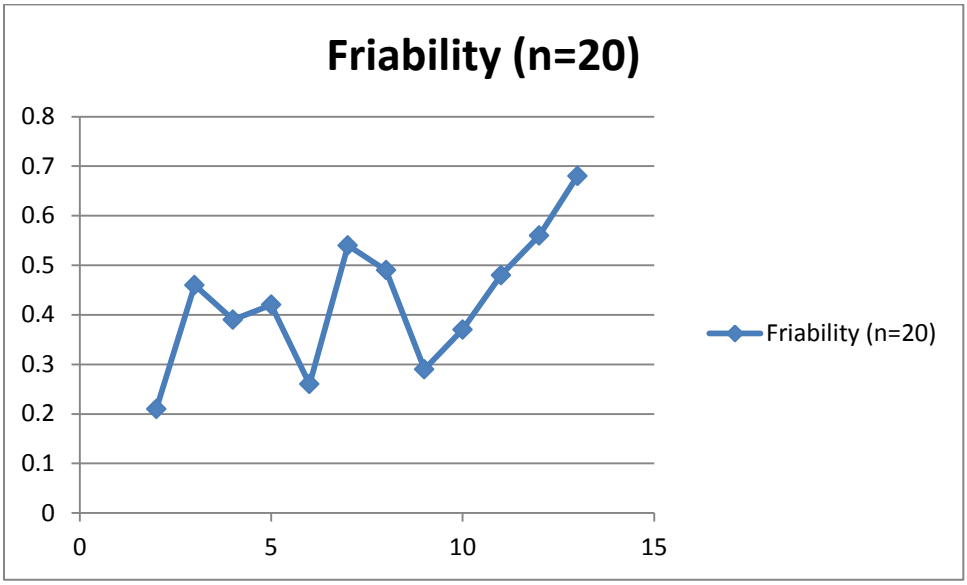


Calibration curve of Eprosartan

EXPERIMENTAL RESULTS

Evaluation data of Eprosartan Buccoadhesive tablets

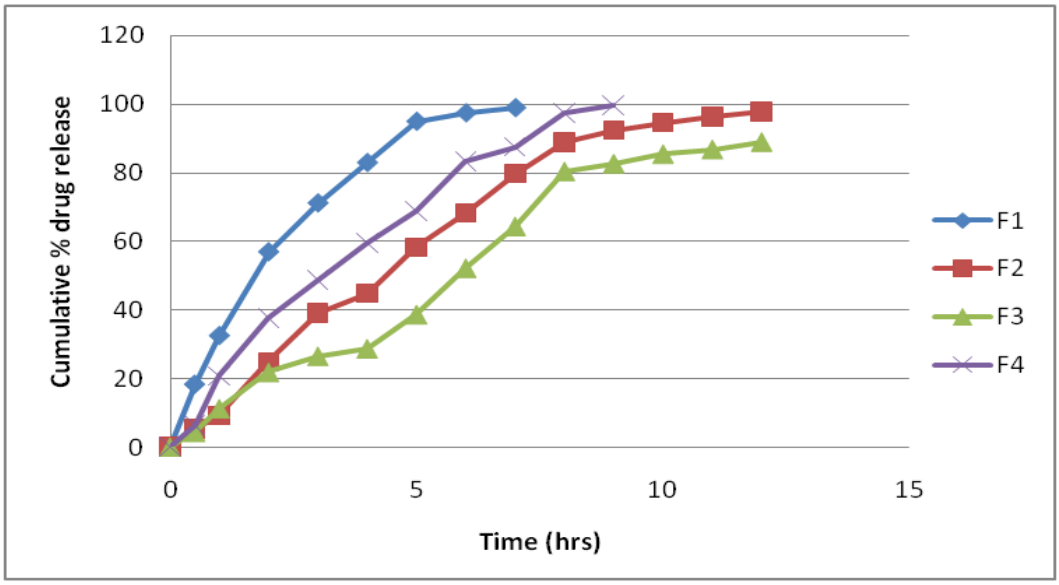
Formulation	Avg. Weight (Mean±S.D) (n=20)	Hardness (Kg/cm$^{2)}$ (n=3)	Friability (n=20)	% Drug content (n=3)
F1	253.4±0.48	10±0.57	0.21	100.2±0.68
F2	257.6±0.74	9±0.62	0.46	99.89±0.58
F3	251.7±0.62	8±0.47	0.39	98.94±0.72
F4	258.4±0.47	7±0.72	0.42	99.80±0.46
F5	258.2±0.23	6±0.48	0.26	99.54±0.62
F6	249.9±0.32	6±0.68	0.54	99.49±0.47
F7	252.1±0.54	7±0.38	0.49	100.24±0.53
F8	253.8±0.37	8±0.48	0.29	99.68±0.71
F9	255.8±0.29	9±0.68	0.37	100.12±0.49
F10	256.4±0.39	8±0.72	0.48	99.9±0.62
F11	258.1±0.32	6±0.56	0.56	99.89±0.54
F12	257.4±0.43	4±0.72	0.68	100.4±0.48



Friability profile of Eprosartan tablets

Dissolution data of Eprosartan buccoadhesive tablets of F1, F2, F3, and F4 formulations

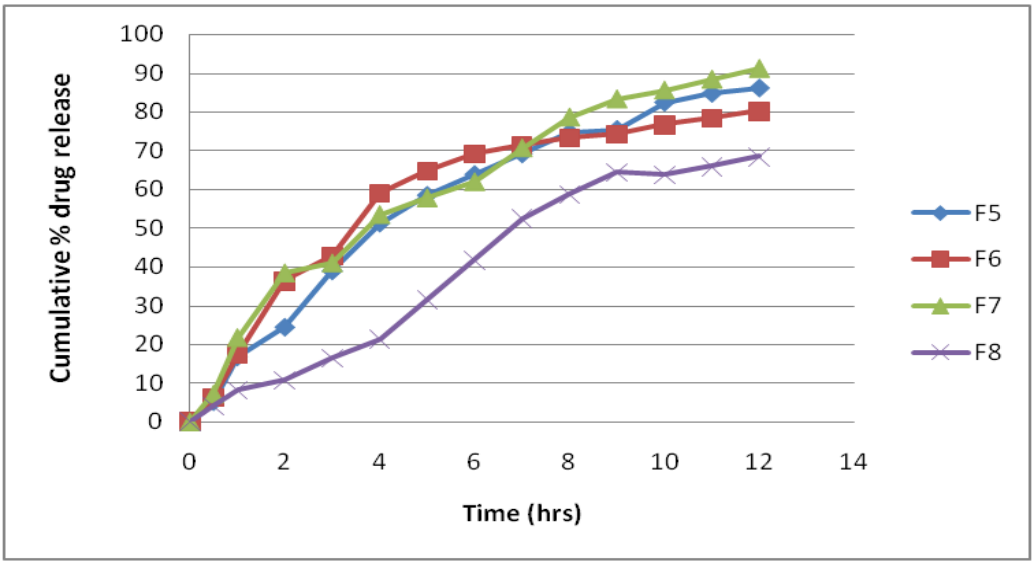
TIME (Hours)	F1	F2	F3	F4
0.5	18.29±0.46	5.23±0.34	4.29±0.52	6.46±0.74
1	32.48±0.78	9.23±0.68	11.19±0.47	20.67±0.68
2	56.87±1.24	24.75±0.47	21.79±0.64	37.46±0.48
3	71.09±1.22	38.96±0.84	26.48±0.74	48.76±0.64
4	82.86±1.09	44.76±0.48	28.67±0.53	59.49±0.84
5	94.86±0.75	58.23±0.57	38.63±1.06	68.62±0.98
6	97.32±.68	68.18±0.38	52.16±1.04	83.16±0.78
7	98.82±.54	79.65±0.47	64.37±1.12	87.49±0.81
8	99.94±0.74	88.79±0.24	80.42±0.98	97.23±0.34
9	----------	92.38±0.68	82.67±0.84	99.59±0.54
10	----------	94.49±0.74	85.46±0.67	----------
11	----------	96.16±0.84	86.79±1.03	----------
12	----------	97.79±0.48	88.97±0.68	----------



Dissolution profile of Eprosartan buccoadhesive tablets of F1, F2, F3, and F4 formulations

Dissolution data of Eprosartan buccoadhesive tablets of F5, F6, F7 and F8 formulations

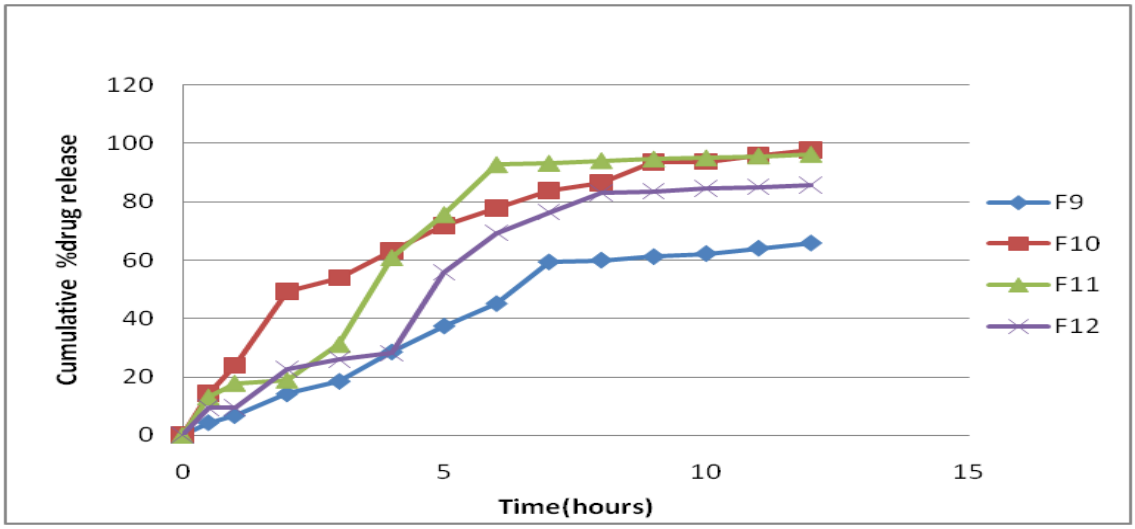
TIME (Hours)	F5	F6	F7	F8
0.5	5.23±0.47	6.23±0.68	7.23±0.43	3.98±0.34
1	16.76±0.68	17.49±0.75	21.76±0.78	8.23±0.74
2	24.43±0.74	36.38±0.43	38.46±1.06	10.75±0.34
3	38.96±0.98	42.76±0.34	41.03±1.08	16.42±0.76
4	51.29±1.02	58.96±0.28	53.49±0.98	21.31±0.84
5	58.46±0.84	64.76±0.98	57.84±0.84	31.47±0.98
6	63.86±0.98	69.23±0.84	61.98±0.68	41.75±0.91
7	69.16±0.48	71.46±0.67	70.72±0.73	52.46±0.1.02
8	74.69±0.68	73.34±0.68	78.67±0.43	58.69±0.77
9	75.46±0.84	74.31±0.84	83.38±0.57	64.46±0.67
10	82.46±0.76	76.69±0.76	85.64±0.48	63.78±0.58
11	84.76±0.84	78.46±0.48	88.46±0.74	65.82±0.84
12	86.16±0.67	80.23±0.78	91.23±0.66	68.49±0.67



Dissolution profile of Eprosartan buccoadhesive tablets of F5, F6, F7 and F8 formulations

Dissolution data of Eprosartan buccoadhesive tablets of F9, F10, F11 and F12 formulations

Time (Hours)	F9	F10	F11	F12
0.5	4.32±0.54	14.39±1.02	13.14±1.04	9.54±1.24
1	6.72±0.84	23.88±0.94	17.82±0.35	9.57±0.84
2	14.16±0.71	49.32±1.32	18.9±0.48	22.68±0.72
3	18.46±0.67	53.92±0.84	31.13±0.78	26.1±0.98
4	28.56±0.87	63.07±0.67	60.84±1.01	28.09±1.04
5	37.44±0.67	71.77±1.24	75.6±1.28	55.8±1.32
6	45.12±0.78	77.85±0.98	92.7±0.68	69.3±0.37
7	59.4±0.49	83.76±1.09	93.18±1.38	76.5±0.67
8	60±0.97	86.34±0.98	94.08±0.84	83.1±0.84
9	61.2±0.54	93.6±1.24	94.59±1.24	83.6±0.47
10	62.25±0.78	93.67±1.42	95±0.84	84.6±1.24
11	64.08±0.38	95.86±0.67	95.67±0.69	85.09±0.86
12	65.86±0.49	97.7±0.82	96.24±0.84	85.79±0.78



Dissolution profile of Eprosartan buccoadhesive tablets of F9, F10, F11 and F12 formulations

Coefficient correlation (r) values from *Invitro* dissolution rate test of eprosartan buccal tablets

Formulation Code	Zero Order	First Order	Higuchi's	Peppas's
F1	0.9037	0.9704	0.9809	0.9769
F2	0.9541	0.9581	0.9679	0.9885
F3	0.9888	0.9751	0.9695	0.9882
F4	0.9689	0.8169	0.9834	0.9913
F5	0.9277	0.99555	0.9797	0.9568
F6	0.8330	0.9388	0.9512	0.9160
F7	0.9308	0.9886	0.9876	0.9459
F8	0.9642	0.9778	0.9394	0.9701
F9	0.9397	0.9544	0.9497	0.9812
F10	0.8756	0.9806	0.9801	0.9637
F11	0.8475	0.9212	0.9067	0.9123
F12	0.9141	0.9443	0.9191	0.9416

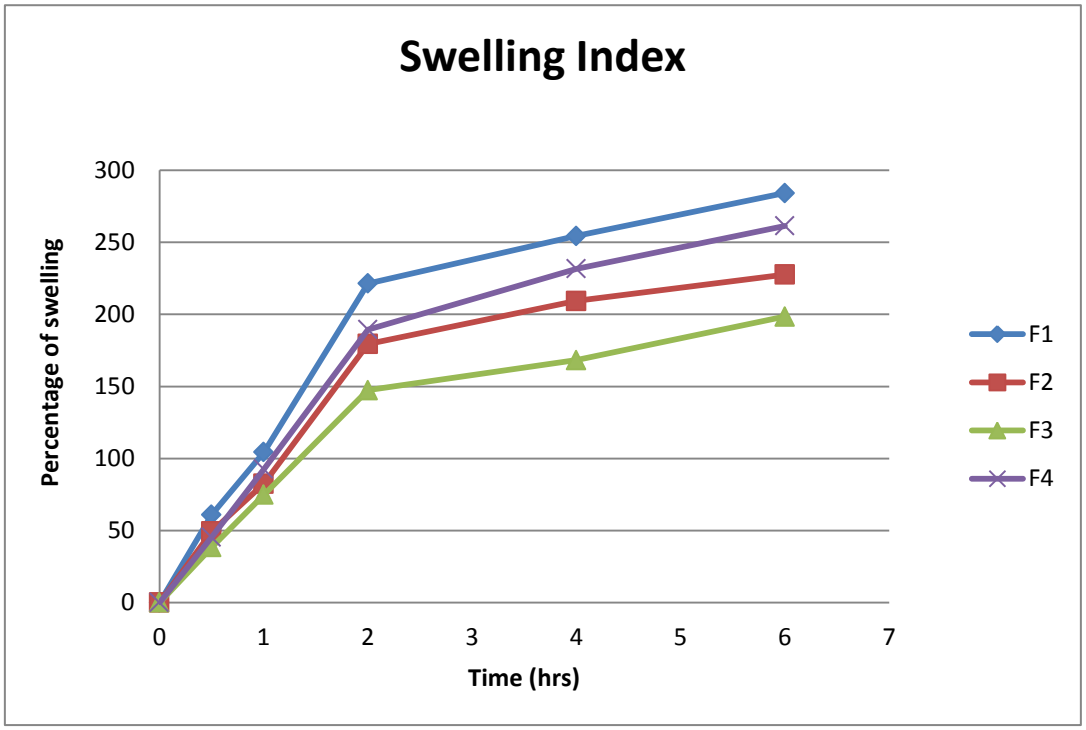
Dissolution parameters of Eprosartan buccoadhesive tablets

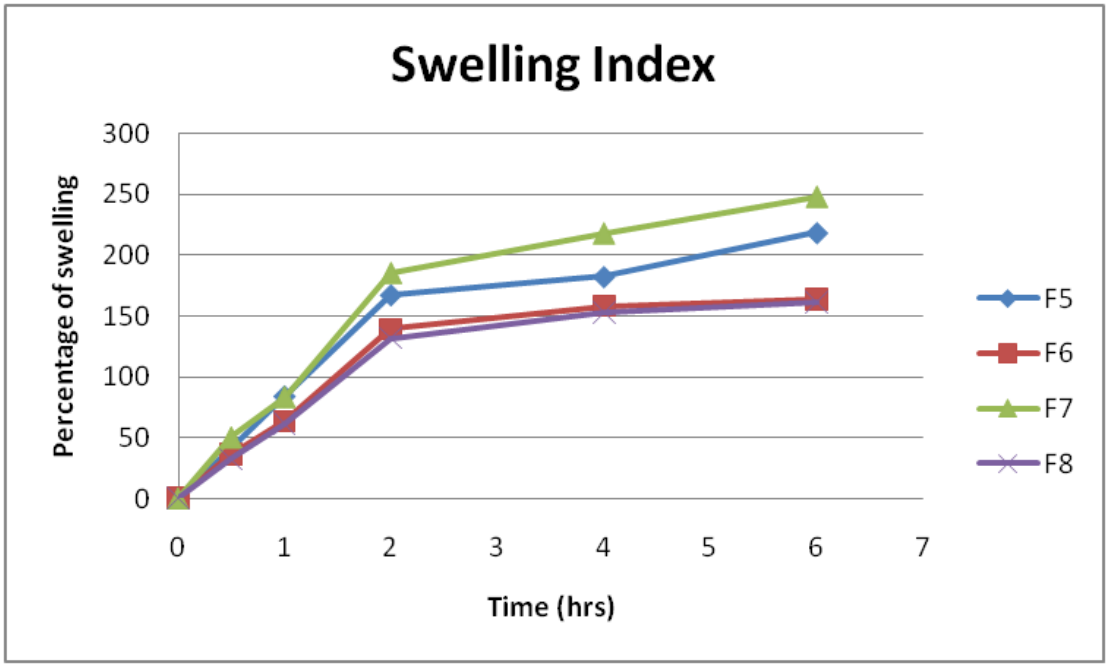
Formulation	n	K_0	K_1	T_{50} (hours)	T_{75} (hours)	T_{90} (hours)
F1	0.6521	14.0033	0.2745	1.83	4.72	4.72
F2	0.7570	8.5195	0.1366	4.62	8.93	8.93
F3	0.7875	7.7547	0.0830	5.84	> 12	> 12
F4	0.7002	10.8721	0.2128	3.27	7.43	7.43
F5	0.8241	7.2101	0.0732	3.91	> 12	> 12
F6	0.7584	6.3691	0.0592	4.52	> 12	> 12
F7	0.7150	7.2660	0.0852	3.91	11.84	11.84
F8	0.8245	6.1054	0.0451	6.93	> 12	> 12
F9	0.7535	5.8126	0.0429	6.87	> 12	> 12
F10	0.5901	7.5088	0.1276	2.19	8.82	8.82
F11	0.7450	8.6560	0.1380	3.93	5.86	5.86
F12	0.8257	7.9658	0.0829	4.84	> 12	> 12

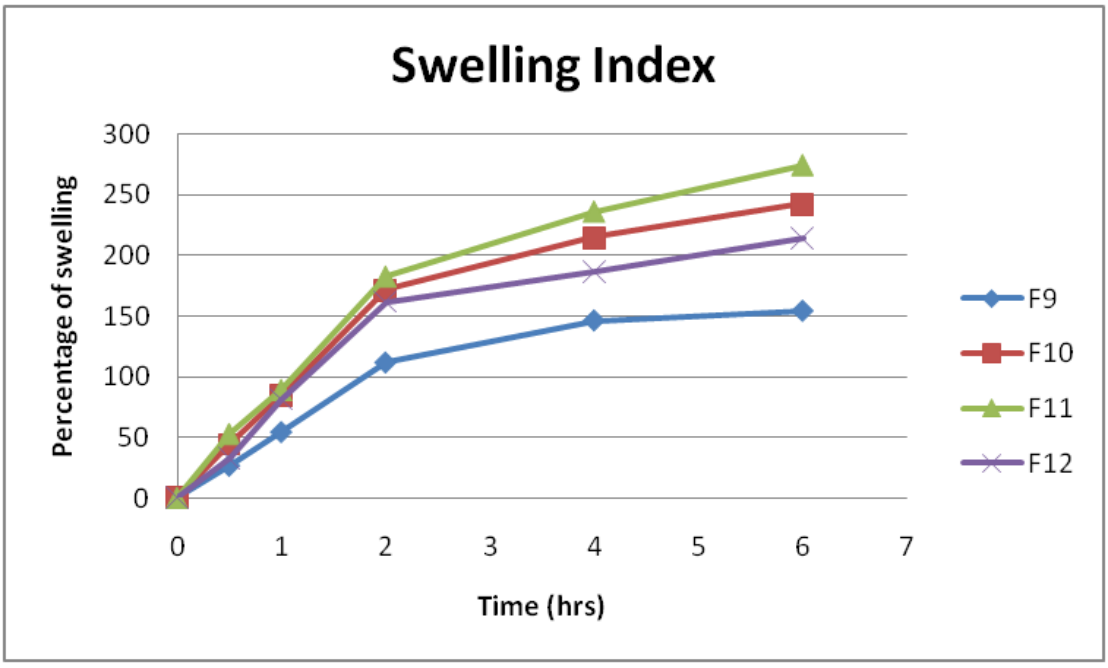
Swelling index of eprosartan buccoadhesive tables

Formulation code	% Swelling index*				
	Time (hours)				
	0.5	1	2	4	6
F1	61.04±0.084	104.46±1.25	221.48±0.098	254.49±.68	284.26±1.48
F2	49.28±0.098	82.48±1.47	179.48±1.21	209.37±2.41	227.64±2.01
F3	38.42±0.95	74.84±0.52	147.43±1.66	168.27±1.41	198.49±1.21
F4	45.49±.09	92.64±1.23	189.49±1.48	231.64±1.34	261.48±1.66
F5	41.42±0.99	84.14±1.48	167.49±1.66	182.43±1.41	218.68±1.98
F6	36.48±0.88	63.74±0.88	139.63±1.37	158.72±0.95	164.38±0.48
F7	50.24±1.16	83.48±1.21	185.67±0.78	218.37±1.23	248.47±1.14
F8	32.14±0.58	61.76±.87	131.64±0.88	152.37±1.02	161.23±1.18
F9	26.49±0.69	54.31±0.28	111.55±2.26	146.29±1.06	154.24±0.39
F10	44.38±1.41	84.56±1.72	171.24±3.14	214.67±2.25	242.67±2.55
F11	52.63±0.88	88.96±2.11	182.46±3.32	236.11±3.45	274.40±3.14
F12	32.67±1.24	81.24±1.46	161.75±3.14	186.34±3.04	214.37±1.33

* Indicates mean±S.D. values





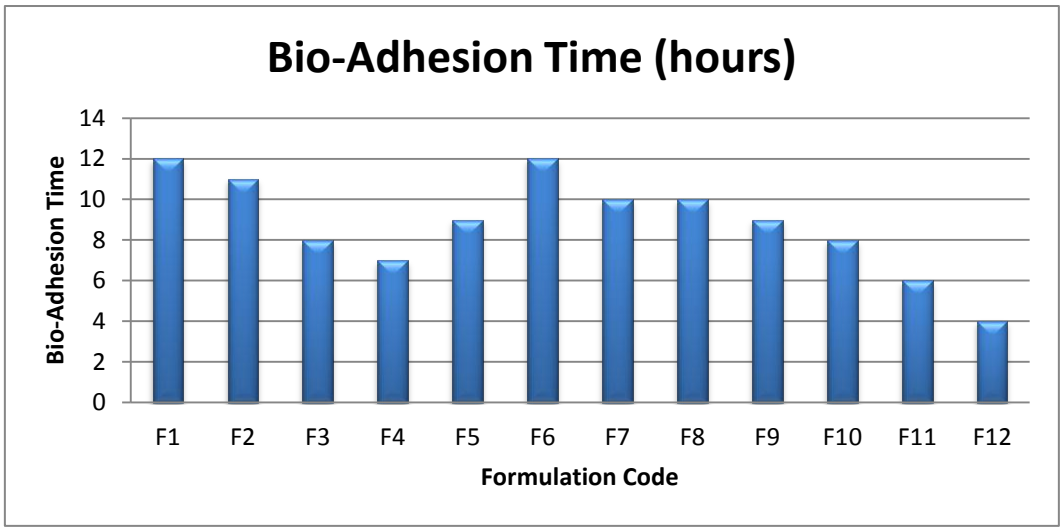


Swelling index profile of Eprosartan buccoadhesive tablets of F1 to F12

In vitro bioadhesion time of Eprosartan buccoadhesive tablets

Formulation	Time (hours)
F1	12
F2	11
F3	8
F4	7

F5	9
F6	12
F7	10
F8	10
F9	9
F10	8
F11	4
F12	7



Bioadhesive profile of Eprosartan buccoadhesive tablets from F1 to F12

IR spectroscopic studies for drug and drug-polymer interactions

From I.R.Spectra, it is evident, that the drug peaks at 3203 cm^{-1}, 2954 cm^{-1}, 2866 cm^{-1}, 1649 cm^{-1}, 1575 cm^{-1}, 1356 cm^{-1}, 1424 cm^{-1}, 1259 cm^{-1}, 1001 cm^{-1}, and 762 cm^{-1} are evident in the drug+polymer mixture also, hence the drug-polymer interactions are absent

SUMMARY AND CONCLUSION

In conclusion, the aim of the present study was to develop buccoadhesive drug delivery system for Eprosartan with a prolonged effect and to avoid first pass metabolism. These buccoadhesive formulations of Eprosartan, in form of buccoadhesive tablets were developed to a satisfactory level in terms of drug release, bioadhesive time, physicochemical properties and surface pH. 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 Eprosartan, prepared using Carbopol 934P and HPMC K4M can successfully be employed as a buccoadhesive controlled released during delivery system. Good bioadhesive time of the formulation is likely to increase it's buccal residence time, and eventually, improve the extent of bioavailability. However, appropriate balancing between various levels of the two polymers is imperative to acquire proper controlled release and bioadhesion. Slow, controlled and complete release of Eprosartan over a period of 12 hours was obtained from matrix

tablets formulated employing HPMC K4M and Carbopol 934P. This tablets exhibited good buccoadhesion time for over 12 hours. Good oral controlled released bilayered buccoadhesive tablet formulation of Eprosartan could be developed using HPMC K4M and Carbopol 934P. Drug release could be obtained upto 10 hrs with a polymer combination of Carbopol 934P and HPMC K4M in the ratio of 1:1 i.e. formulation F2

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How to cite this article: G. Anuhya Goud, Kolikapogu Suvarna roja, G. Venkataih, Dr.A.Yasodha, A.Sivakumar. Formulation and invitro evaluation of bucco adhesive bi layer tablets of eprosartan. Int J of Allied Med Sci and Clin Res 2016; 4(4): 716-726.
Source of Support: Nil. **Conflict of Interest:** None declared.