www.ThePharmaJournal.com

The Pharma Innovation

ISSN: 2277- 7695
TPI 2016; 5(9): 90-95

www.thepharmajournal.com
Received: 13-07-2016
Accepted: 14-08-2016

Sireesha Attuluri
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

P Prem Kumar
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Venkatesh Murukutla
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Manohar Babu S
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Correspondence
Sireesha Attuluri
Department of Pharmaceutics, SIMS College of Pharmacy, SIMS Group of Institutions, Mangaldas Nagar, Guntur, Andhra Pradesh, India

Development and *In Vitro* evaluation of buccoadhesive tablets of losartan potassium

Sireesha Attuluri, P Prem Kumar, Venkatesh Murukutla and Manohar Babu S

Abstract
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. An attempt has been made to develop buccoadhesive bilayered tablets comprising of drug containing bioadhesive layer and drug free backing layer to release the drug for extended period of time with reduction in dosing frequency. Tablets of Losartan potassium were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, Methocel K4M, Methocel K15M and sodium carboxy methyl cellulose either alone or in combinations with backing layer of ethyl cellulose. Slow, controlled and complete release of Losartan potassium 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 Losartan potassium 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.

Keywords: Buccoadhesive bilayered tablets, Buccoadhesion, Losartan Potassium, Presystemic metabolism, Buccal Mucosa

1. Introduction

1.1 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. 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) [3, 4].

1.2 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 bioadhesive buccal delivery systems [4-6].

1.3 Delivery through Buccal Mucosa: Administration of a drug via the buccal mucosa 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, it is relatively more permeable than the skin so it is more desirable site for sustained drug delivery [7, 8].

1.4 Presystemic metabolism/First pass Effects: Before a drug reaches blood circulation, it has to pass for the first time through organs of elimination namely GIT and the liver. The *loss of drug through biotransformation by such eliminating organs during its passage to systemic circulation is called as* First-pass or Presystemic metabolism.

The Four primary systems which affect Presystemic metabolism of a drug are [9, 10]:
Luminal enzymes
Gut wall/mucosal enzymes
Bacterial enzymes
Hepatic enzymes

1.5 Mechanism of Bioadhesion or Bucco Adhesion

Adhesion of a polymer to a tissue involves contribution from three main regions. The surface of the bioadhesive 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 [11-12]:

- Physical or mechanical bonds
- Secondary chemical bonds
- Primary bonds

2. Materials and Methods

2.1. Materials Used

Table 1: Materials used for the formulation development

1	**Losartan potassium**	**Cipla, Goa**	**USP Grade**
2	HPMC K4 M	SD Fine Chemicals Ltd.,Mumbai	Pharmaceutical grade
3	HPMC K15 M	SD Fine Chemicals Ltd.,Mumbai	Pharmaceutical grade
4	Carbopol 934p	SD Fine Chemicals Ltd.,Mumbai	Pharmaceutical grade
5	Magnesium stearate	Yarrow-Chem. Products, Dombivli	Pharmaceutical grade
6	Ethyl cellulose	SD Fine Chemicals Ltd.,Mumbai	Pharmaceutical grade

2.2. Methods Used

2.2.1 Preparation of Buccoadhesive bilayered Tablets:

The buccoadhesive bilayered tablets were prepared using different polymers either alone or in combinations with varying ratios of polymers along with drug. Bilayered tablets were prepared by direct compression procedure involving two consecutive steps. The buccoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 min. Magnesium stearate (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.

2.2.2 Construction of Calibration curve of Losartan Potassium

Accurately weighed 100 mg of Losartan potassium 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.

3. Results

Table 2: Composition of Losartan Potassium 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_{11}	50 mg	-------	-------	50 mg	100 mg	5 mg	50 mg
F_{12}	50 mg	-------	-------	100 mg	50 mg	5 mg	50 mg

Table 3: Calibration curve of Losartan potassium 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

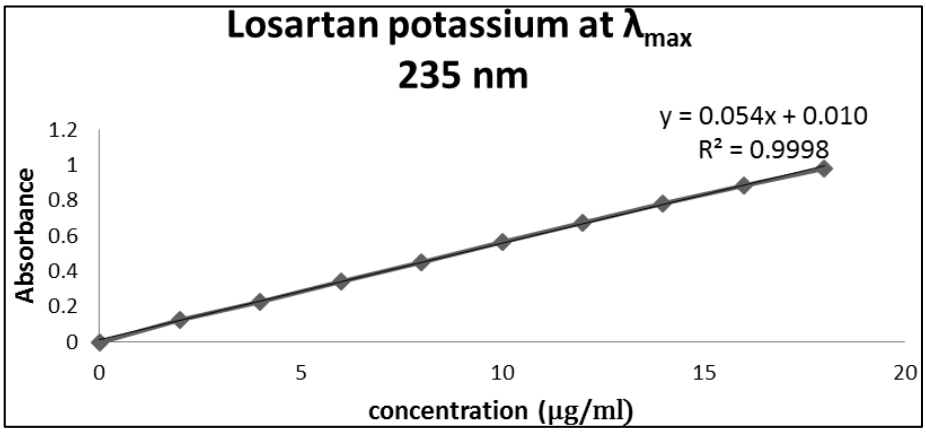

Fig 1: Calibration curve of Losartan potassium

Table 4: Evaluation Data of Losartan Potassium 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

Table 5: Dissolution data of Losartan potassium 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	----------

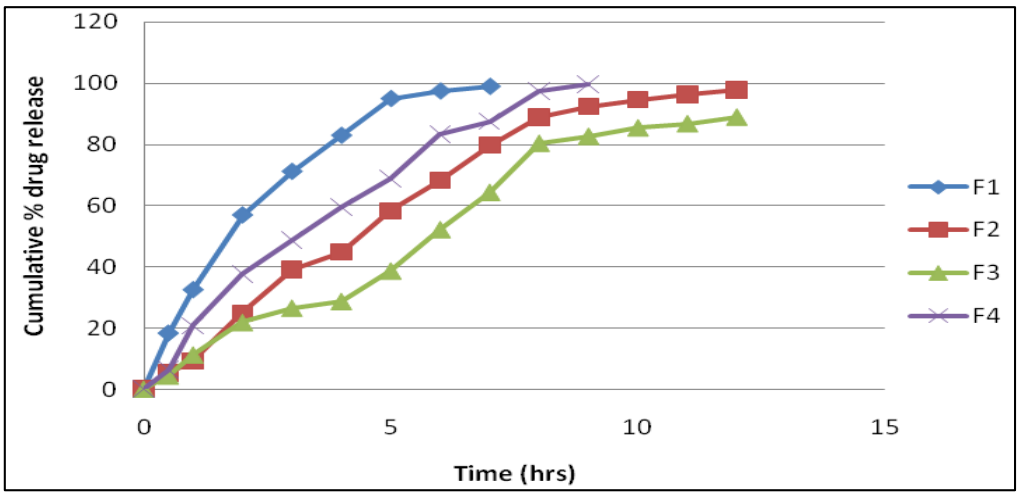

Fig 2: Dissolution profile of Losartan potassium buccoadhesive tablets of F1, F2, F3, and F4 formulations

Table 6: Dissolution data of Losartan potassium 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

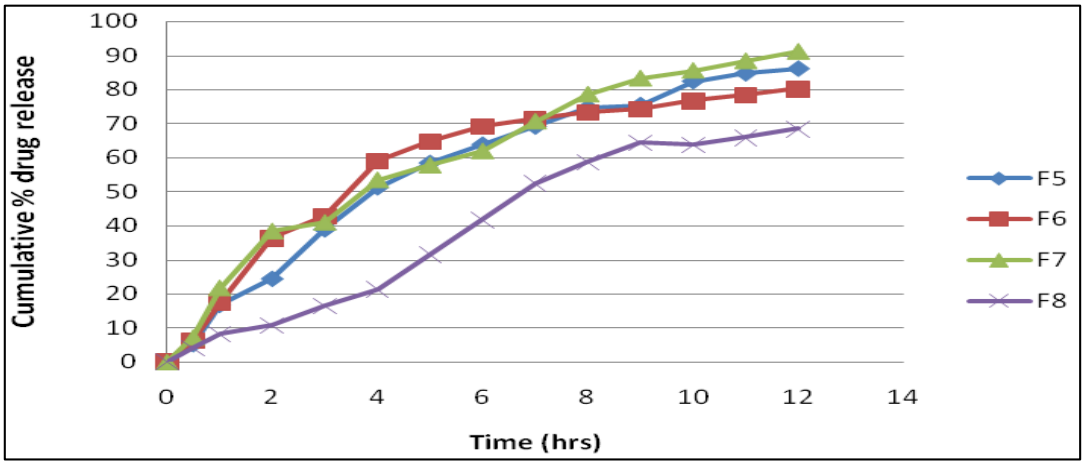

Fig 3: Dissolution profile of Losartan potassium buccoadhesive tablets of F5, F6, F7 and F8 formulations

Table 7: Dissolution data of Losartan potassium 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

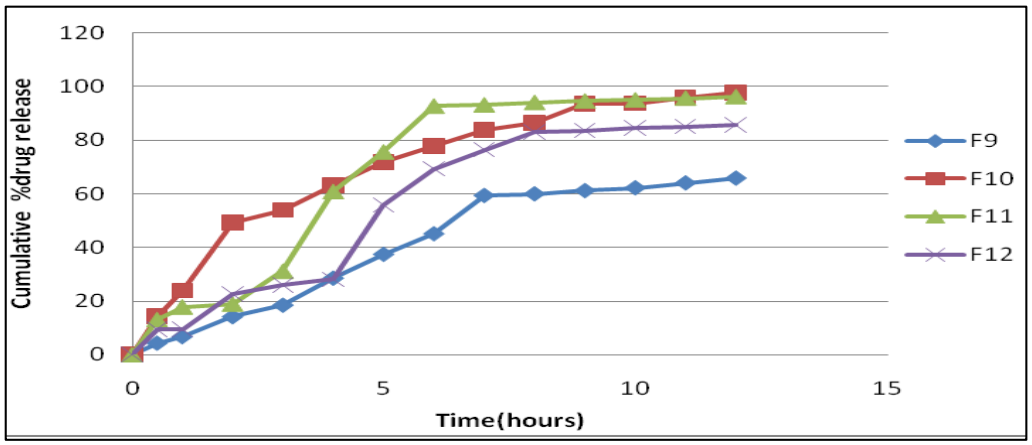

Fig 4: Dissolution profile of Losartan potassium buccoadhesive tablets of F9, F10, F11 and F12 formulations

Table 8: Release Kinetics of Losartan Potassium 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

Table 9: Dissolution parameters of Losartan potassium 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

Table 10: Swelling Index of Losartan Potassium Buccoadhesive Tablets

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

Table 11: *In vitro* bioadhesion time of Losartan potassium 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

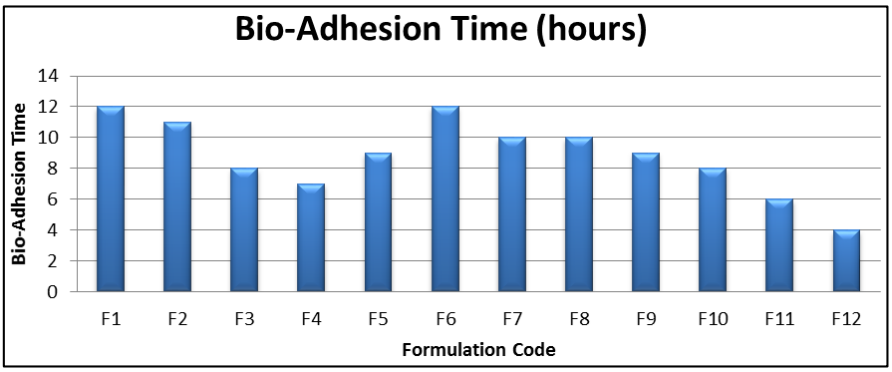

Fig 5: Bioadhesive profile of Losartan potassium buccoadhesive tablets from F1 to F12

4. Conclusion

In conclusion, the aim of the present study was to develop buccoadhesive drug delivery system for Losartan potassium with a prolonged effect and to avoid first pass metabolism. These buccoadhesive formulations of Losartan potassium, 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 Losartan potassium, 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 Losartan potassium 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 Losartan potassium 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.

5. References

1. Pandit JK, Vemuri NM, Wahi SP, Jayachandra Babu R. Mucosal Dosage Form of Ephedrine Hydrochloride using Gantrez-AN 139. Eastern Pharmacist. 1993; 36:169-170.
2. Gupta A, Garg S, Khar RK. Mucoadhesive Buccal Drug Delivery System: A Review. Indian Drugs. 1992; 29(13):586-93.
3. Harris D, Robinson JR. Drug Delivery via Mucous Membrane of the Oral Cavity. J Pharm Sci. 1992; 81:1-10.
4. Wong FC, Yuen KH, Peh KK. Formulation and Evaluation of Controlled Release Eudragit Bucccal Patches. Int J Pharm. 1999; 178:11-2.
5. Marriott C, Gregory NP, Mucus physiology. In: V.Lenaerts and R.Gurny, Bioadhesive Drug Delivery Systems, CRC Press, Boca Raton, FL. 1990, 1-24.
6. Marriott, C, Hughes DRL. Mucus physiology. In: R.Gurny and H.E.Junginger, Bioadhesion-possibilities and Future Trends, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart. 1990, 29-43.
7. Langer RS, Peppas NA. New Drug Delivery Systems. BMES Bull. 1992; 16:3-7.
8. Peppas NA, Buri pa. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Controlled Release. 2:257-275.
9. Nicholas A Peppas, Mounica D Little, Yanbin Huang, Bioadhesive Controlled Released Systems. 255-269.
10. Ponchel G, Irache J. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. Adv Drug Deliv Rev. 1998; 34:191-219.
11. Hwang SJ, Park H, Park K. Gastric Retentive Drug-Delivery Systems, Crit. Rev. Ther. Drug Carrier Syst. 1998; 15(3):243-284.
12. Whitehead L, Fell JT, Collett JH. Development of a Gastroretentive Dosage Form, Eur. J Pharma Sci. 1996; 4(1):182.