Asian J. Pharm. Res. Vol 4, Issue 3, 160-169, 2014.

e-ISSN 2231 – 363X
Print ISSN 2231 – 3621

Asian Journal
of
PHARMACEUTICAL RESEARCH
Journal homepage: - www.ajprjournal.com

FORMULATION AND EVALUATION OF BILAYER BUCCAL ADHESIVE TABLET CONTAINING ATENOLOL

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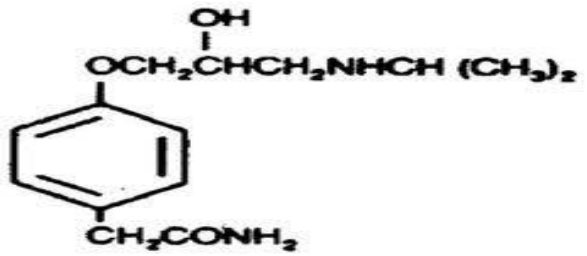
ABSTRACT

The aim of the present research work is to formulate and evaluate bilayered buccal adhesive tablet containing Atenolol as a drug to achieve unidirectional drug release and to increase bioavailability of the drug. Atenolol (beta blocker) is widely used in hypertension. The drug bioavailability is low (54%) due to extensive first pass metabolism. Since the buccal route bypasses first-pass effect, the dose of atenolol could be reduced by 50%. The bilayered buccal tablets were evaluated for physical parameters, swelling index, and surface pH, mucoadhesive strength, drug content uniformity, *in-vitro* release, drug permeation study, stability studies, drug excipient interactions (FTIR). The formulation F5 (containing 1:1 ratio of Chitosan and HPMC K15M) was found to be promising, which showed good bioadhesive strength (35gm), optimum drug permeation (85%), optimum in-*vitro* drug release (97%) with in 8hours and acceptable surface pH. Stability studies of the promising formulation F5 indicated that bilayered buccal tablets are stable and showed no significant changes in drug content.

Keywords: Buccal, Atenolol, Hypertension, Bioadhesive

INTRODUCTION

Atenolol (beta blocker), has been widely used in the management of hypertension. Atenolol has its suitable half-life (6-7 h) [1] and low molecular weight (266.34) and used orally with a dose of 50-100mg.



Chemical Name: 2-(4-{2-hydroxy-3-[(propan-2-yl) amino] propoxy} phenyl) acetamide.

Atenolol is a white powder, odorless and slightly bitter in taste and freely soluble in methanol, acetone and dimethyl sulfoxide, sparingly soluble in water and insoluble in chloroform and ethyl acetate.

Atenolol (2nd generation β blocker) is a β-1selective antagonist (Cardio selective). This slows down strength of the heart's contractions and reduces its oxygen requirements and the volume of blood it has to pump. Hypertension (high blood pressure) may be treated with these drugs because of their ability to increase the diameter of the blood vessels thus allowing blood flow under less pressure. Atenolol is used in the management of hypertension in a dose of 25 to 100 mg daily by mouth, as single or divided doses and in the usual dose for angina pectoris is also same as in hypertension and Atenolol is used in the early management of acute myocardial infarction [2,3].

MATERIALS AND METHODS:

ANALYTICAL METHODS OF ATENOLOL

Preparation of Solutions:

a) pH 6.8 phosphate buffer: 50ml of 0.2M Potassium dihydrogen phosphate was taken in a 200ml volumetric flask, to which 22.4ml of 0.2M Sodium Hydroxide was added and the volume made up to the mark using distilled water.

b) 0.2M potassium dihydrogen phosphate: 27.218g of

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potassium dihydrogen phosphate was added to 1000ml of volumetric flask containing distilled water and the volume was made up to the mark using distilled water.

c) 0.2M Sodium Hydroxide: 8g of Sodium hydroxide was added to 1000ml of volumetric flask containing distilled water and the volume was made up to the mark using distilled water.

PREFORMULATION STUDIES

The following preformulation studies were performed for Atenolol [3,4].

1. Determination of pH
2. Drug-Excipients compatibility studies
3. Determination of λ max
4. *Ex-vivo* permeation of drug solution

PREPARATION OF BUCCAL ATENOLOL TABLETS

Bilayered buccal mucoadhesive tablets were prepared by direct compression method.

- ❖ Preparation of core layer mixture
- ❖ Preparation of backing layer
- ❖ Compression

Procedure

1. Various batches were prepared by varying the ratio and combination of polymers.
2. All the ingredients including drug, polymer and excipients were weighed accurately.
3. Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min.
4. After uniform mixing of ingredients, lubricant was added and again mixed for 2min.
5. The prepared blend (150 mg) of each formulation was pre-compressed using a 9 mm punches in a single punch tablet machine (Rimek mini press-I)
6. Then the upper punch was raised and the backing layer of ethyl cellulose was placed on the above compact; the two layers were compressed into a mucoadhesive bilayered tablet.

Table 1. Formulation Chart for Optimization of Drug to Polymer Ratio

S. No	Drug:Polymer mixture
Trail1	1:1
Trail 2	1:2
Trail 3	1:3
Trail 4	1:4
Trail 5	1:5

Table 2. Formulation chart of Atenolol Buccal tablets (total weight 200mg)

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Atenolol	25	25	25	25	25	25	25	25	25	25
Chitosan	100	50	33.3	66.6	50	33.3	66.6	50	33.3	66.6
Carbopol 934		50	66.6	33.3						
HPMC K15M					50	66.6	33.3			
Sodium CMC								50	66.6	33.3
MCC	23	23	23	23	23	23	23	23	23	23
MagnesiumStearate	2	2	2	2	2	2	2	2	2	2
EthylCellulose	50	50	50	50	50	50	50	50	50	50

EVALUATION OF BUCCAL TABLETS [5-29]

1. Table 3. Determination of weight variation maximum % deviation allowed

Average weight	Average % deviation allowed
130 or less	10
130 – 324	7.5
324	5

2. We also determine thickness, hardness, friability, drug content, swelling index [7-10], Surface pH [11-15], *Ex-vivo* Bioadhesive Strength [16-18].

***3. In-Vitro* Dissolution Studies [19-21]**

Apparatus used- USP II Lab India DS
Dissolution medium- Phosphate buffer pH 6.8
Volume of the dissolution medium-300ml
Speed - 50 rpm
Temperature - 37°C
Sampling intervals-0.5,1,2,3,4,5,6,7 &8hr
Sample withdrawn - 3ml
Measured at- 224nm

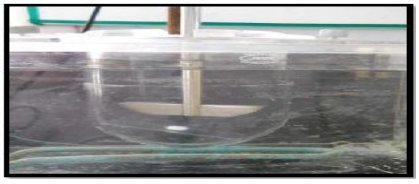

Figure 1. Dissolution apparatus USPII

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4. Table 4. Drug release kinetics [17]

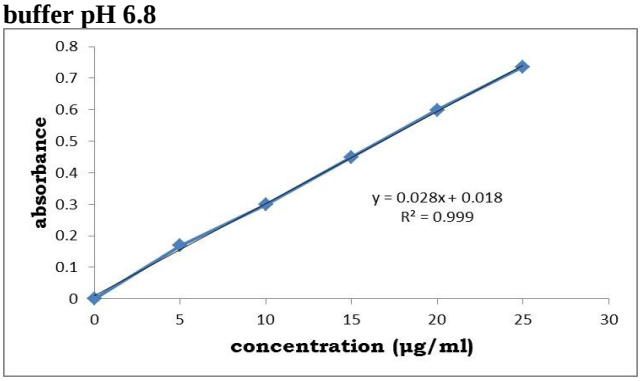
Release Exponent	Drug Release Mechanism	Rate as a function of time
0.5	Fickian Diffusion	0.5
0.5<n<1.0	Non-Fickian Diffusion	tn-1
1.0	Case –IITransport	Zero Order Release
Higher Release	Super Case –IITransport	tn-1

5. *Ex-vivo* drug permeation study [14-16]

Ex-vivo drug permeation through the goat buccal mucosa was performed using modified Franz diffusion cell at 37±0.5°C.

Figure 2. Modified Franz Diffusion Cell

Figure 3. Standard graph of Atenolol in phosphate buffer pH 6.8



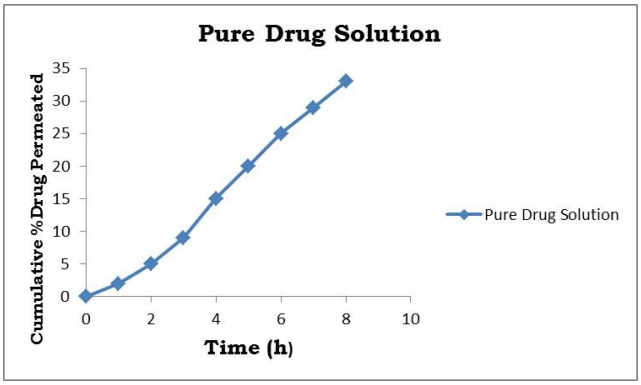
PREFORMULATION STUDIES

1. Determination of pH

The pH of 1% w/v concentration of atenolol is 4.5-5.

2. *Ex-vivo* permeation of Drug Solution

Figure 4. Cumulative % Drug Permeation of Atenolol Drug Solution



3. Drug – Excipient compatibility studies

Figure 5. FTIR spectrum of pure drug Atenolol

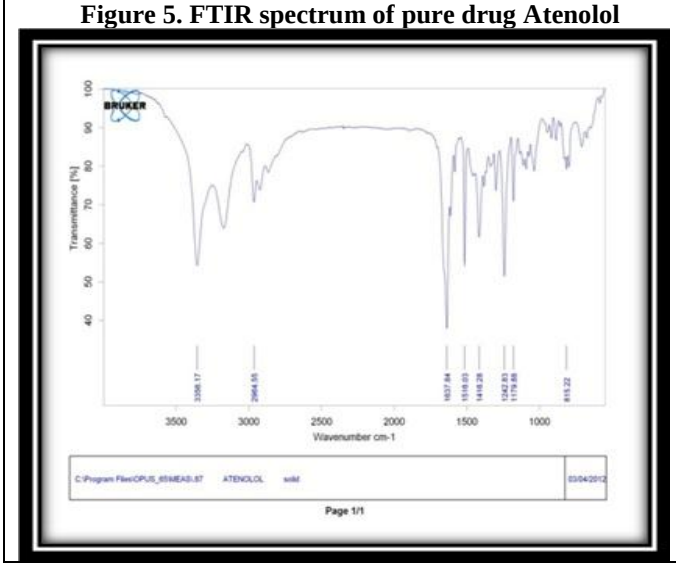


Figure 6. FTIRspectrum of Chitosan

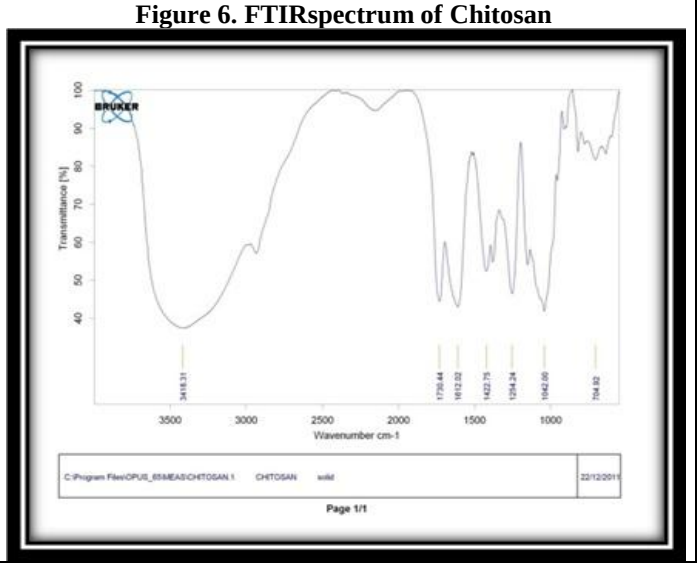


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Figure 7. FTIR spectrum of carbopol 934

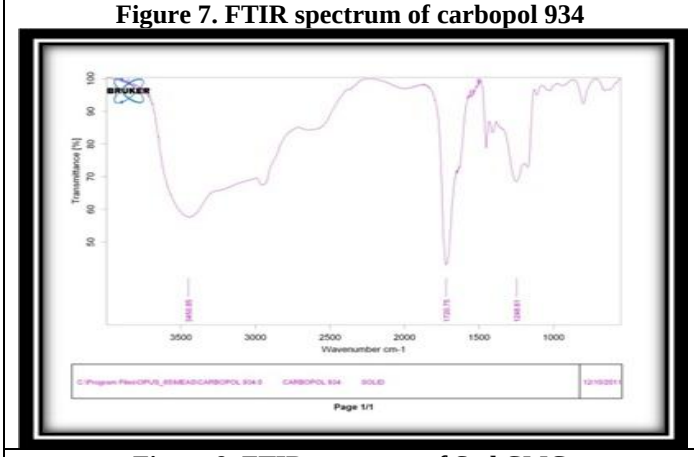


Figure 8. FTIR Spectrum of HPMC K15M

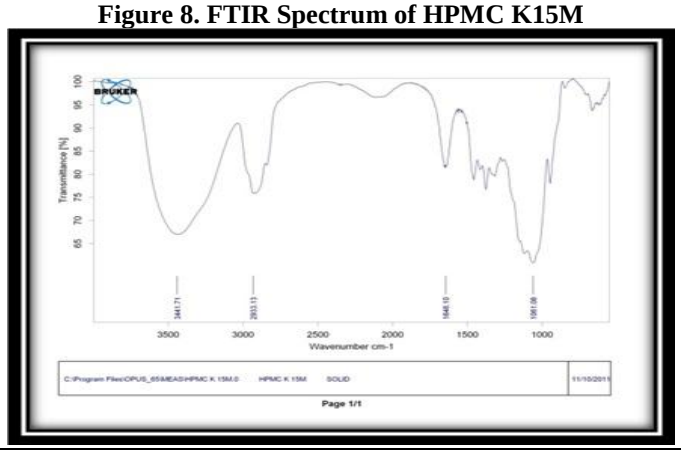


Figure 9. FTIR spectrum of Sod CMC

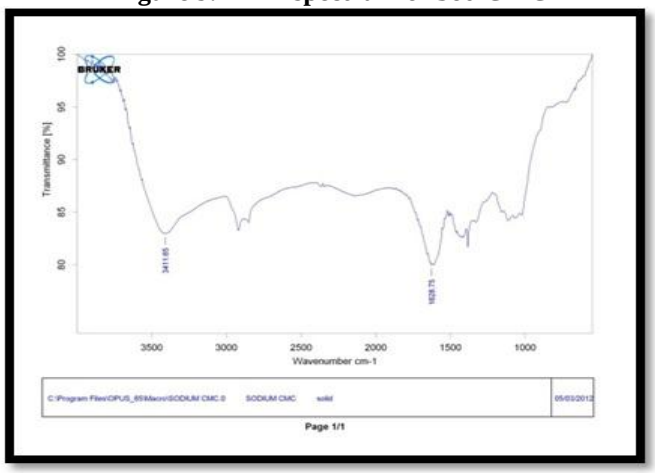


Figure 10. FTIR spectrum of Optimized Formulation

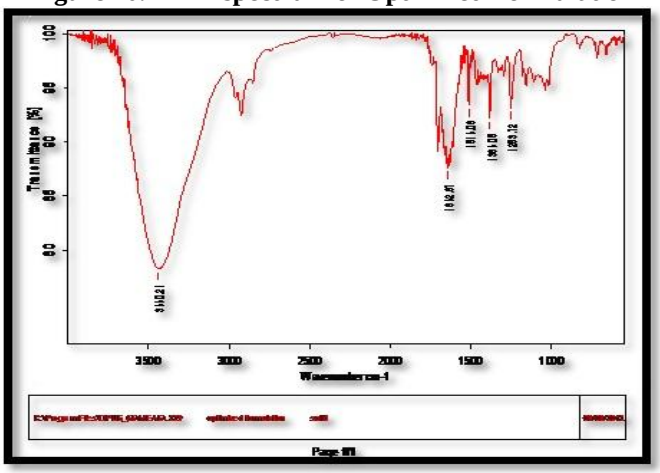


Figure 11. FTIR spectra of Drug and Polymers

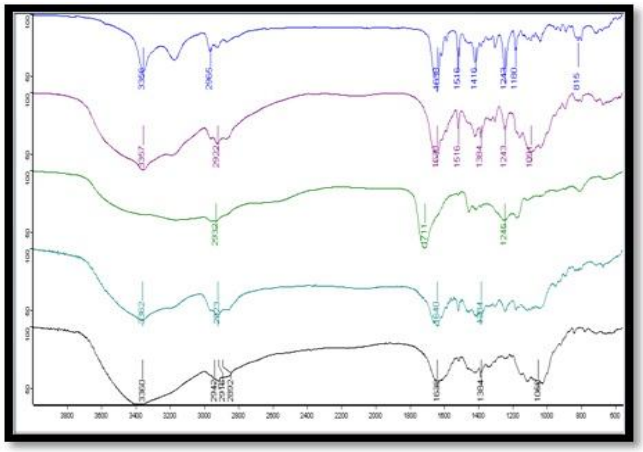
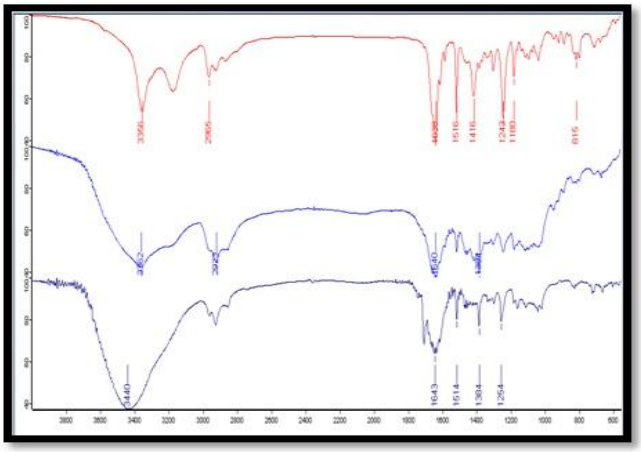


Figure 12. FTIR Spectra of ATENOLOL, Physical Mixture and F5 Formulation



EVALUATION OF ATENOLOL BUCCAL TABLETS

Table 5. Evaluation of Trial Formulations

Code	Hardness(kg/cm^2)	Thickness(mm)	% Drug Content	Bioadhesive Strength (gm)
T1	2.1	2.50	96.5	10.3
T2	2.6	2.52	94.3	14.8
T3	3.5	2.51	97.5	22.5
T4	4.5	2.50	98.2	30
T5	4.9	2.52	97.75	34

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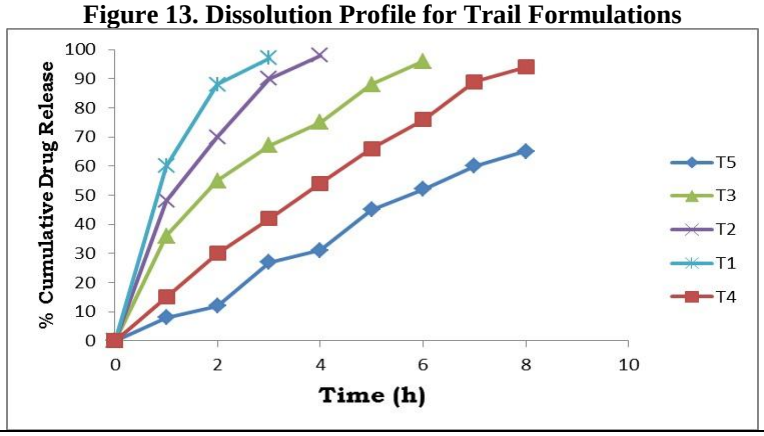
Figure 13. Dissolution Profile for Trail Formulations



By observing the Dissolution profile and Mucoadhesive Strength results mentioned in above table, T4 formulation containing 1: 4 ratio of Drug: Polymer mixture was optimized, and formulations were prepared using drug and different polymer mixtures in the ratio of 1:4.

1. Physical Parameters

The weight variation, thickness, hardness, friability and drug content for the Atenolol Bilayered buccal tablets of each formulation are reported.

Table 6. Results of physical parameters of tablets

Formulation Code	Hardness(kg/cm^2	Thickness (mm}	WeightVariation(mg)	Friability %	% DrugContent
F1	3.5±0.18	2.51±0.02	201±0.47	0.52±0.16	93.85±0.29
F2	4.2±0.22	2.50±0.05	199±0.34	0.74±0.02	97.25±0.45
F3	4.5±0.27	2.52±0.01	202±0.29	0.65±0.05	98.14±0.25
F4	4.2±0.26	2.48±0.08	198±0.81	0.81±0.06	95.50±0.47
F5	4.5±0.24	2.50±0.02	200±0.39	0.68±0.04	98.21±0.81
F6	4.7±0.16	2.51±0.05	201±0.25	0.65±0.02	97.47±0.26
F7	4.5±0.3	2.52±0.01	201±0.45	0.70±0.03	94.95±0.34
F8	3.9±0.22	2.50±0.02	199±0.20	0.72±0.07	96.75±0.39
F9	4.0±0.25	2.51±0.01	201±0.30	0.62±0.12	96.5± 0.29
F10	3.8±0.29	2.52±0.05	202±0.50	0.75±0.08	97.25±0.18

Values are mean ± SD, n=3.

2. Determination of swelling index

Table 7. Result of % Swelling index of tablet formulations F_1-F_{10}

Formulation	1 hour	2 hour	4 hour	6 hour	8 hour
F1	28.01±0.098	50.71±1.10	68.71±1.10	78±0.78	88.00±1.89
F2	32.12±0.084	54.04±1.51	76.9±1.99	83±2.12	92.05±2.22
F3	37.98±1.01	61.14±1.33	83.9±1.33	89.5±1.12	98.07±1.11
F4	30.14±0.088	52.96±0.052	69.5±1.01	82.4±1.23	90.20±1.99
F5	32.36±0.99	58.16±1.05	72.4±1.21	80.6±1.34	94.16±2.01
F6	31.31±0.65	52.53±0.78	73.4±1.57	81.3±0.95	95.00±0.00
F7	30.61±0.95	48.96±1.01	70.0±0.58	76.2±1.04	89.01±1.11
F8	36.66±1.16	57.56±1.47	82.8±1.99	88.5±2.01	98.05±1.66
F9	38.12±0.69	70.03±0.95	85.1±0.49	95.±1.41	102.00±1.59
F10	33.34±0.28	55.16±0.95	74.8±0.27	85.5±2.26	96.00±0.00

Values are mean ± SD, n=3.

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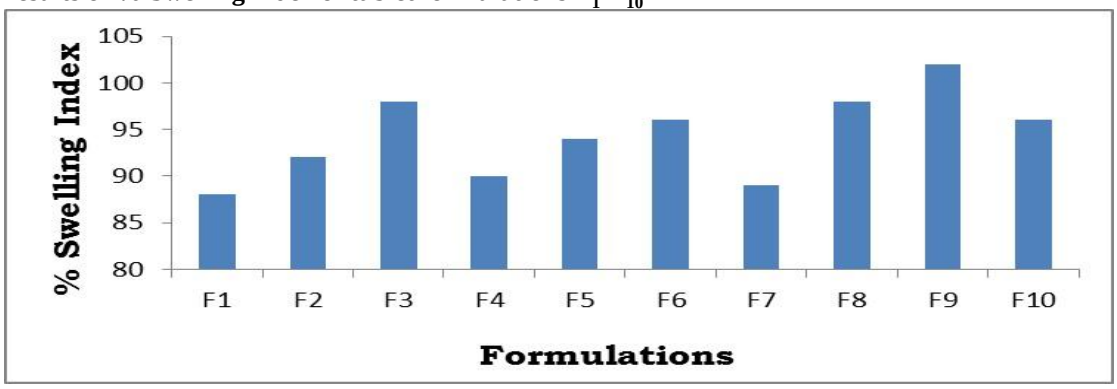
Figure 14. Results of % Swelling index of tablet formulations F_1-F_{10}



3. Determination of Surface pH:

Tablets of all formulations except F_1 had shown a surface pH values in range of 5 to 6.7 that indicates no risk of mucosal damage or irritation.

Table 8. Results of Surface pH of Atenolol Buccal tablet formulations F_1-F_4

Code	Surface pH Mean ± S.D*							
	Time in Hours							
	1	2	3	4	5	6	7	8
F1	4.1±0.11	4.13±0.12	4.21±0.1	4.25±0.13	4.42±0.15	4.45±0.12	4.51±0.11	4.55±0.12
F2	5.30±0.13	5.35±0.11	5.39±0.11	5.44±0.1	5.49±0.12	5.54±0.11	5.58±0.11	5.64±0.12
F3	5.25±0.15	5.30±0.14	5.35±0.11	5.40±0.12	5.45±0.13	5.48±0.13	5.52±0.14	5.55±0.11
F4	5.45±0.15	5.50±0.14	5.53±0.11	5.60±0.12	5.65±0.13	5.70±0.13	5.78±0.14	5.85±0.11

Table 9. Results of Surface pH of Atenolol Buccal tablet formulations F_5-F_{10}

Formulation Code	Surface pH Mean±S.D*							
	Time in Hours							
	1	2	3	4	5	6	7	8
F_5	6.3±0.13	6.31±0.11	6.32±0.13	6.33±0.15	6.34±0.14	6.35±0.13	6.36±0.15	6.37±0.13
F_6	6.61±0.13	6.62±0.12	6.62±0.15	6.63±0.11	6.64±0.15	6.64±0.14	6.64±0.11	6.66±0.12
F_7	5.5±0.11	5.54±0.14	5.60±0.11	5.65±0.11	5.71±0.14	5.75±0.15	5.80±0.13	5.85±0.14
F8	6.20±0.15	6.21±0.14	6.22±0.13	6.23±0.11	6.24±0.14	6.25±0.12	6.26±0.11	6.27±0.14
F9	5.81±0.11	5.82±0.13	5.82±0.11	5.82±0.15	5.83±0.12	5.84±0.14	5.84±0.12	5.84±0.12
F10	6.4±0.11	6.41±0.12	6.42±0.13	6.43±0.14	6.44±0.15	6.45±0.13	6.46±0.12	6.47±0.14

Values are mean ± SD, n=3.

Table 10. Results of *Ex- vivo* mucoadhesive strength of Formulations

Code	Bioadhesive Strength (gm)	Force of bioadhesion
F1	15 ±0.34	0.147
F2	28 ±0.45	0.274
F3	29.75 ±0.75	0.291
F4	26 ±0.25	0.254
F5	35 ±0.18	0.343
F6	32 ±0.12	0.313
F7	28 ±0.29	0.274
F8	25.5 ±0.24	0.245
F9	26.8 ±0.60	0.263
F10	23 ±0.53	0.225

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Figure 15. *Ex vivo* mucoadhesive strength of Tablet Formulation

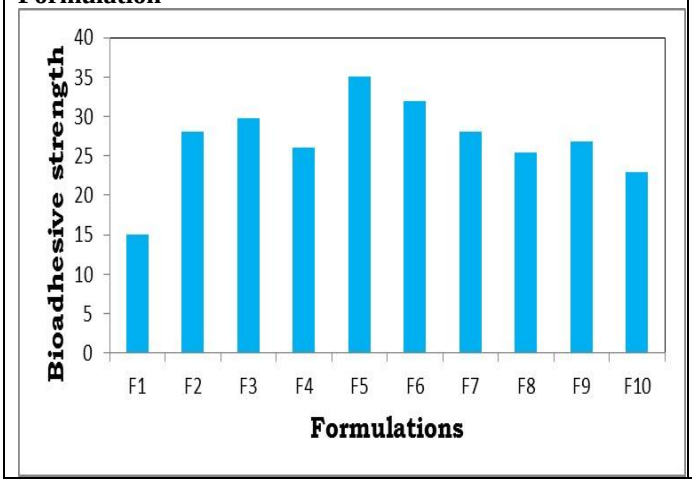
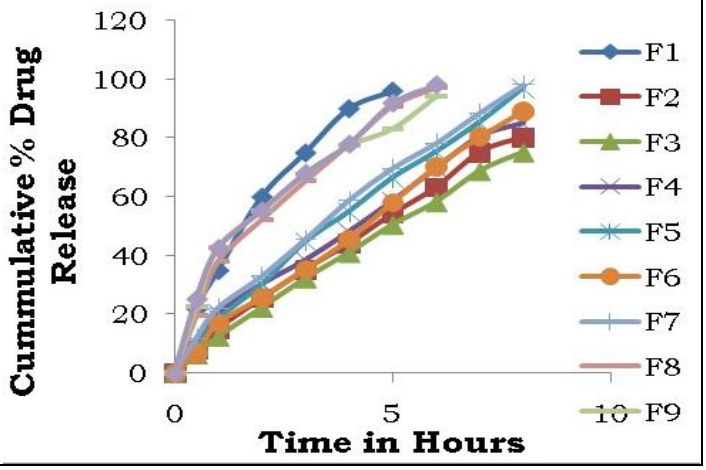


Figure 16. Result of percentage drug release of Formulations F_1-F_{10}



5.*In-Vitro* Dissolution studies

Table 11: Result of percentage drug release of Formulations F_1-F_{10}

Time (h))	% Drug Release									
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
0.5	22	8	6.5	10.24	9.24	7	12	19.5	22.5	25.24
1	35	15.2	12.5	20.25	18.5	17	22.24	38	42.75	42.5
2	60	25.5	22.3	30.3	30.25	25.75	33.3	52.14	55	55.3
3	75	35.3	32.34	38.5	44.85	37.3	45.5	65.3	67.5	68
4	90	44.14	41	48.12	55	45.5	58.75	77.5	77.25	77.85
5	96	54.25	50.5	58.6	66.5	58	69.6	90.75	83	91.25
6	-	63.18	58.25	69.7	75.3	70.24	78.14	97	95.14	98
7	-	75.15	68.75	80.5	85.45	80.25	88.45	-	-	-
8	-	80.3	75.14	85	97	89	98	-	-	-

Dissolution profile of Formulations F1-F10

6. Drug Release Kinetics

Table 12. Data for analysis of drug release mechanism from mucoadhesive buccal tablet formulations

Code	Zero Order R^2	First Order R^2	Higuchi R^2	Korsemeyer-Peppas R^2	Hixon R^2	N Value
F1	0.992	0.956	0.963	0.981	0.899	0.70
F2	0.997	0.966	0.973	0.967	0.969	0.62
F3	0.998	0.977	0.987	0.985	0.962	0.68
F4	0.995	0.991	0.976	0.989	0.979	0.65
F5	0.997	0.965	0.994	0.998	0.965	0.53
F6	0.994	0.929	0.984	0.982	0.954	0.55
F7	0.992	0.936	0.990	0.992	0.955	0.59
F8	0.990	0.916	0.964	0.975	0.971	0.71
F9	0.993	0.930	0.977	0.984	0.976	0.72
F10	0.995	0.876	0.985	0.989	0.979	0.74

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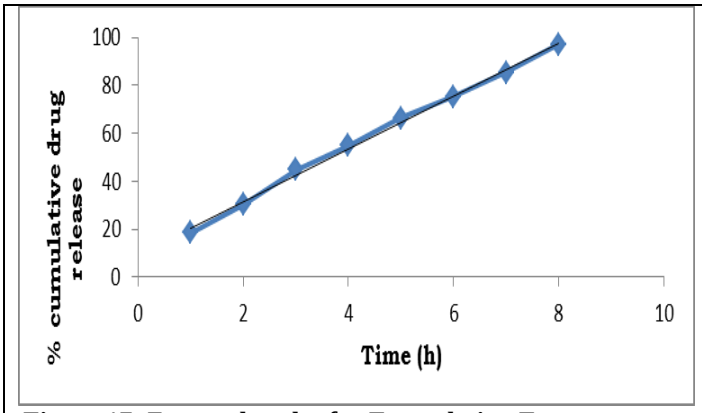

Figure 17. Zero order plot for Formulation F_5

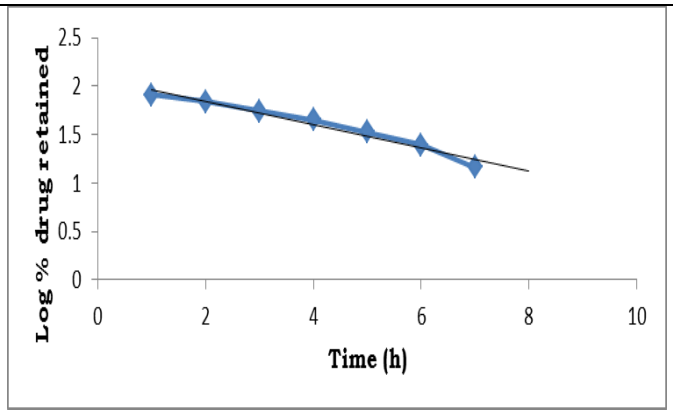

Figure 18. First Order plot for Formulation F_5

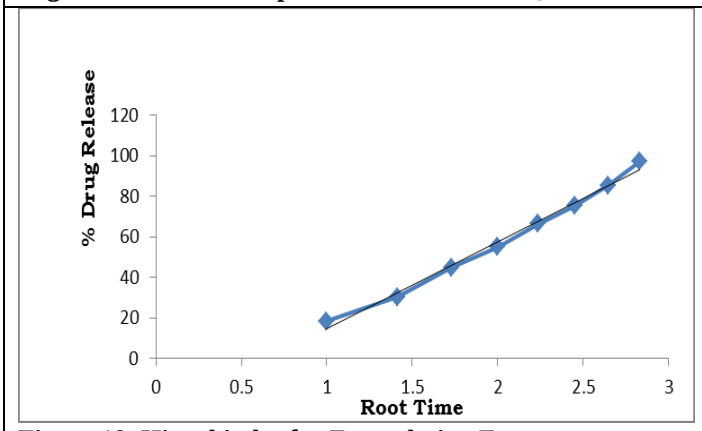

Figure 19. Higuchi plot for Formulation F_5

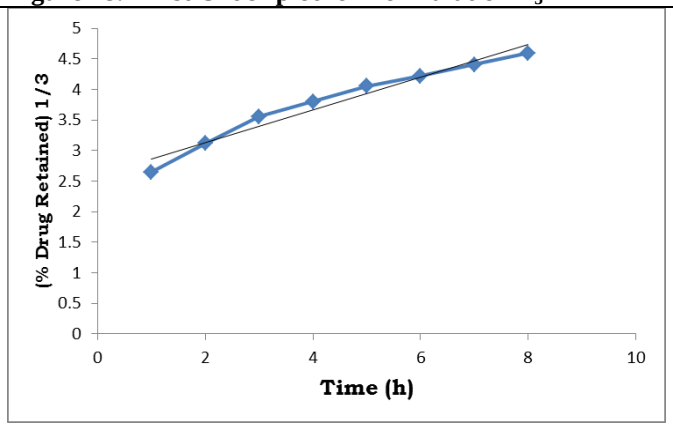

Figure 20.Hixon-crowell plot for Formulation F_5

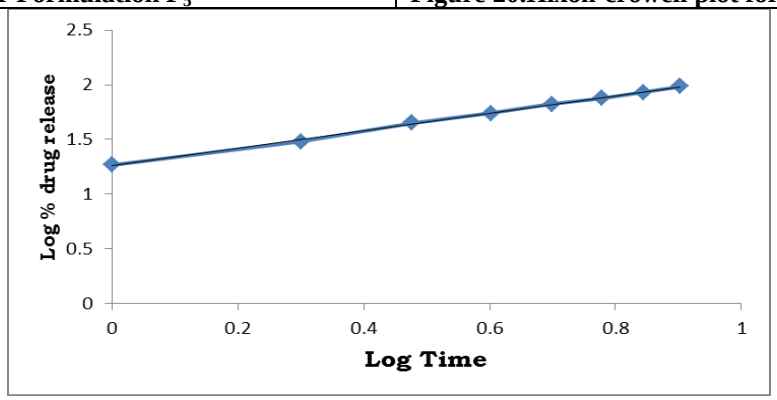

Figure 21. Peppas plot for formulation F_5

***7. Ex-vivo* permeation studies**

Table 13. Results of *Ex- vivo* drug permeation studies of formulations F_1 to F_{10}

Time (h)	% Drug Permeated									
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
0.5	1	5	4	8	13.7	9	6	6	4	7.5
1	3	9.7	7	13	23.7	16.8	11	10	7	13
2	6	18	14.5	20	32	24	18.5	17	13.8	19.5
3	10.5	26	22	30	40.5	32.5	26	21.5	18	25
4	15	35	30	38	56.8	40	32.3	26	22.7	30
5	22	43.5	35.25	48	66.5	52	45	31.3	28	34.75
6	28.8	50	43	56	79	61.8	50	36	33	39
7	2	8	2	63	83	68	54.5	39.85	37.7	43.25
8	35	60	55	66	85	74	60	43	40	46

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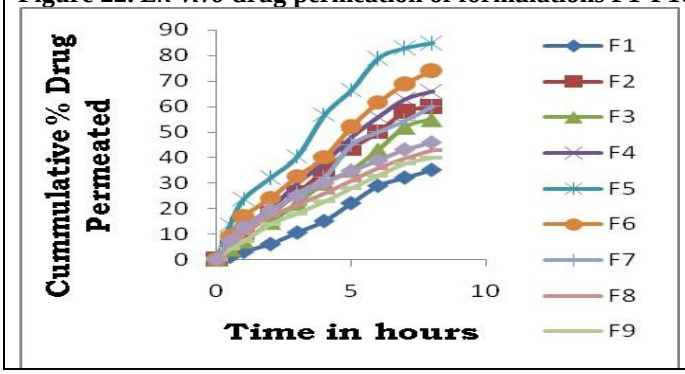
Results of *Ex- vivo* drug permeation studies of formulations F_7 to F_{10}

Figure 22. *Ex-vivo* drug permeation of formulations F1-F10



8. Stability studies

Table 14. Results of Stability studies of Optimized Formulation F_5

Formulation	Time	Percentage Drug Content at		
		5^0C/60 %RH	0^0C /65 %RH	0^0C /75% RH
F5	0^{th} day	8.2	7	6.5

CONCLUSION

In the present study, an attempt was made to prepare bilayer buccal tablets of Atenolol to reduce dose dependent side effects and frequency of administration. Bilayered buccal tablets containing drug was prepared by direct compression method by using Chitosan, carbopol 934, HPMC K15M and sodium CMC as a mucoadhesive polymers and by using ethyl cellulose as backing layer.The bilayered buccal tablets were evaluated for physical parameters, swelling index, and surface pH, mucoadhesive strength, drug content uniformity, *in-vitro* release, drug permeation study, stability studies, drug excipient interactions (FTIR). The release pattern of the formulations was observed to be non-Fickian and released drug by combination of both diffusion and chain relaxation.

The formulations F5 (containing 1:1 ratio of Chitosan and HPMC K15M) were found to be promising, which showed good bioadhesive strength (35gm), optimum drug permeation (85%), optimum in-*vitro* drug release (97%) with in 8hours and acceptable surface pH. Stability studies of the promising formulation F5 indicated that bilayered buccal tablets are stable and showed no significant changes in drug content.

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