WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 7, Issue 1, 761-784. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF CONTROLLED RELASE OF BUCCOADHESIVE BILAYERED BUCCAL TABLET OF NIFEDIPINE

Vineela Sangu*, R. Anusha Naik, Ajay Kumar D., B. Preethi Reddy and B. Dharani Priyanka

Gyana Jyothi College of Pharmacy, Uppal Bus Depot, Hyderabad-500089, Telangana, India.

Article Received on
05 November 2017,

Revised on 26 Nov. 2017,
Accepted on 17 Dec. 2017

DOI: 10.20959/wjpr20181-10496

***Corresponding Author**
Vineela Sangu
Gyana Jyothi College of Pharmacy, Uppal Bus Depot, Hyderabad-500089, Telangana, India.

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 nifedipine were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, Methocel E15, and sodium carboxy methyl cellulose either alone or in combinations with backing layer of ethyl cellulose. The preformulation blend was shown good flow properties with good angle of repose, bulk density and tapped density parameters. The formulated tablets were evaluated for various quality control parameters and they were passed all the tests with standard values as per pharmacopoeia. Slow, controlled and complete release of Nifedipine over a period of 8 hours was obtained from matrix tablets formulated employing HPMC E15 and Carbopol 934P (F7 Formulation). This tablets exhibited good buccoadhesion. Good oral controlled released bilayered buccoadhesive tablet formulation of Nifedipine could be developed using HPMC E15 and Carbopol 934P.

KEYWORDS: Nefidipine, Carbopol, Sodium CMC, Buccal tablets.

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.

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 bioadhesivebuccal delivery systems.

Advantages of Buccal route

- Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
- No first-pass hepatic metabolism.
- No degradation of drugs such as that encountered in the GIT.
- Presence of saliva facilitates both drug dissolution and its subsequent permeation by keeping the oral mucosa moist.
- 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

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

Limitations

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

Nifedipine is a dihydropyridinecalcium channel blocker. Its main uses are as an antianginal (especially in Prinzmetal's angina) and antihypertensive, although a large number of other indications have recently been found for this agent, such as Raynaud's phenomenon, premature labor, and painful spasms of the esophagus such as in cancer and tetanus patients. It is also commonly used for the small subset of pulmonary hypertension patients whose symptoms respond to calcium channel blockers. Nifedipine has been formulated as both a long- and short-acting 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, nifedipine prevents calcium-dependent myocyte contraction and vasoconstriction. A second proposed mechanism for the drug's vasodilator effects involves pH-dependent inhibition of calcium influx via inhibition of smooth muscle carbonic anhydrase. Nifedipine is used to treat hypertension and chronic stable angina.

MATERIALS AND METHODS

Nifedipine was purchased from Karnataka antibiotic centre, hydroxy propyl methyl cellulose was purchased from the keerti agencies uv Scientifics, Sodium CMC was purchased from the zopinax pharma Ltd(Ahemadabad Carbopol and Starch was purchased from the Lab press pharma, MCC was purchased from the Sartourious Lab, Mg stearate was purchased from the Sarco chemical ltd, Ethyl cellulose Sarco chemical ltd.

METHODS

Analytical profile development of drug

UV Scan: Accurately weighed 10 mg of nifedipine and transferred into 10 ml of volumetric flask and dissolved in10 ml ethanolto give stock solution 1 mg/ml. 1 ml was taken from stock solution in another volumetric flask and diluted up to 10 mlwith 6.8 phosphate buffer to give a stock solution 100 µg/ml.1ml taken from solution in another volumetric flask and diluted with bufferup to the 10 ml mark that gives 10 µg/ml. The absorbance of the solutions were scanned in the UV region and found that Nifedipine showed maximum absorbance at 238nm. Thus λmax of Nifedipine was found to be 238 nm.

Construction of Calibration curve of nifedipine

Procedure

Accurately weighed 10 mg of nifedipine and transferred into 10 ml of volumetric flask and dissolved in small quantity of ethanol 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 10 ml to give a stock solution 100 µg/ml. Further dilutions were made from 2-10 µg/ml with 6.8 phosphate buffer and absorbance was measured at 238 nm.

Preparation of Buccoadhesive Bilayered Tablets

The buccoadhesive bilayered tablets were prepared using different polymers either alone or in combinations with varying ratios as summarize. 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 rotary punch tablet compression machine , the upper punch was then allow to up wards and backing layer material ethyl cellulose was added over it and finally compressed at a constant compression force.

Table 1: Composition of Nifedipine Tablets.

Formulation	Drug	HPMC E15	Sodium CMC	Carbopol	Starch	MCC	Mg Stearate	Ethyl cellulose
F_1	30 mg	30 mg	30 mg	-------	30 mg	75 mg	5 mg	50 mg
F_2	30 mg	30 mg	10 mg	---------	30 mg	95 mg	5 mg	50 mg
F_3	30 mg	20 mg	---------	20mg	30 mg	100 mg	5 mg	50 mg
F_4	30 mg	20mg	30 mg	-------	30 mg	95 mg	5 mg	50 mg
F_5	30 mg	15 mg	--------	20 mg	30 mg	100 mg	5 mg	50 mg
F_6	30 mg	15 mg	10 mg	--------	30 mg	110 mg	5 mg	50 mg
F_7	30 mg	10 mg	--------	30 mg	30 mg	95 mg	5 mg	50 mg
F_8	30 mg	10 mg	30 mg	-------	30 mg	95 mg	5 mg	50 mg
F_9	30 mg	10 mg	20 mg	-------	30 mg	105mg	5 mg	50 mg
F_{10}	30 mg		50 mg	--------	30 mg	85 mg	5 mg	50 mg
F_{11}	30 mg	50 mg	-------	--------	30 mg	85 mg	5 mg	50 mg
F_{12}	30 mg		-------	50 mg	30 mg	85 mg	5 mg	50 mg

EVALUATION OF TABLETS

The formulated tablets were evaluated for the following physicochemical parameters:

Weight Variation

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. Form the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is with in permissible limits or not. The results listed in the Table 10.

Table 2: Standard weight variation limits (IP).

S No.	Average mass	Percentage deviation
1.	130mg or less	±10
2.	More than 130 mg and less than 324 mg	±7.5
3.	324 mg or more	±5

Hardness

Hardness of the tablet was determined using the Monsanto harness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The results listed in the table 10.

Friability

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions. After which the tablets were reweighed. The percentage friability was calculated. The results listed in the table 10.

Friability of tablets was calculated by using following equation.

$$\text{Friability} = \frac{W_o - W_f}{W_o} \times 100$$

Where,

Wo = initial weight,

W_f= final weight.

Drug Content

Three tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 100 mg. The equivalent weight Nifedipine was transferred into 100 ml volumetric flask and by using methanol as the extracting solvent and samples was analyzed spectrophotometrically. The results listed in table 10.

***In-vitro* mucoadhesion studies**

Mucoadhesive strength of the buccal tablets was measured on the "Modified Physical Balance method". The method used sheepbuccal mucosa as the model mucosal membrane. The fresh sheepbuccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8.

The both pans were balanced by adding an appropriate weight on the left- hand pan. A piece of mucosa was tied to the surface of the beaker and placed below the left pan which was moistened with phosphate buffer pH 6.8.The tablet was stuck to the lower side of left pan with glue. Previously weighed beaker was placed on the right hand pan and water (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The both pans were balanced by adding an appropriate weight on the left- hand pan. The weight required to detach the tablet from the mucosal surface gave the bio adhesive strength.

Force of adhesion = (mucoadhesive strength/100) ×9.81

***In vitro* swelling studies of buccoadhesive tablets**

Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37°C ±1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula. The results listed in table 12, 13, 14.

% Swelling index = $[(W_2 - W_1)/W_1] \times 100$

IN*VITRO* DISSOLUTION STUDIES OF TABLETS

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP-II, paddle method and 900ml of pH 6.8 phosphate buffers as the dissolution medium and added 0.5% w/v tween 60. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 8hrs in pH 6.8 phosphate buffer at 50 rpm. At definite time intervals i.e. 0.5,1,2,3,4,5,6,7,8 hrsof the aliquot of sample of 5 ml was with drawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 238 nm using uv-spectrophotometer. Cumulative drug release was calculated using the equation (y = 0.045x + 0.001) generated from Beer Lambert's Calibration curve in the linearity range of 2-10 µg/ml.

Dissolution parameters

Apparatus	--	USP-II,
Dissolution Medium	--	pH 6.8 phosphate buffer
RPM	--	50
Sampling intervals	--	0.5,1,2,3,4,5,6,7,8 Hrs.
Temperature	--	37°c + 0.5°c

8. RESULTS AND DISCUSSION

Analytical profile development of drug

UV scan of Nifedipine: The lambda max of nifedipine was found to be 238nm in ph 6.8 phosphate buffer.

Construction of Calibration Curve

Table 1: Calibration curve of Nifedipine in pH 6.8 phosphate buffer at 238 nm.

S.No.	Concentration(µg/ml)	Absorbance(at 238 nm)
1	0 µg/ml	0.00
2	2 µg/ml	0.094
3	4 µg/ml	0.184
4	6 µg/ml	0.270
5	8 µg/ml	0.354
6	10 µg/ml	0.458

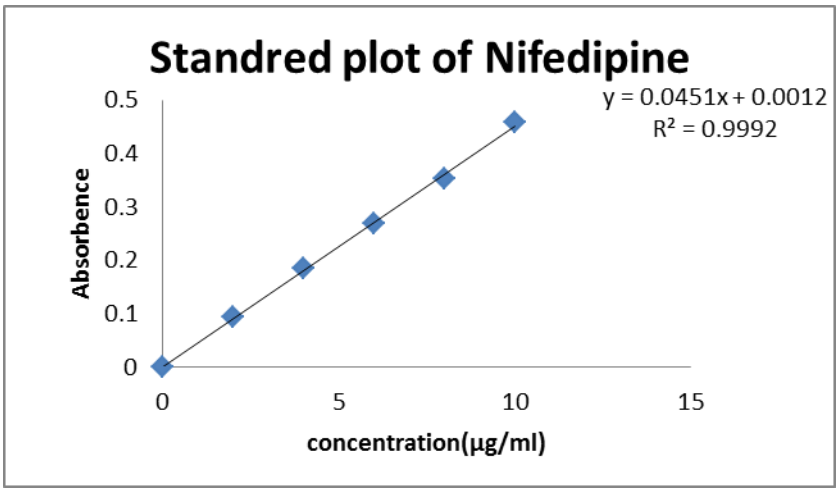

Fig No. 1: Standred Calibration curve of Nifedipine in 6.8 phosphate buffer.

Preformulation study results

Bulk density, Tapped density, % Compressibility index, Hausner ratio and Angle of repose

Table 2: Bulk density, Tapped density, % Compressibility index, Hausner ratio and Angle of repose.

Pre-compression parameters					
Formulations	**Bulk Density (gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle of Repose (Θ)**
F_1	0.50	0.58	13.79	1.16	29.34
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.50	0.58	3.791	1.16	29.34
F_4	0.41	0.50	18	1.21	26.78
F_5	0.41	0.50	18	1.21	26.78
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.50	0.58	13.79	1.16	29.34
F_8	0.46	0.55	16.36	1.19	26.71
F_9	0.45	0.55	18.18	1.22	27.91
F10	0.44	0.52	13.28	1.19	29
F11	0.46	0.55	14.33	1.17	27
F12	0.49	0.57	14.21	1.18	25

Evaluation of Tablets

Evaluation of Avg. Weight, Hardness, Friability, Drug content

Table No.-4.

Formulation	**Avg. Weight (Mean±S.D) (n=20)**	**Hardness ($Kg/cm^{2)}$ (n=3)**	**Friability (n=20)**	**% Drug content (n=3)**
F1	249.6±1.14	4.6±0.1	0.64	98.36
F2	249 ± 1.58	4.63±0.15	0.48	98.56
F3	249± 1.58	5.60±0.10	0.48	98.48
F4	250.4 ± 1.140	5.43±0.20	0.64	98.15
F5	249.4± 1.58	6.60±0.26	0.48	98.76
F6	249.6 ±1.140	4.63±0.15	0.50	99.74
F7	249.4 ± 0.89	6.66±0.15	0.36	98.78
F8	249.4± 1.140	4.10±0.10	0.68	99.76
F9	249.8 ± 1.48	3.63±0.15	0.56	98.98
F10	249.6± 1.140	7.36±0.20	0.32	99.97
F11	249.8± 1.48	6.36±0.20	0.24	99.96
F12	250.4± 1.50	6.66±0.15	0.16	98.97

***In-vitro* mucoadhesion studies**

Table 5: In vitro Mucoadhesion strength of Nifedipine buccoadhesive tablets

Formulation	Bioadhesive strength(gm)
F1	25.8
F2	18.9
F3	30.4
F4	23.6
F5	28.3
F6	19.7
F7	34.6
F8	24.3
F9	22.3
F10	28.6
F11	30.8
F12	40.9

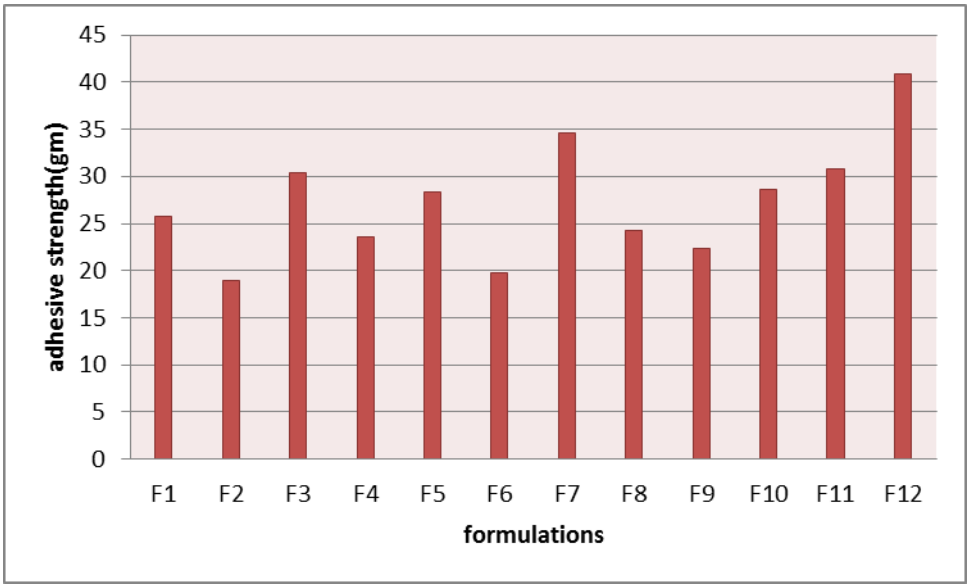

Fig 2: Bioadhesive profile of Nifedipine Mucoadhesive tablets from F1-F12.

Table 7: swelling index results of Nifedipine buccoadhesive tablet formulations from F1-F4.

FORMULATION	0hr	1hr	2hr	3hr	4hr	5hr	6hr
F1	**0**	**0.11**	**0.36**	**0.65**	**0.81**	**0.86**	**0.92**
F2	**0**	**0.08**	**0.12**	**0.19**	**0.23**	**0.45**	**0.68**
F3	**0**	**0.10**	**0.22**	**0.36**	**0.48**	**0.59**	**0.78**
F4	**0**	**0.09**	**0.15**	**0.39**	**0.64**	**0.75**	**0.89**

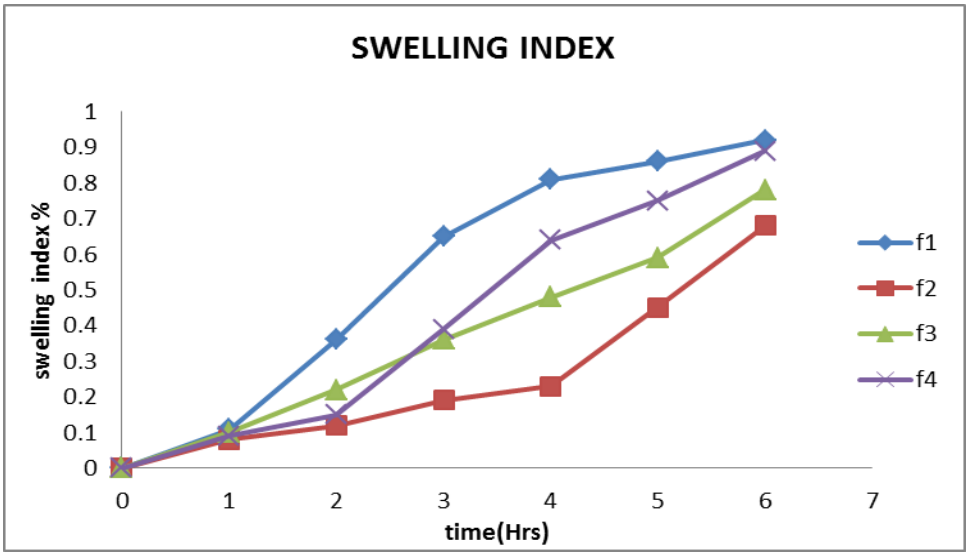

Fig 3: Graph of the Swelling index of formulations from F1 to F4.

Table 8: swelling index results of Nifedipine buccoadhesive tablet formulations from F5-F8.

Formulation	0hr	1hr	2hr	3hr	4hr	5hr	6hr
F5	0	0.07	0.11	0.36	0.45	0.66	0.82
F6	0	0.06	0.11	0.21	0.32	0.54	0.62
F7	0	0.11	0.38	0.63	0.76	0.89	0.96
F8	0	0.12	0.14	0.36	0.59	0.76	0.84

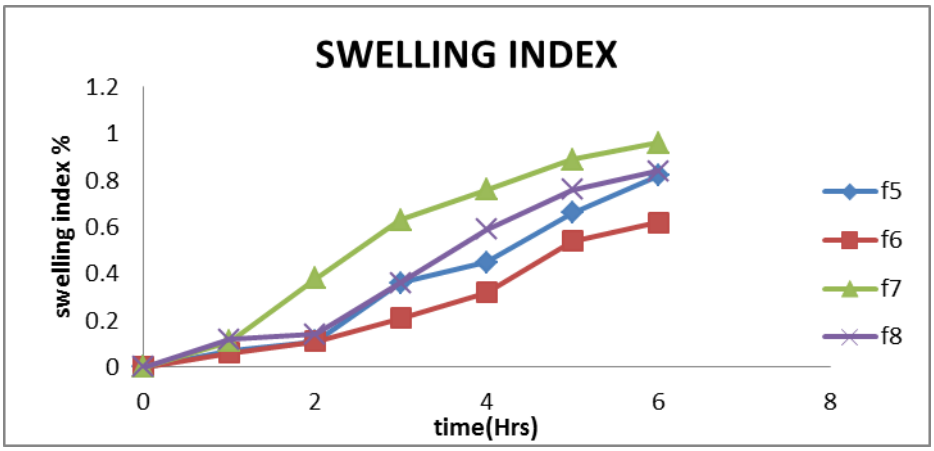

Fig 4: Graph of the Swelling index of formulations from F5 to F8.

Table 9: Swelling index results of Nifedipine buccoadhesive tablet formulations from F9-F12.

Formulation	0hr	1hr	2hr	3hr	4hr	5hr	6hr
F9	0	0.08	0.33	0.54	0.65	0.87	0.92
F10	0	0.06	0.33	0.54	0.65	0.87	0.92
F11	0	0.11	0.22	0.29	0.31	0.49	0.55
F12	0	0.11	0.33	0.67	0.85	1.00	1.21

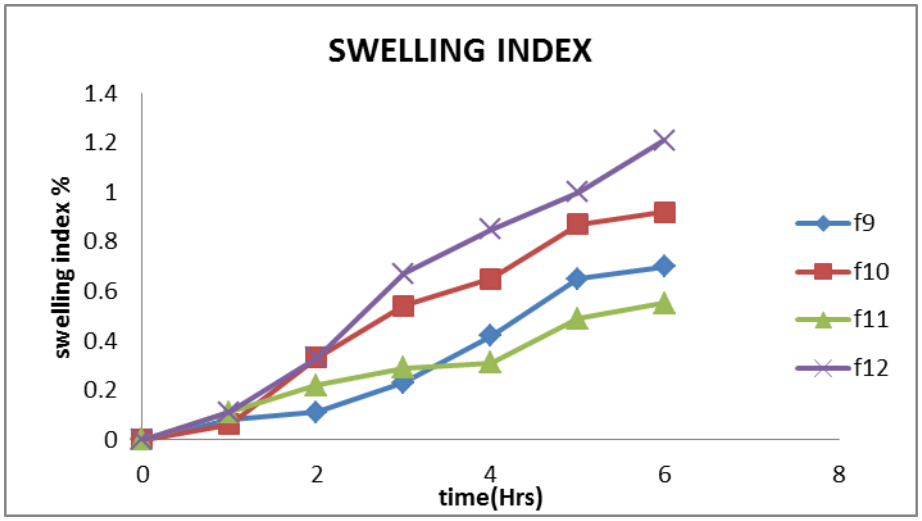

Fig 5: Graph of the Swelling index of formulations from F9 to F12.

***Ex vivo* permeation of buccal tablets**

Table 10: *Ex vivo* permeation data of Nifedipine buccoadhesive tablets of F1, F2, F3, and F4 formulations.

TIME (Hours)ss)	F1	F2	F3	F4
0	0	0	0	0
1	7.53	8.88	10.70	9.75
2	14.08	16.43	22.50	20.50
3	20.50	27.16	30.83	32.00
4	25.33	38.83	40.33	42.50
5	35.83	47.50	47.50	53.33
6	50.50	49.50	56.83	60.50
7	54.00	52.50	61.16	65.83
8	60.50	60.16	65.66	70.33

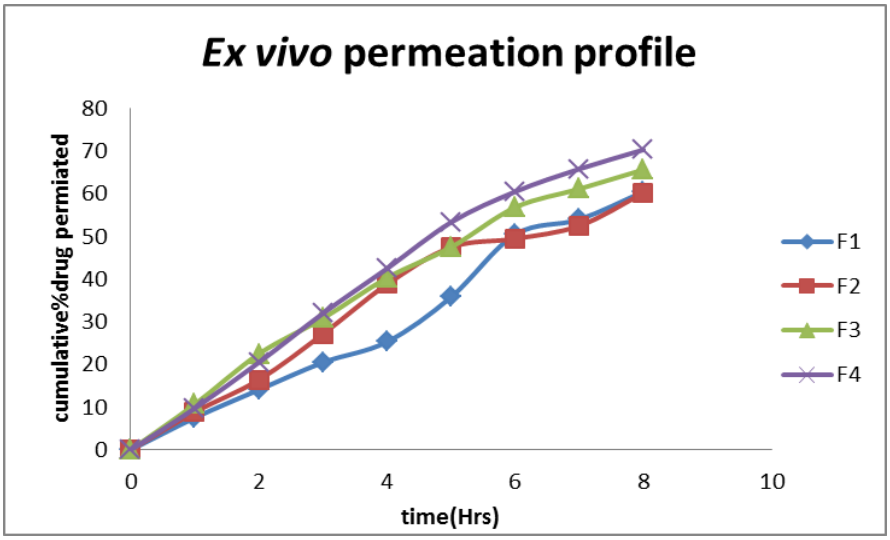

Fig 6: *Ex vivo* permeation profile of tablets of F1, F2, F3 and F4 formulations.

Table 11: *Ex vivo* permeation data of Nifedipine buccoadhesive tablets of F5, F6, F7, and F8 formulations.

TIME (Hours)	F5	F6	F7	F8
0	0	0	0	0
1	12.71	18.00	19.16	12.71
2	25.16	30.83	30.83	25.16
3	37.16	40.33	40.16	36.16
4	49.16	52.16	52.16	52.50
5	57.83	58.50	62.33	64.33
6	68.33	66.16	71.16	70.00
7	70.33	75.83	78.00	82.83
8	76.66	80.33	86.66	92.33

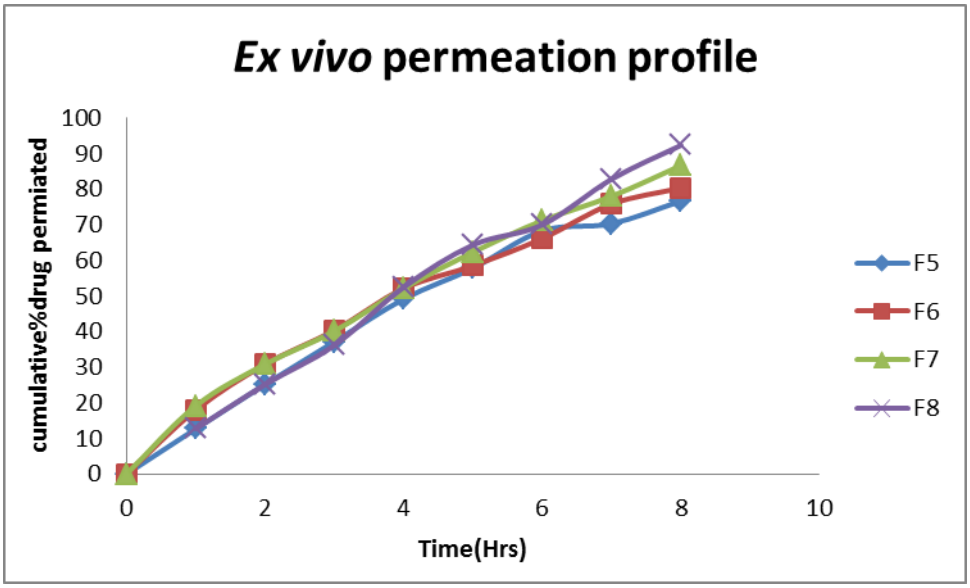

Figure 7: *Ex vivo* permeation profile of Nifedipine buccoadhesive tablets of F5, F6, F7 and F8 formulations.

Table 12: *Ex vivo* permeation data of Nifedipine buccoadhesive tablets of F9, F10, F11, and F12 formulations.

TIME (Hours)	F9	F10	F11	F12
0	0	0	0	0
1	12.90	13.08	13.10	16.61
2	25.83	27.00	30.50	30.50
3	37.00	40.83	39.16	40.83
4	53.3	61.16	52.83	52.83
5	65.00	68.50	58.00	62.83
6	72.16	77.33	65.83	70.33
7	87.00	88.33	75.33	78.00
8	95.66	92.33	80.33	85.33

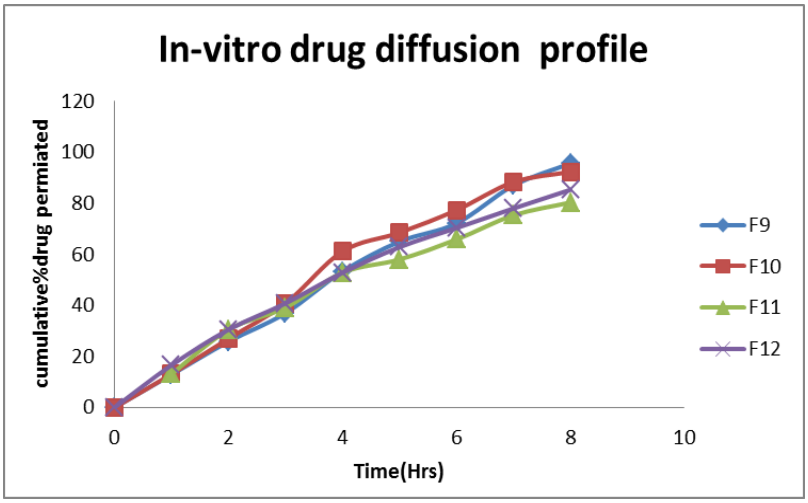

Figure 8: *Ex vivo* permeation profile of Nifedipine buccoadhesive tablets of F9, F10, F11 and F12 formulations.

DISSOLUTION RESULTS

Table 13: Dissolution data of Nifedipine buccoadhesive tablets of F1, F2, F3, and F4 formulations.

TIME (Hours)	F1	F2	F3	F4
0	0	0	0	0
0.5	18.02	15.60	13.06	12.61
1	20.00	23.13	15.53	14.80
2	24.86	27.40	19.80	18.73
3	34.26	33.53	27.40	26.20
4	41.66	37.40	35.01	34.20
5	47.80	39.26	42.93	41.86
6	52.13	45.60	59.40	58.73
7	58.93	54.06	71.33	66.40
8	66.46	68.00	75.33	83.33

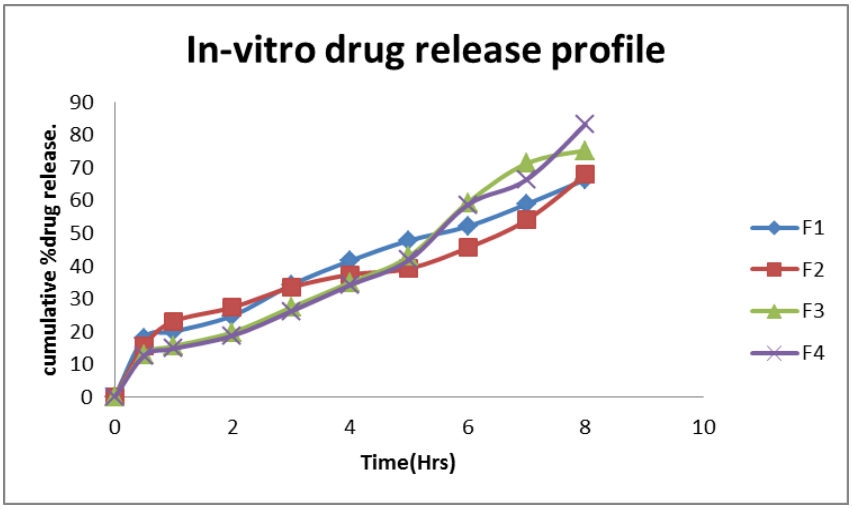

Figure 9: Dissolution profile of Nifedipine buccoadhesive tablets of F1, F2, F3, and F4 formulations.

Table 14: Dissolution data of Nifedipine tablets of F5, F6, F7 and F8 formulations.

TIME(Hours)	F5	F6	F7	F8
0	0	0	0	0
0.5	12.40	13.06	8.26	9.93
1	15.60	16.21	15.66	22.93
2	22.73	22.00	22.80	39.80
3	31.60	29.13	41.33	50.21
4	41.33	40.93	59.73	65.00
5	58.33	57.60	65.26	83.33
6	65.66	65.73	74.00	85.33
7	83.33	74.00	82.00	87.33
8	88.66	87.33	94.66	97.33

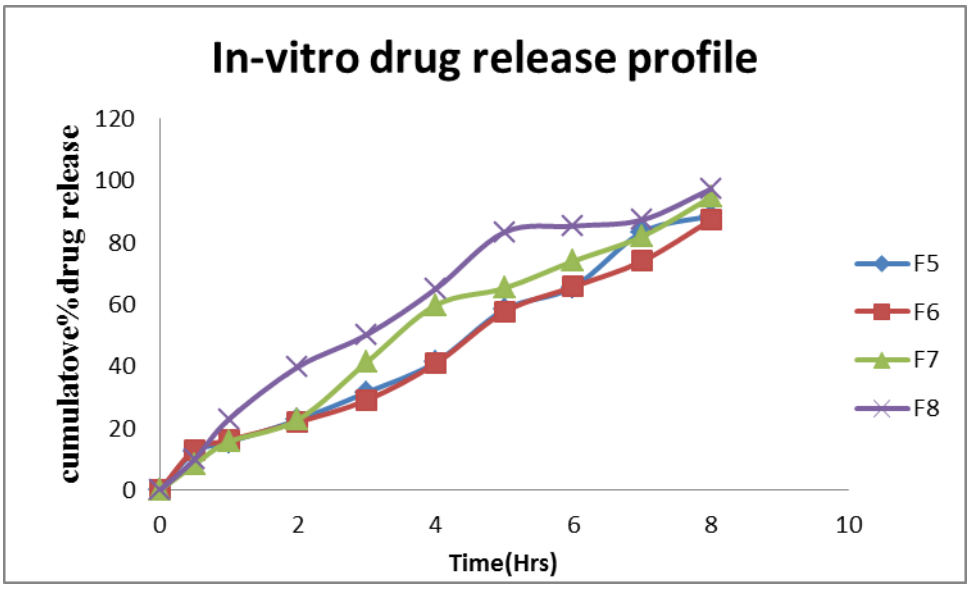

Figure 10: Dissolution profile of Nifedipine buccoadhesive tablets of F5, F6, F7 and F8 formulations.

Table 15: Dissolution data of nifedipine buccoadhesive tablets of F9, F10, F11 and F12 formulations.

Time (Hours)	F9	F10	F11	F12
0	0	0	0	0
0.5	23.26	15	11.60	6.00
1	32.73	24.60	16.66	12.00
2	39.80	32.53	25.86	25.33
3	45.86	39.80	39.20	33.20
4	52.73	49.46	51.06	43.93
5	66.46	59.73	61.33	52.26
6	75.33	66.40	66.46	59.20
7	87.33	83.33	78.00	66.33
8	98.66	94.00	87.33	83.33

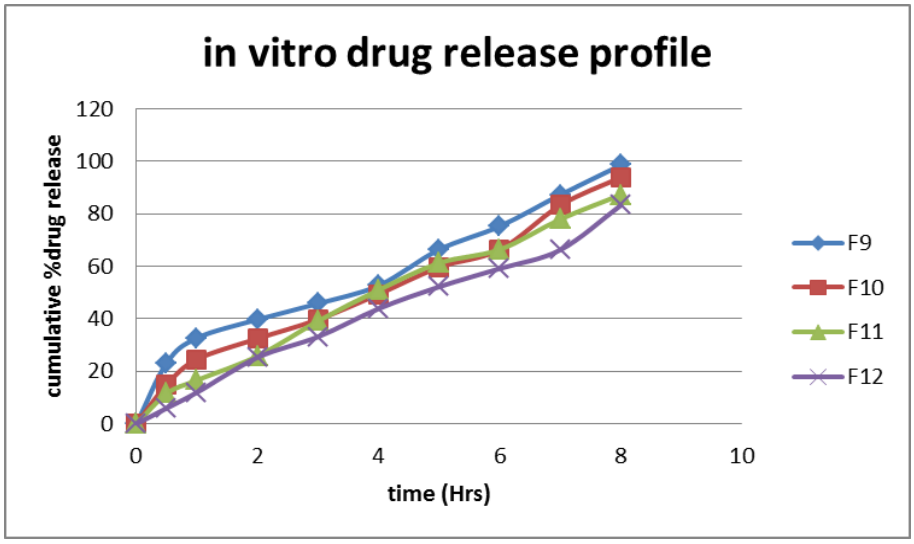

Figure 11: Dissolution profile of Nifedipine buccoadhesive tablets of F9, F10, F11 and F12 formulations.

Release Kinetics

Table 16: Zero order plot of Nifedipine tablet formulation F-9.

Time(Hrs)	Cumulative %drug release
0.5	23.26
1	32.73
2	39.8
3	45.86
4	52.73
5	59.26
6	66
7	87.33
8	98.66

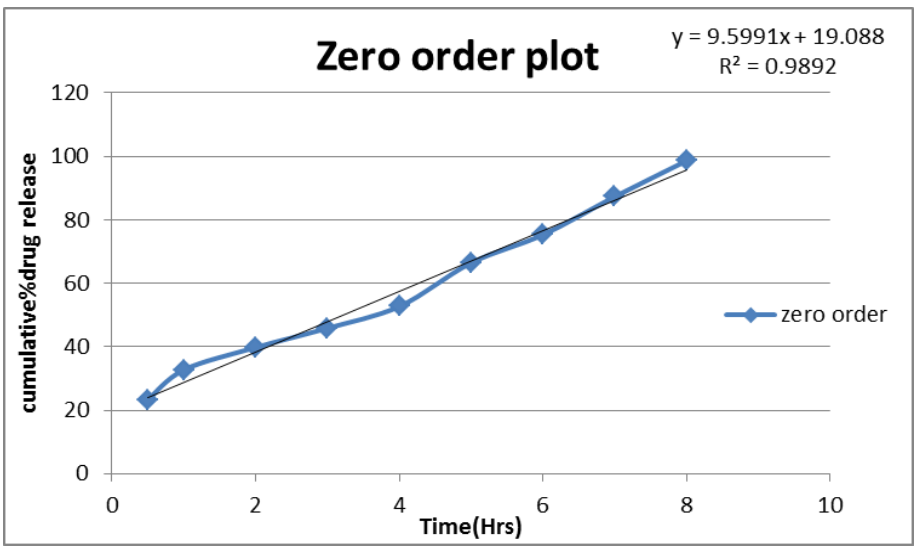

Figure 12: Zero order release kinetics, of Nifedipine tablet formulation F9.

Table 17: First order plot of Nifedipine tablet formulation F-9.

Time(Hrs)	Log cumulative% drug remain
0.5	1.885
1	1.828
2	1.780
3	1.734
4	1.675
5	1.526
6	1.392
7	1.103
8	0.127

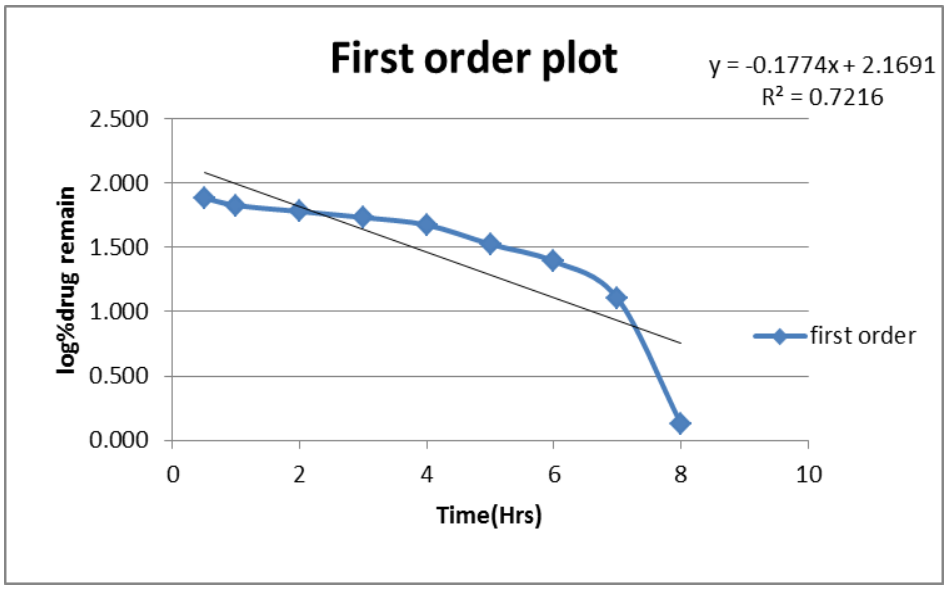

Figure 13: First order release kinetics, of Nifedipine tablet formulation F9.

Table 18: Higuchi plot of Nifedipine tablet formulation f-8.

Root t	Cumulative %drug release
0.707	23.26
1.00	32.73
1.414	39.8
1.732	45.86
2.000	52.73
2.326	59.26
2.449	66
2.646	87.33
2.828	98.66

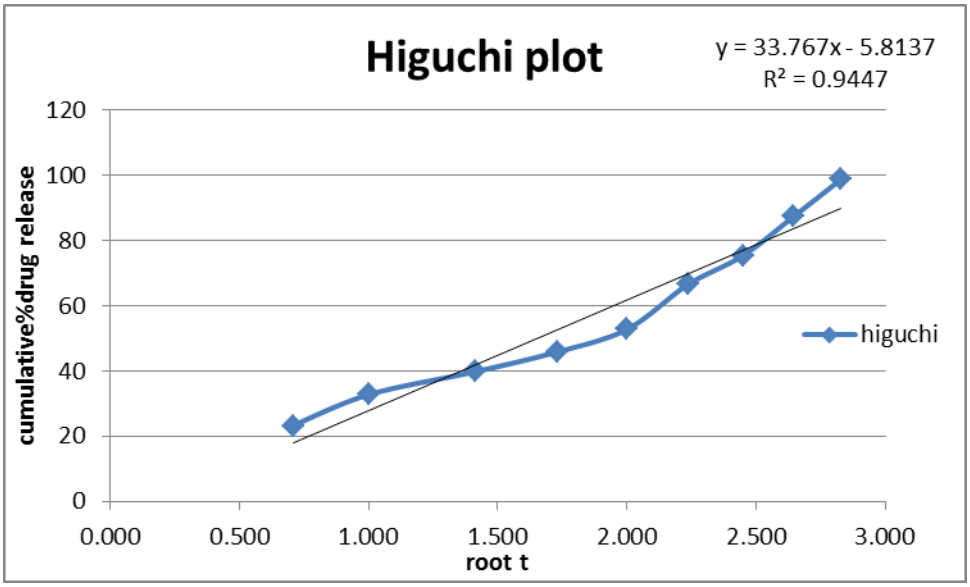

Figure 14: Higuchi drug release kinetics, of Nifedipine tablet formulation F9.

Table 19: Korsmeyer peppas plot of Nifedipine tablet F-8.

Log t	Log cumulative% drug release
-0.301	1.366
0	1.514
0.301	1.599
0.477	1.661
0.602	1.722
0.698	1.772
0.778	1.819
0.845	1.941
0.903	1.994

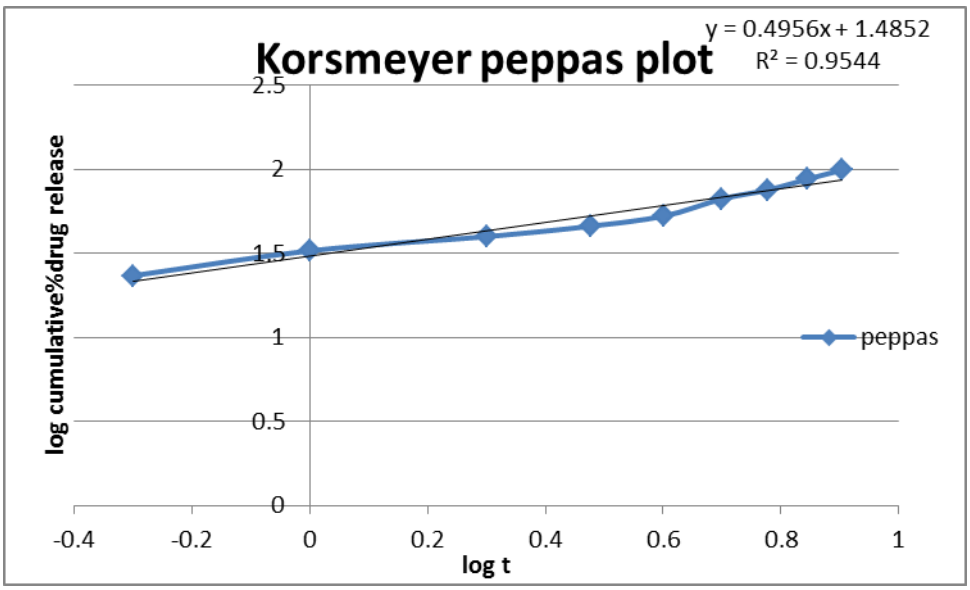

Figure 15: Korsmeyer-Peppas drug release kinetics of Nifedipine tablet f9.

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, HPMC E15 and SodiumCMC were 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.

Drug content and physical evaluation

The assayed drug content in various formulations varied between 98.15% and 99.97%. The average weight of the tablet was found to be between 249.0 mg and 250.4 mg. friability range between 0.16 and 0.68% and thickness of the tablets for all the formulations was found to be between 3.04 mm and 3.22 mm. Buccoadhesive tablets containing Carbopol showed hardness in the range of 7.36 to 5.5 kg/cm ^{2} and it decreased with increasing amounts of SCMC. The hardness of the tablets containing NaCMC was much lower, ranging from 4.60 to 7.2 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.

The bioadhesion and drug release profile are dependent upon swelling behavior of the tablets. Swelling index was calculated with respect to time. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration as shown in [Table -12, 13, 14]. Swelling index measurements could be done up to 6 hours. The swelling indices of the tablets with Carbopol and HPMC increased with increasing amounts of Carbopol. Maximum swelling was seen with the formulations (F12, F7, F10, and F1) containing NaCMC and/or Carbopol, the values increased with increasing amounts of NaCMC and/or Carbopol.[52]

INVITRO DRUG RELEASE STUDIES

In vitro drug release studies revealed that the release of Nifedipine from different formulations varies with characteristics and composition of matrix forming polymers as shown in Figure 18 to 20. The release rate of Nifedipine decreased with increasing concentration of HPMC E15 respectively. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to delay in release of drug from the device. Carbopol is more hydrophilic than HPMC; it can swell rapidly, therefore decrease of

Carbopol content decrease the drug release in F3 and F5 to F7. Drug release rate was increased with increasing amount of hydrophilic polymer. The maximum cumulative percent release of Nifedipine from formulation F9 could be attributed due to ionization of sodium car boxy methylcellulose at pH environment of the dissolution medium. Ionization of sodium carboxymethycellulose and carbopol leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counter ion diffusion inside the gel creates an additional osmotic pressure difference across the gel leading to the high water uptake. This water uptake leads to the considerable swelling of the polymer. The continued swelling of polymer matrix causes the drug to diffuse out from the formulation at a faster rate. Formulations F9, F8, F7, and F10 showed relatively high rate of release of Nifedipine which is due to rapid swelling and erosion of SCMC. Further, the increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water soluble drug. Moreover, the hydrophilic polymers would leach out and hence, create more pores and channels for the drug to diffuse out of the device. Formulation F10 which contains high amounts of NaCMC gets eroded during dissolution study before stipulated study period. Thus higher concentration of NaCMC cannot be incorporated into such formulations for sustaining the release.

Various dissolution parameters computed for all the controlled release buccoadhesive tablets. To examine further the release mechanism of Nifedipine from buccoadhesive tablets, the results were analyzed according to the equation, proposed by Peppa's and Korsemeyer.[40] The obtained values of release rate exponent (n) lie between 0.5901 and 0.8257 in all formulations for the release of Nifedipine. In general, the released pattern found to be non-Fickian tending to approach first order.

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' value in various models is in table 11. The 'r' values obtained for fitting the drug release data to zero order, indicating that the drug release mechanism follows zero 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.

From the above results it is concluded that the drug release from the formulated buccoadhesive tablets of Nifedipine followed first order kinetics and was diffusion controlled.

CONCLUSION

In conclusion, the aim of the present study was to develop buccoadhesive drug delivery system for Nifedipine with a prolonged effect and to avoid first pass metabolism. These buccoadhesive formulations of Nifedipine, in form of buccoadhesive tablets were developed to a satisfactory level in terms of drug release, bioadhesive time, and physicochemical properties.

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 Nifedipine, prepared using Carbopol 934P and HPMC E15 can successfully be employed as a buccoadhesive controlled released during delivery system. Good bioadhesive time of the formulation is likely to increase its buckle 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 Nifedipine over a period of 8 hours was obtained from matrix tablets formulated employing HPMC E15 and Carbopol 934P (F7 Formulation). This tablets exhibited good buccoadhesion. Good oral controlled released bilayered buccoadhesive tablet formulation of Nifedipine could be developed using HPMC E15 and Carbopol 934P.

REFERENCES

1. Ahmad MAHMOOD Mumtaz, hug-sengChng, Evaluation of bioadhesivebuccal tablets containing triamcinolone acetonide in healthy volunteers: International journal of pharmaceutics, 1995; 121: 249-254.
2. B.Taylan, Y.Capan, O.Guven, S.Kes, A.Atillahincal Desion and Evaluation of Sustained release and buccal adhesive propranolol hydrochloride tablets: journal of controlled release, 1996; 38: 11-20.
3. Han gonchoi, J.Jung, C.S.Yong, C.Rhee, M.Lee, J.Han, K.Park, C.Kim: Formulation and invivo evaluation of omiprazolebuccaladhesive Tablet: journal of controlled release, 2000; 68: 405-412.
4. J.Varshosaz, Z.Dehghan: Development and characterization of buccoadhesive nifedipine Tablets: European journal of pharmaceutics and biopharmaceutics, 2002; 54: 135-141.
5. K.P.R. Chowdary, B.Suresh, B.Sangeeta and G.Kamalakara Reddy "*Design and Evaluation of DiltiazemMucoadhesive Tablets for Oral Controlled Release"*of Saudi Pharmaceutical Journal, October 2003; 11(4).
6. G.ikinci, S.Senel, C.G.Wilson, M.Summu Development of a buccalbioadhesive nicotine tablet formulation for smookingcessatlon: international journalof pharmaceutics, 2004; 277: 173-178.
7. SA Sreenivas and KV Pai Thiolated Chitosans: Novel Polymers for Mucoadhesive Drug Delivery – A ReviewTropical Journal of Pharmaceutical Research, September 2008; 7(3): 1077-1088.
8. R Manivannan1, a Balasubramaniam1, DC Prem Anand1, G Sandeepand Rajkumar. Formulation and *In-Vitro* Evaluation of Mucoadhesive Buccal Tablets of Diltiazem Hydrochloride *Research J. Pharm. and Tech*, Oct.-Dec. 2008; 1(4).
9. M.Chandira, Mehul, Debjit, Chiranjib, Kumudhavalli, B.Jayakar, Formulation, Desion And Development of buccoadhesive tablets of virapamil hydrochloride: International journal of pharmatech and research, Oct-Dec 2009; 1(4): 1663-1677.
10. Bhavanipatel, piyushpatel, ashokbhosale, shrawareehardikar, swatimutha, ganeshchaulang: Evaluation of tamarind seed polysaccharide (TSP) as mucoadhesive and sustained release component of nifedipine buccoadhesive tablet & comparision with HPMC and Na CMC.: Int. J. Pharm Tech Res, 2009; 1(3).
11. Harikrishna.B, N.Ravikumar, Pranavb. DennisD.: Controlled release from directly compressible theophylline buccal tablets colloids and surfaces b.biointerfaces, 2010; 77: 227-233.

12. B.Satyabrata, Ellaiah, Mohantychandan, K.V.R Murthy, P.Bibuthibushan and P.Sudhirkumar: desion and in vitro evaluation of mucoadhesivebuccal tablets of perindopril prepared by sintering technique: Asian journal of pharmaceutical and clinical research, 2010; 3(4).
13. A.ankarao, CH.baburao and K.Devanna: formulation and evaluation of buccoadhesivebilayered tablets of carvidilol.
14. Ganesh g. n. k design and development of buccal drug delivery system for Labetalol usingnatural polymer Ganeshg.N.K. IJPRD, 6 May 2011; 3(3): 37-49. international standard serial number 0974 – 9446.
15. Rahul saxena, T.A. Premchandani, R.C. Saxena formulation and evaluation of buccoadhesivetablet of montelukast sodium asian journal of pharmaceuticaland clinical research, 2011; 4(4).
16. Swamy P.V.*, Kinagi M. B., Biradar S. S., Gada S. N. and Shilpa H Formulation Design and Evaluation of Bilayer Buccal Tablets of Granisetron Hydrochloride Indian Journal of Pharmaceutical Education and Research *Submitted: 26/4/2010 Revised: 3/7/2010 Accepted: 11/1/2011*.
17. 17.B. ArunPrasanth*, R. Sankaranand, V. Venugopal, M. Anoosha, P. Sunitha, T.Swetha, P. Laxmi and A. Lalitha Effect of Moringa Gum in Enhancing Buccal Drug Delivery of Propranolol Hydrochloride IJRPC, 2011; 1(2): ISSN: 2231-2781.
18. B. AGAIAH GOUD*, KUMARA SWAMY.S* AND PRAVEEN KUMAR. V* FORMULATION AND EVALUATION OF BIOADHESIVE BUCCALTABLETS OF SIMVASTATIN Journal of Advanced Pharmaceutical Sciences JAPS, 2011; 1(1).
19. Surender Verma, Mahima Kaul*, Aruna Rawat and Sapna Saini: AN OVERVIEW ONBUCC AL DRUG DELIVERY SYSTEM Kaul*et al*., IJPSR, 2011; 2(6): 1303-1321.
20. RAJESH MUJORIYA: A Review on study of Buccal Drug Delivery System ISSN 2222-1727 (Paper) ISSN 2222-2871 (Online), 2(3).
21. Pranshu Tangri*,1, N.V. Satheesh Madhav1 ORAL MUCOADHESIVE DRUG DELIVERY SYSTEMS: A REVIE *International Journal of Biopharmaceutics*, 2011; 2(1): 36-46.
22. S.D.Gandhi, PriyankaR.Pandya, rahulumbarkar, tanvitambawala, monojA.Shah Wong FC, Yuen KH, Peh KK. Formulation and Evaluation of Controlled Release Eudragit Bucccal Patches. Int J Pharm, 1999; 178: 11-2.
23. Naveet Verma, Pronobesh Chattopadhyay: Polymericplotform for mucoadhesivebuccal drug delivery system: a review: ISSN 0975-7066, 2011; 3(3).

24. Stuti Gupta Singh*1, Ravindra Pal Singh2, Shivjee Kumar Gupta1, Renu Kalyanwat1, Sudhir Yadav1: Buccal Mucosa as a route for Drug Delivery: Mechanism, Design and Evaluation: RJPBCS, July – September 2011; 2(3).
25. Nahid Sharmin, Md. Elias-al-Mamun, Md. Saiful Islam and Reza-ul Jail: Preparation and Charecterization of lidocaine double layer buccal tablet using mucoadhesive Carbopol Polymers: Dhaka univ. J. Pharm. Sci, 20011, June; 10(1): 29-34.
26. Marriott, C. and Gregory, N.P., Mucus physiology. In: V.Lenaerts and R.Gurny, Bioadhesive Drug Delivery Systems, CRC Press, Boca Raton, FL, 1990; 1-24.
27. Marriott, C.and Hughes, D.R.L., Mucus physiology. In: R.Gurny and H.E.Junginger, Bioadhesion-possibilities and Future Trends, Wissenschaftliche Verlagsgesellschaftmb H, Stuttgart, 1990; 29-43.
28. Langer, R.S. and Peppas, N.A., New Drug Delivery Systems. BMES Bull., 1992; 16: 3-7.
29. Peppas, N.A and Buri, p.a., Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J. Controlled Release, 2: 257-275.
30. Nicholas A. Peppas, Mounica D.Little, and Yanbin Huang, Bioadhesive Controlled Released Systems, 255-269.
31. 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.
32. S. J.Hwang, H. Park and K. Park, "Gastric Retentive Drug-Delivery Systems", Crit. Rev. Ther. Drug Carrier Syst, 1998; 15(3): 243–284.
33. L. Whitehead, J. T. Fell and J H Collett, "Development of a Gastroretentive Dosage Form", Eur. J. Pharma. Sci., 1996; 4(1): 182.
34. P. Mojaverian, P. H. Vlasses, P. E. Kellner and M. Rocci, "Effects of gender, posture and age on gastric residence time of an indigestible solid: pharmaceutical considerations", Pharm. Res., 1988; 10: 639–644.
35. Singh B, Ahuja N. Response surface optimization of drug delivery system. In: Jain NK, ed. *Progress in Controlled and Novel Drug Delivery Systems.* New Delhi, India: CBS Publishers and Distributors, 2004; 20: 240.
36. N. R. Jimenez-Castellanos, H. Zia and C. T. Rhodes, "Mucoadhesive drug Delivery Systems", Drug Dev. Ind. Pharm, 1993; 19: 143.
37. Vasir JK, Tambwekar K, GargS. Bioadhesive microspheres as a controlled drug delivery. J Control Release, 1998; 55: 143-52.
38. Polymer profile Good R.J. Adhesion, 8(1): 1976.
39. Choudary KPR., Srinivas L. Indian Drugs, 2000; 37(9): 400.

40. S.B.Patil, R.S.R.Murthy, pharma times, Apr. 2006; 38(4)
41. Vyas and Khar, targetted drug delivery systems, 2004; 124.
42. Das, N.G., Das, S.K., Controlled Release of Oral Dosage forms, Pharm. Tech., 2003; 6: 10-16.
43. Berressem, P., The Birth of New Delivery Systems, Chem. Britain, 1999; 35(2): 29-32.
44. Jha, S.K, Intellectual Property Rights and Globalization of the Pharmaceutical Industry, Pharma Times, 2003; 35(3): 13-22.
45. Shukla, S., Prasad, S., Sharma, E.K., The Opportunities for Indian Pharma., Out Look, 2002 Oct.-13; 41-49. 5. Nagai, T. and Machida, Y., Mucosal Adhesive Dosage Forms, Pharm. Int., 1985; 196-200.
46. Bodde, H.E., De Vries, M.E. and Junginger, H.E., Mucoadhesive Polymers for the Buccal Delivery of Peptides, Structure-Adhesiveness Relationships, J. Control. Rel., 1990; 13: 225-231.
47. Mathiowitz, E., Chickering, D., Jacob, J. S.and Santos, C., In; Mathiowitz, E., Eds, Encyclopedia of Controlled Drug Delivery, Vol. 1, John Willey & Sons, New York, 1999; 9-44.
48. Devarajan, P.V. and Adani, M.H., In; Jain, N.K., Eds, Controlled and Novel Drug Delivery, CBS Publishers & Distributors, New Delhi, 2002; 52-81.
49. Squier, C.A., The Permeability of Oral Mucosa, Crit. Rev. Oral Biol. Med., 1991; 2: 13-32.
50. Squier, C.A. and Wertz, P.W., Structure and Function of the Oral Mucosa and Implications for Drug Delivery, in, M.J. Rathbone, Eds; Oral Mucosal Drug Delivery, Marcel Dekker, Inc., New York, 1996; 1-26.
51. SB Shirsand, Sarasija Suresh, GG Keshavshetti, PV Swamy, P Vijay Prakash Reddy: Formulation and optimization of mucoadhesive bilayer buccal tablets of atenolol using simplex design method: International journal of pharmaceutical investigation. 2012; 2(1): 34-41.