Research Article
ISSN: 0974-6943

Bangale G.S et al. / Journal of Pharmacy Research 2011,4(1),33-38

Available online through
http://jprsolutions.info

Natural Mucoadhesive Material Based Buccal Tablets of Nitrendipine-Formulation and *In-vitro* Evaluation.

Bangale G.S*[1], Shinde G.V.[1] Umalkar D.G.[1], Rajesh K.S.[2]
[1.] *Dept.of Pharmaceutics, Parul institute of Pharmacy, Vadodara, Gujarat.*
[2.] *Indo Soviet Friendship College of Pharmacy, Ghalkalan Moga, Punjab.*

Received on: 15-09-2010; Revised on: 14-10-2010; Accepted on:13-12-2010

ABSTRACT

In present investigation an attempt was made to formulate and evaluate oral buccoadhesive tablets of Nitrendipine using some natural mucoadhesive material like Zizyphus maurtiana(Jujube), Tamarind seed polysaccharide(TSP),also synthetic polymers like sodium CMC and HPMCK15M was tried .Prepared buccal tablets were comparatively evaluated for their physicochemical parameters like weight variation, hardness, friability, drug content uniformity test. The surface pH,swelling index,bioadheive strength ,in-vitro residence time ,ex-vivo permeation test also carried out which has been important aspect for success of mucoadhesive buccal tablets all these parameters were evaluated shows comparatively better results in formulation containing natural mucoadhesive material than synthetic polymers. In vitro drug release rate of Nitrendipine prepared from this material was studied in isotonic phosphate buffers solution of pH 6.6 at 37 ± 0.5^{0}c from this it was found that mucoadhesive buccal tablets prepared from natural mucoadhesive material exhibited extended drug (85%) release up to 10 hrs compared to tablets prepared from synthetic material like sodium CMC and HPMCK15M.Drug release from tablets followed non-fickian diffusion controlled and zero order kinetics pattern up to 10 hrs.

Key words: Buccal tablet, Zizyphus maurtiana(Jujube), Tamarind seed polysaccharide (TSP), Swelling index, Nitrendipine.

INTRODUCTION

The term of bioadhesion is used to describe to describe the attachment of synthetic and natural polymers to biological surface like eye ,nose ,buccal,intenstine ,rectum vagina[1].If the adhesion surface is mucous membrane coated with thin layer of mucus the term mucoadhesion is employed [2] .Among above system buccal mucosa offers many advantages relatively large surface area for absorption ,easy accessibility, simple delivery devices, avoid first pass metabolism due to direct absorption via buccal mucosa and reaches into systemic circulation and feasibility of controlled drug delivery [3].Recent years have seen an increasing interest in the development of mucoadhesive buccal dosage forms like buccal films.gel,patches used both systemic delivery of drug as well as local treatment of buccal cavity .The bioadhesive potential of different material is an important parameter and to determine the same several techniques are reported [4].Few drug that has been attempted as buccal tablets and films were nifedipine,propanolol hydrochloride,carvedilol ,diltiazem hydrochloride[5].Nitrendipine is a calcium channel blocker used in treatment of mild to moderate hypertension, chronic stable angina pectoris and Prinz metals variant angina [6].It undergoes extensive hepatic first pass metabolism with its oral bioavailability 11% with duration of action ranges from 4-48 hrs.Hence there is need of alternative route for administration. It is a potent molecule with dose 20 mg daily with low molecular weight and lipid solubility [7].These drug characteristics favour its absorption via buccal route. Since the biodegradability of the synthetic polymers is questionable, some natural mucoadhesive materials extracted from edible fruits and tamarind seed meal having good mucoadhesive properties are used for this purpose [8]. Hence objective of present study to develop mucoadhesive buccal tablet of Nitrendipine using various natural as well as synthetic mucoadhesive polymers to circumvent of first pass metabolism of drug and improve its bioavailability by controlling the release rate for prolong period of time with desired therapeutics effect.

MATERIAL AND METHOD.

Nitredipine was obtained as gift sample from M/s Camlin ltd.Mumbai.HPMCK15M, SodiumCMC was obtained from loba chemicals,Mumbai,Tamarind seed polysaccharide powder (TSP) was isolated from tamrindus indica seed. The fruits of Zizyphus mauritiana Lam. were purchased from local market. All other chemicals and material used are of analytical grade.

Methodology.

Extraction of Z.mauritiana. The mucilage from above materials was extracted as per method reported Rao et al. [9] with little modifications. In this method, 250 g edible fruits of *Z.* Mauritiana were soaked in double distilled water and boiled for 5 h in a water bath until slurry was formed. The slurry was cooled and kept in refrigerator overnight so that most of the undissolved portion was settled out. The upper clear solution was decanted off and centrifuged at 500 rpm 20 min. The supernatant was concentrated at 60ºC on a water bath until the volume reduced to one third of its original volume. Solution was cooled down to the room temperature and was poured into thrice the volume of acetone by continuous starring. The precipitate was washed repeatedly with acetone and dried at 50º C under vacuum. The dried material was powdered and kept in desiccators.

Isolation of TSP. The alcohol-insoluble fraction from the water extract of tamarind seed meal, constituting 60 to 65 per cent of the husked kernel, has been described as a rich source of polysaccharides. TSP was prepared following methods by Rao et al., [10,11] in three batches on a laboratory scale. To 20g of tamarind kernel powder, 200ml of cold distilled water was added and slurry was prepared. The slurry was poured into 800ml of boiling distilled water. The solution was boiled for 20 minutes under stirring condition in a water bath. The resulting thin clear solution was kept overnight so that most of the proteins and fibres settled out. The solution was then centrifuged at 5000 rpm for 20 minutes. The supernatant was separated and poured into twice the volume of absolute alcohol by continuous stirring. The product was pressed between felt. The precipitate was washed with absolute ethanol, diethyl ether and petroleum ether and then dried at 50-60° C under vacuum. The dried material was ground and sieved to obtain granules of different particle size range. The particle size range of 150-75 microns was used for preparation of tablets.

Preparation of Mucoadhesive buccal tablets of Nitredipine.

Buccal tablets, each containing 20 mg of Nitredipine, were prepared by conventional wet granulation method using flat face 6 mm punch (Cadmach Machinery Co Pvt. Ltd., India) employing synthetic mucoadhesive polymer as sodium CMC,HPMC K15M.and natural material like Z. mauritiana and TSP (table 1) The tablets weight was adjusted for 120 mg.

Table No.1- Composition of Buccoadhesive tablets of Nitrendipine

Ingredient (mg/tablet.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Nitrendipine	20	20	20	20	20	20	20	20	20	20
Sodium.CMC	40	60	—-	—-	30	—-	—-	—-	—-	—-
HPMC K15M	—-	—-	40	60	30	—-	—-	—-	—-	—-
Z.mauritiana	—-	—-	—-	—-	—-	40	60	—-	—-	30
T.S.P.	—-	—-	—-	—-	—-	—-	—-	40	60	30
D.C.P.	56	36	56	36	36	56	36	56	36	36
Talc	2	2	2	2	2	2	2	2	2	2
Mg.Sterate	2	2	2	2	2	2	2	2	2	2
Ratio	1:2	1:3	1:2	1:3	1:1.5:1.5	1:2	1:3	1:2	1:3	1:1.5:1.5

Total weight. 120 mg.

***Corresponding author.**
Bangale G.S
Dept.of Pharmaceutics,
Parul institute of Pharmacy, Vadodara, Gujarat.
***Tel.: + 91**-09377157022*
***E-mail:**gsbangale@yahoo.co.in*

Evaluation of Mucoadhesive buccal tablets of Nitrendipine.

Preformulation studies.

Bulk density.[12] A sample of powder of drug/polymer was introduced into 25 ml graduated cylinder. The bulk volume (vb) of material was noted on graduated cylinder. The bulk density was calculated by the formula,

$$\text{Bulk density (?) } (gm/cm^3) = \frac{\text{Weight of drug /polymers}}{\text{Bulk volume of drug /polymers}} = \frac{M}{Vb}$$

Tapped density .[13] Drug /polymers powder was filled in graduated cylinder and then tapping was done 500 times initially and the tapped volume (Vt) was measured to nearest graduated unit. The tapped density was calculated by the formula,

$$\text{Tapped density (rt)} = \frac{\text{Bulk volume (Vb)}}{\text{Tapped volume (Vt)}}$$

Compressibility index:[14]- The compressibility index is measures of the propensity of a powder to be compressed. Compressibility index of drug / polymers was calculated by the formula,

$$\text{Compressibility index (I)} = \frac{\text{Tapped density (rt)} - \text{Fluff density(rb)}}{\text{Tapped density (rt)}} \times 100$$

Hausner ratio:[15]- The Hausner ratio is an index of ease of powder flow. It is calculated by following formula.

$$\text{Hausner ratio} = \frac{\text{Tapped density (rt)}}{\text{Bulk density (rb)}}$$

Table No.2 Preformulation studies of Drug and Polymers.

Sr no	Drug and Polymers	Bulk density* (gm/cm ^{3})	Tapped density* (gm/cm^3)	Compressibility Index* (%)	Hausner Ratio	Angle of repose(?)
1.	Nitrendipine	0.277± 0.021	0.326 ± 0.051	15.08 ± 1.04	1.17	$21^0 39'$
2.	SodiumCMC	0.357 ± 0.01	0.442 ± 0.0131	19.20 ± 0.298	1.23	$25^0 74'$
4.	HPMCK15M	0.333 ± 0.015	0.486 ± 0.0125	31.48 ± 0.305	1.45	$28^0 58'$
5.	T.S.P.	0.256 ± 0.019	0.381 ± 0.129	32.39 ± 1.86	1.48	$32^0 74'$
6.	Z. mauritiana	0.312 ± 0.05	0.445 ± 0.0331	29.42 ± 0.041	1.41	$30^0 17'$

Each value represents Mean ±S.D. (n =3)

Drug content uniformity.[16] An (UV) ultraviolet spectrophotometric method based on measurement of absorbance at 235nm in isotonic phosphate buffer of pH 6.6 was used for estimation of Nitredipine. The method obeys Beers-Lamberts law in concentration range from 10 to 50 µm.

Weight variation.[17] For evaluation of weight variation twenty tablets from each batch were taken and weight individually on digital balance (fisher brand PS -200) they were calculated and measured as per I.P. specification.

Hardness and Friability.[18] Hardness was determined using Monsanto hardness tester and friability test was performed using Roche friabilator.

Thickness.[19] Three tablets were selected from each batch and thickness was measured by using vernical calliper.

Table No. 3 -Physicochemical evaluation of buccal tablets.

Batch no.	Weight variation*	Thickness* (mm)	Hardness* kg/cm 2	Friability (%)	Drug content uniformity*(%)
F1	Pass	1.82±0.01	6.4±0.02	0.26	99.8±0.4
F2	Pass	1.91±0.02	7.2±0.01	0.29	97.2±0.5
F3	Pass	1.98±0.01	6.3±0.04	0.33	100.4±0.5
F4	Pass	2.00±0.03	6.1±0.03	0.27	101.2±1.0
F5	Pass	1.96±0.04	7.1±0.02	0.32	99.8±0.4
F6	Pass	1.83±0.03	6.3±0.01	0.40	100±1.1
F7	Pass	1.86±0.02	6.6±0.02	0.50	98.6±0.3
F8	Pass	1.84±0.05	7.5±0.05	0.56	100±0.4
F9	Pass	1.89±0.01	7.3±0.01	0.63	98.1±0.2
F10	Pass	1.91±0.01	7.6±0.03	0.52	100±0.3

Each value represents Mean ±S.D. (n =3)

Surface pH.[20] To investigate the possibility of any side effect on oral cavity due to acidic or alkaline pH is found to cause irritation to buccal mucosa ,hence surface pH of tablets was determined Buccal tablets were left to swell for 2 hrs.on the surface of Agar (2% w/v) plate the surface pH was measured by means of pH paper placed on the core surface of swollen tablets .

Swelling index study.[21,22] Swelling study was performed on 1% agar gel plates. Twenty tablets were weighed and average weight of each four tablets was calculated. The tablets were placed on the gel surface in five Petri dishes (each containing four tablets), which were placed in an incubator at 37°C. Four tablets were removed at time intervals of 1, 2,3, 4,5 and 6 hrs, excess water from the surface was carefully soaked using filter paper, and swollen tablets were weighed. The swelling index was calculated by using formula,

$$\text{Swelling index} = \frac{\text{Wet weight - Dry weight}}{\text{Wet weight}} \times 100$$

In vitro residence time.[23,24] In vitro residence time for tablets was determined using USP disintegration apparatus. The disintegration medium was composed of 800 ml of isotonic phosphate buffer of pH 6.6 maintained at 37°C .A segment of goat buccal mucosa ,3 cm length was glutted to glass slab. The tablet surface was hydrated using 15 ml pH 6.6 I.P.B.and then hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to tablets was completely immersed in the buffers solution at lowest and wash out at highest point the time necessary for complete erosion or detachment of tablets from mucosal surface was determined.

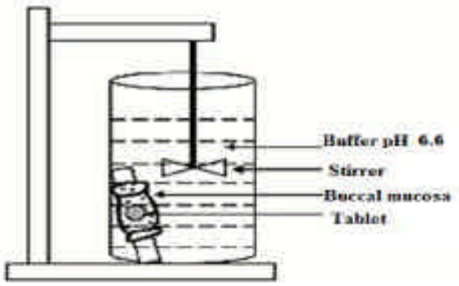

Figure 1.Schematic representation of in-vitro Residence Time.

Bioadhesive strength.[25,26] Bioadhesive strength of the tablets was measured on a modified physical balance . The apparatus consist of a modified double pan physical balance in which a lighter pan has replaced the right pan and left pan had been replaced by a Teflon cylinder (diameter and height) suspended by Teflon ring and copper wire. The left side of the balance was exactly 5 g heavier than the right side. Another Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on one side. This was kept in Petri dish, which was then placed below the left hand set of the balance. Porcine buccal mucosa was used as the model membrane and isotonic phosphate buffer pH 6.6 solutions were used as a moistening fluid. Porcine buccal mucosa was obtained from slaughterhouse was kept in Kerb's buffer of pH 7.4 at 37^0C for 2 hours. The underlying mucus membrane was separated and washes thoroughly with phosphate buffer pH 6.6 solutions. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in Petri dish. Two side of the balance were made equal, before the study keeping a 5 g weight was placed on the right pan. Petri dish with Teflon block was kept below the left hand set up of the balance. The tablet was stuck on to the lower side of the hanging Teflon cylinder. Five-gram weight from the right pan was then removed. This lowered the Teflon cylinder along the tablet over the membrane with a weight of 5 g. this was kept undisturbed for five minutes. Then the weight on the right hand side was slowly added in an increase weight of 0.5 g until the tablet just separated from the membrane surface. The excess weight on the right pan i.e. total weight minus 5 g was taken as a measure of the mucoadhesive strength. From the mucoadhesive strength following parameter was calculated and given in table no.4.

$$\text{Force of adhesion (N)} = \frac{\text{Bioadhesive strength}}{100} \times 9.81$$

Figure 2.In-vitro mucoadhesive strength measurement apparatus

FOOTNOTES; A – Pointer, B – Pan, C – Teflon ring for balancing, D – Teflon cylinder for sticking the tablet, E – Teflon block with protrusion, F – Copper wire

Table No.4 - Mucoadhesive strength, swelling index and In-vitro residence times.

Formulation code	Mucoadhesive strength (gm)	In-vitro residence time	%Swelling index. (after 6 hrs study)
F1	16.50	3 hrs 7 min.	Tablets breaks
F2	18.23	3 hrs 18 min.	58.66
F3	17.33	4 hrs	197.17
F4	17.97	4 hrs 23 min.	216.50
F5	18.92	4 hrs 34 min	198.10
F6	19.05	6 hrs	237.47
F7	19.86	6 hrs 32 min.	250.11
F8	20.12	6 hrs 48 min	269.29
F9	20.88	6 hrs 43 min	277.12
F10	21.57	7 hrs 13 min	298.50

In-vitro release study.[27,28] Standard USP or IP dissolution apparatus have been used to study in vitro release profile using both basket and rotating paddle. In vitro release rate study of buccal tablets of nitrendipine was carried out using the Apparatus 2 (Basket apparatus) method. Place the tablet in a dry basket at the beginning of each test. Lower the Basket before rotation operates the apparatus immediately at 50 rpm. Medium used for release rate study was 900 ml isotonic phosphate buffer pH 6.6 during the course of study whole assembly was maintained at 37±0.5 ^{0}C. Withdraw a 5 ml of sample at time interval of 1,2,3,4, up to 10 hr and replaced with 5 ml of fresh dissolution medium. The withdrawn samples were appropriately dilute with dissolution medium and then filter it with whattman filter paper and % release of nitrendipine was determined spectrophotometrically at 235nm.against isotonic phosphate buffers pH 6.6 as blank.

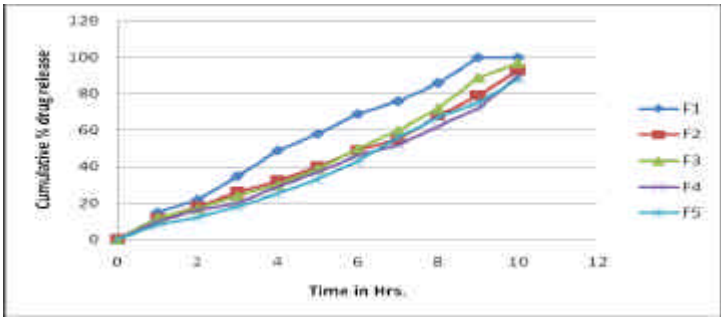

Figure 3 . In-vitro release profile of tablets (F1toF5) -Zero order plot.

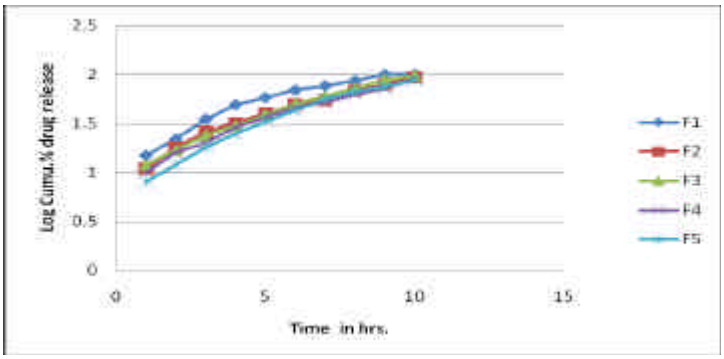

Figure.4- In-vitro release profile of tablets (F1to F5)-First order plot.

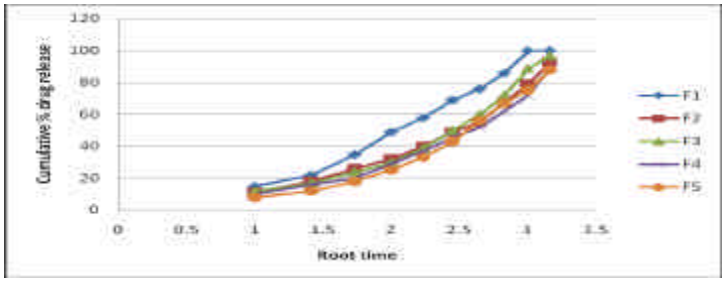

Figure.5- In-vitro release profile of tablets (F1to F5)- Higuchi's plot

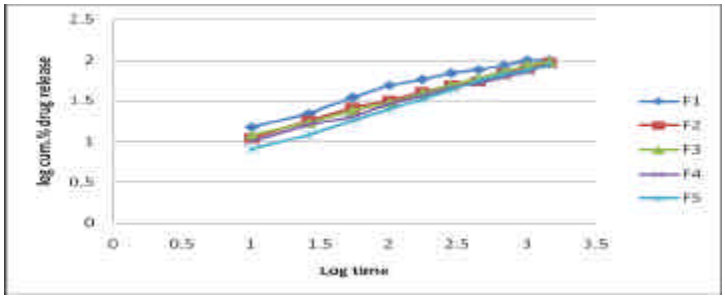

Figure.6- In-vitro release profile of tablets (F1to F5)-Peppas plot.

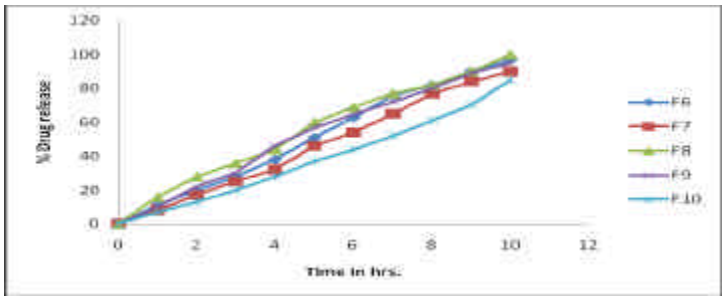

Figure.7- In-vitro release profile of tablets (F6to F10)-Zero order plot

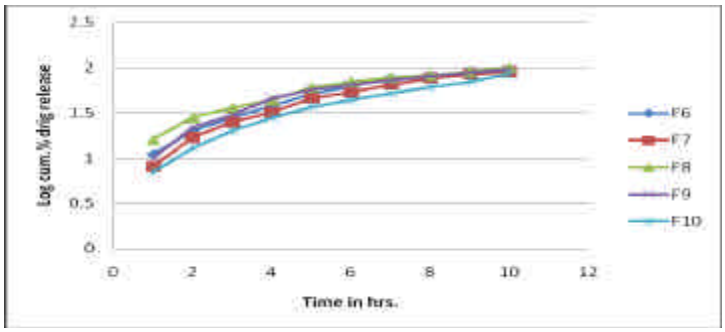

Figure.8- In-vitro release profile of tablets (F6to F10)-First order plot.

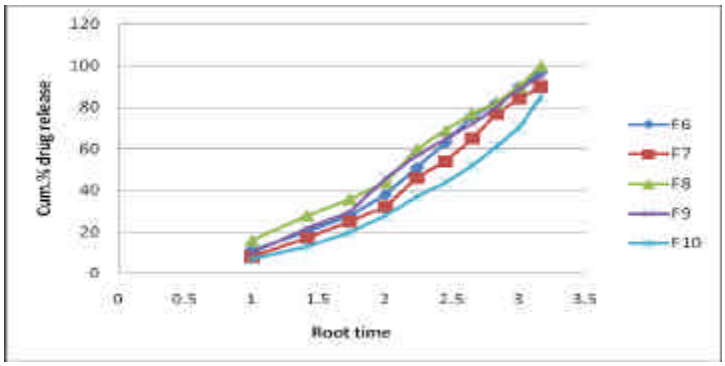

Figure.9- In-vitro release profile of tablets (F6to F10)-Higuchi's plot.

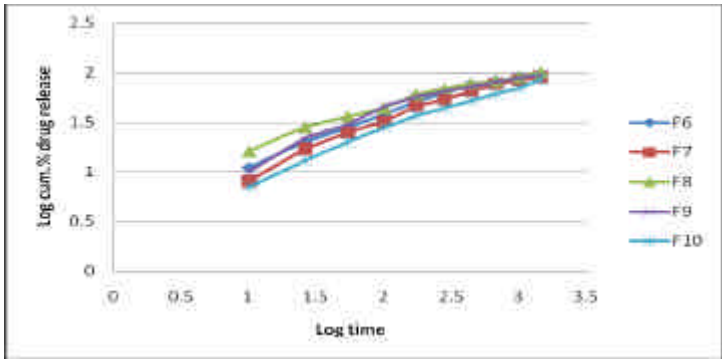

Figure.10- In-vitro release profile of tablets (F6to F10)-Peppas plot.

Ex-vivo Permeation study of optimized batch (F-10).[29]

Ex-vivo diffusion study of buccal tablet was carried out using fresh porcine oral mucosa tissue, which was procured from local slaughterhouse and placed in Krebs buffer pH 7.4. Isolation of the epithelium was done mechanically by using scissors and forceps. These studied were carried out using open end cylinder method .The mucous membrane was tied to one end of the two sided open ended cylinder, which acted as donor compartment. The buccal tablet containing 20 mg of Nitrendipine was kept on the mucous membrane, in such a way that the lower surface of the tablet was in contact with the mucous membrane then the donor compartment was fixed, so that mucous membrane was in contact with the receptor medium (Beaker), 100 ml of isotonic phosphate buffer, (pH 6.6) in the receptor compartment. Samples of 5 ml were withdrawn at periodic intervals from the receptor compartment and replaced with the fresh isotonic phosphate buffer immediately and after suitable dilution the drug content was analyzed spectrophotometrically at 235nm against a blank.

Table No.5- Ex-vivo % drug permeation through buccal mucosa of optimized batch (F10)

Time (hrs)	Cumulative % drug permeate.*
1	1.97
2	2.65
3	6.30
4	10.72
5	12.41
6	17.00
7	20.10
8	24.22
9	27.28
10	31.27

Each value represents Mean ±S.D. (n =3)

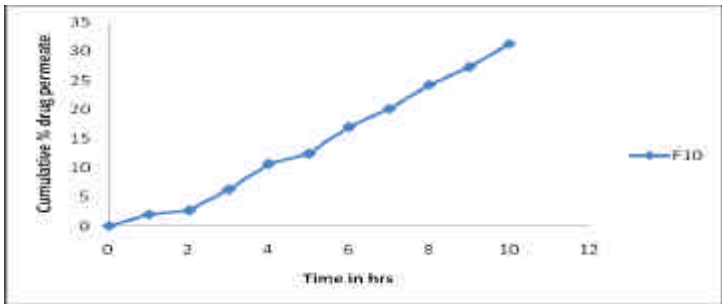

Figure.11-Cumulative % drug permeate from optimized batch (F10)

Stability studies.[30,31] Stability studies was carried out on the optimized formulation (F-10)as per ICH guidelines. The tablets were wrapped in aluminium foil placed in ambers colour bottle and finally stored at 40±2^{0}c and 75+6% RH for 6 month. The tablets were evaluated for bioadhesive strength, in vitro drug release and Physical parameters as drug content, thickness, hardness, friability studies.

Table No.6. Bioadhesive strength study of optimized formulation (F10)

Time (Month)	Bioadhesive strength (gm)
0	21.57
2	20.05
4	19.16
6	19.00

Table No.7- Cumulative % drug release of optimized formulation (F10)

Time (hrs)	0 Month	2 Month	4 Month	6 Month
1	8	8.00	7.15	6.00
2	12	11.29	11.00	10.10
3	18	17.47	16.50	14.87
4	25	25.00	24.30	22.34
5	33	32.33	31.30	29.88
6	43	42.00	41.11	39.00
7	56	45.66	44.33	41.59
8	67	65.00	64.12	63.66
9	75	74.20	71.09	68.31
10	88	87.59	86.03	83.00

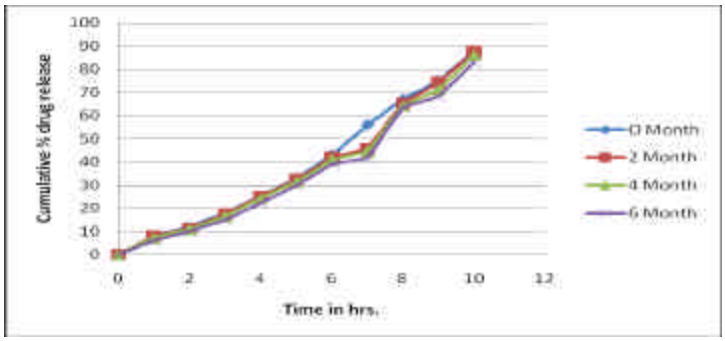

Figure.12-Cumulative % drug release from optimized batch (F10)

Data analysis.

The release data obtained from various batches were studied with respect to effect of drug: polymer ratio, diluents ratio. To analyze the mechanism of drug release from the formulation, the dissolution profile of all the batches were fitted to zero order, first-order, Higuchi, Korsemeyer and Peppas, to ascertain the kinetic modeling of drug release.

Zero Order:[32]

In many of the modified release dosage form particularly controlled or sustained release dosage form (those dosage forms that release the drug in planned, predictable and slower than normal manner) is zero order kinetics.

$Q = K_o t$

Where, Q is the amount of drug release at time, t and K_o is the release rate constant.

The results are shown in table no.8

First Order:[33]

Most conventional dosage form exhibits this dissolution mechanism some modified release preparations, particularly prolonged release formulation adhere to this type of dissolution pattern.

$\text{Log } Q = K_1 t$

Where Q is the percent of drug release at time, t and K_1 is the release rate constant.

The results are shown in table no.8

Higuchi Equation :[34]

A Large number of modified release dosage form contain some sort of matrix system is such instances the drug dissolves from this matrix. The dissolution pattern of the drug is dictated by water penetration rate (diffusion control) and thus the following relationship applies.

$Q = K_2 t^{1/2}$

Where, Q is the percentage of drug release at time t and K_2 is the diffusion rate constant. The results are shown in table no.9

Peppas Equation :[35,36,37]

$Q = Ktn$

Where, Q is the percent of drug release at time, t and K is the diffusion rate constant and n is diffusional exponent. If n is equal to one the release is zero order. If n is equal to 0.5 the release is best explained by fickian diffusion and if $0.5 < n < 1$ then the release is through anomalous diffusion or case II diffusion in this model a plot of % drug released versus log time is linear.

Table No.8- Kinetic values obtained from In-vitro release data of buccal tablets (F1 to F10)

Formulation	Zero order plot Slope	Regression coefficient (R)	First order plot Slope	Regression coefficient(R)
F1	10.309	0.9903	0.1445	0.6764
F2	8.7455	0.9870	0.144	0.7372
F3	9.5455	0.9810	0.1483	0.7593
F4	8.3364	0.9812	0.1454	0.7656
F5	8.7909	0.9806	0.1552	0.8389
F6	10.07	0.9943	0.1501	0.7288
F7	9.4182	0.9958	0.1535	0.7661
F8	9.6818	0.9876	0.1387	0.6440
F9	9.701	0.9894	0.1480	0.7023
F10	8.1909	0.9908	0.1517	0.7980

Table No.9- Kinetic values obtained from In-vitro release data of buccal tablets (F1 to F10)

Formulation	Higuchi plot Slope	Regression coefficient (R)	Peppas plot Release exponent(n)	Regression coefficient(R)	Transport mechanism
F1	34.921	0.9408	0.5795	0.9008	Anomalous or non-fickian
F2	28.75	0.8839	0.5634	0.9337	Anomalous or non-fickian
F3	31.027	0.8581	0.5746	0.9436	Anomalous or non-fickian
F4	27.20	0.8651	0.5627	0.9491	Anomalous or non-fickian
F5	28.34	0.8440	0.5876	0.9767	Anomalous or non-fickian
F6	33.62	0.9173	0.5904	0.9336	Anomalous or non-fickian
F7	31.14	0.9096	0.5952	0.9540	Anomalous or non-fickian
F8	33.09	0.9553	0.5629	0.9484	Anomalous or non-fickian
F9	32.92	0.9173	0.5884	0.9192	Anomalous or non-fickian
F10	26.75	0.8754	0.5809	0.9689	Anomalous or non-fickian

Table No.10 - Physical parameters of optimized formulation (F10)

Physical parameters	0 Month	2 Month	4 Month	6 Month
Drug content uniformity*(%)	100±0.3	99.57 ± 0.33	99.24 ±0.24	98.11±0.66
Thickness* (mm)	1.91±0.01	1.90±0.03	1.90±0.07	1.90±0.44
Hardness* kg/cm2	7.6±0.03	7.4±0.02	7.4±0.34	7.2±0.73
Friability(%)	0.52	0.57	0.62	0.69

Each value represents Mean ±S.D. (n =3)

RESULTS AND DISCUSSION.

Preformulation studies of buccal tablets. Interparticulate interactions that influence the bulking properties of a powder with powder flow. A comparison of the bulk density and tapped density can give a measure of the relative importance of this interaction in a given powder; such a comparison is often used as an index of the ability of the powder to flow. The bulk density and tapped density for nitrendipine was found to be 0.277 ± 0.02 and 0.326 ± 0.051 gm/cm^3 respectively. A simple indication of ease with which a material can be induced to flow is given by application of a compressibility index. The value for compressibility index of nitrendipine was found to be 15.08 ± 1.04 that reflects the good flow property which was supported by the Hausner ratio of 1.17.Its indicated higher the potential of particle for compression due to lower compressibility index.

The bulk density and tapped density for Sodium CMC,HPMC K15M, was found to be 0.357 ± 0.011 gm/ cm^3, 0.442 ± 0.0131 gm/ cm^3 0.333± 0.015 ,0.486 ± 0.0125 gm/ cm^3 respectively. Compressibility index values for all polymers were found between 15 to 32 % and Hausner ratio above 1.47 to 1.48. Compressibility index value of natural polymer like T.S.P.and Z.mauritiana was 32^{0}39,30^{0}17 indicate poor. It conclude that the potential strength of polymer particle or not satisfactory for compression which also supported by lower density value and Hausner ratio above 1.25.The angle of repose of both polymers are come in under poor flow properties. Hence this fact suggested that necessity of addition glidant to improve flow properties. The Compressibility index, Hausner ratio, angle of repose, Sodium CMC, HPMCK15M was in acceptable limits.Carrs index of this polymer is 19.20 and 31.48 was in passable range. But Hausner ratio and angle of repose value indicate as good and acceptable one. It concluded that there is less friction and cohesiveness between the particles. All above properties mentioned above and value obtained for PVP was near to boundary of standard limit.

Evaluation Physical Parameters.

* **Hardness test.** The hardness of tablets was found to in the ranges of 6.3 to7.6 kg/cm^2 the optimized formulation (F-10) shows maximum hardness as 7.6±0.03 kg/cm^2.

* **Friability test.** The % weight loss in friability test was found to be less than 1% indicate tablets can withstand the mechanical shock or during handling.

* **Weight Variation Test.** The average weight of tablets was found to be 120 mg for all batches and % deviation within specified limits. Overall the all prepared formulation were good quality with regard to drug content.

***Drug Content Uniformity.** The percentage drug content for batches F1 to F10 was found to be in the range of 97.2 % to 101.2% .Hence it complies with official specification.

Evaluation of surface pH. The surface pH of all formulation was in the range of 5 to 7 except formulation F1,F2 shows less than 5 due to presence of carboxylic acid group present in the polymer NaCMC. Rest of formulation provide an acceptable pH in the range of salivary pH (5.0 to 7.0) hence can not produce any irritation to buccal mucosa.

In-vitro swelling index study. Swelling index was calculated with respect to time the swelling index increased as weight gain by tablets increased proportionally with rate of hydration or erosion of polymers in swelling medium. The maximum % swelling was attained in 6 hrs.The formulation containing Sodium CMC polymer series i.e. .(F1,F2) The SodiumCMC was break down after 3 hrs due to uncontrollable swelling because polymer having higher charged density resulting in large inter polymer chain spaces through population of charged substitution group and eventually least resistance to permission of water also SodiumCMC has viscosity less results in low binding forces between the molecules. The optimized formulation (F10) contain natural mucoadhesive material as T.S.P.and Z.mauritiana with ratio 1:1.5:1.5 shows maximum % swelling as 298.50% after 6 hrs.indicating synergistic hydration and erosion effect as well as slow uptake of water with controllable manners up to 6 hrs with max.% swelling. The series of formulation (F6 to F10) prepared by using natural material shows comparatively maximum % swelling than formulation (F1 to F5) containing synthetic polymers indicate that natural mucoadhesive material s potential choice for buccal tablets.

In-vitro Residence time study. In- vitro residence time is one of important physical parameters of buccoadhesive tablets .The result shows F1,F2 formulation shows lower residence time up to 3 hrs.due to faster erosion and dissolution of tablets as well as poor bioadhesion force with mucosal membrane while formulation contain natural material as T.S.P.and Z.mauritiana shows acceptable residence time up to the 6 hrs.The optimized formulation (F10) contain equal proportion of natural mucoadhesive material having residence time up to 8 hrs.due formulation contain polymer as HPMCK15M series also shows residence time more than 4 hrs also acceptable one.

In-vitro Bioadhesion strength study. The bioadhesion characteristics were affected by types and ratio of polymers the highest bioadhesive strength i.e. 21.53gm was possessed by optimized formulation (F10) due to possibility of proper hydration and erosion of natural polymer adhere to mucosal surface with strong bond which have been supported by maximum bioadhesive force. The table no.4 shows value of in-vitro residence time and biadhesive force of all formulation.

Ex-vivo permeation studies. In-vivo permeation studies was carried out by using open end cylinder method. The cumulative % of drug diffused across the buccal mucosa was 31.27% with respect to time up to 10 hrs.

In-vitro Dissolution study. The figure no.3 shows drug release studies from formulation containing synthetic polymers. The formulation contain Sodium CMC polymer (F1,F2) shows near about 100% drug release during 10 hours study shown in figure no.3 .This may due to SodiumCMC it gets swell by forming a gel layer on exposed tablet surfaces. The loosely found polymer molecules were easily eroded allowing the release of drug rapidly it attributed that it create pores and tortuous pathways which aided faster release by maximum uptake of water and inadequate swelling and poor residence time (3 hrs.).The formulation contain HPMCK15M polymer (F3,F4) shows 97%, and 90% of drug release. This is due to higher hygroscopic nature and hydrophilicity of polymer cause slower hydration with low viscosity. The cumulative % drug release from tablets containing natural material like *Z.* Mauritiana and TSP (F6 to F10) are shown in figure no.7.The results indicate that tablets (F6 ,F7) prepared from *Z.* Mauritiana shows 97% and 98% release the at controllable manner up to 10 hrs.followed by 100% and 97% drug was release from tablets (F8,F9) contain TSP as rate controlling polymer indicate that higher hydration and erosion of polymer with low viscosity compare to *Z.* Mauritiana hence almost 100% drug was release from tablets contain TSP.The above dissolution profile suggested that as conc. of polymer both natural and synthetic polymer increases release rate of drug from tablets are retarded .The 4.

formulation (F10) which was prepared from the mucoadhesive materials extracted from the edible fruits of *Z.* mauritiana and Tamarind seed polysaccharide (TSP) used in 1:1.5:1.5 drug: material ratio have shown promising results (released about 85 % of the drug in 10 h) with reasonably good mucoadhesive properties of natural material. This is due to natural material absorbed water rapidly with maximum swelling at 6 hours and start to welling erosion and finally drug release of at constant manner by zero order kinetic and swelling gel diffusion mechanism by applying zero order regression and Peppas value of regression is correlated with each other hence formulation (F10) as a optimized formulation due to above parameters and selected for further studies. The kinetic parameters of drug release for different formulations are presented in Table III.The dissolution data of all formulation when fitted in accordance with first order equation it is evident that Regression coefficient (R) value not close to unity(0.6440 to 0.8389) and less than the zero-order plots shows that it was follows first order release kinetics i.e. amount of drug release is non dependent on the matrix drug load.Higuchi′s square root kinetics describe the release from matrix system hence all the formulation expressed by Higuchi classical diffusion equation as the plot shows linearity with regression coefficient (R) value as (0.8440 to 0.9558) also not close to infinity indicate drug release process is not as per Higuchi′s nature. The zero order plot of all formulation were found to be closely linear, as indicated by their high regression(R)values as (0.9806 to 0.9943) Therefore it was ascertained that the drug release from these formulations could follow either near zero or zero-order kinetics. Hence, to confirm the exact mechanism of drug release from these tablets, the data were fitted according to the Korsemeyer-Peppas model. A simple empirical equation to describe the general solute release behaviour from controlled release polymer matrices: $Q = Ktn$ .Where, Q is the percent of drug release at time, t and K is the diffusion rate constant and n is diffusional exponent. The value of n gives an indication of the release mechanism: when $n = 1$, the release rate is independent of time (zero-order) (case II transport), $n = 0.5$ stands for Fickian diffusion and when $0.5 < n < 1.0$, diffusion and non-Fickian transport are implicated. Lastly, when $n > 1.0$, super case II transport is apparent. In the present study, the regression coefficient (R) was found to in the range of (0.9192 to 0.9767) for the Korsemeyer-Peppas equation. Slope values (n) ranging from (0.5627 to 0.5952) suggest that the drug release from buccal tablets (F1 to F10) followed anomalous or non-fickian transport mechanism therefore both diffusion and erosion mechanism play role in nitrendipine release from natural material.

CONCLUSION.

Mucoadhesive buccal tablets of Nitrendipine were prepared with object of to avoid first pass metabolism and prolonged effect of drug. The tablets were developed by using both natural and synthetic polymer but satisfactory level in terms of drug release, mucoadhesive strength ,swelling index ,physiochemical parameters was proposed in tablets containing natural material like *Z.* Mauritiana and T.S.P.than tablets contain synthetic polymer like NaCMC and HPMCK15M.Hence it proposed that natural polymer is successively incorporated in mucoadhesive drug delivery system with avoidance of questionable biodegradability problem associated in synthetic polymers.

ACKNOWLEDGEMENT.

Author are thankful to Managing trustee of Parul group of Institutes for providing all the facilities for this research project.

REFERENCES.

1. Mathiowitz E,Chickering D,Jacob J.S. Bioadhesive drug delivery system .In:Mathiowitz E editor,Encyclopedia of controlled drug delivery system. New York;John wiely and sons,Inc.(1998) 9-13.
2. Peepas NA,Buri PA. Surface ,interfacial and molecular aspect of polymer bioadhesion on soft tissue .J.control release. (1985) 2:257-275
3. Hoogstraale J.Benes L,Burgaud S. Oral transmucosal drug delivery system .In:Hilierys A.M.Lloyd A.W. Swarbrick J.editors.drug delivery and targeting .London :Taylor and Francis .(2001) 186-200
4. Park K,Robinson JR.Bioadhesive polymer as platforms oral controlled drug delivery :method to study bioadhesion .Int.J.Pharm (1984).198:107-27
5. Chaudary KPR,Srinivas L,Mucoadhesive drug delivery system;A review of current status .Indian drug. (2000) 37:400-406
6. The Drug Bank(Database on the Internet) supported by Wishart D.Department of computer science and biological science, University of Alberta (cited on 2006 may 07);Available from http/ /redpoll.pharmacy.ualbarta.ca/drugbank/drugBank/.
7. Santiago TM, Lopez LM . Nitrendipine: a new dihydropyridine calcium-channel antagonist for the treatment of hypertension.DICP-The annals of pharmacotherapy.(1990) 24;(2):167-75
8. Khullar P, Khar RK, Agarwal SP. Evaluation of guar gum in the preparation of sustained-release matrix tablets. Drug Dev Ind Pharm. (1998). 24: 1095-9.
9. Rao PS, Srivastav HC, Tamarind. In Industrial Gums, (Ed.) R.L. Whistler, Academic Press, 2nd Ed, New York. (1973). 369-411
10. Nandi RC. A Process for preparation of polyose from the seeds of Tamarindus indica, Ind. Pat. (1975) 142092,
11. 11.Rao PS. Extraction and purification of tamarind seed polysaccharide. J Sci Ind Research, (1946). 4:705.
12. Cooper J and gunn G. Powder flow and compaction, In; Tutorial pharmacy (carter SJ; Eds.) New Delhi. India; CBS Publisers and distributers. (1986):211-233.
13. Shah D, Shah Y and Rampadhan M. Development and evaluation of controlled
14. release diltiazem hydrochloride microparticles using cross-linked polymer (vinayl alcohol). Drug Dev. Ind. Pharm. (1997); 23(6): 567-574
15. Carr RL.Evaluating flow properties of colloids. Chem Eng. J. (1965) 72:163-8
16. Hausner HH. Friction condition in a mass of metal powder.Int J Powder Metall.(1967) 3: 7- 13
17. Chaudary KP,Girish KK,Rao DG.Spectrophotometric determination of nitrendipine in pharmaceutical dosage forms. Indian Drug (1998) .35:645-7
18. Gilbert S. Banker and Neil R.Anderson Lachman, L, Liberman, H.A. and Knaig, J.L Eds., "The Theory and practice of Industrial Pharmacy**"**, (3rd edn), Varghese Publishing House, Bombay, (1990) 293-345.
19. Subrahmanyam CVS. "Text Book of Physical Pharmaceutics". 2nd ed. New Delhi : Vallabh Prakashan. (2001). 253-261
20. United States Pharmacopeia, XXIV NF 19,United State Pharmacopeia Convention, Rockville, (2000) 2388-2389.
21. Nozaki, Y, Ohta M, Chien YW. Transmucosal controlled systemic delivery of isosorbide dinitrate:in vivo-in vitro correlation.J. Control. Rel. (1997) 43: 105-114.
22. Noha AN, Fatma AS and Nabila AB. Mucoadhesive delivery systems. II formulation and invitro / invivo evaluation of Buccal Mucoadhesive tablets containing water soluble drugs. Drug Development and Industrial Pharmacy.(2004) 30 (9) : 995-100422.
23. Lalla JK and Gurnancy RA. Polymers for mucosal delivery-Swelling and mucoadhesive evaluation. Indian Drug (2002) 39 (5) : 270- 276.
24. Patel B, BhosaleA, Hardikar S, Evaluation of Tamarind Seed Polysaccharide (TSP) as a Mucoadhesive and sustained release component of nifedipine buccoadhesive tablet & Comparison. International Journal of PharmTech Research.(2009) 1 (3):404-410
25. Mohammed FA,Khedr H.Preparation and in-vitro /in-vivo evaluation of the buccal bioadhesive properties of slow release tablets containing miconazole nitrate. Drug Develop Ind Pharm (2003) ;29:321-327
26. Gupta A, Garg S, Khar R. Measurement of bioadhesive strength of mucoadhesive buccal tablets :Design of in-vitro assembly. Indian Drug .(1992) 30:152-5
27. Vermani K,Garg S,Lourence JD. Assembly for Invitro measurement of bioadhesive strength & retention characteristics in simulated vaginal environment. Drug Ind Pham (2002).28:1133-46
28. United States Pharmacopeia, XXIV NF 19, United State Pharmacopeia Convention, Rockville.(2000) : 264.
29. Indian Pharmacopeia, Vol. II, Controller of Publication, Delhi, (1996). A-82-83.
30. Madgulkar A,Kadam S,Pokharkar V. Development of buccal adhesive tablet with prolonged antifungal activity :optimization and ex-vivo deposition studies.Indian J of Pharm Sci.(2009);71(3):290-294
31. Crowley MM, Schroedar B, Talariko M. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot melt extrusion. Int J Pharm.(2004); 269(2): 509-522.
32. Krajalic A, Jacker IG. Matrix formation in sustained release tablets: possible mechanism of dose dumping. Int J Pharm. (2003);251(1) : 67-78
33. Merchant HA, Shoaib HM, Yousuf RI. Once-daily tablet formulation and in vitro release evaluation of cefpodoxime using hydroxypropyl methylcellulose: A technical note. AAPS Pharm. Sci. Tech. (2006) ; 78: 10-28
34. Bourne DW. Pharmacokinetics. In: Banker GS, Rhodes CT, eds. Modern Pharmaceutical. 4th ed. New York, NY: Marcel Dekker Inc. (2002):67-92.
35. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspension. J Pharma Sci. **(**1961) 50: 874 – 875.
36. Korsemeyer R, Gurny R, Peppas N. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. **(**1983) 15: 25-35.
37. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv.(1985) 60: 110 – 111.
38. Ritger PL and Peppas NA. Simple equation for solute release. Part 1. Fickian and non-fickian release from non-swellable devices in the form of slabs, spheres, cylinders or disks, J. Control.Rel. (1987) 5: 37-42.

Source of support: Nil, Conflict of interest: None Declared