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FORMULATION AND EVALUATION OF BIOADHESIVE DRUG DELIVERY OF NISOLDIPINE

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Abstract: The aim of study was to prepare and characterize bioadhesive buccal tablets of Nisoldipine using combination of bioadhesive polymer carbopol 934P and sustained release polymers like HPMC K_4M, HPMC$K_{15}M$, sodium alginate in different ratio by direct compression method. Eighteen formulation were developed with different concentration of bioadhesive polymers in each formulation. The formulated buccal tablets were tested for surface pH, swelling index. The prepared tablets also evaluated for bioadhesive strength, ex-vivo bioadhesion time and drug permeation through porcine buccal mucosa. In vitro bioadhesive strength, ex-vivo residence time and in vitro release studies showed that formulation F13 containing 1:1 ratio of drug and polymer combination showed satisfactory bioadhesive property. FTIR results showed no evidence of strong interaction between the drug and polymers. The results indicated that suitable bioadhesive buccal tablets with desired permeability could be prepared. Stability study of Nisoldipine bioadhesive buccal tablets was performed at 40 ± 2 °C / 75 ± 5 % RH for 1 month. At the end of study; it was found that there are no significant changes in drug content and in vitro dissolution, bioadhesive strength.

Keywords: Bioadhesive, Nisoldipine, Carbopol 934P:HPMC K_4M

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1. INTRODUCTION

There are various routes of drug administration meant for different pharmaceutical dosage forms like parentral, topical and oral route. Among these the later one is the most preferred and convenient route for drug administration. This route however has certain demerits like drug inactivation by the hepatic first pass effect, degradation of drugs by gastro- intestinal tract enzyme. These factors affect the drug absorption and hence cause the poor bioavailability of active drugs which may lead to the formation of the therapeutically inactive drug molecule. advances in emerging trends in pharmaceutical science has designed different approaches to avoid the first pass metabolism bioadhesive drug delivery seems to be more convenient and beneficial. Buccal mucosa is a potential site for the delivery of drugs to the systemic circulation. A drug administered via bioadhesive drug Delivery system through the buccal mucosa enters directly in the systemic circulation thereby minimizing the first-pass hepatic metabolism and adverse gastro-intestinal effect. Buccal cavity possess ideal characteristics for drug absorption and hence it acts as an excellent site for the absorption of drugs. Nisoldipine is a 1, 4 Dihydropyridine calcium channel blocker class of drug used as a antihypertensive agent. It works by inhibiting the influx of calcium in smooth muscle and prevents calcium channel dependent smooth muscle contraction and vasoconstriction. Nisoldipine belongs to BCS class-II,

Low solubility and Low bioavailability (3.7 to 8.4%).Physicochemical Properties of drug like,

Low Dose (8.5 mg) Low molecular weight (388.41gm/mol).make it suitable candidate for administration by buccal route.

2. MATERIAL AND METHOD

2.1 Materials

Nisoldipine obtained from shri ram chemicals, Ghaziabad. Carbopol (934), sodi. Alginate, mg stearate, Talc from sulab corporation,baroda.HPMCK_4M and HPMCK_{15}M from dow. fine chemicals,Mumbai.ECfromLOBAchemia,Mumbai.avicel(102)fromS.D.finechemicals,mumbai.Aspartame from ACME chemicals Bombay.

2.2 Method

2.2.1 Bioadhesive buccal tablets prepration[2]

Bioadhesive buccal tablets containing Nisoldipine were prepared by direct compression method.The ingredients of the core layer were weighed accurately and mixed properly. Carbopol 934P was used as bioadhesive polymer and HPMCK_4M, HPMC K_{15}M polymers were used as sustained release polymers. The mixture was then pre compressed using 6 mm die by a tablet

press after precompression of tablet the upper punch was removed carefully without disturbing the set up and ethyl cellulose for the backing layer was added over the tablet and compressed again.

Table 2.1 Composition of Nisoldipine buccal tablets:

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nisoldipine	1 0	10	10	10	10	10	10	10	10
Carbopol 934P	10	20	30	-	-	-	-	-	-
HPMCK$_4$M	-			10	20	30	-	-	-
HPMCK$_{15}$M	-	-	-	-	-	-	10	20	30
Sodium Alginate	-	-	-	-	-	-	-	-	
Avicel 102	46	36	26	46	36	26	46	36	26
Aspartame	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Mg Stearate	1	1	1	1	1	1	1	1	1
Ethyl Cellulose	30	30	30	30	30	30	30	30	30
Total	100	100	100	100	100	100	100	100	100

Ingredients (mg)	F10	F11	F12	F13	F14	F15	F16	F17	F18
Nisoldipine	10	10	10	10	10	10	10	10	10
Carbopol 934P	-	-	-	10	10	10	10	10	10
HPMCK$_4$M	-	-	-	10	20	30	-	-	-
HPMCK$_{15}$M	-	-	-	-	-	-	10	20	30
SodiumAlginate	10	20	30	-	-	-	-	-	-
Avicel 102	46	36	26	36	26	16	36	26	16
Aspartame	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Mg Stearate	1	1	1	1	1	1	1	1	1
Ethyl Cellulose	30	30	30	30	30	30	30	30	30
Total	100	100	100	100	100	100	100	100	100

3. IDENTIFICATION, ESTIMATION AND EVALUATION OF BUCCAL TABLET

3.1 IDENTIFICATION OF DRUG

By Open Capillary Method Melting point of Nisoldipine was found to be 153-156°C which was in the range as given in literature, hence the drug could be stated as pure.

3.2 FTIR Spectroscopy

The Infrared spectroscopy of the sample was carried out to as certain identity of the Drugs. A pellet of approximately 1mm diameter of drug was prepared by compressing 3-5 mg of the drug with 100-150mg of potassium bromide in KBR pross. The pellet was mounted in IR compartment and scanned between wave number 4000-400 cm^{-1} using a FTIR Spectrophotometer.

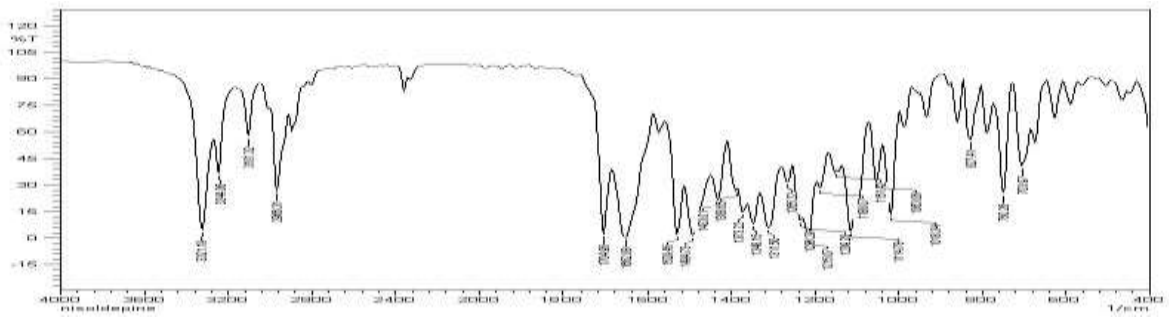


Figure 3.1 FTIR spectra of Nisoldipine

Functional group	Literature(cm-1)	Frequency(cm-1)
N-H streaching	3400-3250	3321.19
C-H streaching	2850-3000	2966.31
Esterified carbonyl	1735-1750	1704.96
Aryl nitro group	1550-1475	1529.45
Ether absorption	1000-1300	1215.07

Table 3.1 IR interpretation

The peaks of nisoldipine shown in the table 3.1 matches with the peaks mentioned in the literature which confirms the identification of drug with its functional groups.

3.3 DRUG-EXCIPIENT COMPATIBILITY STUDY

FTIR absorption spectra of pure drug and physical mixture were recorded in the range of 400 to 4000 cm-1 by KBr disc method using FTIR spectrophotometer. FTIR study was carried out individually for drug and physical mixture of drug with all polymers. FTIR spectra of physical mixture of drug with all polymers were compared with FTIR spectra of pure drug.

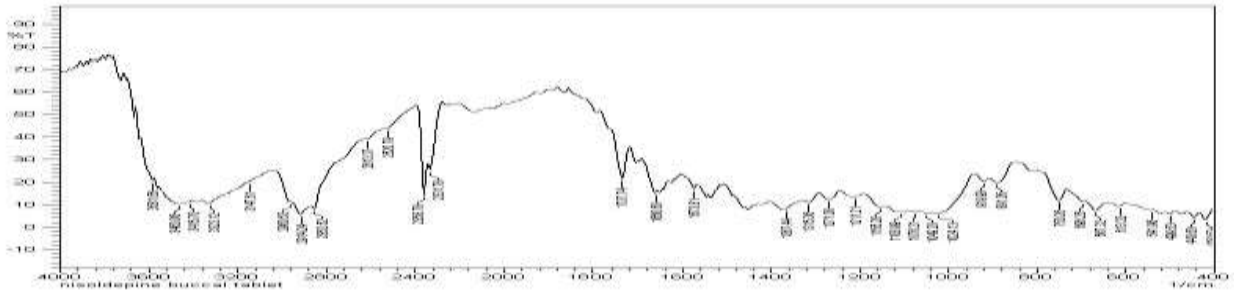


Figure 3.2 FTIR spectra of physical mixture of Nisoldipine and excipients

Table 3.2 Comparison of interpretation of FTIR spectra of Nisoldipine and Physical mixture

Functional group	Frequency(cm-1)	
	Pure Nisoldipine	Physical mixture
N-H streaching	3321.19	3323.12
C-H streaching	2966.31	2960.53
Esterified carbonyl group	170496	1737.74
Aryl nitro group	1529.45	1573.81
Ether absorption group	1215.07	1211.80

The FTIR spectrum of the physical mixture and pure nisoldipine are similar and are in range with respect to the values specified in the literature, suggesting that the drug and polymers are compatible with each other. There are no interactions between them.

3.4 ESTIMATION OF NISOLDIPINE IN PHOSPHATE BUFFER pH 6.8

3.4.1 Determination of UV absorption maxima (λ max)

The UV absorption maxima of nisoldipine in phosphate buffer pH 6.8 was found to be 229.39 nm, when scanned between 200-400 nm by UV-visible double beam spectrophotometer as shown in Figure 3.3 The said λmax was used for preparation of calibration curve.

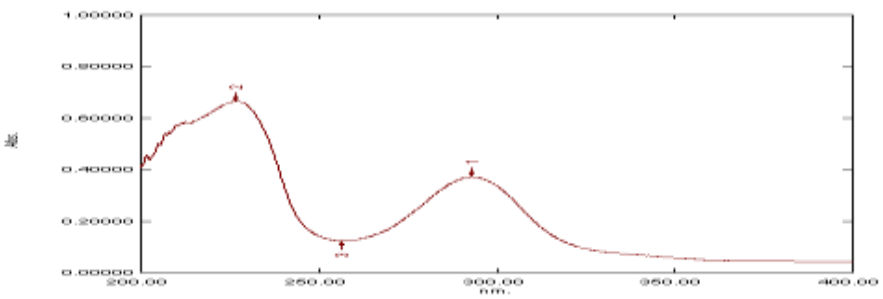


Figure 3.3 Absorption maxima (λmax) of Nisoldipine in phosphate buffer pH6.8

λmax = 235.20 nm,

Abs = 0.635,

Conc = 8 µg/ml in phosphate buffer pH 6.8

λmax = Experimental: 229.39 nm

Literature: 238 nm

3.4.2 ESTIMATION OF NISOLDIPINE

3.4.2.1 Preparation of Calibration curve of Nisoldipine in phosphate buffer pH 6.8

100 mg of Nisoldipine was accurately weighed and transferred to 100 ml volumetric flask. The drug was dissolved in 5 ml methanol and the volume was made up to100ml with phosphate buffer pH 6.8 to obtain a stock solution of 1000 µg/ml. 10 ml of stock solution was diluted up to 100 ml with phosphate buffer pH 6.8 (Stock solution II). From stock solution II aliquots of 0.2, 0.4,0.6,0.8,1.0 and 1.2 ml were transferred to a series of 10 ml volumetric flasks. The volume was made up with phosphate buffer pH 6.8 to give 2,4,6,8,10 and 12 µg/ml of concentration. The absorbance of these solutions was measured at 238 nm against blank.

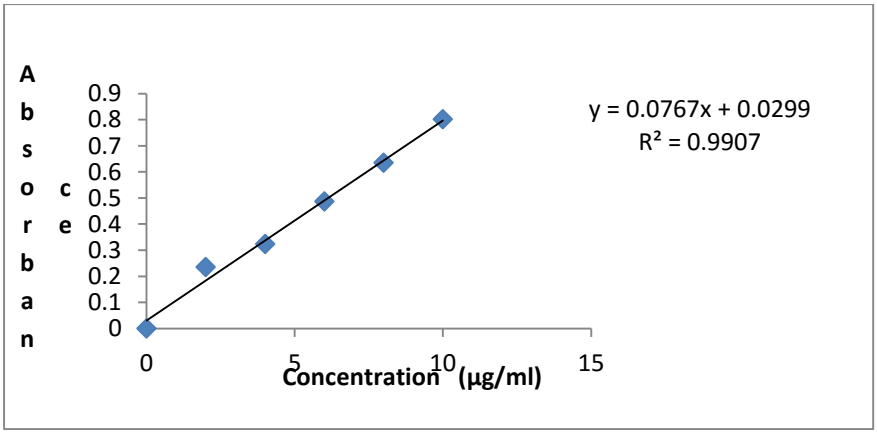


Figure 3.4 Linearity curve of Nisoldipine in phosphate buffer pH 6.8

It can be seen from the results of calibration curve data that the relationship between concentration and absorbance was linear. (R^2=0.9907)

3.5 Post compression parameter

1) Thickness and diameter

The thickness and diameter of the tablet was measured using Vernier calipers. Three tablets were selected randomly from individual formulations, thickness and diameter was measured using Vernier calipers. It was measured in mm.

2) Weight variation

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown. The pharmacopoieal specification of weight variation is given in Table 3.5.

Table 3.5 IP standards of uniformity of weight

Sr. No.	Average wt. of tablet	%of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

3) Hardness

The Pfizer hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm^2

4) Friability (%F)

Friability of the tablet determined using friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at a height of 6 inches in each revolution. Pre weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were reweight and the loss in the weight of tablet is the measure of friability and is expressed in percentage.

% friability=(Initial weight of tablets-Final weight of tablets)/Initial weight of tablets× 100

5) Assay

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder, powder equivalent to the mass of one tablet was dissolved in methanol by sonication for 5 mins and filtered through Whatman filter paper. The drug content was analyzed spectrophotometrically at 238 nm using an UV spectrophotometer.

6) Surface pH study[3]

The surface pH study for buccal tablets was performed to investigate the possibility of any side-effect in vivo. An acidic or alkaline pH may irritate the buccal mucosa, so the surface pH of tablet should be almost neutral. In this method the tablet was allowed to swell by placing it in contact with 1 ml of phosphate buffer pH 6.8 for 2hrs at room temperature. The pH was determined by bringing the electrode into contact with the tablet surface and allowing the surface to equilibrate for 1 minute.

7) Swelling index[4]

At first the buccal tablets are weighed individually (W1) and then the tablets are placed in an agar gel plates 1% or 2% in a petri-dish with the core (drug-polymer layer) facing the gel surface, incubated at 37±1°C for up to 6 hrs. At regular intervals of time, the swollen tablets are removed from petri-dish and weighed again(W2). The Swelling Index (SI) can be calculated using the formula.

$$\text{Swelling Index} = \frac{W2 - W1}{W1} \times 100$$

Where W2= weight of tablet after time at 't'.

W1 = weight of tablet before placing in the petri dish

8) In vitro drug release study[5]

The USP dissolution apparatus is used for the drug release study. It can be either a rotating paddle type, where backing layer of buccal tablet is to be attached to a glass disk with adhesive material and the disk is placed at the bottom of the rotating basket type. The dissolution study is to be performed by suitable amount of phosphate buffer pH 6.8, samples at pre-determined time intervals are taken out and replaced with fresh buffer medium. The samples are filtered and suitable dilution is made and analyzed by an U.V Spectrophotometer.

9) Ex vivo Bioadhesion strength[6]

Bioadhesive strength of the tablets was measured on a modified physical balance. The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) The left-hand side of the balance was exactly 5 gm heavier than the right side. In order to find out the bioadhesion strength first buccal tablet (n=3) was stacked to the glass slide with the help of knob, which was situated at the base of physical balance. Now five grams of weight from the right pan was then removed. This lowere the glass slide along with the tablet over the membrane with a weight of 5.0 gm. This was kept undisturbed for 5 min. Then the weights on the right-hand side were slowly added in increments of 0.1 gm till the tablet just separated from the membrane surface. The excess weight on the right pan ,i.e. total weight minus 5gm was taken as a measure of the bioadhesive strength.

10) Ex vivo Bioadhesion time[7]

The Ex vivo Bioadhesion time for biooadhesive buccal tablets was determined by modified USP dissolution apparatus. The dissolution medium was composed of 500 ml of phosphate buffer pH 6.8 maintained at 37°C. A segment of porcine buccal mucosa each of 3 cm length was glued to the surface of glass slab which was then vertically attached to the apparatus.

Three tablets of each batch were hydrated using 1.5 ml of pH 6.8 buffer on one side and hydrated surface was brought into contact with mucosal membrane for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing phosphate buffer pH 6.8 The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time necessary for complete erosion or detachment of the buccal tablet from the mucosal surface was recorded.

11) RELEASE KINETICS[8]

In order to understand the mechanism and kinetics of drug release, the results of in vitro drug release study were fitted with various kinetic models namely zero order (% release vs t), first order (log% unrelease vs t), Higuchi matrix (% release vs square root of time). In order to define a model which will represent a better fit for the formulation, drug release data further analyzed by Korsmeyer Peppas equation, $Mt/M\infty = ktn$, where Mt is the amount of drug released at time t and $M\infty$ is the amount released at time ∞, the $Mt/M\infty$ is the fraction of drug released at time t, k is the kinetic constant and n is the diffusional exponent, a measure of the primary mechanism of drug release. R^2 values were calculated for the linear curves obtained by regression analysis of the above plots.

12) EX VIVO PERMEATION STUDY[9]

Ex vivo permeation study of bioadhesive buccal tablet was carried out on porcine buccal membrane using modified Franz diffusion cell with a diffusion area of 17.35 cm^2 and the acceptor compartment volume of 22 ml. A semi permeable membrane was clamped between the donor and acceptor compartments. The water in the acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer and maintained at 37 ± 5°C. The buccal tablet was placed into the donor compartment and was wetted with 1ml of water. The diffusion was carried out for 8 h. The amount of Nisoldipine permeated through the membrane was determined by removing samples periodically and replaced with an equal volume of water. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically at 238 nm.

13) STABILITY STUDY[10]

The stability study was carried out on the optimized formulation as per ICH guidelines Q1C. Optimized formulation were packed in rubber stoppered vials kept in stability chamber. The stability study was performed at 40 ± 2 °C / 75 ± 5 % RH for 1 month. At the end of study sample were analyzed for drug content, in vitro drug release, bioadhesive strength and swelling inde

4. RESULT AND DISCUSSION

4.1 Post compression parameter

Table 4.1 Post-compression parameters

Batch	Hardness* (Kg/cm2)	Thickness* (mm)	Average weight* (mg)	Friability* (%)
F1	4.46±0.01	3.04±0.055	106.68±1.64	0.72±0.03
F2	4.67±0.04	3.07±0.036	101.12±2.07	0.69±0.04
F3	4.48±0.86	3.02±0.045	99.14±0.93	0.58±0.01
F4	4.72±0.35	3.03±0.050	96.64±0.93	0.58±0.01
F5	4.47±0.57	3.06±0.028	100.31±0.76	0.55±0.09
F6	4.12±0.66	3.05±0.025	106.44±1.97	0.77±0.58
F7	4.66±0.05	3.05±0.020	97.33±3.51	0.71±0.05
F8	4.16±0.35	3.04±0.051	104.33±1.08	0.66±0.04
F9	4.10±0.10	3.02±0.010	101.00±2.64	0.82±0.06
F10	4.67±0.05	3.06±0.026	94.66±2.08	0.82±0.03
F11	4.00±0.05	3.06±0.026	94.63±4.21	0.81±0.04
F12	4.70±0.05	3.06±0.032	105.02±0.02	0.76±0.04

F13	4.57±0.04	3.05±0.025	100.66±6.02	0.62±0.16
F14	4.57±0.04	3.01±0.041	101.64±6.02	0.76±0.06
F15	4.13±0.03	3.00±0.046	97.80±0.98	0.74±0.09
F16	4.35±0.50	3.01±0.051	96.23±3.08	0.64±0.06
F17	4.46±0.04	3.07±0.036	98.72±3.04	0.77±0.06
F18	4.26±0.05	3.02±0.036	104.18±0.80	0.65±0.05

*Values are means ± SD,(n=3)

Tablets were found to be satisfactory when evaluated for weight variation, thickness, hardness, friability. The results for these parameters are given in table 4.1. The hardness of tablets ranged from 4.10 to 4.72 kg/cm2 and the friability values were less than 0.82% indicating that the tablets were compact and hard.

Table 4.2 Post-compression parameters of all formulations

Batch	Drug content* (%)	Surface pH*	Swelling index* (6 hrs)	Bioadhesive residence Time* (hrs)	Bioadhesive strength* (gm)
F1	96.63±1.18	6.11±0.02	69.5±0.05	6.2±0.73	10.0±1.2
F2	94.06±1.34	6.33±0.03	78.4±0.02	6.6±0.91	12.3±1.4
F3	97.70±0.76	6.36±0.07	82.7±0.10	7.3±0.51	15.0±1.3
F4	93.87±1.02	6.42±0.05	70.3±0.03	6.2±0.69	13.5±1.3
F5	95.67±0.84	6.11±0.02	87.3±0.04	8.0±0.81	18.6±1.2
F6	94.47±0.86	6.39±0.02	77.4±0.02	6.5±0.93	16.4±1.6
F7	96.99±0.70	6.23±0.05	86.0±0.02	7.2±0.50	21.7±2.2
F8	94.37±0.70	6.43±0.05	80.7±0.03	6.5±0.90	18.0±1.3
F9	99.69±0.96	6.36±0.23	73.2±0.02	6.0±0.60	14.3±1.5
F10	99.68±1.06	6.60±0.34	91.2±0.01	8.5±0.73	20.6±1.3
F11	95.52±1.16	6.66±0.25	85.5±0.03	7.6±0.58	17.3±1.1
F12	94.59±0.70	6.56±0.28	72.2±0.10	6.2±0.62	12.20±1.6
F13	99.52±0.70	6.53±0.15	94.2±0.02	8.7±0.70	22.9±1.5
F14	95.52±0.70	6.46±0.11	79.5±0.04	6.8±0.57	15.0±1.2
F15	96.98±0.96	6.13±0.03	88.3±0.03	8.1±0.79	20.5±1.4
F16	95.49±0.76	6.227±0.01	83.2±0.02	7.4±0.51	18.4±1.3
F17	94.65±0.92	6.36±0.05	70.2±0.02	6.0±0.57	13.4±1.6
F18	96.45±0.92	6.56±0.05	78.6±0.02	6.0±0.94	16.5±1.3

*Values are means ± SD,(n=3)

Drug content

The assay values were within the limits 93.87 to 99.52 % with good uniformity. The surface pH of all the tablets was within a range of 6-7 as shown in the Table 4 that indicates no risk of mucosal damage or irritation.

Surface pH study of buccal tablets

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. Surface pH of the optimized formulation F13 was found to be 6.53±0.15.This pH is near to the neutral, so the formulation does not cause any irritation on the mucosa. Surface pH values for all the formulations (F1-F18) are represented in table 4.2.

Swelling studies of buccal tablets

Swelling index was performed for all the batches (F1 to F18) up to 6 hr. In the present study, the higher swelling index was found for tablets of batch F13 containing Carbopol 934P with HPMC K_4M (1:1 ratio) compare to other formulation.

The bioadhesion and drug release profile are dependent upon swelling behavior of the buccal tablets. As the proportion of polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. An increase in the viscosity of the gel as well as formation of gel layer with a longer diffusion path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. The values of all formulations were found in ranged of 69.5 to 94.2 respectively.

Ex vivo residence time

The ex vivo residence time for selected formulations varied from 6-8 hrs. The maximum residence time (8.7±0.70 hrs) was found for formulations F13 are represented in table Bilayered tablets containing higher proportion of carbopol 934P:HPMCK_4M, the bioadhesion time was found to be increased. This is because of the high bioadhesive nature of the polymer and interpenetration of polymeric chains into the mucus membrane.

Measurement of bioadhesion strength

The maximum bioadhesion strength for formulations containing carbopol 934P:HPMC K_4M (F13) batch were found to be 22.9±1.5.The force of adhesion gradually decreased with the increase in carbopol 934P, HPMC K_4M, HPMC $K_{15}M$ and sodium alginate percentage in the formulations.

Comparatively weak bioadhesion force of the non ionic polymer HPMC may be attributed to the absence of a proton-donating carboxyl group which reduce its ability for the formation of hydrogen bonds where as carbopol 934P exhibits stronger bioadhesion force as it contains branched molecules with more or less cross-linked segments of comparable length. The difference observed in adhesion force reflect their structural difference as carbopol 934P is a polyacrylic acid crosslinked with allyl sucrose.

In all the formulations (F1-F18) as the polymer concentration increased, the bioadhesive strength also increased. The order of bioadhesion was sodium alginate<HPMCK_4M< HPMCK_{15}M < carbopol 934P. Buccal tablets formulated with carbopol 934P showed stronger bioadhesion than HPMCK_4M and HPMC K_{15}M. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa. Optimized tablet (F13) showed 22.9±1.5g of bioadhesion strength. Bioadhesion strength values of all the formulations (F1-F18) are represented in Figure 4.1.

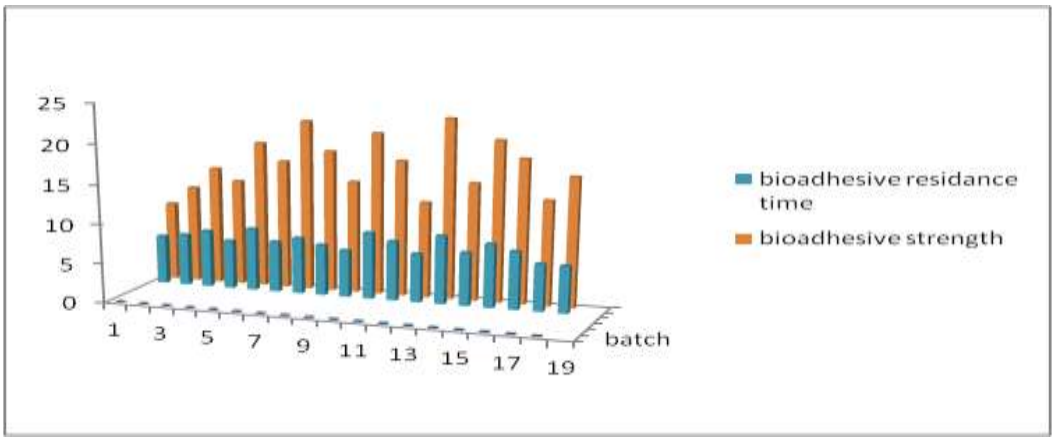


Figure 4.1 Bioadhesive residence time and bioadhesive strength of batch F1-F18

4.2 Ex vivo permeation of buccal tablets

The results of drug permeation from buccal tablet of Nisoldipine through the porcine buccal mucosa reveal that drug was released from the formulation and permeated through the porcine buccal membrane and hence can possibly permeate through the human buccal membrane. Following Figure represent comparison of cumulative percent drug permeated from drug selected formulations. The results indicated that the cumulative percentage drug permeation was more in F13 among the selected formulations and about 97.96 % of Nisoldipine was be

Permeated through the buccal membrane in 6 hrs respectively.

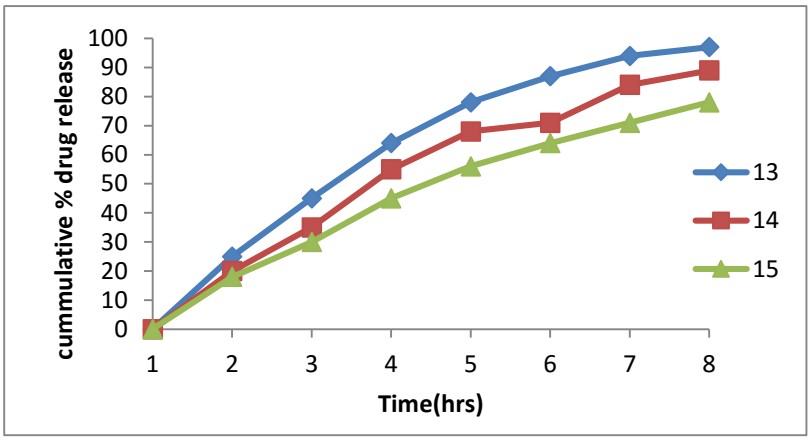


Figure 4. 2 Comparison of release profile of different batche

From the above comparison of release profile of F13 to F15 formulations, it was found that F13 formulation containing CP 934P:HPMC K_4M in the ratio of 1:1 giving better drug release of about 97.96 % at 6 hrs.

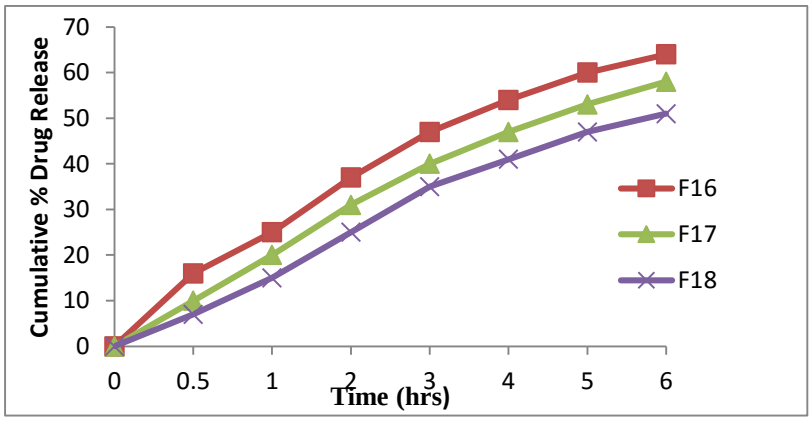


Figure 4. 3 Comparison of release profile of different batches

From the above comparison of release profile of F16 to F18 formulations, it was found that F16 formulation containing CP 934P:HPMC $K_{15}M$ in the ratio of 1:1 giving better drug release of about 58.86% at 6 hrs.

4.3 In vitro dissolution studies

The in vitro dissolution was carried out in phosphate buffer pH 6.8. In vitro dissolution studies clearly indicated that the formulation containing CP 934P: HPMC K_4M (1:1 ratio) showed higher drug release as compared to formulations containing CP 934P : HPMC $K_{15}M$. From result it was

concluded that the in vitro drug release, the formulation containing CP and HPMC K_4M is suitable for buccal drug delivery. The release rate of Nisoldipine decreased with increasing amount of HPMC $K_{15}M$, Sodium Alginate. Carbopol is more hydrophilic than Sodium Alginate swells rapidly, therefore decrease in carbopol content may delay in the drug release.

4.3.1 RELEASE KINETICS

The results of curve fitting into the mathematical models are given in Table 4.3.The results indicate the drug release behavior from the formulated buccal tablet of Nisoldipine.

Table 4.3 In vitro dissolution studies for release kinetic

Batch	Zero order	First order	Higuchi	Hixon Crowel	Koresmeyer Peppas
	R^2	**R^2**	**R^2**	**R^2**	**R^2**
F13	0.8721	0.4925	0.9876	0.9524	0.9885

The results of curve fitting into the mathematical models are given in Table 4.3.The results indicate the drug release behavior from the formulated buccal tablet of Nisoldipine. The results of curve fitting into the mathematical models indicate the drug release behavior from the formulated buccal tablet of Nisoldipine.. When the release rate of Nisoldipine and their respective correlation coefficients were compared, it was found to follow Koresmeyer Peppas model kinetics (R2 = 0.9885). From result it was concluded that in vitro drug release of tablet containing CP and HPMC K4M followed by Koresmeyer Peppas kinetics model

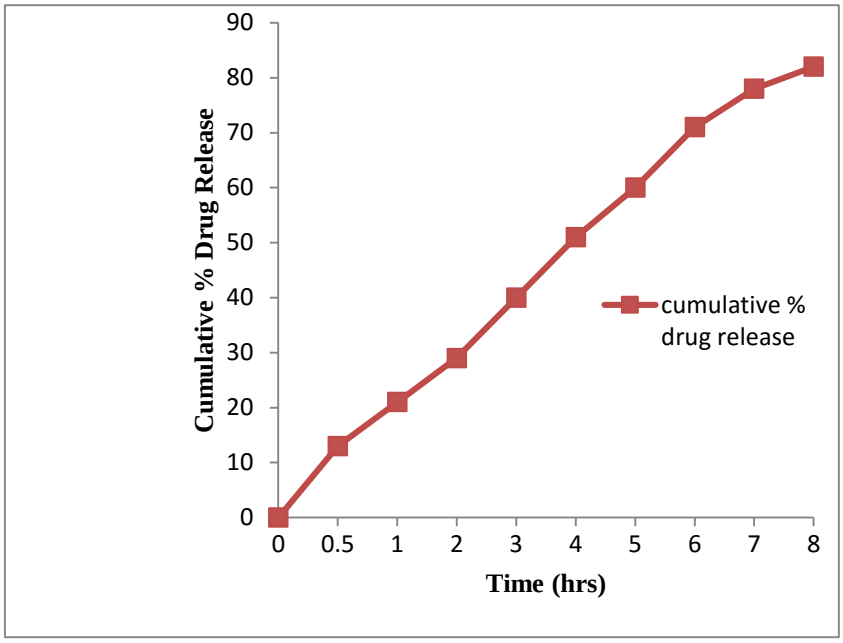
4.4 EX VIVO PERMEATION STUDY FOR F13 BATCH

Table 4.5 Ex vivo permeation of F13 batch

Time	Cumulative % drug permeation
0	00.00±0.00
0.5	13.89±0.961
1	21.96±0.489
2	29.68±0.691
3	40.56±0.856
4	51.75±0.654
5	60.95±1.045
6	71.76±0.981
7	78.65±0.865
8	82.78±0.958

*Values are means ± SD,(n=3)

Figure 4.5 Ex vivo drug permeation of F13 batch



The results of drug permeation from buccal tablet of Nisoldipine through the porcine buccal mucosa reveal that drug was released from the formulation and permeated through the porcine buccal membrane and hence can possibly permeate through the human buccal membrane. Following Figure 4.5 represent comparison of cumulative percent drug permeated from drug selected formulations. The results indicated that the cumulative percentage drug permeation was more in F13 among the selected formulations and about 82.78 % of Nisoldipine was be Permeated through the buccal membrane in 8 hrs respectively.

4.5 Comparison of F13 formulation with Marketed product

4.5.1 Comparing parameter:

In vitro drug release profile: The release profile of F13 formulation is compared with marketed product Sular®.

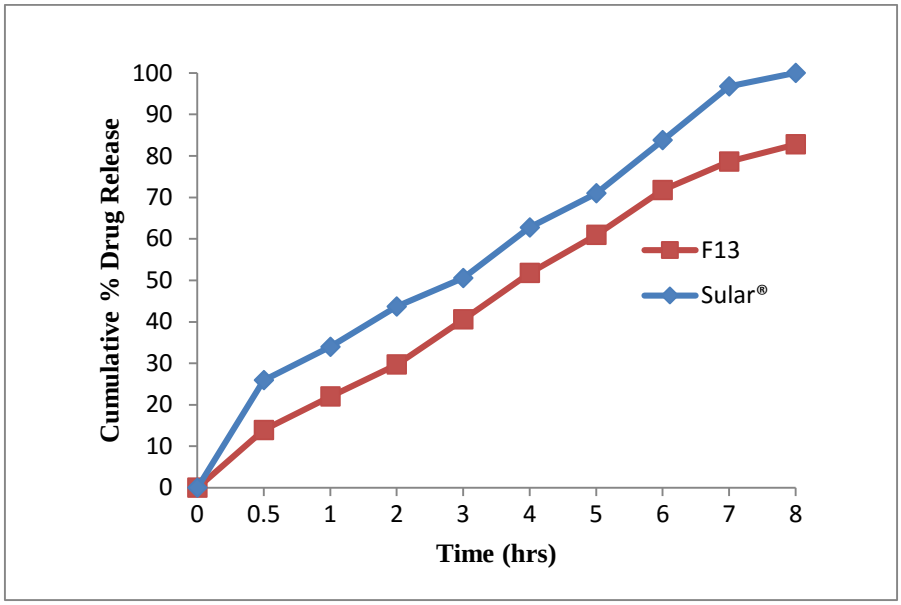


Figure 4.6 In vitro drug release comparison of F13 with Sular®

The above figure 4.6 shows the comparison of in vitro release of F13 batch with the marketed product.That shows100.96% drug release was observed in 8 hrs.In contrast to that, the release of F13 batch which shown 82.78% gave sustained release 8 hrs.

4.5.2 Difference factor (f1) and Similarity (f2) factor

A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (Moore 1996). The difference factor (f_1) calculates the percent (%) difference between the two curves at each time point and is a measurement of the relative error between the two curves; The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. For Curves to be considered similar f_1 values should be close to 0, and f_2 values should be close to 100.generally, f1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) insure sameness or equivalence of the two curves and , thus of the performance of the test (post change) and reference (pre change) product.

Here Sular® is taken as reference product and F13 formulation was taken as test product .

Table 4.7 f_1 and f_2 values for F13 formulation (test) and marketed product (reference)

Parameters	values
f_1	9.1
f_2	79.058

From the table no4.7 result showed that difference factor(f_1) was found to be 9.1 is comply within the official range (0-15) while similarity factor (f_2) was found to be 79.058 is also comply within the official range(50-100).so it ensures sameness or equivalence of the two curves and the performance of the test and reference products.

4.6 STABILITY STUDY FOR OPTIMIZED FORMULATION

Table 4.8 Results of stability study

Batch F1	In vitro drug release*	Drug content*	Bioadhesive strength*	Swelling index*
Initial	97.96 ± 0.891	99.52±0.70	23.5± 1.5	94.2±0.02
After 1 months	96.87± 0.785	98.12±0.60	23.1±1.2	93.2±0.04

*Values are means ± SD,(n=3)

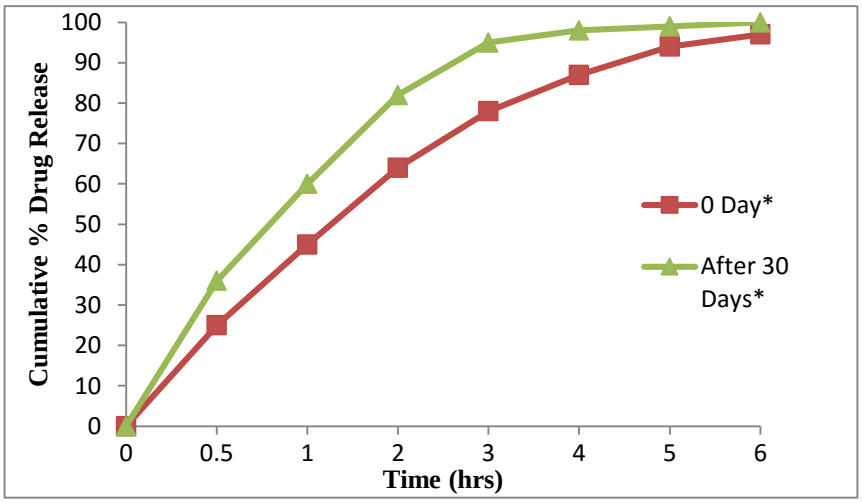


Figure 4.7 Release profile of optimized batch at 0 day and after 30 days

Stability studies on the promising formulation was performed at 40 ± 2 °C / 75 ± 5% RH* for a period of 1 months* according to ICH guideline indicated that there are no significant changes in drug content and in vitro dissolution, bioadhesive strength.

5 CONCLUSION

The results of the present study indicate that buccal tablets of Nisoldipine can be prepared by direct compression method using CP as a bioadhesive polymer and HPMC K_4M as a release modifying polymer and EC as backing layer. Carbopol 934P and HPMC K_4Min the ratio of 1:1 can be used to prepare bioadhesive buccal tablets of Nisoldipine having prolonged therapeutic effect with optimum release profile giving enhanced patient compliance by avoiding first pass metabolism.

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