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MUCOADHESIVE BUCCAL TABLETS OF NISOLDIPINE FOR ORAL DELIVERY: PREPARATION, IN-VITRO AND IN-VIVO EVALUATION

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ABSTRACT
Nisoldipine (ND) is calcium channel blocker used in treatment of hypertension. ND has poor oral bioavailability (BA) of about 5% due to extensive first-pass metabolism and limits its therapeutic use. Hence, the buccal delivery was considered as an alternative used to enhance the BA of ND. ND buccal tablets (ND-BT) were prepared by direct compression technique, using carbopol 934P HPMC K_4M and K15M as muco-adhesive polymers. Prepared ND-BT formulations were evaluated for an optimized system based on physico-chemical, *ex-vivo* residence time, *in-vitro* and ex vivo permeation studies. Further, in vivo studies of optimized ND-BT were conducted in pig's comparison with ND marketed formulation. The evaluation parameters of the tablets were within the pharmacoepial acceptable limits. However, the swelling and bio-adhesive strength were increased with increasing polymer concentrations. From the *in-vitro* release studies it is shown that, tablets with HPMC K_4M (N2) exhibited better release profile than all other formulation, and were considered as optimized BT formulation. The release mechanism from kinetic methods suggests that, the drug release follows zero-order kinetics with diffusion mechanism. Further, about 2.63-folds enhancement in the oral bioavailability of ND from buccal tablet was observed when compared with marketed formulation. Thus, the buccal tablets of ND showed enhanced BA and could be another delivery approach for oral administration.

KEYWORDS: Nisoldipine, first-pass metabolism, Buccal tablets, *in vitro*, *ex vivo*, *in vivo.*

INTRODUCTION
The oral cavity is easily accessible for self-medication and is well accepted by patients. In the last three decades, there is a great interest in the research of buccal drug delivery system (Senel, Hincal, 2001). The oral cavity is the most attractive route for drug delivery due to its ease of administration. Both locally acting and systemic acting drugs can be administered by this route. The site-specific release of drug at mucosa is achieved when used for local activity and systemic action requires drug absorption through the mucosal barrier to reach systemic circulation (Chaitanya et al., 2011).

Oral route is most preferred and widely applicable route for the delivery of majority of the drugs. But the problems such as poor aqueous solubility, less residence time, chemical instability in the gastrointestinal tract minimizes the bioavailability (BA) of orally administered drugs (Narendar and Kishan, 2015). Further, metabolism through various barriers or enzymes also degrade the drug before reaching site of action. Hence, various alternative drug delivery systems are developed to enhance the oral BA of these drugs. The delivery systems include; enhancement of solubility through solid dispersions (Ettireeddy*et al.,* 2017), complexation with cyclodextrins (Palem*et al.,* 2016), liquisolid compacts (Arun*et al.,* 2015); increase the stability and prolonged residence time through floating systems (Narendar et al., 2011; Reddy *et al.,* 2016), increase the mucoadhesive property (Bomma*et al.,* 2016); lipid based delivery systems for by passing metabolism with solid lipid nano particles (Narendar and Kishan, 2017), transfersomes (Pitta *et al.,* 2018), nanostructured lipid carriers (Reddy *et al.,* 2018) and micronization for reducing particle size using nanosuspensions (Nagaraj et al., 2017; Arun*et al.,* 2018).

Nisoldipine (ND) is dihydropyridine derivative of calcium channel blocker. It is used for the treatment of hypertension. It has poor oral bioavailability (less than 5%) due to poor aqueous solubility and first-pass metabolism. Previously, various delivery lipid systems like solid lipid nano particles (Narendar and Kishan, 2015), nano structured lipid carriers (Narendar et al., 2018), proliposomes (Nekkanti et al., 2016), transdermal delivery (El Maghraby et al., 2015) were reported

enhance the BA. There are no buccal delivery systems reported till now. Hence, the bioavailability of drug was enhanced by formulating as buccal tablets to avoid first pass metabolism and also prolong the drug release for 6h. Therefore, the aim of the investigation was to prepare and evaluate buccal tablets of nisoldipine to enhance the oral bioavailability.

The main objective of the present investigation was to design the formulation and evaluation of bioadhesive buccal tablets of ND(ND-BT) to improve the oral bioavailability. Accordingly, ND-BT were prepared and evaluated for an optimized system based on physical parameters, assay, swelling, surface pH, ex vivo residence time. In vitro release studies using dissolution and permeation studies through porcine membrane using diffusion cells were performed. Further, in vivo performance of optimized ND-BT was conducted in pig across buccal mucosa.

MATERIALS AND METHODS

Nisoldipine was obtained as a gift sample from Stride's lab, Bangalore India. Carbopol 934P was obtained from S.D. Fine Chemicals, Mumbai. Hydroxy propyl methyl cellulose (HPMC K4M and K15M) was obtained from Loba chemicals, Mumbai. Micro crystalline cellulose (MCC) obtained from Laksmi chemicals, India PEG 6000 obtained from India glycol Pvt Ltd., Mumbai, India. All other ingredients used in formulations were of analytical grade.

Preparation of ND Buccal Adhesive tablets (ND-BT)

Buccal tablets of ND (ND-BT) were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Drug was mixed manually with different ratios of mucoadhesive polymers and diluent for 10 min. The blend was mixed with magnesium stearate for 3-5 min and then compressed into tablets by the direct compression method using 6 mm flat faced punches. The tablets were compressed using a sixteen station CEMACH rotary tablet-punching machine. The mass of the tablets was determined using a digital balance (SHIMADZU) and thickness with digital screw gauge. The composition is depicted in Table 1.

Table 1: Formulation of mucoadhesive tablets of nisoldipine.

Ingredients	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12
Nisoldipine	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M	25	37.5	50	75	---	---	--	--	--	---	---	---
Carbopol	---	---	---	--	12.5	25	37.5	50	---	--	--	---
HPMC $K_{15}M$	---	---	---	---	---	---	---	---	12.5	25	37.5	50
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3

Total weight equal to 150 mg by using MCC

Evaluation of muco-adhesive buccal tablets

Determination of weight variation: This is an important quality control test to be checked for any variation in the weight of tablets that leads to either under or overdose. So every batch should have a uniform weight (USP, 1990).

Method: Twenty tablets were randomly selected from each formulation and their average weight and standard deviation were calculated from the total weight of all tablets. The % difference in the weight variation should be within the permissible limits. The % deviation was calculated.

Thickness

The thickness of buccal tablets was determined with the help of vernier calipers. Three individual tablets from each formulation were used and the results averaged.

Hardness

Hardness is an important quality control test to be indicated for measuring the ability of a tablet to withstand mechanical shocks while handling. The test was conducted for 3 tablets from each formulation using Monsanto hardness tester; the average and standard deviation values were calculated (Lachman, 2009).

Friability

It is a measure of mechanical strength of tablets. Roche friabilator was used to determine the friability by the following procedure. Pre-weighed tablets (10 tablets) were placed in the friabilator. This device consists of a plastic chamber that is set to revolve around 100 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. At the end of the test, tablets were reweighed; loss in the weight of the tablet is the measure of friability and is expressed in percentage as:

$$F\ (\%) = [1\text{-}W_F/Wo] \times 100$$

Where Wo is the weight of the tablets before the test and W_F is the weight of the tablets after test

Drug content

Ten tablets were weighed and grounded in a mortar with a pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in phosphate buffer pH 6.8 for 10 minutes, added sufficient buffer and filtered through filter paper, 1ml of filtrate was suitably diluted with buffer and drug content was analyzed

spectrophotometrically at 260nm using a UV spectrophotometer (IP, 1996).

Swelling studies of buccal tablets

Appropriate swelling behavior of a buccal adhesive system is an essential property for uniform and effective muco-adhesion (Kashappa, Pramod, 2004). Swelling of tablet involves the absorption of a liquid resulting in an increase in weight and volume. The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bio-adhesiveness. The agar plate model used in this study resembles the secreting fluid around the buccal mucosa (Emami, Varshosaz, Saljoughian, 2008). For each formulation, three buccal tablets were weighed individually (W_1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 1°C. After every 1 hr time interval until 6 hr, the tablet was removed from the petri-dish and excess surface water was removed carefully with blotting paper. The swollen tablet was then reweighed (W_2) and the swelling index (SI) was calculated using the following formula (Vishnu et al., 2007, Luana*et al.*, 2004, Chinna Reddy *et al.*, 2011).

Swelling Index = $[(W_2-W_1) \div W_1] \times 100$

Where, W_1 = initial weight of the tablet

W_2 = final weight of the swollen tablet

***Ex-vivo* bioadhesion strength:** Bioadhesion strength of tablets were evaluated using a microprocessor based on advanced force gauge equipped with a motorized test stand (Ultra Test Tensile strength tester, Mecmesin, West Sussex, UK) according to method describe as it is fitted with 25kg load cell, in this test porcine membrane was secured tightly to a circular stainless steel adaptor and the buccal tablet to be tested was adhered to another cylindrical stainless steel adaptor similar in diameter using a cyanoacrylate bioadhesive. Mucin 100 µl of 1 %w/v solution was spread over the surface of the buccal mucosa and the tablet immediately brought in contact with the mucosa. At the end of the contact time, upper support was withdrawn at 0.5mm/sec until the tablet was completely detached from the mucosa. The work of adhesion was determined from the area under the force distance curve.

The peak detachment force was maximum force to detach the tablet from the mucosa.

$$\text{Force of adhesion} = \frac{\text{Bioadhesion strength x 9.8}}{1000}$$

$$\text{Bond strength} = \frac{\text{Force of adhesion}}{\text{surface area}}$$

Surface pH

The bioadhesive tablets were allowed to swell by keeping it in contact with 1 mL of distilled water for 2hr at room temperature. Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3).

Moisture absorption

Agar (5% m/V) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\%\text{Moisture Absorption} = \frac{\text{Final weight–Initial weight x 100}}{\text{Initial weight}}$$

***Ex-vivo* residence time**

The *Ex-vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised pig mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 500 ml of phosphate buffer, pH 6.8, at 37^0C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (Fig 5). The time for complete erosion or detachment from the mucosa was recorded.

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

Ex-vivo permeation study of ND buccal tablets through the porcine buccal mucosa was performed using Franz-type diffusion cell with a diffusion area of 30.02 cm^2 and the receptor compartment volume of 21 ml at 37°C ± 0.2°C and 50rpm. This temperature and rpm was maintained by using magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2hr of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the Franz-type diffusion cell. After the buccal membrane was equilibrated for 30 min with Krebs buffer solution between both the chambers, the receiver chamber was filled with fresh pH 7.4 buffer solution.

The buccal tablet was placed in donor chamber and wetted with 1ml of buffer solution (pH 6.8) (Palem et al., 2011).The amount of drug permeated through the membrane was determined by removing aliquots (5mL) were collected from the receiver chamber at predetermined time intervals and filtered through a filter paper and the medium of the same volume (5mL), which was pre-warmed at 37°C, was then replaced into the receiver chamber. The amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 236 nm using a UV

spectrophotometer. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the flux (J), permeability coefficient (P).

$$J = \frac{(dQ/dt)}{A}$$

$$P = \frac{(dQ/dt)}{\Delta CA}$$

Where, J is the steady-state flux ($mg.hrs^{-1}cm^{-2}$)
P is permeability coefficient (cm/h)

dQ/dt is the slope obtained from the steady state portion of the curve
ΔC is the concentration difference across the mucosa and

A - the area of diffusion (cm^2).

Stability studies

Stability studies were performed at a temperature of 40^0C at 75% RH, over a period of three months (90 days) for the optimized buccal tablet. Sufficient number of tablets (15) was packed in amber colored screw capped bottle sand kept in stability chamber maintained at $40^o \pm 1^o$ C & 75% RH. Samples were taken at monthly intervals for drug content estimation. At the end of three months' period, dissolution test and drug content studies were performed to determine the drug release profiles and drug content.

Comparative bioavailability study in pigs

The study protocol was reviewed and approved by the Creature moral advisory group, Browns college of Pharmacy, Khammam, Telangana. White healthy pigs weighing 30 ± 5 kg were selected from the slaughter house for the study. The bioavailability of optimized mucoadhesive buccal tablet (ND-BT) was compared with marketed tablet formulation (Sular®). They were allowed free access to food and water, until the night prior to dosing, and were fasted for 10 h. Latin square cross-over design was followed; the animals were divided into two groups, each group consisting of six pigs. To one group, marketed formulation was administered through feeding tube followed by rinsing with 10 ml of water and ND-BT to another group in the first phase. The pigs were anesthetized during sample collection until the third hour sample. In the second phase vice versa was followed and was conducted after 15 days of wash out period. Blood samples (5 mL) from the tail vein were collected at pre-set time intervals. All blood samples were allowed to clot and centrifuged for 10 min at 5000 rpm (MIKRO 220R, Hettich, Germany). The serum was separated and transferred into clean micro-centrifuge tubes and stored at −20°C until HPLC analysis. The amount of HH in the samples was analyzed using HPLC.

Pharmacokinetic analysis

Pharmacokinetic parameters of ND after administration of bioadhesive buccal and marketed tablet formulations were estimated for each volunteer using a computer program, KINETICA 2000 (Version 3.0, Innaphase Corporation, PA, USA). Non-compartmental analysis was used to calculate the pharmacokinetic parameters: mean peak plasma concentration (C_{max}), time to reach peak plasma concentration (T_{max}), and area under the curve (AUC). The relative bioavailability (F) for buccal delivery was calculated using equation (3).

$$\text{Relative bioavailability} = \frac{[AUC]\ \text{buccal tablet formulation}}{[AUC]\text{Marketed tablet formulation}}$$

Differential Scanning Calorimetry (DSC)

For DSC study, Universal V4 TA instruments was used, samples 2–4 mg was weighed accurately, placed in aluminum pans and heated at 10°C per min rate in the range of 30-300°C in a nitrogen purging gas environment.

RESULTS AND DISCUSSION

Compatibility Studies

The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations (Figure 1). The DSC thermogram of pure nisoldipine showed endothermic peak at a temperature of 154.5°C, which is corresponding to its melting range (152 – 157^oC). The pure HPMC K_4M polymer showed decomposed endothermic peak at 76.88^oC. In case of physical mixture, the drug showed an endothermic peak at 152.6^oC and polymer at 73.67^oC. The optimized formulation showed drug peak at 152.5^oC and HPMC K_4M polymer at 74.79^oC, respectively. From this observation, there was no interaction takes place between drug and polymer.

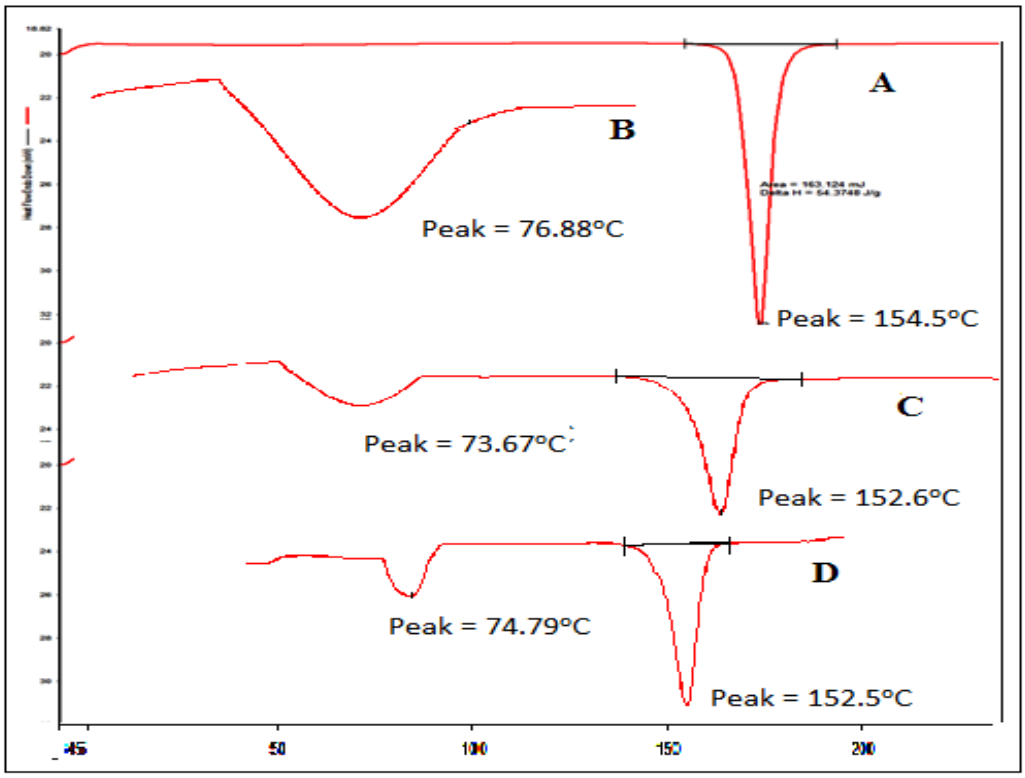

Figure 1: DSC thermogram of A) pure ND, B) pure HPMC K4M, C) physical mixture of drug and polymer (1:1) and D) optimized formulation (N2).

Characterization of Blend

The blends for buccal tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Angle of repose was less than 30° and Carr's index values were less than 15 for the blend of all the batches indicating excellent to good flowability and compressibility. Hausner's ratio was less than 1.11 for all the batches indicating excellent flow properties. The results are showed in Table 2.

Table 2: Physical properties of pre-compression blend.

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio	Flow property
N1	30.25^0	0.342	0.386	11.39	1.12	Good
N2	30.43^0	0.358	0.412	13.10	1.15	Good
N3	22.87^0	0.326	0.334	2.39	1.02	Excellent
N4	22.45^0	0.334	0.348	4.022	1.04	Excellent
N5	24.37^0	0.442	0.499	11.43	1.12	Excellent
N6	29.41^0	0.321	0.334	3.88	1.04	Good
N7	22.88^0	0.326	0.333	2.32	1.02	Excellent
N8	30.13^0	0.360	0.414	13.11	1.15	Good
N9	24.30^0	0.447	0.500	11.42	1.13	Excellent
N10	22.87^0	0.326	0.334	2.32	1.02	Excellent
N11	22.45^0	0.334	0.348	4.02	1.04	Excellent
N12	30.43^0	0.358	0.412	13.23	1.15	Good

Physical parameters and drug content

The results of uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 148.6±0.41and 151.6±1.14mg. The hardness of the tablets ranged from 6.34±0.57 to 6.86±0.55kg/cm^2 and the friability values were less than 0.5% indicating that the Buccoadhesive tablets were compact and hard. The thickness of the tablets ranged from 2.52±0.17 to 2.65±0.66 mm. All the formulations satisfied the content of the drug as they contained 98 to 101 % of ND and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table 3: Physical evaluation parameters of ND buccal tablets.

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Drug content (%)
N1	6.50 ±0.44	2.52±0.17	150.8±1.48	0.36	98.25±1.37
N2	6.60±0.31	2.57±0.25	149.4±0.54	0.39	99.48±0.80
N3	6.72±0.40	2.54±0.80	148.6±0.41	0.43	99.12±2.47
N4	6.86±0.55	2.50±0.20	148.8±1.64	0.12	100.22±0.88
N5	6.34±0.57	2.65±0.66	150.6±1.14	0.54	100.24±1.25
N6	6.49±0.30	2.63±0.25	148.2±0.83	0.58	99.53±1.87
N7	6.51±0.32	2.57±0.81	148.7±0.46	0.36	99.50±0.60
N8	6.53±0.35	2.58±0.80	148.9±0.64	0.39	99.32±0.87
N9	6.52±0.31	2.57±0.82	148.9±0.44	0.43	99.58±0.60
N10	6.76±0.55	2.30±0.20	149.8±1.64	0.12	99.22±0.88
N11	6.44±0.57	2.45±0.66	151.6±1.14	0.18	100.24±1.0
N12	6.59±0.30	2.33±0.25	149.2±0.83	0.26	100.53±1.0

Microenvironment pH study

The surface pH of all formulations was found to be within ± 1units of neutral pH. The values are tabulated in the Table 4. Hence, these formulations should not cause any irritation in buccal cavity.

Table 4: Microenvironment pH of ND buccal tablets (mean±SD, n=3).

Formulation	Surface pH	Mucoadhesion time (h)
N1	6.4±0.2	6
N2	6.6±0.09	8
N3	6.2±0.3	9
N4	6.6±0.4	5
N5	6.5±0.3	7
N6	6.3±0.1	>9
N7	6.5±0.3	6
N8	6.4±0.2	7
N9	6.6±0.1	9
N10	6.3±0.08	5
N11	6.6±0.16	6
N12	6.9±0.3	6

***Ex-vivo* mucoadhesion time**

Ex vivo residence time was determined by using porcine buccal mucosa. The mucoadhesion time is important to know how long the tablet could able to stick to the buccal mucosa. This adhesion time relates to the release rate of drug. The bioadhesive tablet is important for good mucoadhesion. Bioadhesion characteristics are affected by the type and ratios of bioadhesive polymers. The results were tabulated in the Table 4.

Swelling index

The swelling behavior of a buccal adhesive system is an important properties uniform and prolonged release and effective mucoadhesion. The swelling index study indicated that the rate of swelling was directly proportional to polymer content. Swelling index was calculated with respect to time. The swelling index gives an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption. The results of present formulation were tabulated in the Table 5. The swelling index of the formulations ranged from 65.8 to 99.6 % at the end of 6 h.

Table 5: Percent swelling index of ND buccal tablets (mean±SD, n=3).

Time (h)	Swelling index (%)											
	N1	**N2**	**N3**	**N4**	**N5**	**N6**	**N7**	**N8**	**N9**	**N10**	**N11**	**N12**
1	20.8	24.6	30.4	14.8	18.3	20.7	20.1	21.3	18.4	30.4	24.6	20.7
2	48.1	51	56.2	30.1	35.3	38.5	46.2	55.2	56.7	56.2	51	38.5
4	59.6	63.8	67.5	50.4	54.4	60.6	68.5	76.5	67.9	67.5	63.8	60.6
6	76.45	79.4	85.6	65.8	70.7	74.4	88.3	99.6	85.6	85.6	79.4	74.4

***In-vitro* release studies of ND buccal tablets**

The *In-vitro* drug release study has been done for various formulations (N1-N12) in pH 6.8 phosphate buffer. The different ratios of polymers were used. The results are presented in Figure 2, 3 and 4. The results shown that as the proportion of polymers in the formulation increases, cumulative percent drug release was found to be reduced. Among the twelve batches, formulation N1, N2, N3 and N4 developed with HPMC K4M polymer. As the concentration of polymer increased from 37.5 to 75 mg, the drug release was retarded. The N1 formulation released 98.2±2.01% drug during 6 h. N2, N3 and N4 formulations showed 97.1±2.88, 86.7±1.93 and 80.6±1.74% drug release, respectively. This might be due to the swelling of the polymer and diffusion takes place. Similarly, in case of N5–N8 formulations, developed with carbopol showed 94.8, 88.6 and 81.3 % except N5 showed 98.5% release during 6h and remaining three showed in 8 h. From N9-N12, the N9 formulations showed release upto 6h but, remaining three prolonged the drug release up to 8h.

Among all N2, N5 and N10 were optimized based on sustained drug release and highest drug respectively at 8 h. But mucoadhesion time for N2 formulation was less than 8 h hence, N2 was considered as best formulation.

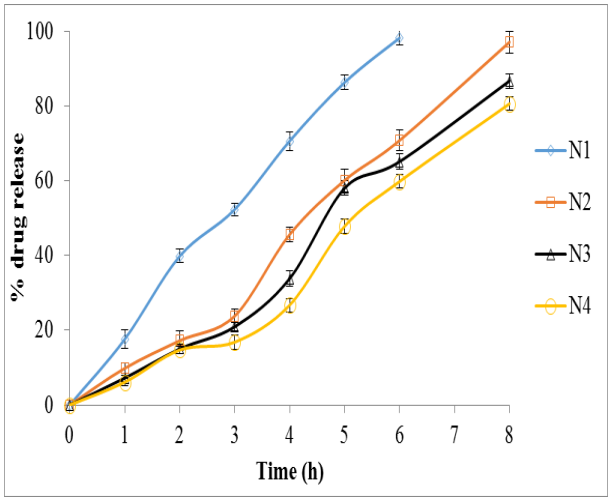

Figure 2: In vitro release profiles of ND from ND buccal tablets (N1-N4) (Mean±SD, n=3).

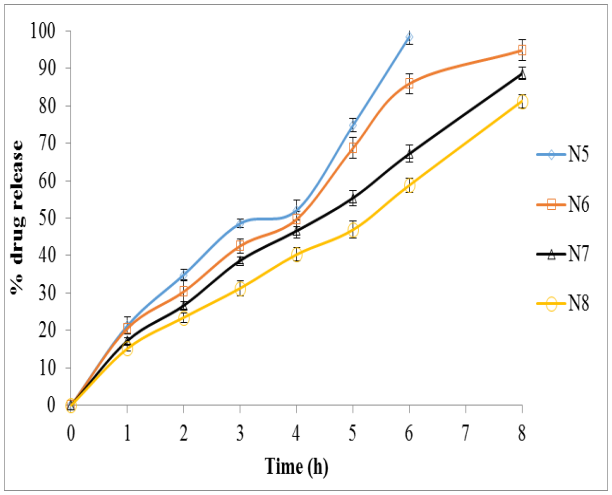

Figure 3: In vitro release profiles of ND from ND buccal tablets (N5-N8) (Mean±SD, n=3).

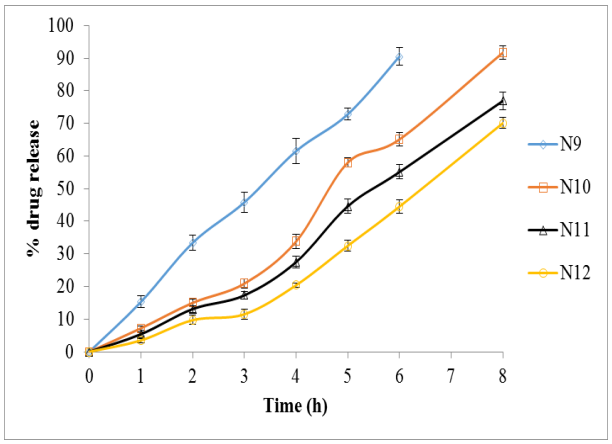

Figure 4: In vitro release profiles of ND from ND buccal tablets (N9-N12) (Mean±SD, n=3).

***Ex-vivo* permeation studies of ND buccal tablet (N2) through porcine buccal mucosa formulation**

Ex vivo permeation of N2 formulation was condcuted through porcine buccal mucosa by usin franz diffusion apparatues. Cumulative amount of drug permeated was found to be 84.01±2.13% in 8 h. Prior to the study, the permeation of pure ND drug solution also studied and was found to be 81.66% in 8 h.

***Ex-vivo* bioadhesion strength**

In vitro bioadhesion for optimized ND buccal tablets was conducted and displayed good bioadhesion i.e., work of adhesion 4.77 ±0.83 mJ, peak detachment force 1.66±0.17 N.

Moisture absorption

Moisture absorption studies evaluated the integrity of the formulation upon exposure to moisture. Formulations N2 were eroded in 2 hours with 54.77% w/w. When the tablets were positioned without the backing membrane complete swelling followed by erosion was observed, indicating that the drug release mechanism involves swelling of the polymer initially followed by drug release from the swollen matrix by diffusion.

Stability studies

Results from stability studies indicate that the formulated ND buccal tablets are stable for a period of 3 months under 2 different conditions at 25±2^{o}C and 65±5%RH and 40±2^{o}C and 75±5%RH (Table 6). There were no remarkable changes observed during the period of storage.

Table 6: Stability studies of optimized nisoldipine buccal tablet (N2) formulation.

Time (days)	Assay		Cumulative % drug release		Surface pH	
	25±2°C&65±5%RH	40±2°C&75±5%RH	25±2°C& 65±5%RH	40±2°C&75±5%RH	25±2°C& 65±5%RH	40±2°C& 75±5%RH
Initia	99.48	99.48	97.6	98.6	6.6	6.6
30	99.40	99.30	99.1	97.9	6.6	6.6
60	99.31	99.2	97.2	97.1	6.6	6.6
90	98.5	98.0	98	97.8	6.6	6.6

Bioavailability study in pigs

Mean serum concentration and time profiles of nisoldipine buccal tablets and marketed tablet (Sular®) formulation were showed in Table 7 and Figure 5. PK parameters of study are represented in table 7. From PK parameters, the $C_{max,}$ $t_{max,}$ t_{half} (h) and MRT of the N2 and marketed tablet was found to be 6.43±1.10 and 3.21±0.83 µg/mL; 2.50±0.54 and 1.33±0.51 h; 12.55±1.65 and 6.08±0.85 h; 14.11±2.10 and 7.60±1.04, respectively. All these parameters are twice when compared with marketed tablet. This might be due to the prolonged release of the ND from the N2 formulation. AUC_{tot} of the formulations was 42.15±3.11and 15.98±2.03 µg.h/mL, receptively for N2 and marketed tablet. From this evidenced that about 2.63-folds enhancement in the oral bioavailability of buccal tablet when compared with marketed tablet formulation of ND.

Table 7: Pharmacokinetic parameters of nisoldipine in pigs after administration of marketed tablet (Sular®) and optimized buccal tablet (N2)(mean± SD, n=6)

Parameter	N2 buccal tablet	Marketed tablet (Sular®)
C_{max}(µg/mL)	6.43±1.10*	3.21±0.83
t_{max}(h)	2.50±0.54#	1.33±0.51
AUC_{tot} (µg.h/mL)	42.15±3.11*	15.98±2.03
t_{half} (h)	12.55±1.65*	6.08±0.85
MRT (h)	14.11±2.10*	7.60±1.04

* - indicates p<0.001 and # - indicates p<0.01 statistically significant compared with Marketed tablet (Sular®)

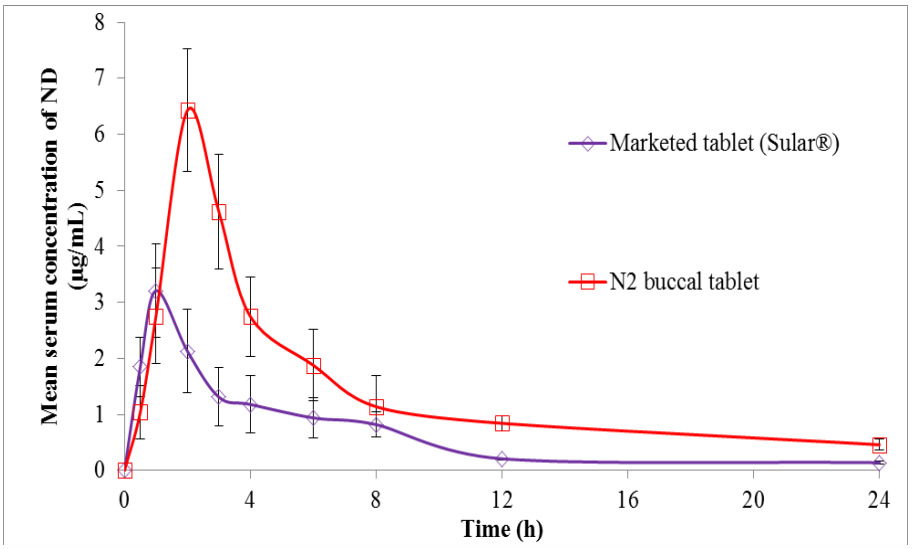

Figure 5: Mean serum concentrations of ND buccal tablet (N2) and marketed tablet formulation (Sular®)in pigs after oral administration (mean±SD, n=6).

CONCLUSION

The present investigation designed to develop the buccal drug delivery system of ND with controlled effect and to avoid first pass metabolism to improve the oral BA. All the prepared tables were within the acceptable pharmacopeial limits for evaluation parameters.The optimized formulation N2 was best in terms of drug release, mucoadhesive permeationacross the mucosal membrane and in vivo performance in pigs buccal mucosa. Hence, it can be concluded that the formulations of ND mucoadhesive buccal tablets are promising one as the controlled drug delivery, improve bioavailability and may be a good candidate for buccal delivery.

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