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FORMULATION AND OPTIMIZATION OF MUCOADHESIVE BUCCAL TABLETS OF NIFEDIPINE USING 2^3 FULL FACTORIAL DESIGNS

[*1]Muthukumaran M, [2]Dhachinamoorthi D, [1]Chandra Sekhar K B

[1]Jawaharlal Nehru Technological University Anantapur, Anantapur, A.P, India.

[2]QIS College of Pharmacy, Vengamukkapalem, Ongole, A.P, India.

Abstract

The objective of this current investigation is to highlights the novel sustained release mucoadhesive buccal tablets containing nifedipine by using various proportions of mucoadhesive polymers such as xanthan gum, HPMC-K4M, carbopol-974P, along with ethyl cellulose and magnesium sterate as impermeable backing membrane. The 2^3 full factorial designs were applied to carry out systematic studies. The *FTIR* and *DSC* studies confirmed that the absence of chemical interactions with drug and excipients. Further, the optimized buccal tablets were evaluated for various physicochemical parameters such surface pH, swelling index, *ex - vivo* mucoadhesive strength, *in vitro drug* release, *ex-vivo* permeation studies, release kinetics and short–term stability studies. The results from the present investigation reveals that capable mucoadhesive buccal tablets of nifedipine, it could be a better approach to bypass the extensive hepatic first-pass metabolism, thereby improve the bioavailability.

Keywords: Buccal tablets, 2^3optimizationtechnique, Nifedipine, Xanthan gum, angina pectoris.

Introduction

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as carriers. Amongst various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike parenteral, mucosal, and transdermal routes circumvent hepatic first-pass metabolism and offer alternative routes for the systemic delivery of drugs [1]. These include routes such as pulmonary, ocular, nasal, rectal, buccal, sublingual, vaginal, and transdermal. Hence the mucoadhesive drug delivery system can be classified according to its potential site of applications [2]. The buccal region of oral cavity is an attractive site for the delivery of drugs owing to the ease of the administration. Buccal drug delivery involves the administration of desired drug through the buccal mucosal membrane lining of the oral cavity. This route is useful for mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation[3]. Suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration and should release the drug in a unidirectional way toward the

Author for Correspondence:
Muthukumaran M,
Jawaharlal Nehru Technological University Anantapur,
Anantapur, A.P, India.
Email: muthuviyas@gmail.com

mucosa, in a controlled and predictable manner, to elicit the required therapeutic response.

Nifedipine, a systemic calcium channel blocker, is a practically water insoluble and light-sensitive drug which belongs to the dihydropyridine class of compounds, used in the treatment of angina pectoris and hypertension[4]. As its biological half-life is about 2 h and is eliminated rapidly, repeated daily administrations are needed to maintain effective plasma levels [5]. It shows a low and irregular bioavailability of about 50% after oral administration with a high first pass effect[6]. It has been suggested that drugs with biological half-lives in the range of 2–8 h are good candidates for sustained-release formulations [7].

Materials and methods

Nifedipine, Xanthan gum, Carbopol 974P (CP) was obtained as a gift samples from Micro labs-Bangalore. Hydroxypropylmethyl cellulose (HPMC K4M) (Colorcon Asia ltd. Goa) were obtained as a gift sample. Ethyl cellulose (EC) (Loba Chemie Pvt. Ltd.), magnesium stearate (Himedia laboratories Pvt ltd. Mumbai) and all other reagents and chemicals used were of analytical grade.

Design of Experiments

A 2^3 Full Factorial design was employed to study the effect of three independent polymer variable factors [(A=Xanthan gum), (B=HPMCK4M), (C=Carbopol-974P)] was kept at two levels, as low and high. The experimental trials were performed at all 8 possible combinations.

Preparation of mucoadhesive buccal tablets of nifedipine[8]

Mucoadhesive buccal tablets were formulated by a direct compression technique. All the ingredient of the formulations was passed through a sieve # 85 and was blended in a glass mortar with a pestle to obtain uniform mixing. In the first step, drug was incorporated in the adhesive layer of the tablet, which faces toward the mucosal surface.

The blended powder of the core was compression into tablets on a Rotary, 10 **-** station tablet punching machine. In the second step, the upper punch was raised and the ethyl cellulose and magnesium sterate as backing layer was added over it and finally compressed at a constant compression into a mucoadhesive buccal tablets. The compositions of buccoadhesive buccal tablets of nifedipine are given in table 1.

Table No. 01: Composition variables of nifedipine buccal tablets

	Drug reservoir(mg)				Drug free backing layer(mg)	
Formula code	**Drug**	**Xanthan gum**	**HPMC K4M**	**CP-974P**	**EC**	**Mg.Sterate**
FNX1	30	35	25	20	20	10
FNX2	30	60	25	20	20	10
FNX3	30	35	40	20	20	10
FNX4	30	60	40	20	20	10
FNX5	30	35	25	40	20	10
FNX6	30	60	25	40	20	10
FNX7	30	35	40	40	20	10
FNX8	30	60	40	40	20	10

HPMCK4M- Hydroxyl propyl methyl cellulose, CP-974P – Carbopol-974P,
EC – Ethyl cellulose, Mg.Sterate-Magnesium sterate.

Drug-polymers Compatibility Studies

This study has been done to check whether there is any compatibility related problems are associated with drug and excipients used for the formulation of buccal tablet. The drug-excipients compatibility studies[9] were carried out by using Fourier Transform Infrared Spectrophotometer (FTIR) and Differential scanning calorimetry (DSC).Drug-Polymers compatibility studies were performed by Fourier transforms infrared spectroscopy (FTIR). A physical mixture of drug, polymer and other excipients were prepared and mixed with suitable quantity of potassium bromide. It was scanned from 4000 to 400 cm-1 in a FTIR spectrophotometer, in order to confirm that the entrapment of drug within the polymeric system involves only the physical process. The IR spectrum of the physical mixture was compared with those of pure drug and polymers and peak matching was done to detect any appearance or disappearance of peaks. DSC in which the difference in the amount of heat required to

increase the temperature of a sample and reference are measured as a function of temperature whether more or less heat must flow to the sample depends on whether the process is exothermic or endothermic.

Post compression evaluation of buccal tablets[10, 11]

All the prepared buccal tablets were evaluated for thickness, hardness, friability, and drug content.

Surface pH[12]

The surface pH of the buccoadhesive system was determined to predict the comfort of the formulation with the buccal mucosa. The buccal tablet was allowed to swell by keeping in contact with 5ml of phosphate buffer pH 6.8 ± 0.01 for 2 hours at room temperature. The pH was deliberate by bringing the electrode in contact with the surface of the buccal tablet and allowing it to equilibrate for 1 minute.

Swelling behaviour of buccal tablets[13]

The extent of swelling was measured in terms of % weight gain by the tablet. The buccal tablet from each formulation was kept in a Petri dish containing 1% agar gel plates. At the end of every 2 hours, the tablet was withdrawn, kept on tissue paper and weighed, till 6 hours.

The degree of swelling was computed using the formula:

Swelling Index (S.I) = [(W2-W1)/W1] x 100

Where, W1- initial weight of tablet, W2- weight of tablet at time

Mucoadhesive tensile strength Measurement[14]

Measurement of the force required to break the adhesive bond between a membrane and buccal tablets was carried by modifying balance method. Sheep buccal mucosa was used as model membrane. Buccal mucosa freshly excised from buccal portion of sheep and mucus side was exposed, washed thoroughly with phosphate buffer pH 6.8, placed to the beaker, which was filled with phosphate buffer so that it was just touched the mucosal surface. The buccal tablet was stuck to the lower side of a thread with cyanoacrylate adhesive. The two sides of the balance were made equal by keeping a 5 g weight on the right hand pan. Next, weight of 5 g was removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. Then weight was increased slowly to the right hand pan until the tablet detached from the mucosal surface.

Fig. No. 01: Mucoadhesive Strength measurement modified balance

In vitro release study of nifedipine buccal tablets[15]

The in vitro dissolution study was conducted for all formulation using USP dissolution test apparatus type II. The backing layer of buccal tablet was stick in to the glass disk by instant adhesive. The glass disk was allocated to the bottom of the dissolution container such that tablet core faced to the 900 ml dissolution medium (pH 6.8 Phosphate buffer) and temperature was maintained at 37 ± 5°C with stirring at 50 rpm. Release of studies was carried out for 10hrs. The nifedipine was evaluated spectrophotometrically at 238 nm.

Ex vivo Drug Permeation study[16]

The modified Franz diffusion cell was used for drug permeation study. The receptor compartment was cover with water jacket to maintain temperature 37± 5°C. The separated sheep buccal membrane was mounted between the chamber and in the receptor chamber, phosphate buffer solution (pH 6.8) was filled and buccal membrane was allow stabilizing for the period of 1 h. After stabilization, the tablet was kept on membrane and samples were withdrawn from sample portal of diffusion cell at predetermine time and replaced sample volume by replacing fresh medium to

maintained sink condition. The aliquot were analyzed spectrophotometrically. The drug permeation was correlated with cumulative drug released.

Drug release kinetic study[17, 18]

To ascertain the kinetic of the drug release from all the formulated buccal tablets, kinetic models such as zero-order, first order, Higuchi, Korsemeyer-Peppas models are computed with drug release data. The criterion for selecting the most appropriate model was on the basis of the goodness-or fit test.

Stability Studies[19, 20]

Mucoadhesive buccal tablets of optimized batch were selected for short-term stability study. It was carried out at accelerated condition of 40 ±2°C for a period of three months. After each month interval, tablet sample was analyzed for physical characters, drug content, and tensile strength of mucoadhesive and in- vitro drug release.

Results and discussion

In the present work, an antihypertensive drug nifedipine and the mucoadhesive polymers were selected on the basis of bioadhesive property, non-irritancy, swelling index property, stability and compatibility with the drug for the development of buccal tablets. FTIR spectroscopic analysis was carried out to ascertain whether there is any interaction between drug and excipients used in the formulations. The IR spectra of nifedipine pure drug shows characteristic functional peaks at 3331.18 (N-H Stretching), 3100.67 (C-H Stretching), 1680.05 (C=N Stretching), 1529.60 (N-H bending), 1495.85 (C=C Stretching), 1310.67 (C-O Stretching), 1226.77 (C-N Vibration), 830.38(C-H bending) even as physical mixtures of drug and polymers show characteristic peaks at 3324.42 (N-H Stretching), 3099.71 (C-H stretching), 1685.84 (C=N Stretching),1529.60 (N-H bending), 1495.85 (C=C Stretching), 1349.25 (C-O Stretching), 1227.73 (C-N Vibration), 830.38 (C-H bending) with negligible shift in wave numbers, reflects that there is no drug-excipients interaction in formulation.

DSC scans of the nifedipine pure drug are presented in fig 3. The thermogram of nifedipine exhibited an endothermic peak at 175.8ºC corresponding to its melting point range. In the physical mixtures of drug and polymers, the sharp peak was observed in the same melting point range, suggesting that drug had not interacted with the polymers, which indicate its compatibility with excipients.

The pre-compression evaluation on blend of ingredients was analyzed for physical characteristics. The angle of repose of formulation blends F1 to F8 were in the range 22º17'± 0.86 to 29º21' ± 1.83, The bulk density, Tapped density, Carr's index, Hausner's ratio were found in the range of 0.403 ± 1.01 to 0.453±0.37 g/cc, 0.473 ± 0.53 to 0.542 ± 0.87 g/cc 9.42 ±1.11% to 13.54 ± 1.87% 1.024±0.03% to 1.181 ± 0.94%, respectively. It reveals that all formulations possess good flow property and compressibility.

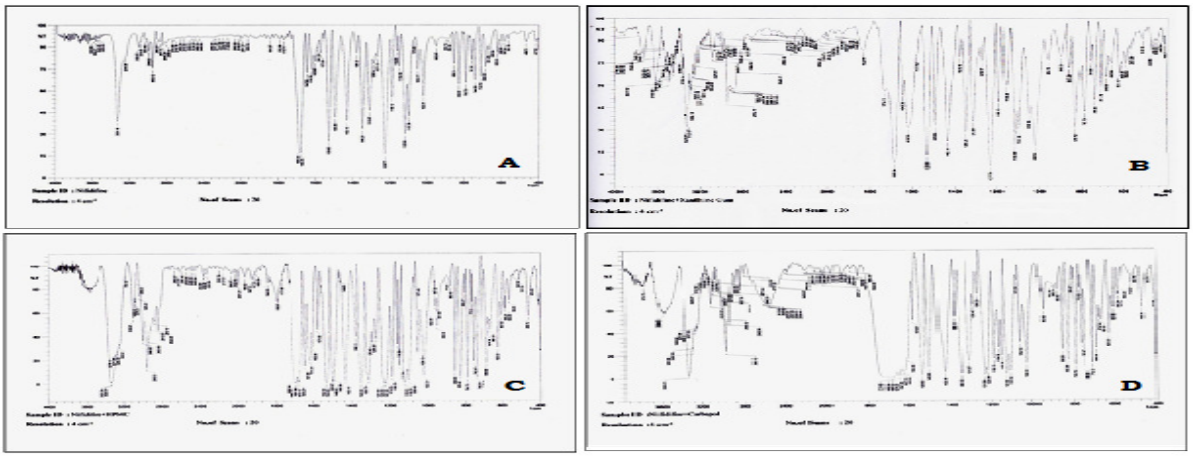

Fig. No. 02: FTIR Spectrum of A) nifedipine Pure B) Physical mixture of nifedipine and xanthan gum C) Physical mixture of nifedipine and HPMCK4M D) Physical mixture of nifedipine and carbopol 974P

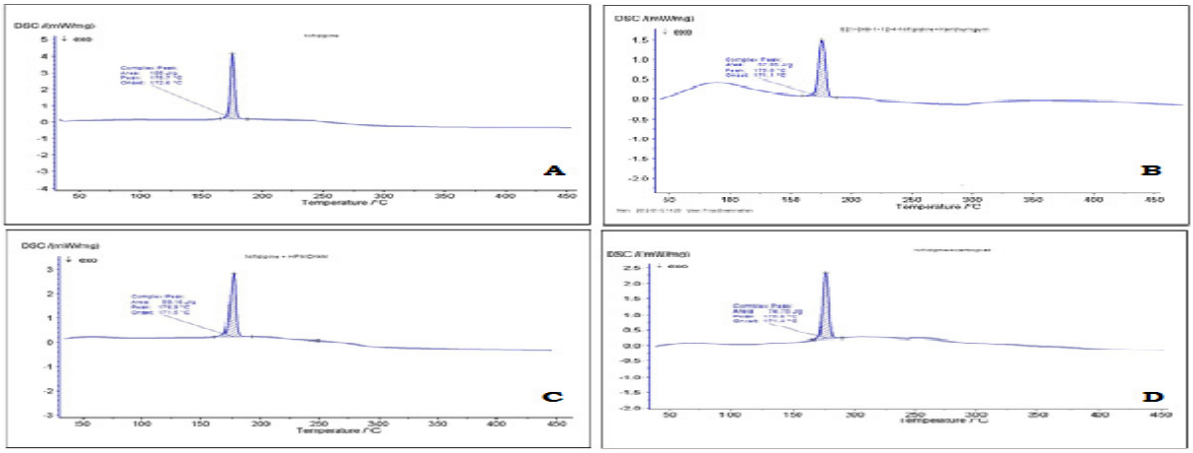

Fig. No. 03: DSC Thermogram of A) nifedipine Pure B) Physical mixture of nifedipine and xanthan gum C) Physical mixture of nifedipine and HPMCK4M D) Physical mixture of nifedipine and carbopol 974P

Table No. 02: Post compression evaluation of nifedipine buccal tablets

Formulation code	Thickness (mm)	Friability (%)	Hardness (Kg/cm^2)	Drug content (%)	Surface pH
FNX1	2.23±1.04	0.52±0. 11	4.2±0.351	91.77±1.23	6.71±0.56
FNX2	2.29±1.16	0.42±0. 29	3.7±0.152	93.85±1.03	6.53±0. 98
FNX3	2.19±1.05	0.60±0. 75	4.3±0.305	91.62±0.94	6.79±0. 69
FNX4	2.28±1.09	0.44±0. 87	3.9±0.30	93.81±1.06	6.41±0.98
FNX5	2.31±1.37	0.58±0. 49	4.3±0.450	94.69±1. 81	6.76±0. 17
FNX6	2.22±1.11	0.42±0.62	3.8±0.550	93.97±1. 17	6.47±0.94
FNX7	2.26±1.61	0.52±0.92	4.1±0.351	92.76±1.03	6.76±0.74
FNX8	2.24±0.03	0.49±1.02	3.7±0.568	91.93±1. 17	6.51±0.95

Mean±SD (n=3)

Mucoadhesive buccal tablets of nifedipine were found to be satisfactory when evaluated for thickness (2.19±1.05 to 2.31±1.37 mm), hardness (3.7±0.152 to 4.3±0.305 kg/cm^2), friability (0.42±0.62 to 0.60±0.75 %) and drug content (91.62±0.94 to 94.69±1. 81%).

Surface pH determination

Surface pH of all the formulations was ranging between 6.41±0.98 to 6.79±0.69 which are fine within the limit of acceptable salivary pH range. Hence, it can be interpreted that none of formulation would cause any local irritation to buccal mucosal surface.

Swelling Studies

The swelling[21] state of the polymer was essential for its bioadhesive behaviour. Results of swelling index study are represented in fig 4. Higher level of xanthan gum and carbopol concentration containing formulation showed slower water uptake initially and followed by fully hydrated on time course. The maximum swelling index was observed with this formulation may chances of xanthane gum, due to its an anionic hydrophilic nature, has greater affinity to forms hydrogen bounding of water and draw more water leadings to development of gels. In case of effect of CP concentration on response was observed to be more considerable than that of HPMC concentration.

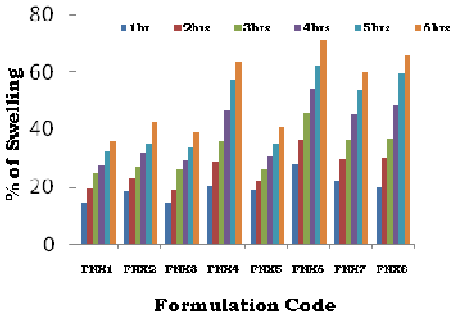

Fig. No. 04: Comparison of swelling index of various formulations containing nifedipine buccal tablets

***In vitro* mucoadhesion studies**

The mucoadhesion characteristic of formulations is influenced by the concentration of the polymers. The high degree mucoadhesive strength was

observed with the formulation contains high level concentration of xanthan gum and carbopol, which may possibly due to uncoiling of the structure of xanthan gum molecules at pH 6.8 could formed secondary bonds with mucin and interpenetration of the polymer chains in the interfacial region of mucin, while other polymers may simply involved superficial bioadhesion.

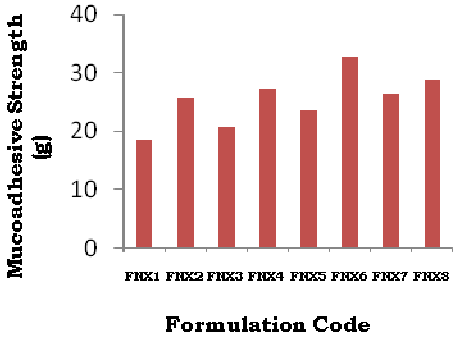

Fig. No. 05: Comparison of in- vitro mucoadhesion strength of nifedipine buccal tablets

In vitro drug release studies

The release data of nifedipine from all the formulation is shown in fig 6. from the results *in vitro* drug release of nifedipine from buccal tablets, it was observed that increment in the concentration of xanthan gum and carbopol increases[22, 23] the sustain of drug release, this might be due to the carbopol, which is carboxyl groups highly dissociate repulsion between the negatively charged carboxyl groups causing uncoiling and expansion of molecules and thus result in gel formation. The gel thus formed consists of closely packed swollen particles. This particular property may partially be responsible for the retarded drug release from the tablets.

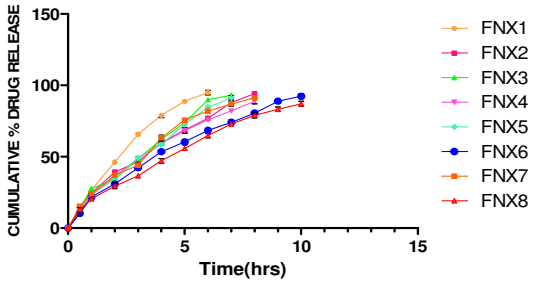

Fig. No. 06: Comparison of in- vitro nifedipine release from buccal tablets of various formulations

In vitro drug permeation study

The optimized formulation was subjected to an in vitro buccal permeation study using a diffusion cell. The result was compared with in vitro drug release as shown in figure. In vitro drug permeation rate of nifedipine optimized formulation through mucosal membrane was found to be inconsiderably less as compared to in vitro dissolution, this may also due to presence of barriers such as membrane coating granules, and lipids may cause hindrance in permeation. However, the correlation between in vitro drug release rate and in vitro drug permeation across the sheep buccal mucosa were found to be satisfactory with a correlation coefficient (R^2) respectively.

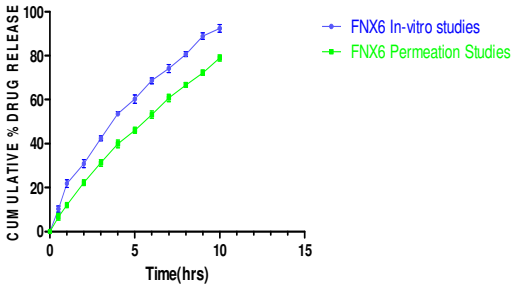

Fig. No. 07: Comparison of in vitro dissolution profile and in vitro permeation of nifedipine buccal tablets

The obtained in vitro drug release data's of all the formulations were computed to different kinetic models, such as zero order, first order, higuchi matrix, and peppas models to predict the mechanism of drug release. The results are shown in table 3. A higher correlation coefficient for Higuchi model where a linear relationship existed between cumulative amounts of drug released from the prepared tablets and square root of time. The stability study was carried out on optimized buccal tablets formulation and its results indicate that there is no change in the appearance, drug content, and mucoadhesive strength and on drug release rate of the tablet.

Conclusion

In the present work efforts have been made to design and evaluate mucoadhesive buccal tablets of nifedipine. A 2^3 full factorial design was applied to study the effect of formulation variables (concentration of polymers) on the release properties by applying optimization technique. The observed independent variables were found to be very close to predicted values of optimized formulation which demonstrates the feasibility of the optimization procedure in successful development of buccal tablets containing nifedipine by using Xanthan gum and carbopol 974P. The prepared dosage form was found to stable with

respect to drug content, mucoadhesive strength and drug release kinetics at an accelerated storage condition. It may be concluded that buccal route is one of the alternatives available for administration of nifedipine.

Table No. 03: Correlation coefficient of kinetic models for nifedipine buccal tablets

Formulation Code	Zero order	First order	Higuchi	Krosmeyer-Peppas
	R^2	R^2	R^2	R^2
FNX1	0.938	0.973	0.956	0.895
FNX2	0.938	0.936	0.966	0.905
FNX3	0.929	0.928	0.946	0.924
FNX4	0.923	0.985	0.986	0.907
FNX5	0.967	0.949	0.947	0.938
FNX6	0.924	0.962	0.986	0.927
FNX7	0.918	0.983	0.976	0.956
FNX8	0.933	0.984	0.967	0.969

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