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Fabrication and evaluation of sustained release mucoadhesive bilayer tablets containing nifedipine

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

[1]Jawaharlal Nehru Technological University Anantapur, Anantapur, A.P, India
[2]QIS College of Pharmacy, Vengamukkapalem, Ongole, A.P, India

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ABSTRACT

The purpose of the study was to formulate and evaluate mucoadhesive bi-layer buccal tablets of Nifedipine using the Natural bioadhesive polymers such as Pectin to compare the synthetic polymer like Carbopol 971-P, HPMC-K4M and Polyvinyl pyrrolidone (PVP- K30) along with ethyl cellulose and magnesiumsterate as an impermeable backing layer to improve the oral bioavailability. The preformulation study was performed by FTIR and DSC. The first layer which adheres to mucosa was obtained by direct compression of mucoadhesive polymers and drug. The second layer containing water impermeable agent was compressed on the first layer. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, in vitro drug release. The surface pH of all the tablets was close to neutral pH the mechanism of drug release was found to be non-Fickian diffusion for buccal tablets. The present study concludes that mucoadhesive buccal tablets of Nifedipine can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of Nifedipine

Keywords: Mucoadhesion bi-layer tablet, buccal drug delivery, Nifedipine.

INTRODUCTION

Buccal delivery of drug provides an alternative to the oral route of drug administration. In recent years, delivery of therapeutic agents through various trans-mucosal routes gained significant attention owing to their pre-systemic metabolism or instability in the acidic environment associated with oral administration. Buccal delivery provides direct entry of drug into the systemic circulation, avoiding the hepatic first-pass effect, ensuring ease of administration, and making it possible to terminate delivery when required. 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 mucosa, in a controlled and predictable manner, to elicit the required therapeutic response. This unidirectional drug release can be achieved using bi- layer tablet dosage form Nifedipine, a calcium channel blocker used in the treatment of angina pectoris and hypertension. The treatment requires a constant release of the drug into systemic circulation. Since, its half life is 2-4 hrs requires frequent dosing of the drug. Even though nifedipine is rapidly and almost completely absorbed from GI tract it undergoes extensive first pass metabolism (around60%) resulting in a poor bioavailability (45%) after oral administration. Hence, to improve its therapeutic efficacy, patient compliance and to reduce the frequency of dosing and side effects as well as to avoid its extensive first pass metabolism, Mucoadhesive buccal drug delivery approach was considered to be better suitable for nifedipine.[1-3]

MATERIALS AND METHODS

Nifedipine , Pectin , Carbopol 971-P (CP) were obtained as a gift samples from Micro labs-Bangalore. hydroxyl propylmethyl cellulose (HPMC K4M) (Colorcon Asia ltd. Goa) and Polyvinylpyrrolidone (PVP- K30) (Sanofi-aventis ltd Goa) were obtained as a gift sample. Ethyl cellulose (EC) (Loba Chemie Pvt. Ltd.), magnesium stearate (Himedia laboratories Pvt ltd. Mumbai) andAllother reagents and chemicals used were of analytical grade.

Preparation of buccal tablets [4]

Mucoadhesive buccal tablets containing nifedipine were prepared by a direct compression method using two steps. Various batches were prepared by varying the ratio of Pectin and Carbopal,HPMC ,Pvpk30 to identify the most effective formulation. The mucoadhesive drug polymer mixture was prepared by homogeneously mixing the drug with Pectin,CP, HPMC,PVP,Ethyl Cellulose in a polybag for 15 minutes as shown in Table 1. The mixture 170 mg was then compressed using a 12 mm diameter die in a single stroke multistation tablet machine (Cadmech, Ahmedabad, India). The upper punch was raised and the backing layer of EC and magnesium sterate was placed on the above compact the two layers were then compressed into a mucoadhesive bilayer tablet. Each tablet weighed 170 mg with a thickness of 1.5 to 1.6 mm.

Methodology

Preformulation studies[5]

IR Spectral Study

I.R spectroscopy can be used to investigate and predict any physiochemical interaction between different excipients. *I.R* spectra matching approach was used for detection of any possible chemical interaction between the drugs and polymer. A physical mixture of drug, polymer and other excipients were prepared and mixed with suitable quantity of potassium bromide. This mixture was compressed to form a transparent pellet using a hydraulic press at 15 tons pressure. It was scanned from 4000 to 400 cm-1 in a FTIR spectrophotometer (FTIR 8400 S, Shimadzu). The IR spectrum of the physical mixture was compared with those of pure drug and polymer and peak matching was done to detect any appearance or disappearance of peaks.

Differential scanning calorimetry

DSC is a thermo analytical technique 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. For example, as a solid sample melts to a liquid it will require more heat flowing to the sample to increase its temperature at the same rate as the reference. This is due to the absorption of heat by the sample as it undergoes the endothermic phase transition from solid to liquid. Likewise, as the sample undergoes exothermic processes (such as crystallization) less heat is required to raise the sample temperature.By observing the difference in heat flow between the sample and reference, differential scanning calorimeters are able to measure the amount of heat absorbed or released during such transitions.

Evaluation of bi-layered tablets[6,7]

Weight variation:

Collect 10 tablets from each formulation of varying concentration of natural polymer. Weigh the tablets individually from all the selected formulations; calculate the average weight and comparing the individual tablet weights to the average**.**

Thickness:

Collect 5 tablets from each batch of formulation and the thickness of the tablets were measured with the help of vernier caliper. The average thickness is calculated.

Friability

Friability of the tablets was determined by using Roche friabilator. From each batch, 10 tablets were weighed accurately which was W1 then placed in the friabilator and rotated at 25 rpm for 4 min. After completing the rotation weight of tablets were weighed which is W2. The percentage friability was determined.

Hardness
Monsanto hardness tester was used for this purpose. The hardness of five tablets in each batch was measured and the average hardness was calculated.

Swelling study
Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37 ± 0.1^{o} C. The tablet was removed from the petri-dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (W2), and the swelling index (SI) or percent hydration.

% of hydration = (W2-W1) X 100 / W2

Where
W1- initial weight of tablet
W2- weight of disks at time t

Surface pH study:
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. The method adopted by *Bottenberg et al* was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

Content uniformity
Drug content uniformity was determined by dissolving the tablets in ethanol and filtering with whattman filter paper (0.45 nm). The filtrate was evaporated and the drug residue dissolved in 100 ml phosphate buffer pH 6.8. The 5 ml solution was then diluted with phosphate buffer pH 6.8 up to 20 ml, filtered through whattman filter paper, and analyzed at 234 nm using a UV Double beam spectrophotometer (Shimadzu 2501 PC, Japan.). The experiments were performed in triplicate, and average values reported.

Fig no.1: Modified Physical balance

Ex -vivo mucoadhesive strength[8]
Bioadhesive strength of the buccal tablets was measured on modified physical balance used for determining the ex vivo mucoadhesive strength of prepared buccal tablets. Fresh sheep buccal mucosa was obtained from a local slaughterhouse. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37 ±1°C. Sheep buccal mucosa was tied to the glass petri dish, which was filled with phosphate buffer so that it 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 m contact time. Then weight was added slowly to the right hand pan until the tablet detached from the mucosal surface.

In- vitro dissolution studies[9]

The *in vitro* dissolution was carried out by using Tablets Dissolution Tester (USP-II). The tablet is placed such that core faced to the dissolution medium (900 ml of 6.8 Phosphate buffer). Dissolution medium temperature was maintained at 37 ± 5°C and stirring at 50 rpm. An aliquot of the sample was periodically with drawn at suitable time intervals and the volume was replaced with fresh dissolution medium. The samples were analyzed spectrophotometrically at 234nm.

Release kinetics

In-vitro dissolution has been recognized as an important element in drug development. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence. Several theories/kinetic models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where *ft* is the function of *t* (time) related to the amount of drug dissolved from the pharmaceutical dosage system. In order to elucidate mode and mechanism of drug release, the *in-vitro* data was transformed and interpreted at graphical interface constructed using various kinetic models. The zero order release Eq. (1) describes the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of transdermal systems, matrix tablets with low soluble drugs, coated forms, osmotic systems etc., where the drug release is independent of concentration.

$$Qt = Qo + Kot \quad (1)$$

Where, *Qt* is the amount of drug released in time *t*, *Qo* is the initial amount of the drug in the solution and *Ko* is the zero order release constant The first order Eq. (2) describes the release from the system where release is concentration dependent e.g.pharmaceutical dosage forms containing water soluble drugs in porous matrices.

$$\log Qt = \log Qo + K1\ t\ /2.303 \quad (2)$$

Where *Qt* is the amount of drug released in time *t*, *Q* is the initial amount of drug in the solution and *K* is the first *s* order release constant. Higuchi described the release of drug from insoluble matrix as a square root of time

Table No 1 Composition of Formulations of Mucoadhesive Buccal Tablets

DRUG RESERVOIR							DRUG FREE BACKING LAYER
Formula code	**Drug(mg)**	**Pectin**	**CP-934**	**HPMC K4M**	**PVPK30**	**EC**	**Mg.Sterarate**
D1	20	35	40	25	20	20	10
D2	20	60	20	25	15	20	10
D3	20	35	30	40	15	20	10
D4	20	60	20	25	15	20	10
D5	20	40	40	25	15	20	10
D6	20	60	20	25	15	20	10
D7	20	35	30	40	15	20	10
D8	20	60	25	20	15	20	10

HPMCK4M- Hydroxyl propyl methyl cellulose, CP-971p – Carbopol-971p, PVPK30 – Polyvinyl pyrolidine, EC – Ethyl cellulose,Mg.Sterate-Magnesium stearate

Table No 2 Evaluation parameters of Nifedipine buccal tablets from D1-D8

Batch Code	Thickness (mm)	Hardness (kg/cm2)	% Drug Content	Surface pH	Mucoadhesive Strength (g)
D1	2.34 ± 0.128	4.2 ± 0.447	99.3 ± 1.31	7.0 ± 0.10	11.72± 0.8
D2	3.36 ± 0.203	5.4 ± 0.548	98.9± 1.52	7.2 ± 0.23	12.19 ± 0.6
D3	3.40 ± 0.057	3.8 ± 0.447	96.8 ± 1.31	7.3 ± 0.10	14.09 ± 0.6
D4	3.39 ± 0.061	4.6 ± 0.548	95.1 ± 1.46	7.1 ± 0.11	15.0 ± 1.5
D5	3.50 ± 0.147	5.4 ± 0.548	94.8 ± 1.45	6.9 ± 0.10	18.50 ± 1.7
D6	3.35 ± 0.106	5.6 ± 0.548	92.3 ± 1.00	7.4 ± 0.05	17.50± 0.7
D7	2.95± 0.158	4.8± 0.257	94.3±0.6	7.2± 0.25	17.50± 0.74
D8	2.750± 0.7	4.6± 0.7	97.50± 0.7	7.0± 0.7	17.50± 0.7

$$Qt = KH\sqrt{t} \quad (3)$$

Where, *Qt* is the amount of drug released in time *t*, *KH* is Higuchi's dissolution constant. The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model)19,20.

Table No 3

Drug release Kinetics							
Formula Code	**Zero order**		**First order**		**Higuchi**	**Peppa's**	
	K0	**r**	**K1**	**r**	**R**	**n**	**R**
D1	8.3036	0.99079	0.4429	0.732653	0.9804	0.66007	0.99994
D2	8.17987	0.99571	0.369	0.856278	0.98607	0.76813	0.99652
D3	9.44584	0.99561	0.1635	0.747604	0.98609	0.8558	0.9998
D4	9.67705	0.99746	0.21105	0.855399	0.98477	0.85626	0.99693
D5	10.323	0.99688	0.38107	0.891977	0.97015	0.82223	0.9971
D6	8.6549	0.99617	0.31972	0.817707	0.96283	0.84842	0.99894
D7	8.954	0.994	0.3521	0.7671	0.9701	0.8512	0.9941
D8	8.523	0.9905	0.4123	0.8124	0.9881	0.8621	0.9971

K0- Zero order rate constant K1- First order rate constant
r – Coefficient of Correlation n- diffusional exponent

RESULTS AND DISCUSSION

Drug polymer compatibility studies using *FTIR* and *DSC*

FTIR studies revealed that the characteristic absorbance bands of various functional groups of . Nifedipine were found in the vicinity of standard absorbance range (Fig 2). Hence the FTIR studies indicated that there was no interaction between drugs and polymers under study. DSC studies revealed that the drug exhibit sharp melting endotherm at 175.7°C and thermograms of the physical mixture of Nifedipine with polymers exhibited exothermic peak in the vicinity of its melting point range indicates absence of any drug-polymer interactions (Fig 7).

Figure No 2: FTIR Spectrum of Nifedipne

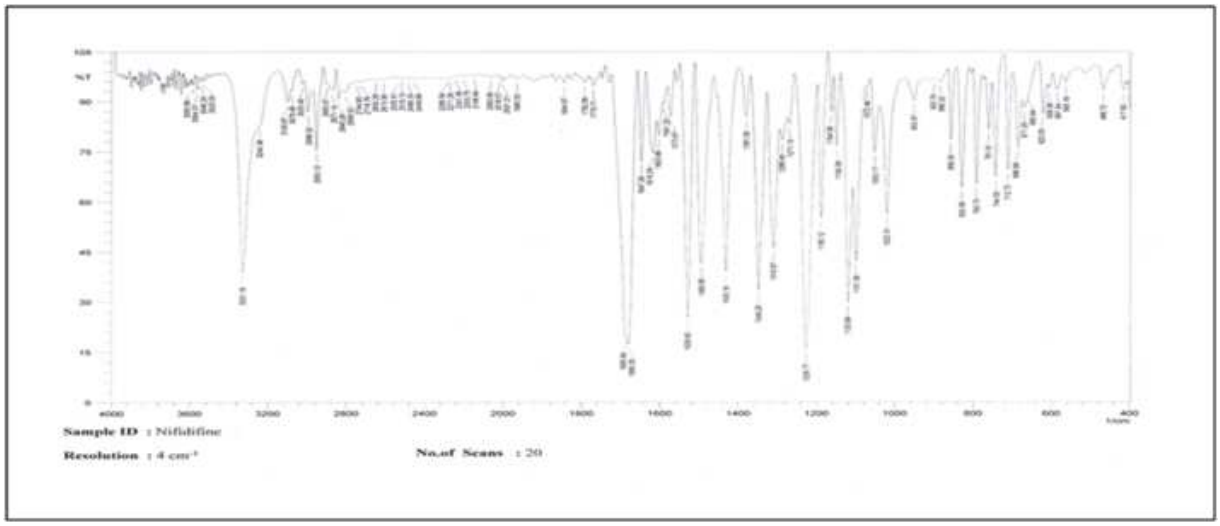


Figure No 3: FTIR Spectrum of Nifedipne+Carbopol

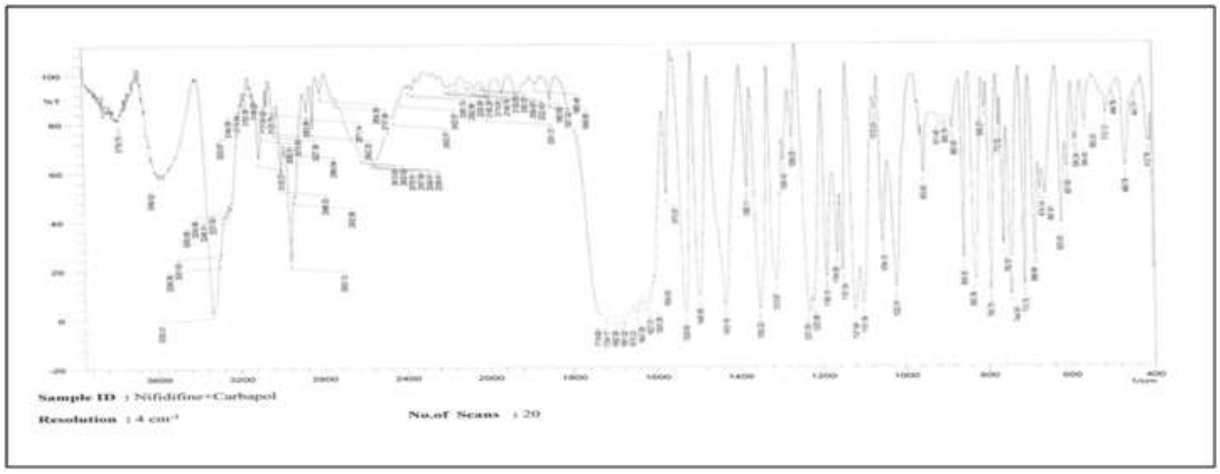


Figure No 4: FTIR Spectrum of Nifedipine+HPMC

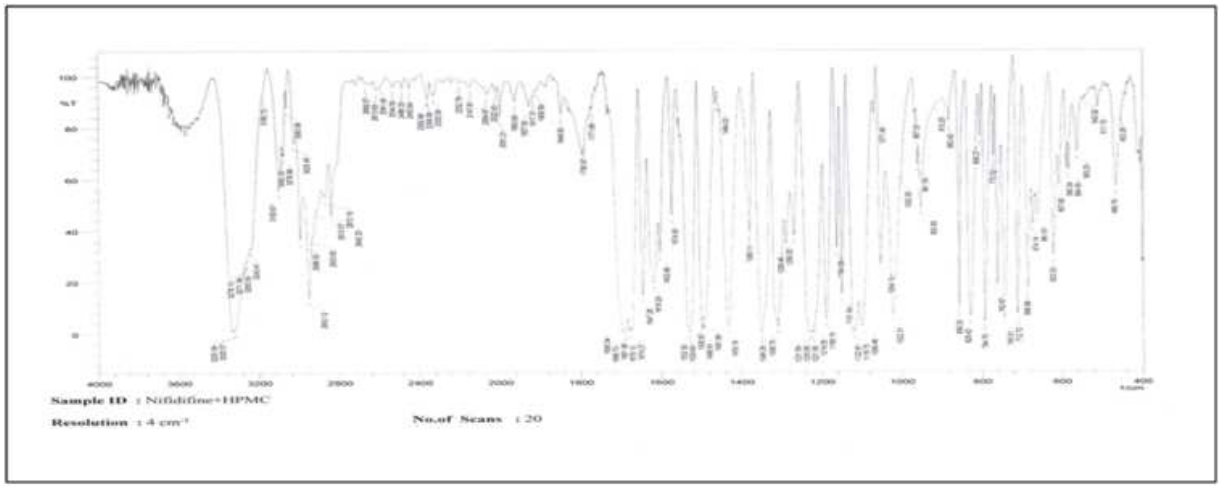


Figure No 5: FTIR Spectrum of Nifedipne+Pectin

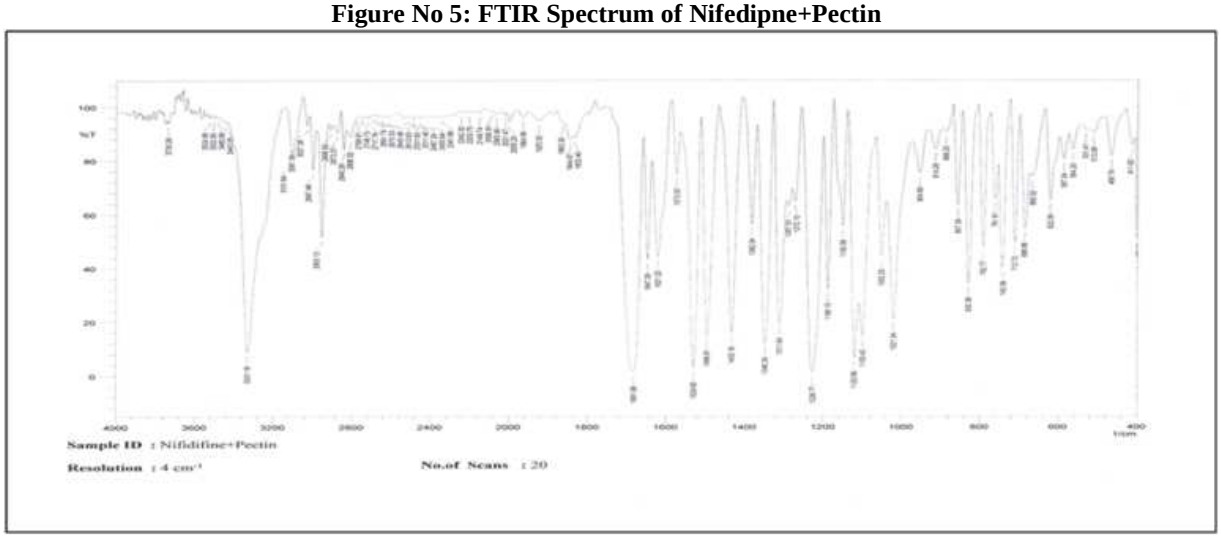


Figure No 6: FTIR Spectrum of Nifedipne+Pvp

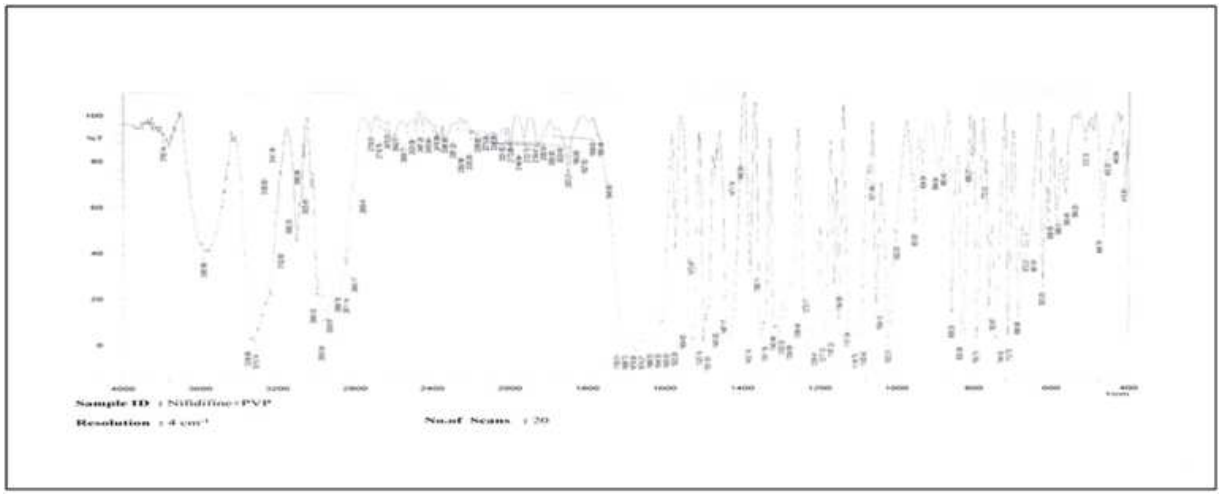
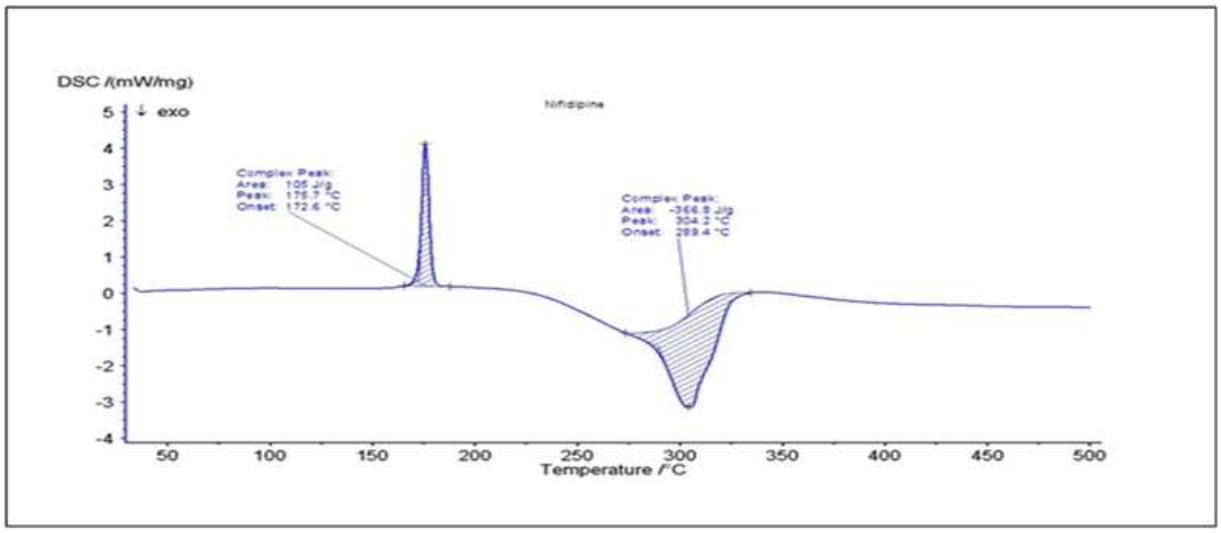


Figure No 7: DSC Studies on Nifedipine



Physical properties of Bilayer tablets

The blend of ingredients was analyzed for physical characteristics. The angle of repose of formulation blends D1 toD6 were in the range of 30º59' ± 1.464 to 31º20' ± 1.103. The bulk density, tapped density, Corr's index were found in the range of 0.433 to 0.317 gm/cc, 0.52-0.47gm/cc, and 16.66 – 14.28 respectively. It reveals that all the formulation blends were having good flow characteristics and flow rates. All the formulations pass the test for weight variation as per the IP standard ± 7.5 % deviation. Percentage of drug content for all formulations F1 to F6 was in the range of 99.3-92.3%. Thickness of F1 to F6 formulations was found to be 3.50 to 2.34 ± 0.128 mm. Hardness of all formulations F1-F6 was found to be 5.6 ± 0.447 to 3.8 ± 0.447 kg/sq.cm.

Surface pH determination:

Surface pH of bilayered tablets was found to be in between 7.4 to 6.9 the investigated results indicated that the developed buccal tablets will not cause any irritation to mucosal surface.

Figure No 8: DSC Studies on Nifedipine+HPMCK4M

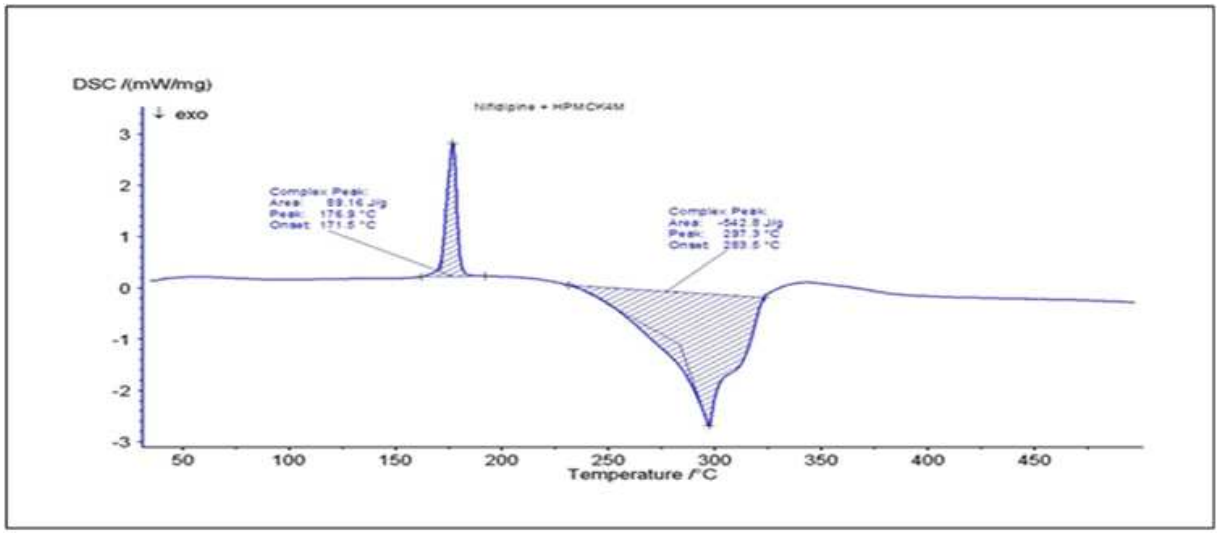
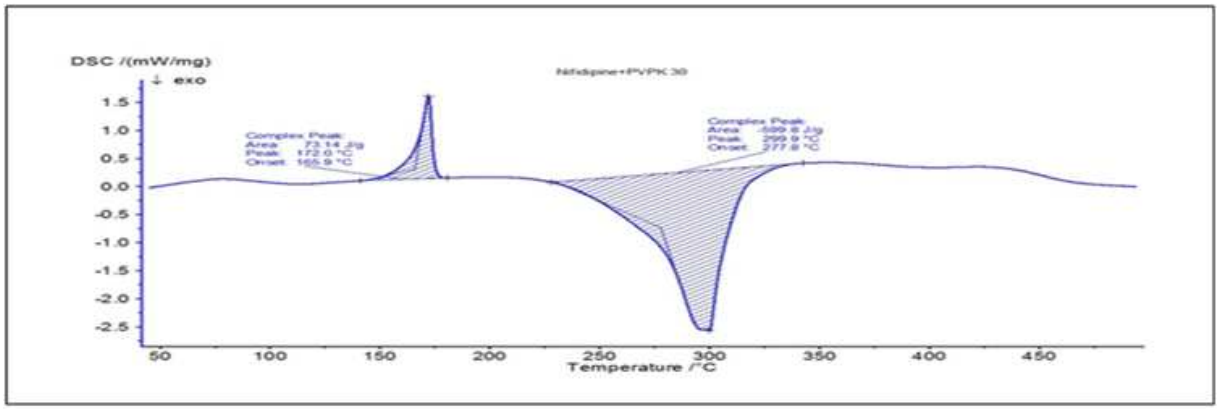


Figure No 9: DSC Studies on Nifedipine+Pvpk30



Swelling Studies:

The bioadhesion and drug release profile are dependent upon swelling behavior of the tablets.Swelling index was calculated with respect to time. The Swelling index was for all formulations D1 toD6 (After 4 hours) were in the range 38.06 to 72.71%.

In-vitro mucoadhesion studies:

The in-vitro mucoadhesive strength study was performed by using specially modified physical balance to measure the force (N) required to detach the tablet. The adhesion was mainly affected by the concentration of mucoadhesive polymer. The results were shown in the table 2. In all the formulations, as the polymer concentration increased, the mucoadhesive strength increased. The higher bioadhesive strength of the Pectin may be due to the formation of secondary bonds with mucin and entanglement and interpenetration of polymeric chain with mucin.

***In vitro* drug release studies:**

The *in-vitro* drug release were carried out by using the USP type II rotating paddle method by little modification of tablet attaching to glass slide. The dissolution medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the periphery to wards the centre, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into the dissolution medium. The hydrated gel layer thickness determines the diffusional path length of the drug. Release of drug from the buccal mucoadhesive tablets varied according to the concentration of matrix-forming polymer. The drug release was governed by amount of matrix

forming polymers. The most important factor affecting the rate of release from buccal tablets is the drug and polymer ratio. As increase in the polymer concentration increases the viscosity of the gel as well as the formation of gel layer with longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of drug and therefore reduction in drug release rate.

Figure No 10: DSC Studies on Nifedipine+Pectin

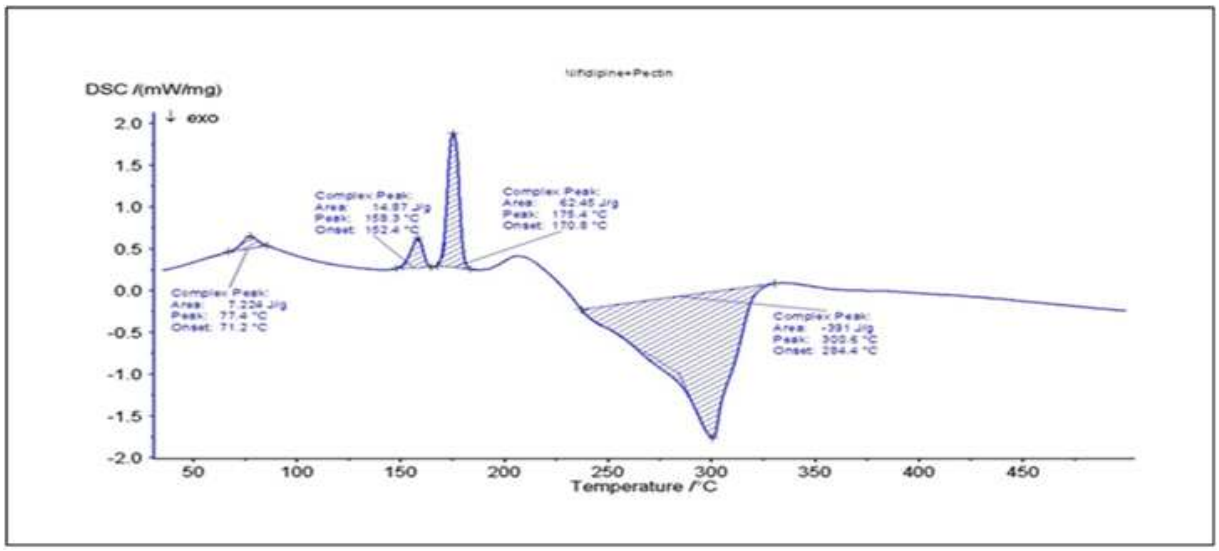
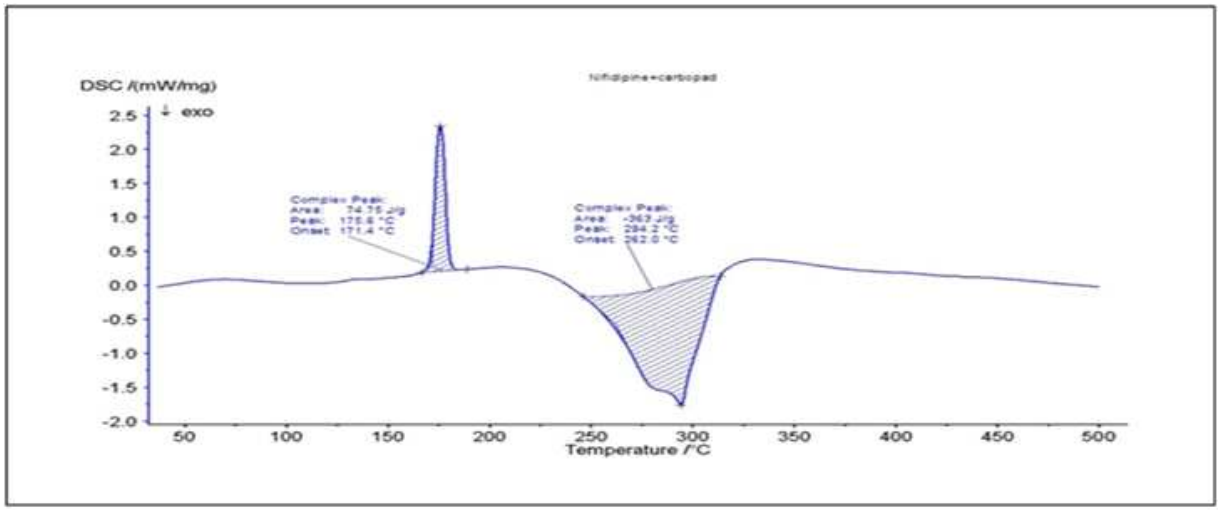


Figure No 11: DSC Studies on Nifedipine+Carbopol

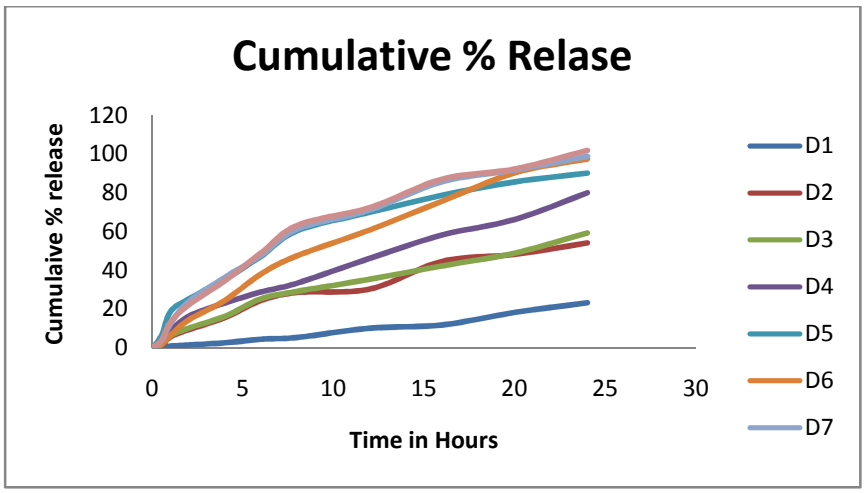


Release kinetics

In order to elucidate mode and mechanism of drug release, the *in-vitro* data was transformed and interpreted at graphical interface constructed using various kinetic models. The *in vitro* release data obtained for buccal formulations, in phosphate buffer pH 6.8, was fitted into various kinetic models.

Release mechanism: By incorporating the release data in Korsmeyer-Peppa's equation, the mechanism of the drug release can be indicated according the value of release exponent 'n' Peppa's plot for buccal tablets.

Fig No 12 Comparative Invitro Drug Release Profile for D1-D8 Formulations



CONCLUSION

This study has demonstrated that direct compression technique was suitable for producing bilayered buccal tablets. Nifedipine can be successfully penetrated through the buccal membrane. The formulated Nifedipine buccal tablets showed a significant increase in oral bioavailability. Higher bioavailability would be due to avoidance of first-pass hepatic metabolism by intestinal lymphatic transport, which circumvents the liver. The dose of Nifedipine buccal tablets needs to be decreased in accordance with increased bioavailability, to minimize its dose related adverse effects.

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