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Research Article

DESIGN, DEVELOPMENT AND EVALUATION OF MUCCOADHESIVE PATCHES OF NIFEDIPINE FOR BUCCAL DELIVERY

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Abstract

The buccal region offers an attractive route of administration for systemic drug delivery. Nifedipine is a calcium channel blocker and its oral bioavailability is 45-56% because of first pass metabolism. Buccal route of drug delivery provides direct access to the systemic circulation and thus bypasses liver and avoids pre-systemic elimination in the GI tract and liver and a high bioavailability is obtained. FTIR and UV spectroscopic methods revealed that there was no interaction between nifedipine and polymers. Nifedipine patches were prepared using polymers like Chitosan, PVP K 30, PVA, and HPMC. The patches were evaluated for their thickness uniformity, folding endurance, weight uniformity, content uniformity, swelling behaviour, tensile strength, and surface pH. *In vitro* release studies were conducted for nifedipine loaded patches in phosphate buffer (pH, 6.8) solution. Patches exhibited drug release in the range of 86.26 to 98.32% in 90 min. Data of *in vitro* release from patches were fit to different equations and kinetic models to explain release profiles. Kinetic models used were zero and first-order equations, Higuchi, and Korsmeyer-Peppas models. The selected patches were further studied for temperature dependant stability studies. It was found that the drug loss was less through the patches stored for one month.

Key Words: Nifedipine; buccal patches; *in vitro* release; bioadhesive strength.

Introduction

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs.The mucosa is relatively permeable with a rich blood supply. Buccal route of drug delivery provides direct access to the systemic circulation through the internal jugular vein and thus bypasses liver and avoids pre-

systemic elimination in the GI tract and liver and a high bioavailability is obtained. The ease of administration and ability to terminate drug delivery when required makes it a potential and attractive route of drug delivery.[1,3]

Nifedipine is a cardio-vascular drug coming under the class of calcium channel blocker which is widely used to treat essential hypertension and angina pectoris. Although it is completely absorbed from the gastrointestinal tract, the systemic availability is approximately 45-56% because of high first-pass metabolism. Nifedipine was selected as a suitable candidate for the present investigation because of its low oral therapeutic dose (5-20), it's having low molecular weight (346.3). A suitable buccal drug delivery system should be flexible and possess good bio adhesive properties, so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a predictable manner to elicit the required therapeutic response.

Drug delivery through the buccal mucosa offers a novel route of drug administration. Various synthetic polymers are under investigation as carrier for buccal drug delivery. In the present study, polymers such as, hitosan, hydroxyl propyl methyl cellulose (HPMC), polyvinyl pyrolidone (PVP), and polyvinyl alcohol (PVA) were employed. These polymers are seen to have potential and are comparatively economical. It is a cheap non-toxic biodegradable polymer, widely available in Indian coastal areas and gives wide opportunities for development of better drug delivery systems. Thus, the objective of this work was to design and characterize the buccal patches of nifedipine employing chitosan as main polymeric substrate.

Materials and Methods

Materials

Nifedipine was procured from Alkem pharmaceuticals, Mumbai. Chitosan was obtained from yarrow chem. Pdts, Mumbai. PVP K 30, PVA and HPMC were obtained from HiMedia laboratories Pvt.ltd, Mumbai. Propylene glycol and acetic acid was purchased from Nice chemicals Pvt. Ltd, Cochin.

Methods

Drug- Polymer Compatibility

Drug –polymer interaction was observed by IR spectrophotometry. An FTIR study of pure nifedipine, pure polymers and physical mixture of drug and polymers were performed by KBr pellet technique.

Preparation of the blank patches

The plain polymeric patches were prepared by solvent casting technique. 1.5% acetic acid solution was prepared in which weighed quantity of chitosan was properly dissolved. The solution was filtered through muslin cloth to remove debris. Different polymers like PVP K 30, PVA, and HPMC were added at different ratios to get different combinations of patches as shown in the table 2. Propylene glycol was added as plasticizer. The polymers were weighed accurately and dissolved properly. The required quantity of propylene glycol was added. This polymeric solution was kept overnight to remove air bubbles, and then it was added uniformly to a Petri plate containing mercury as substrate. The plate was then kept in an oven at 45^0C for 24 hours. After drying the film was peeled off with a sharp blade and kept in a self sealed cover.

Table-2: Composition of various prepared buccal films with different polymers.

Formulation code		Chitosan(w/v)	PVP K 30 (w/v)	PVA(w/v)	HPMC(w/v)	Propylene glycol(w/v)
I	C_1	1%	0.2%	-	-	5%
	C_2	1%	0.3%	-	-	5%
	C_3	1%	0.4%	-	-	5%
	C_4	1%	0.6%	-	-	5%
II	C_5	1%	0.6%	-	-	5%
	C_6	0.8%	0.6%	-	-	5%
	C_7	0.6%	0.6%	-	-	5%
	C_8	0.4%	0.6%	-	-	5%
III	C_9	1%	0.6%	0.2%	-	5%
	C_{10}	1%	0.6%	0.4%	-	5%
	C_{11}	1%	0.6%	0.6%	-	5%
	C_{12}	1%	0.6%	0.8%	-	5%
IV	C_{13}	1%	0.6%	-	0.2%	5%
	C_{14}	1%	0.6%	-	0.4%	5%
	C_{15}	1%	0.6%	-	0.6%	5%
	C_{16}	1%	0.6%	-	0.8%	5%

Preparation of drug loaded patches

The plain polymeric patches were prepared by solvent casting technique. 1.5% acetic acid solution was prepared in which weighed quantity of chitosan was properly dissolved. The solution was filtered through muslin cloth to remove debris. Different polymers like PVP K 30, PVA, and HPMC were added at different ratios to get different combinations of patches. Propylene glycol was added as plasticizer. The polymers were weighed accurately and dissolved properly. 5%w/v of propylene glycol was added. Required quantity of nifedipine was added and stirred well for uniform mixing. This polymeric solution was kept overnight to remove air bubbles, and then it was added uniformly to a petri plate containing mercury as substrate. The plate was then kept in an oven at 45^0C for 24 hours. After drying the film was peeled off with a sharp blade and kept in a self sealed cover.

Formulation of ethyl cellulose backing membrane:

The ethyl cellulose backing membrane was prepared by casting technique. Ethyl cellulose was soaked in 20 ml of alcohol-toluene mixture and kept for 24 hours. To this remaining quantity of solvent and glycerol in required amount was added and mixed thoroughly using mechanical stirrer till finally dispersed thick solution is obtained. This solution was poured on plain glass mould lined with aluminium foil; the solution was then dried immediately in an oven at 40ºC. The composition of ethyl cellulose backing membrane is illustrated in table1.

Table1: Formula of ingredients ethyl cellulose backing membrane

Sl. No.	Ingredients	Concentration
1	Ethyl cellulose	4%w/v
2	Glycerol	10%w/w of polymer weight
3	Alcohol : Toluene (1:4)	QS to 100 ml

Evaluation of the blank patches

Physical Appearance and Surface Texture:

Physical appearance and surface texture evaluation includes visual inspection and evaluation of texture by feel or touch.

Weight Variation:

Ten patches of 1cm^2 were weighed individually and average of those of those patches measured.

Thickness: [4, 14]

The thickness of the patch was measured using screw gauge with a least count of 0.01mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

Percent Swelling Index: [5,6]

The polymeric patches are cut in to small patches of 1.5cm diameter. This patch was placed on the surface of the agar plate and the diameter at different time intervals where taken up to 5hrs and the percentage swelling index was calculated using the formula,

$$SD\% = \frac{Dt - Do \times 100}{Do}$$

SD% = % swelling by diameter method

Dt = diameter of swollen patch after time t

Do = original patch diameter.

Folding Endurance: [7,8]

The flexibility of patches can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

Surface pH: [9,10]

Buccal patches were left to swell for 1 hour on the surface of the agar plate, the agar plate prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer of pH 6.6 under stirring and the solution was poured into the petridish, it was allowed to stand until it solidified to form a gel at room temperature. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

Moisture Content & Moisture Absorption Studies:[15]

i. Moisture Content: The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After three days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss using the formula:

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

ii. Moisture Absorption: The buccal patches were weighed accurately and placed in the desiccators containing 100ml of saturated solution of aluminium chloride, which maintains 76% relative humidity (RH). After three days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Water Vapour Transmission Rate (VTR): [16,17]

Vapour transmission method was employed for determination of vapour transmission from the patch. Glass-bottle (length =5cm, narrow mouth with internal diameter =0.8cm) filled with 2g anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37 ± 2^0C. The difference in weight after three days was calculated. The vapour transmission rate was obtained as follow.

$$\text{Vapour transmission rate (VTR)} = \frac{\text{(Amount of moisture transmitted)}}{\text{Area} \times \text{Time}}$$

Tensile Strength:[11,12]

The tensile strength of buccal patch refers to tension or force required to tear of the patch apart into two pieces. The instrument used to measure the tensile strength designed in our laboratory especially for this project work. The instrument is a modification of chemical balance. One pan of the balance was replaced with one metallic

plate having a hook for attaching the film. The equilibrium of the balance was adjusted by adding weight to the right pan of balance. The instrument was modified in such a way that the patch can be fixed up between two hooks of horizontal beams to hold the test film. A film of 2.5cm length was attached to oneside hook of the balance and the other side hook was attached to plate fixed up to the pan. The weights are added to the other side pan of the balance. Thus, tensile strength,

$$T = \frac{M \times g}{B \times t} \quad \text{Dynes/cm}^2$$

T= force at break/ initial cross-sectional area of sample.

Where,

m = mass in grams

g = acceleration due to gravity 980 cm/sec^2

b = breadth of the specimen in cm

t = thickness of sample in cm.

Percent Elongation at Break: [13]

The percent elongation at break is defined as the elongation at the moment of rupture of the specimen divided by the initial gauge length of the specimen and multiplying by 100.

$$\text{Percent elongation at break} = \frac{LB - L0}{L0} \times 100$$

LB = length of the specimen in cm when it breaks.

L0 = original length of the specimen in cm.

The instrument and procedure is similar to that used for tensile strength.

Evaluation of Drug Loaded Patches:

Drug Content Determination: [18]

The weight of whole patch was determined and cut in to 2cm^2. For determining the drug content, a single piece of patch was taken and crushed in a mortar using pestle. Methanol was added and triturated to completely dissolve the drug, it was then diluted to 100ml. The solution was filtered. The absorbance of the solution was measured using UV spectrophotometer at 235nm and the drug loading was calculated. Percentage drug loading was calculated using formula.

$$\% \text{ drug loading} = \frac{\text{Practical loading}}{\text{Theoretical drug loading}} \times 100$$

***In vitro* release**:

The *in vitro* release study was carried out using USP dissolution apparatus type 2 in 400ml phosphate buffer pH 6.8 at 100 rpm. A $2cm^2$ patch was taken and attached to a glass slide in order to prevent floating of patch over the dissolution media. The in vitro release study was carried out for 8 hours. 5ml of samples were withdrawn at various times interval, replacing with fresh medium each interval, absorbance of the samples were measured at 235nm, and the cumulative percentage release was calculated.

Bio-adhesive Strength of Selected Patches: [19]

The tensile strength required to detach the polymeric patch from the mucosal surface was applied as measure of the bioadhesive performance. The apparatus was locally assembled and was a modification of the physical balance. The device was mainly composed of a two-arm balance. The left arm of the balance was replaced by small stainless steel lamina vertically suspended. At the same side, a platform was maintained in the bottom in order to fix the model mucosal membrane. The bovine cheek pouch excised and washed was fixed to the platform. The mucoadhesive patch was fixed of $3cm^2$, was fixed to the stainless steel lamina using an adhesive. The exposed patch surface was moistened with 1ml of isotonic phosphate buffer for 30 seconds for initial hydration and swelling. The platform was then raised upward until the hydrated patch was brought into the contact with the mucosal surface. A preload of 20gms was placed over the stainless steel lamina for 3 minutes as initial pressure. And then weights were slowly increased on the right pan, till the patch detaches from the mucosal membrane. Force required detaching the patch from the mucosa give the bioadhesive strength of the mucoadhesive patch. The procedure is repeated for 3 times for each patch and mean value of the 3-trials was taken for each set of formulation. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before taking reading.

$$\text{Bioadhesive force, } F = \frac{(W_w \times G)}{A}$$

W_w –Weight applied (g)

G- Acceleration due to gravity (cm/s^2)

A- Surface area of the patch(cm^2)

Stability Study of the Selected Patches:[1]

Optimized medicated patches were subjected to stability testing. Patches were placed in a beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 ± 2^0C and 75±5% relative humidity for 1 month. Changes in the appearance and drug content of the stored patches were investigated at the end of every week.

Drug Release Kinetic Study:

To describe the kinetics of the drug release from the buccal patches the data were treated on the basis of mathematical models such as zero-order, first order, Higuchi, Korsmeyer- Peppas models.

Results and Discussion

Drug Estimation:

Calibration curves of nifedipine in methanol and phosphate buffer (pH 6.8) solutions were obtained at 235nm with UV spectrophotometer. Beer's law obeyed to construct the calibration curve was in the concentration range of 2-10µg/ml.

Drug – Polymer Compatability:

IR spectra of nifedipine alone and its combination with polymers are shown in Fig.1-Fig4. An IR spectrum of nifedipine showed the peaks 3331.07cm^{-1} (N-H, str), 2953.02cm^{-1} (C=C str), 1678.07cm^{-1} (C=O str), and 1529.55cm^{-1} (Ar-NO_2 str). These peaks can be considered as characteristic peaks of nifedipine and were not affected and prominently observed in IR spectra of nifedipine along with polymers as shown in Fig.1-Fig4.

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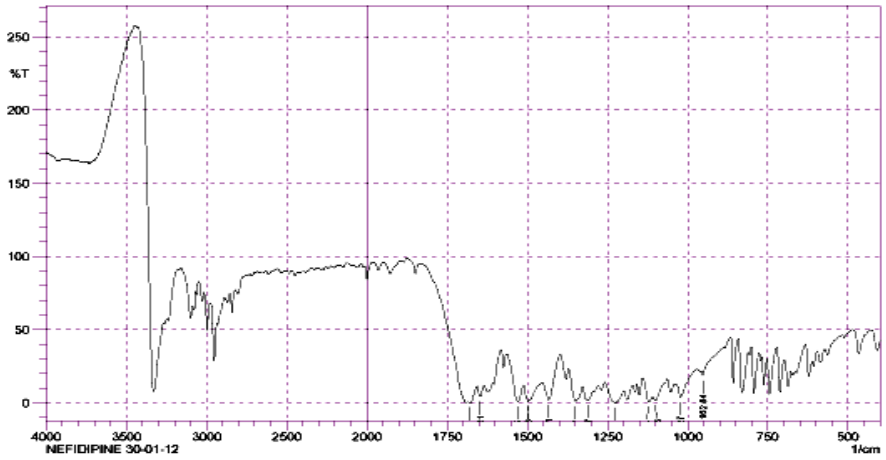

Fig.1-IR spectrum of nifedipine.

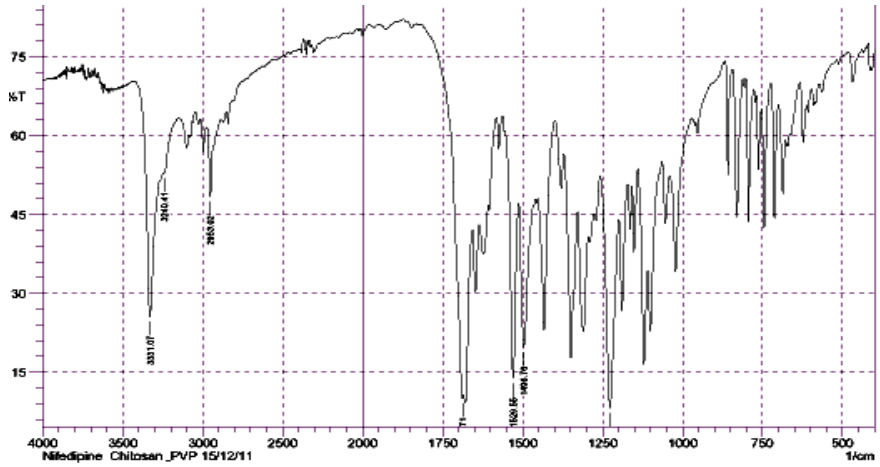

Fig.2-IR spectrum of nifedipine+chitosan+PVP

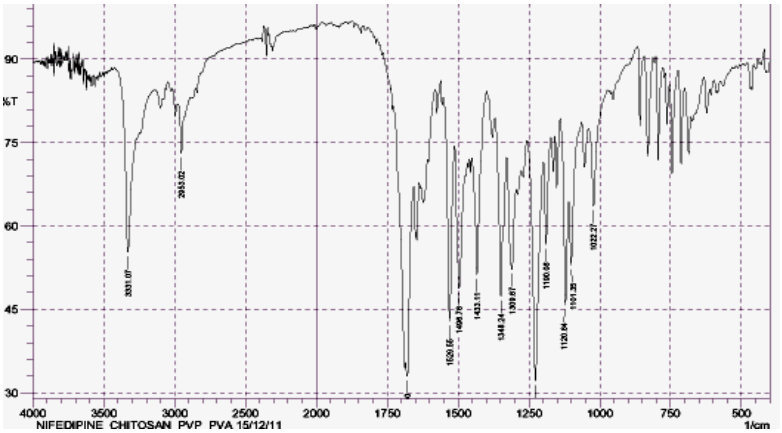

Fig. 3-IR spectrum of nifedipine+chitosan+PVP+PVA

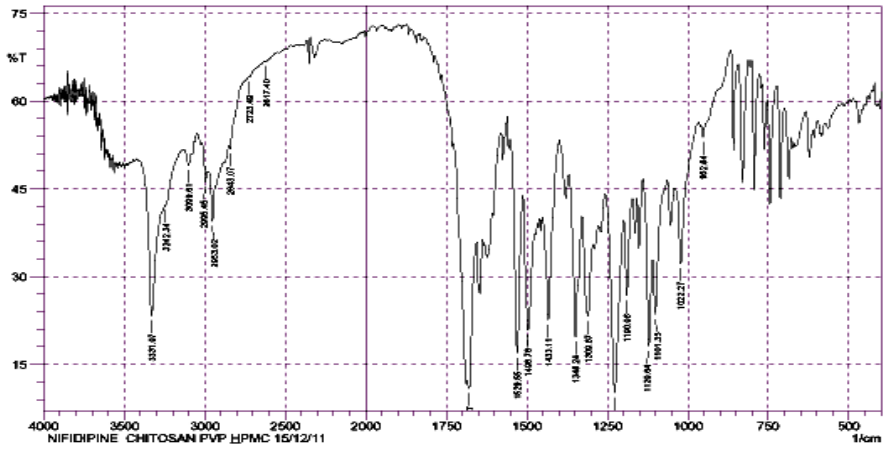

Fig. 4-IR specrum of nifedipine+chitosan+PVP+HPMC

Preparation of the Patches:

The prepared patches were evaluated for physical and mechanical parameters. Based on the results of physical evaluation one patch from each group was selected as right candidate for drug loading. Thus formulations C_4, C_{12}, and C_{16} were selected which showed satisfactory results. The selected formulations were loaded with different doses of drug, nifedipine as shown in table 3.

Table-3: Preparation of drug loaded patches.

Formulation code	Dose of nifedipine (mg)	Percentage drug loading
C_4D_1	5	32.1%
C_4D_2	10	55.9%
C_4D_3	20	51.75%
C_4D_4	30	54.13%
$C_{12}D_1$	5	44.67%
$C_{12}D_2$	10	56.6%
$C_{12}D_3$	20	57.81%
$C_{12}D_4$	30	56.3%
$C_{16}D_1$	5	46.5%
$C_{16}D_2$	10	58.11%
$C_{16}D_3$	20	55.73%
$C_{16}D_4$	30	56.7%

Evaluation of the Patches

Physical appearance and surface texture: All the prepared patches were translucent and visually smooth surfaced. A few numbers of patches were brittle and less flexible. All other formulations were smooth and flexible in nature.

Weight variation: The average weight of film from each group of formulation was reported in table 4 by taking the weights five times for standard deviation. The weights of the patches range from 7.2±1.3mg to 8.8±2.04mg. Results indicated that group-IV (Chitosan, PVP, HPMC) have the least mass among the different formulations.

Thickness: The thickness (table 4) of films varied from 0.24±0.01mm to0.27±1.3mm. Group I having highest thickness while group IV having least among all formulations.

Table-4: Physical evaluation of formulation C_1- C_{16}.

Formulation code	texture	Thickness (mm)	Weight variation(mg)	Folding endurance	Swelling index(5hr)	Surface pH
C_1	brittle	0.27±1.1	8.8±2.04	101±1	13.3%±3.8	7
C_2	Less flexible	0.27±1	8.8±0.84	182±1.5	26.6%±3.8	7
C_3	flexible	0.27±1.1	8.8±1.3	188±2.1	40%±7.6	7
C_4	flexible	0.27±1.3	8.8±0.83	210±2.5	53.3%±7.6	7
C_5	flexible	0.25±0.005	8.6±1.1	217±2.5	60%±3.8	7
C_6	flexible	0.25±0.005	8.6±1.1	205±2.5	53.3%±3.8	7
C_7	sticky	0.25±0.01	8.6±1.1	185±1.2	40%±3.8	7
C_8	sticky	0.25±0.84	8.6±1.5	188±2.1	40%±3.8	7
C_9	Less flexible	0.25±1.3	8.6±1.8	217±1.2	40%±3.8	7
C_{10}	Less flexible	0.25±1.3	8.6±1.3	205±2.2	33.3%±6.3	7
C_{11}	flexible	0.26±0.01	8.8±1.1	224±2	46.6%±3.8	7
C_{12}	flexible	0.26±0.01	8.8±1.3	255±2.5	60%±3.8	7
C_{13}	flexible	0.24±0.01	7.2±1.3	250±2.5	26.6%±3.9	7
C_{14}	flexible	0.24±0.02	7.4±0.84	235±2.8	33.3%±7.6	7
C_{15}	flexible	0.24±0.01	7.2±1.3	264±2.1	46.6%±7.7	7
C_{16}	flexible	0.24±0.01	7.4±1.1	295±1.5	60%±3.8	7

Swelling index: Any polymer with good swelling property is expected to be a good candidate for bioadhesive application. Among all formulations from each group C_4, C_5, C_{12}, and C_{16} showed more pronounced percentage swelling index. It was observed that there was proportionate increase in swelling of film as the increase in concentration of film.

Folding endurance: Films which showed folding endurance above 200 were selected for drug loading. Thus formulations C_4, C_5, C_{12}, and C_{16} from each group was selected which showed maximum folding endurance. The results indicate that an increase in polymer concentration increased the folding endurance.

Surface pH: The surface pH of all the films exhibited uniformity in their values and they were found to be 7 which shows neutral pH and indicates its compatibility with buccal pH.

Moisture content & moisture absorption studies:

Moisture content: The percentage of moisture content (table-5) was varied between 0.98%±0.017 and 1.5%±0.06. in most cases, the moisture content was found to increase with increase in concentration of polymers that are more hydrophilic in nature. Low moisture content in the formulations helps them to remain stable from being a completely dried and brittle film.

Table-5: Physical and mechanical evaluation of formulation C1-C16.

Formulation code	Moisture content	Moisture absorption	Vapour transmission rate ($gcm^{-2}h^{-1}$)	Tensile strength (N/m^2)	Percentage elongation at break
C_1	0.97%±0.02	0.98%±0.017	$1.4\times10^{-2}\pm0.75\times10^{-2}$	$1.2\times10^{3}\pm0.25\times10^{3}$	10%±2.8
C_2	0.97%±0.02	1.01%±0.005	$2.7\times10^{-2}\pm0.81\times10^{-2}$	$1.6\times10^{3}\pm0.15\times10^{3}$	15%±2.8
C_3	1.4%±0.025	1.45%±0.006	$2.7\times10^{-2}\pm0.81\times10^{-2}$	$2.6\times10^{3}\pm0.15\times10^{3}$	30%±8.6
C_4	1.5%±0.06	1.48%±0.011	$4.1\times10^{-2}\pm0.7\times10^{-2}$	$3.6\times10^{3}\pm0.2\times10^{3}$	45%±8.6
C_5	1.4%±0.1	1.46%±0.015	$4.1\times10^{-2}\pm0.81\pm10^{-2}$	$3.6\times10^{3}\pm0.2\times10^{3}$	45%±8.6
C_6	1.2%±0.1	1.4%±0.005	$2.7\times10^{-2}\pm0.81\pm10^{-2}$	$2.6\times10^{3}\pm0.15\times10^{3}$	25%±2.8
C_7	1.01%±0.02	1.01%±0.017	$2.7\times10^{-2}\pm0.7\times10^{-2}$	$2.6\times10^{3}\pm0.15\times10$	25%±2.8
C_8	0.98%±0.02	0.98%±0.017	$1.4\times10^{-2}\pm0.75\times10^{-2}$	$1.6\times10^{3}\pm0.15\times10^{3}$	15%±2.8
C_9	0.98%±0.07	1.45%±0.005	$1.4\times10^{-2}\pm0.75\times10^{-2}$	$4.7\times10^{3}\pm0.15\times10^{3}$	15%±2.8
C_{10}	1.2%±0.07	1.46%±0.011	$2.7\times10^{-2}\pm0.81\times10^{-2}$	$5.4\times10^{3}\pm0.2\times10^{3}$	25%±2.8
C_{11}	1.2%±0.07	1.46%±0.015	$2.7\times10^{-2}\pm0.81\times10^{-2}$	$5.7\times10^{3}\pm0.15\times10^{3}$	20%±2.8
C_{12}	1.4%±0.2	1.48%±0.011	$4.1\times10^{-2}\pm0.7\times10^{-2}$	$6.1\times10^{3}\pm0.12\times10^{3}$	40%±8.6
C_{13}	0.98%±0.02	1.01%±0.017	$1.4\times10^{-2}\pm0.75\times10^{-2}$	$4.3\times10^{3}\pm0.15\times10^{3}$	15%±2.8
C_{14}	1.01%±0.02	1.45%±0.005	$2.7\times10^{-2}\pm0.81\times10^{-2}$	$4.7\times10^{3}\pm0.2\times10^{3}$	25%±2.8

C_{15}	1.2%±0.1	1.46%±0.006	$4.1\times10^{-2}\pm0.7\times10^{-2}$	$5.4\times10^{3}\pm0.2\times10^{3}$	25%±2.8
C_{16}	1.4%±0.1	1.5%±0.012	$5.5\times10^{-2}\pm0.7\times10^{-2}$	$6.5\times10^{3}\pm0.12\times10^{3}$	35%±8.6

Moisture absorption: The moisture absorption study of patches was done at a relative humidity of 75% for a period of three days. The low moisture uptake by all the formulations was observed at 75% relative humidity. The low moisture uptake by all the buccal patches can help to retard any hydrolytic degradation, and patches will remain stable.

Water vapour transmission rate: In this study, the formulation C_4 and C_5 that contain higher concentration of chitosan showed the highest transmission rate of $4.1\times10^{-2}\pm0.7\times10^{-2}$ $gcm^{-2}h^{-1}$ (table5). Similarly among groupVI the formulation C_{16} which contain highest concentration of HPMC showed highest transmission rate.

Tensile strength: Tensile strength measures the strength of film as a diametric tension or tearing force. It is measured in gm or N/m^2. The tensile strengths of patches were studied. The tensile strengths of patches were in the order of $C_4 > C_3 > C_2 > C_1$ in groupI. This indicates chitosan and polyvinyl pyrollidone produce effective cross-linking. Among all the patches studied patch C_4, C_5, C_{12}, and C_{16} showed highest tensile strength and patch C_1 showed lowest tensile strength.

Percent elongation at break: The elongation at break test provides an indication of the strength and elasticity of the film which is reflected by the elongation of the break. Films suitable for buccal application should preferably be strong but flexible. The evaluation of different formulations in each group showed highest elongation in formulations C_4, C_5, C_{12} and C_{16}.

Evaluation of Drug Loaded Patches

Drug content determination: The selected formulations were loaded with different doses of nifedipine like 5mg,10mg, 20mg and 30mg.(table 3). The drug loading efficiency of all the formulations of each combination were studied and result showed that the highest drug loading was found to be produced by batch C_4D_2, $C_{12}D_3$, and $C_{16}D_2$ and it was 55.9%, 57.81%, and 58.11% respectively.

***In vitro* drug release:** The release data of nifedipine from all the patches are calculated and the graph of cumulative percentage release vs. time for each combination is shown in fig.5, fig.6, and fig.7. All the formulations of chitosan, PVP combination showed release up to 7hr. The maximum percentage release was

shown by formulation C_4D_2. Combinations C_{12} and C_{16} showed release up to 8hr. The maximum release was shown by formulation C_{12} D_3, and C_{16} D_2. The optimimized patches gave Non Fickian analomous diffusion type model. (Table7.) Thus formulations C_4D_2, $C_{12}D_3$, and $C_{16}D_2$ from each combination which showed maximum percentage loading and drug release were selected for further studies.

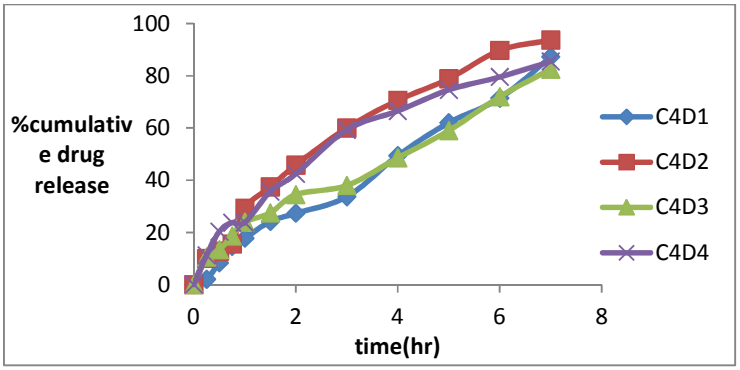

Fig.5- *in vitro* release of nifedipine from buccal patches of C_4D_1 - C_4D_4

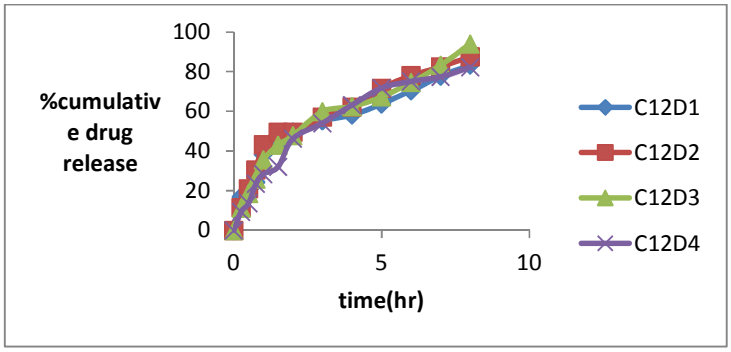

Fig.6- *in vitro* release of nifedipine from buccal patches of $C_{12}D_1 – C_{12}D_4$

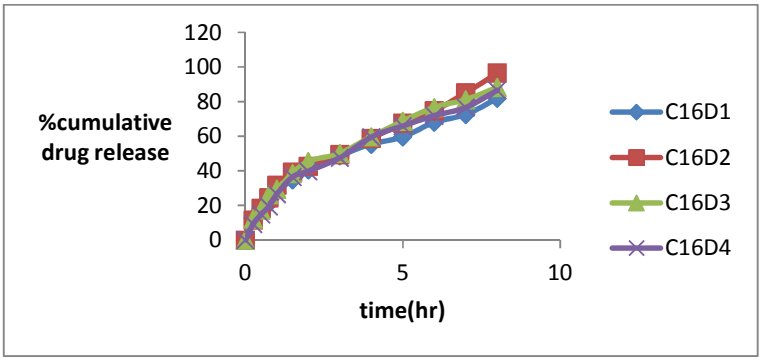

Fig.7- *in vitro* release of nifedipine from buccal patches of $C_{16}D_1 – C_{16}D_4$

Bio-adhesive strength of selected patches: In general, the strength of mucoadhesion is affected by various factors such as contact time with mucus, swelling rate of the polymer and the biological membrane used in the study. The bio-adhesive strength of the selected formulations is showed in the table 6. The highest bioadhesive strength was showed by formulation $C_{16}D_2$, which was 9.1N. It indicate that, HPMC base have good bioadhesion properties in combination with chitosan and PVP.

Table-6: Bio-adhesive strength of selected patches.

Formulation code	Bioadhesive strength(N)
C_4D_2	6.5±0.17
$C_{12}D_3$	7.8±0.75
$C_{16}D_2$	9.1±0.75

Stability study of selected patches: Patches that were placed in specified temperature and humidity conditions for stability studies were withdrawn every week and analysed for their drug content. Percentage drug present in the patches was determined spectrometrically. It was found that the drug loss was less through the patches stored for one month. The patches were also observed for their appearance and texture. The patches prepared using chitosan, PVP and HPMC combination showed satisfactory characteristics without being influenced by ageing.

Conclusion

Among the various polymeric combinations, the combination $C_{16}D_2$ was found to be most suitable. The formulation $C_{16}D_2$ comprising polymers chitosan, PVP K 30, and HPMC fulfil the requirement of good buccal film. It showed highest bioadhesive strength. Stability studies also showed satisfactory results. It follows *in vitro* drug release up to 96.52% for 8hr.

Thus from the present study it can be concluded that, bucco adhesive system for nifedipine with chitosan, PVP K 30 and HPMC meet the ideal requirement for buccal devices which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability.

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