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Design, Prepare and Characterization of Nefidipine Buccal Patches

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Abstract

Research work was design, prepare and characterization of antihypertensive buccal patches. Nefidipine used in treatment of blood pressure, congestive cardiac failure and angina. BDDS can be effectively utilized for the drug which undergoes first pass metabolism. The quality of API with regard to solubility and short half-life makes this drug as a suitable candidate for administration by Buccal route. These Nefidipine buccal patches were optimized for their thickness, folding endurance, content uniformity and release rate of the drug. Drug and excipient compatibility measured by using FTIR. Release rate of the drug were carried out with Franz diffusion cell utilizing pH 6.8 phosphate buffers as drug release medium.

Keywords

Nifedipine, FTIR studies, solvent casting technique, Eudragit RS 100, HPMC k 15M, carbopol 934, Franz diffusion cell.

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1.INTRODUCTION

The buccal region, within the oral cavity, offers an attractive route of administration for systemic drug delivery Consequently, buccal drug delivery requires the use of mucoadhesive polymers as these dosage forms should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period of time.[1] The buccal route was chosen because of its good accessibility, robustness of the epithelium, facile removal of the dosage form, relatively low enzymatic activity, and natural clearance mechanism for elimination of the drug from buccal area, satisfactory patient compliance, and avoidance of hepatic first pass metabolism . [2] Buccal films are flexible, comfortable compared to the tablets and can circumvent shorter residence time of oral gels [3]. Few drugs that have been attempted as buccal films were nifedipine, isosorbide dinitrate, diltiazem hydrochloride and propranolol hydrochloride.[4] It is believed that the Mucoadhesive nature of the device can increase the residence time of the drug in the body. The bioavailability of the drug is improved because of the combined effects of the direct drug absorption and the decrease in excretion rate. Increased residence time and adhesion may lead to lower API concentrations and lower administration frequency to achieve the desired therapeutic outcome.[5,6] Nifedipine, a calcium channel blocking agent, is frequently used for the treatment of angina pectoris and hypertension. Nifedipine is absorbed rapidly in gastrointestinal tract after an oral administration with a bioavailability of 45% to 75% due to its significant first-pass metabolism. Conventional preparations, which would increase heart rate reflect and activate the sympathetic nervous system, are not convenient clinically. Nifedipine sustained-release preparation is relatively

safe, well in compliance with mild adverse effects owing to its less variation of blood concentration and longer maintenance time.[8,9]

2. MATERIALS AND METHOD

2.1 MATERIALS

Nefidipine was collected as a gift sample from Hetero labs, Hyderabad, PMC k 15M, eudragit, carbopol 934 and other excipients were purchased from AR chemicals.

2.2 METHODODOLOGY [10,11,12]

Compatibility study (IR spectroscopy)

In the formulation of Nefidipine patch formation, API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between Nefidipine and the selected polymers. The pure drug and drug with excipients were scanned separately.

Method of preparation of nefidine buccal patches

Formulation design

Table-1: Formulation Design of Nefidipine buccal Patches

S. No	F.Code	Ingredients (mg)					
		Drug (mg)	HPMC k15M	Carbopol 934	Eudragit RS100	DMSO	PEG
1	F1	50	500	-	-	0.1ml	1ml
2	F2	50		500	-	0.1ml	1ml
3	F3	50	-	-	500	0.1ml	1ml
4	F4	50	250	250	-	0.1ml	1ml
5	F5	50	-	250	250	0.1ml	1ml
6	F6	50	250	-	250	0.1ml	1ml
7	F7	50	200	-	300	0.1ml	1ml
8	F8	50	300	-	000	0.1ml	1ml

Preparation method

Solvent casting method:

Nefidipine buccal patches were formulated by the solvent casting evaporation technique. The drug Nefidipine was diffuse in methanol. Polymers HPMC K15, carbopol 934 and eudragit RS 100 were taken in a boiling tube, to this add Nefidipine drug which was previously dissolved in methanol. Sufficient care was taken to prevent the creation of lumps. PEG was taken as a plasticizer and Dimethylsulfoxide as permeation enhancer and added to the mixture and mixed well. It was set aside for 2 hours to exclude any entrapped air and was then transferred into a previously cleaned petri plate (40cm^2), drying of patches was carried out in vacuum oven at room temperature. Dried patches were packed in aluminium foil and stored in a desiccator for further evaluation.

Characterization of Buccal formulation [13,14,15,16]

Physical appearance

All the formulated Nefidipine films were observed for color, clarity, flexibility, and smoothness.

Folding endurance

Buccal patches folding endurance was estimated by frequently double over at the same place till it broke. The number of times the film could be folded at the same place without breaking is the folding endurance. This was restating on all the films for three times and the mean values plus standard deviation was calculated.

Thickness of the film

The thickness of each film was measured by using screw gauze. Buccal patches thickness was estimated at various sites on each patch and the average thickness of the Buccal patch was capture as the thickness of the patch.

Weight uniformity

The formulated Buccal patches are to be dried at 60^{0}C for 6 hours before trial. A identify the area of 4.52 cm^2 of film is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Drug content

The Buccal films (4.52 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4 contain 0.5% SLS. This was then stirred with magnetic bead at 400 rpm for 2 hrs. The contents were filtered, and the filtrate was analyzed spectrophotometrically for drug content at 252 nm. Similarly, a blank was prepared from Buccal films without drug.

Moisture absorption studies

The buccal patches were weighed exactly and placed in a desiccator containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were

taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Percentage moisture uptake} = \frac{\text{Final weight- Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies

Three patches were weighed separately and kept in a desiccator contains calcium chloride at 37^{0}C for 24 hours. Then the last weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight-Final weight}}{\text{Final weight}} \times 100$$

***In vitro* release study**

The release rate of the drug was determined by using Franz diffusion cell apparatus temperature maintained at 37 ± 0.5 ^{0}C and stirred at a rate of 200 rpm. Sink conditions was maintained all over the study. The vessel containing 10ml of phosphate buffer pH 6.8 phosphate buffer solution. Aliquots of 1ml of samples were withdrawn at various time meanwhile and then analyzed using a UV Spectrophotometer at 230 nm against blank.

% release rate of drug was determined using the following formula.

$$\text{Percentage drug release} = \frac{Da}{Dt} \times 100$$

Here, Dt = Total amount of the drug in the film; Da = The amount of drug released

Release kinetics

Drug release mechanisms and kinetics are the two important characteristics of a drug delivery system in describing drug dissolution profile. The models that have show high 'R' value was considered as the best fit on the release data.

% drug release = concentration × no.of dilutions × volume of dissolution fluid/1000

Various mathematical models are

Zero Order Release Equation

The equation for zero order release is

$Q_t = Q_o + K_o t$ Where , Q_o = Initial amount of drug; Q_t = Cumulative amount of drug release at time "t"

K_o= Zero order release constant; T= Time in hours

First Order Release Equation

$$\text{Log } Q_t = \text{Log } Q_o + K_t / 2.303$$

Where,Q_o = Initial amount of drug;Q_t = Cumulative amount of drug release at time "t"; K= First order release constant;T= Time in hours

Higuchi Release Equation

The Higuchi release equation is

$$Q_t = K_H\sqrt{t}$$

Where , Q = Cumulative amount of drug release at time "t";K_H = Higuchi constant;T = Time in hrs

Korsmeyer -Peppas Release Equation:

Korsmeyer –Peppas equation is $F = M_t / M = K_m t^n$

Where, F = fraction of drug released at time 't'; Mt = amount of drug released at time 't' ;M = total amount of drug in dosage form;K_m= kinetic constant;n = diffusion or release exponent;t = time in hrs.

Stability studies

Optimized medicated films were subjected to short term stability testing. The Buccal films were sealed in aluminium foils and kept in a humidity chamber maintained at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months as per ICH guidelines.

3.RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

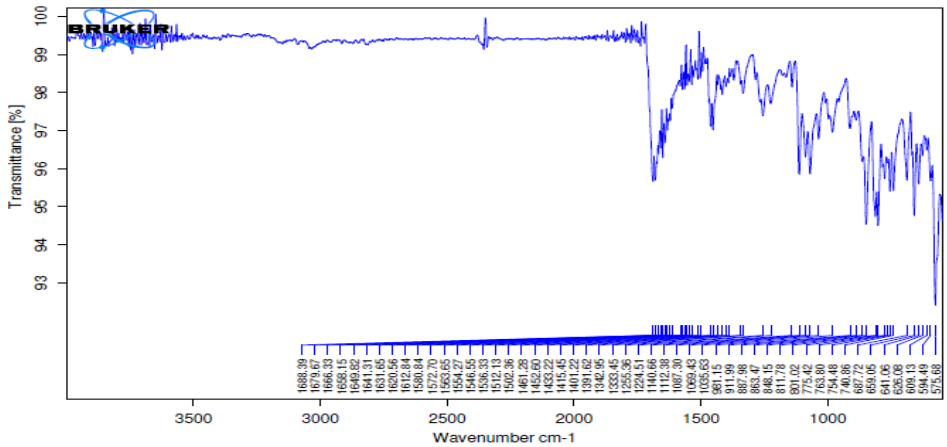

Fig-1: FTIR spectra of Pure drug

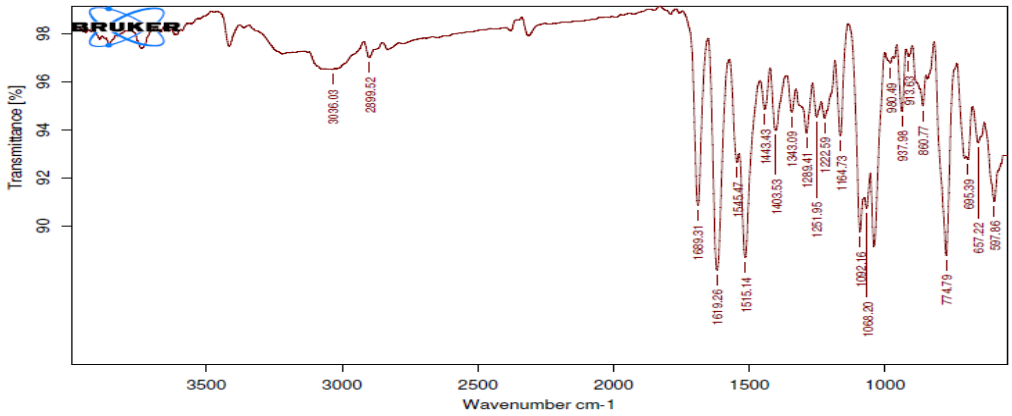

Fig-2: FTIR spectra Optimized formula

Evaluation of Buccal formulation

Table-2: Physicochemical evaluation of nefidipine buccal patches

Formulation code	Weight (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% Moisture loss	% Moisture absorption
F1	245.9	0.90	192	101	6.85	9.95
F2	265.4	0.96	190	99.89	9.20	10.20
F3	286.2	0.91	189	99.65	10.85	10.95
F4	274.7	0.95	191	98.42	9.85	11.85
F5	241.9	0.99	192	99.10	10.29	12.32
F6	230	0.96	190	98.78	11.85	13.98
F8	256.7	0.95	191	98.85	11.15	12.72

***In vitro* release study**

The buccal films (2 cm^2) were added to conical flask containing 100 ml of phosphate buffer pH 7.4 contain 0.5% SLS. This was then stirred with magnetic bead at 400 rpm for 8 hrs. The contents were filtered, and the filtrate was analysed spectrophotometrically for drug content at 242 nm. Similarly, a blank was prepared from buccal films without drug.

Drug content= (Weight of drug in patch)/(Total weight of patch) ×100

Where, Dt = Total amount of the drug in the patch;
Da = The amount of drug released.

Table-3: *In vitro* release data of film F_1 to F_8

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F8
0	0	0	0	0	0	0	0	0
1	14.90	15.15	15.80	15.56	16.13	15.58	14.89	15.10
2	26.70	25.89	26.50	25.55	26.45	25.55	25.60	24.65
3	37.89	36.87	37.70	38.25	37.89	38.55	33.59	35.65
4	48.18	45.23	44.50	47.59	48.89	48.66	49.89	48.24
5	69.75	68.35	67.65	66.55	68.98	67.55	69.12	69.32
6	76.89	79.34	71.98	78.32	79.21	80.55	81.25	82.65
7	88.86	86.77	85.32	84.28	85.90	86.99	88.96	89.23
8	94.45	97.50	98.12	97.22	98.24	99.32	96.92	98.25

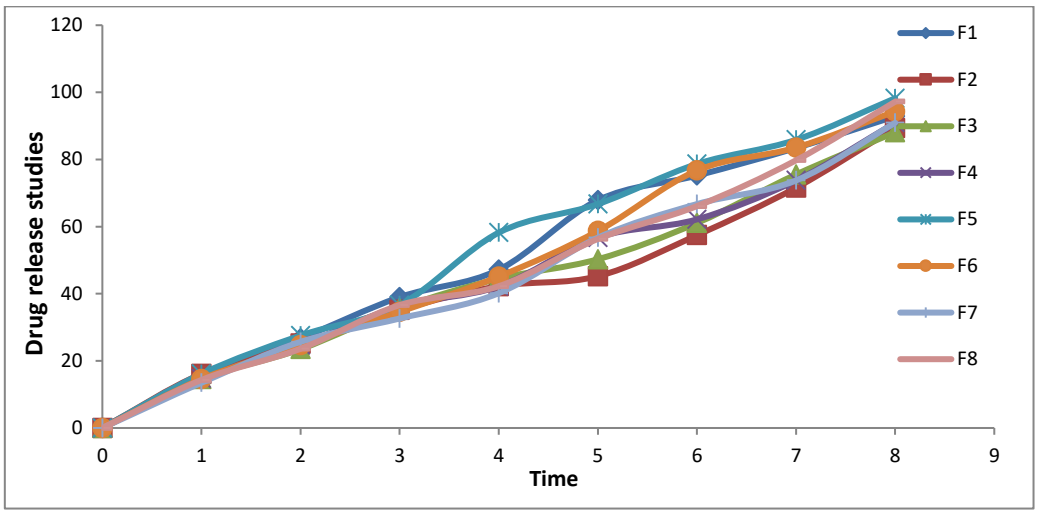

Fig-3: In vitro drug release of all formulation

Release order kinetics

Table-4: In vitro release profile of Nifedipine of 13ptimized formulation

Time (hrs)	Root T	Log T	Cum % drug release	Cum % drug retained	Log Cum % drug release	Log Cum % drug retained	(% retained)$^{1\backslash 3}$
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	1	0	15.58	88.96	1.6541	1.9429	4.9843
2	1.2134	0.3110	25.55	76.24	1.3454	1.7143	4.3321
3	1.4328	0.4671	38.55	69.73	1.4705	1.7639	4.2189
4	2	0.6010	48.66	62.53	1.4858	1.8521	3.4128
5	2.4568	0.6889	67.55	52.66	1.6789	1.8543	3.7264
6	2.3585	0.7681	80.55	45.92	1.7543	1.9750	3.4321
7	2.5158	0.8250	86.99	37.00	1.7814	1.5698	3.2175
8	2.6275	0.9132	99.32	26.15	1.8830	1.1342	2.7984

Zero order kinetics

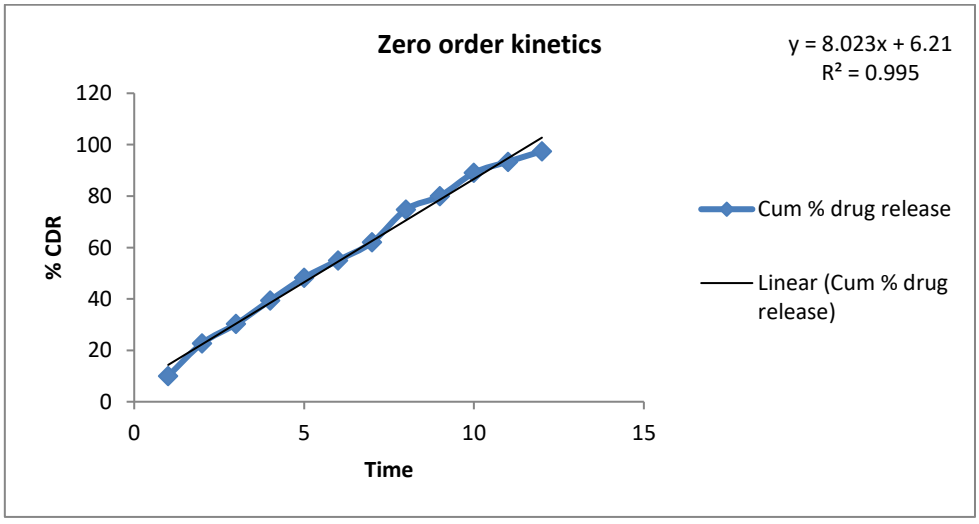

Fig-4: Drug release of Zero order kinetics

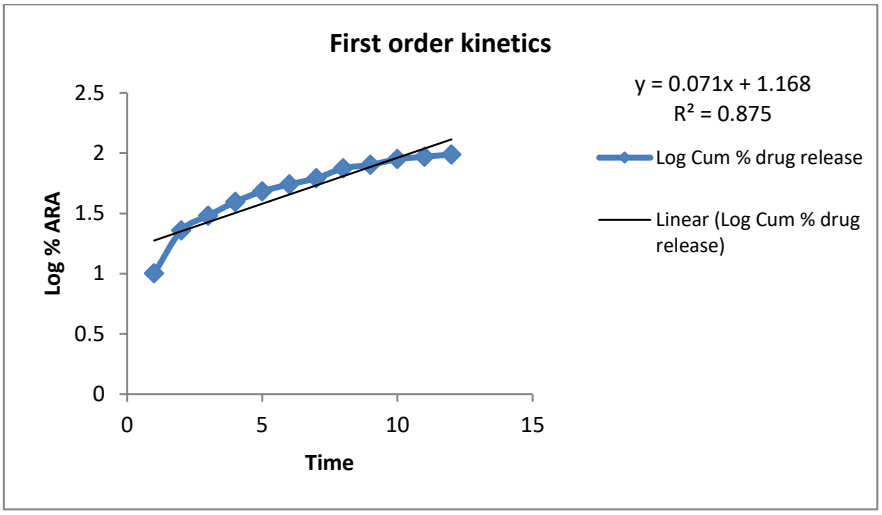

Fig-5: Drug release of First order kinetics

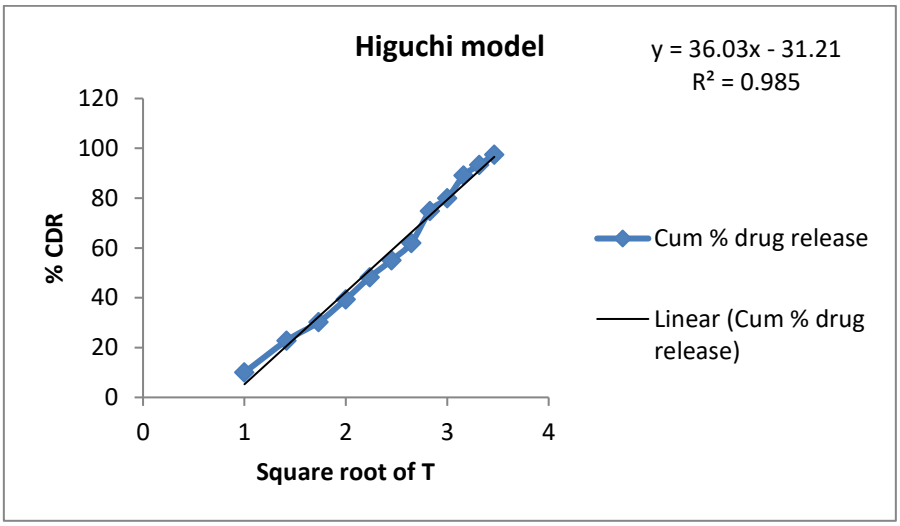

Fig-6: Drug release of Higuchi model

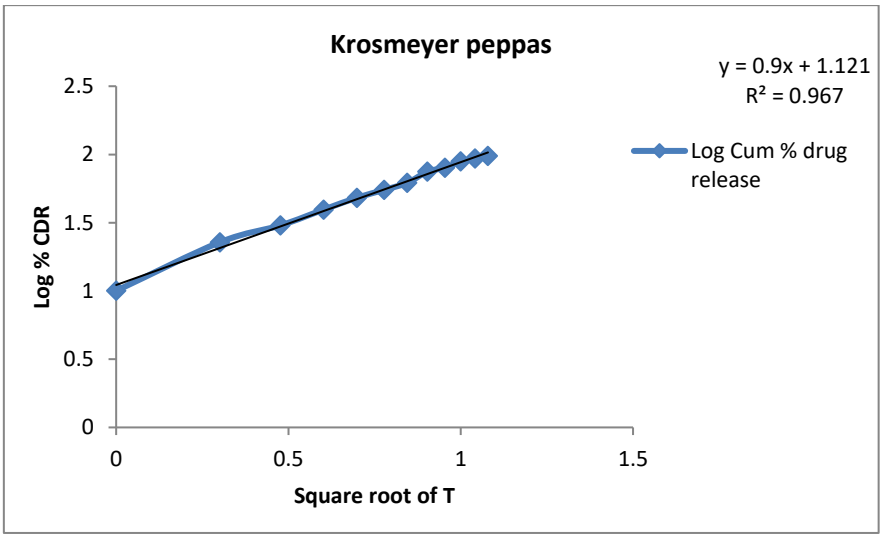

Fig-7: Drug release of Krossmayer peppas

Table-5: Drug release kinetics

S.no	Kinetic model	R^2 value
1	Zero order kinetics	0.995
2	First order kinetics	0.875
3	Higuchi model	0.985
4	Krossmayer peppas	0.967

Stability studies

Optimized formulations F6 was selected for accelerated stability studies as per ICH guidelines. The patches were observed for color, appearance and flexibility for a period of three months. The folding endurance, weight, drug content, % cumulative drug release of the formulation was found to be decreasing. This decrease may be attributed to the harsh environment (40^0C) maintained during the studies. The results are tabulated in table 25.

Table-6: Stability study of optimized formulation

Formulation Code	Initial	1st Month	2nd Month	3rd Month
F6	99.32	99.33	99.34	99.35
F6	99.32	99.34	99.35	99.36
F6	99.32	99.36	99.36	99.37

4.CONCLUSION

Buccal films of Nefidipine were formulated by solvent casting technique. The I.R spectra let out that, there was no interaction between polymers and drug. All the polymers used were consistent with the drug. Characterization parameters like thickness, tensile strength, folding endurance, percentage moisture loss indicates that films were mechanically stable. In-vitro drug release showed a sudden release in the first day. There after the delivery profile was controlled and extended till the end of static delivery. Among the seven formulations, the formulated patch F6 showed 99.32 % of release. Throughout the *in-vitro* release studies, the films remained intact without any disintegration. All the films were found to be stable over the storage period and conditions tested. Overall study suggests that among the films prepared F6 was found to show the best results. Hence it was considered as optimized formulation.

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