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DEVELOPMENT OF MUCCOADHESIVE PATCHES FOR BUCCAL ADMINISTRATION OF FELODIPINE

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ABSTRACT

The aim of the study is to formulate mucoadhesive Buccal patches for Felodipine which is an anti hypertensive drug with low bioavailability of 20%. Mucoadhesive patches were prepared by solvent casting method using Carbopol 971P and HPMC E5. Various parameters like film weight, thickness, drug content, surface pH, swelling index, folding endurance, buccal residence time and *ex vivo* permeation studies were evaluated. The patches were found to be smooth even surface, uniformity in thickness, drug content and the *ex vivo* permeation study was found to be 66% and the release pattern was non fickian**.**

Key words: Mucoadhesive, Buccal patches, Felodipine

1. INTRODUCTION

To any drug moiety to elicit its pharmacological action, it has to reach the systemic circulation without change, oral route of administration is the safe method of systemic delivery of drugs but one of the main disadvantage of the oral route is presystemic metabolism of certain drugs, as a result a drug may be absorbed but incompletely available to the systemic circulation to elicit its pharmacological response.

Buccal drug delivery systems are useful for the administration of drug which is susceptible to extensive first pass metabolism. Buccal bioadhesive system appears to be especially attractive because of the easy accessibility and the robust nature of the oral mucosa. It is less prone to irritation or irreversible damage by a dosage form and therefore it may lead to better patient acceptance and compliance.

Felodipine has chosen for the present formulation development study, which is a selective calcium channel blocker and antihypertensive drug. Oral administration of Felodipine undergoes extensive hepatic first pass elimination with the result of which only 20-25% of the oral administration drug reaches the systemic circulation. It is therefore, considered to be a potential candidate for the mucoadhesive drug delivery.

The objective of the present study is to formulate mucoadhesive delivery system for Felodipine using HPMC, Carbopol etc to evaluate its potential in bypassing the first pass effect associated with oral administration.

2. MATERIALS AND METHODS

Felodipine was gifted from Cipla, Carbopol was obtained from SD fine chemicals, HPMC gifted by Colorcon, All other chemicals and reagents used were of analytical grade; double-distilled water was used throughout the study.

Formulation of Felodipine buccal patches: Buccal patches of Felodipine were prepared by solvent casting technique by using Hydroxypropylmethyl cellulose-E5 (HPMC) and Carbopol-971P. Calculated amounts of HPMC and Carbopol were dispersed in ethanol and stirred to form polymer solution. Felodipine was incorporated in the polymeric solutions after levigation with propylene glycol which served the purpose of plasticizer as well as penetration enhancer under occasional stirring for 24hrs. The medicated gels were left overnight at room temperature to obtain clear, bubble-free gels. The gels were caste into Petri-dish (4.5 cm diameter), and solvent was allowed to evaporate at controlled rate by covering the Petri-dish with inverted glass funnel to avoid blistering effect on dried film. The medicated gel is allowed to dry at 40˚c temperature to form a flexible film.

Film weight and thickness: For evaluation of film weight, three films from every formulation were taken and weighed individually on a digital balance. The average weights were calculated .similarly three films of each formulation were taken and the film thickness was measured using digimatic verneir caliper at three spot on film and the mean is calculated.

Drug content: Three film (each of 2 cm diameter) of each formulation were taken in separate 100 ml volumetric flask ,100 ml of pH 6.5 phosphate buffer was added continuously stirred until patch get dissolved. The solution were filtered ,diluted suitably and analyzed at 241 nm in UV spectrophotometer. The average of drug contents of three films was taken as final reading.

Surface pH of film: For determination of surface pH three films of each formulation were allowed to swell for 2 hrs on the surface of pH 6.5solution using cover slip. The surface pH was measured by using a pH paper placed on the surface of the swollen patch. Mean of three reading was recorded.

Swelling index: The films were allowed to swell on the surface of pH 6.5 phosphate buffer kept in an incubator maintained at 37±0.2°. Increase in the weight of the film was determined at preset time intervals (1-3hrs) the percentage swelling (%S) was calculated using the following equation.

$$\text{Percentage swelling (\%S)} = \frac{Xt - X}{X}$$

X_t is the weight of the swollen film after time't'

X is the initial film weight at time 0

Folding endurance: The films of each formulation of size (2 sq.cm diameter) were cut and folding endurance was determined by repeatedly folding a small strip of film at the same place till it broke. Number of times the film could be folded at the same place without breaking gives the value of folding endurance.

Buccal residence time: The *in-vitro* residence time was evaluated after application of the patches onto freshly cut rat peritoneal membrane. The fresh mucosa was fixed in the inner side of the beaker, above 2.5 cm from the bottom, with cynoacrylate glue. One side of each patch was wetted with one drop of pH 6.5 phosphate buffer and pasted to the mucous membrane by applying alight force with a fingertip for 30 seconds .the beaker was filled with 500 ml of phosphate buffer and it was kept at 37±2 °c. After 2 min a 50 rpm stirring rate was applied using magnetic stirrer to stimulate buccal cavity environment and patch adhesion was monitored. The time required for the patch to detach from the mucosal membrane was recorded as the mucoadhesive time.

***Ex-vivo* permeation studies:** In this study, peritoneal membrane of rat used as mucous membrane .the membrane was excised and trimmed evenly from the sides. It was then washed in buffer solution and used immediately. The *ex vivo* permeation studies of mucoadhesive Buccal patch of Felodipine through an excised layer of rat peritoneal membrane were carried out using the modified Franz diffusion cell. A patch of each formulation under study was placed in intimate contact with the excised mucosal membrane and the top side was covered with aluminium foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 10 ml of phosphate buffer .the cell contents were stirred with a magnetic stirrer and temperature of 37±1° was maintained throughout the experiment. The samples were withdrawn at 5,15,30,60,120,190 minutes, filtered, diluted suitably and then analyzed using UV spectrophotometer at 241 nm.

3. RESULTS AND DISSCUSSION

The compatibility between the drug and selected polymers was evaluated using FTIR peak matching method. The IR spectra of pure drug, polymer and the physical mixture are shown in figure.3. There was no appearance of disappearance of peaks in the polymer-drug mixture, which confirmed the absence of any chemical interaction between the drug and the polymers. Hence they are compatible. The film weight was found to be in the range of 1.4±0.61 mg, 1.20±0.025 mg, 1.29±0.26 and thickness were observed to be in the range of 0.25±0.015mm, 0.25±0.026mm and 0.27±0.008 mm are shown in the table 2. Drug content in the formulation were F1 2.35±0.028 mg/2 sq.cm, F2 2.39±0.03 mg/2 sq.cm and F3 2.37±0.029 mg/2 sq.cm diameter. On this basis, it was found that the drug was dispersed uniformly throughout the patch, are shown in the table 2. Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa, the surface pH of the buccal films were made to keep the surface pH as close to Buccal /salivary pH as possible, by the proper selection of the polymers for developing the buccal films. The surface pH of patches was 6.49±0.034, 6.56±0.020, 6.7± 010. The comparative percentage swelling for various formulations was in order of F1>F2>F3. The percentage swelling of HPMC-E5 films was reduced by the addition of Carbopol 934P. Folding endurance was found to be highest for F3 (245±4.910) and lowest for F1 207±5.04). It was found that folding endurance of HPMC films was increased by the addition of polymer carbopol934P. The folding endurance values of the films were found to be optimum and therefore the films exhibited good physical and mechanical properties.

In-vitro residence time of the patch was found to be satisfactory in all formulation, which shows 3.5 hrs for formulation I, 4.20 hrs for formulation F2 and 5.5 hrs for formulation F3.

In *ex-vivo* release studies of various formulations were performed using pH 6.5 phosphate buffer as dissolution medium and measuring drug concentration by UV spectroscopy at 241 nm. Distinguishable difference was observed in the release of Felodipine patch containing HPMC and Carbopol. In the graph plotted between the percentage drug release *vs* time which shown in figure.4. After three hours the cumulative drug release of formulations were found to be F1 (66.17), F2 (62.81) and F3 (56.98) Table 2. To determine the exact mechanism of diffusion, the slope was calculated for the peppas' plot. From the table, it shows the values were greater than 0.5 which indicates that the release was anomalous diffusion not obeying fick's law Table 3.

4. CONCLUSION

The present study indicates a good potential of swellable mucoadhesive buccal patch containing Felodipine for systemic delivery with an added advantage of bypassing the hepatic first pass metabolism. The results of the study show that therapeutic levels of Felodipine can be delivered buccal route. It may be concluded that the films containing 2.5 mg Felodipine with 1:1 ratio of HPMC-E5 and Carbopol 971 P, show good swelling, a convenient residence time and promising drug release, thus seems to be a potential candidate for the development of buccal film for effective therapeutic use.

Table.1. Formulation table of Felodipine mucoadhesive patch

Ingredients	F1	F2	F3
Felodipine	78.5 mg	78.5mg	78.5mg
HPMC-E5	100mg	100mg	100mg
Carbopol-971 P	100 mg	200mg	300mg
Propylene glycol	2 ml	2 ml	2ml
Ethanol	25 ml	25ml	25ml

Table.2. Parameters showing the successful formulation of mucoadhesive path of Felodipine

Parameters	F1	F2	F3
Weight variation(mg)	1.14±0.061	1.20±0.025	1.29±0.026
Thickness(mm)	0.25±0.018	0.25±0.026	0.27±0.008
Drug Content(mg)	2.35±0.028	2.39±0.03	2.37±0.29
Folding endurance	207±5.049	230±1.732	245±4.910
Surface pH	6.49±0.034	6.56±0.020	6.7±0.010
Residence Time(hrs)	3.5	4.2	>5.5
Swelling Index (%)	38.50±0.562	35.89±0.657	31.87±0.858
Ex-vivo release (%)	66.81	62.81	56.98±

Table.3. Mechanism of drug release from mucoadhesive path of Felodipine

Formulation	First order plot		Peppas plot	
	k	R	r	N
F1	0.5×10^{-2}	0.9892	0.9821	1.005
F2	0.52×10^{-2}	0.9912	0.9981	1.139
F3	0.46×10^{-2}	0.9855	0.9014	1.550

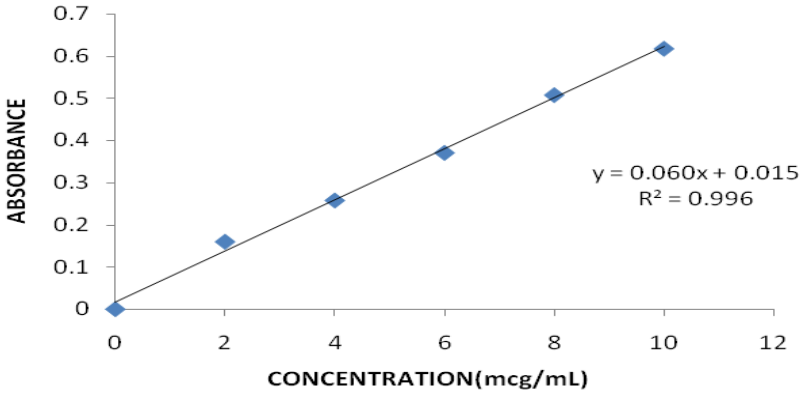


Figure.1.Standard curve of Felodipine in phosphate buffer ph 6.5

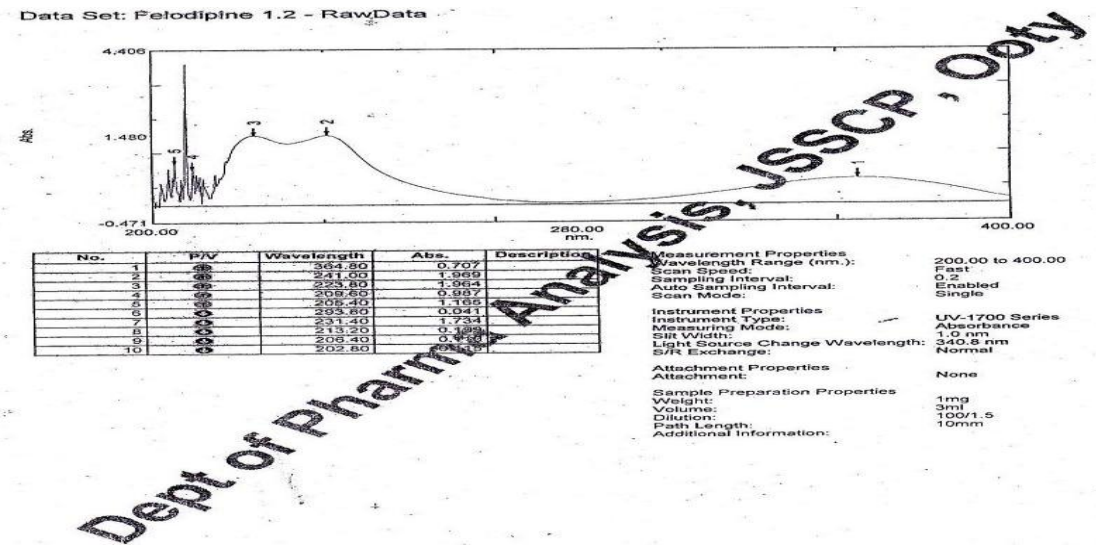
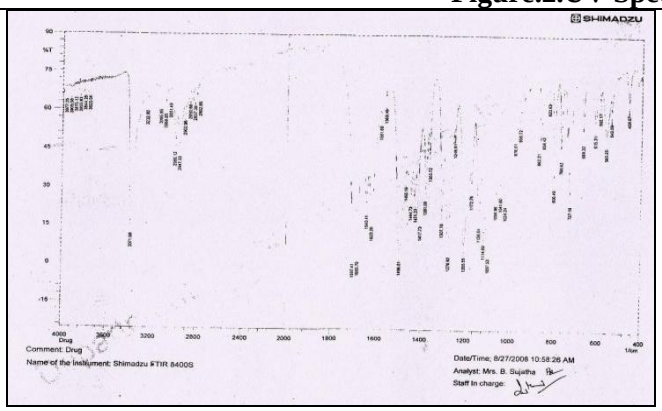
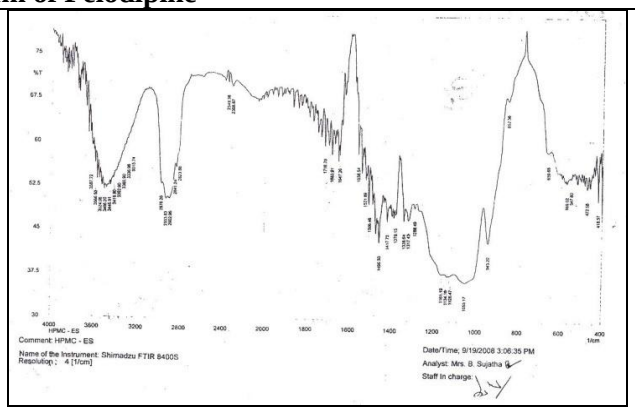


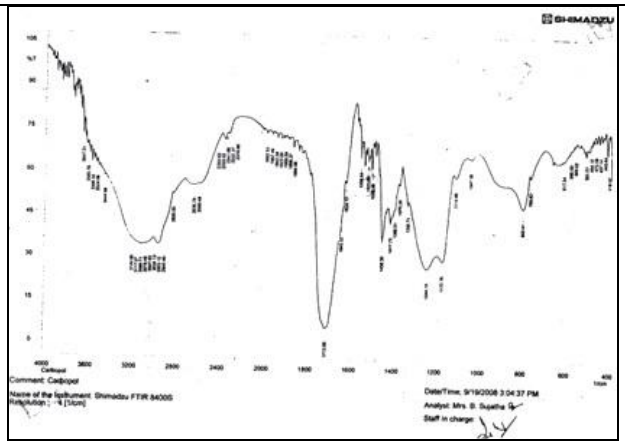
Figure.2.UV Spectrum of Felodipine



A



B



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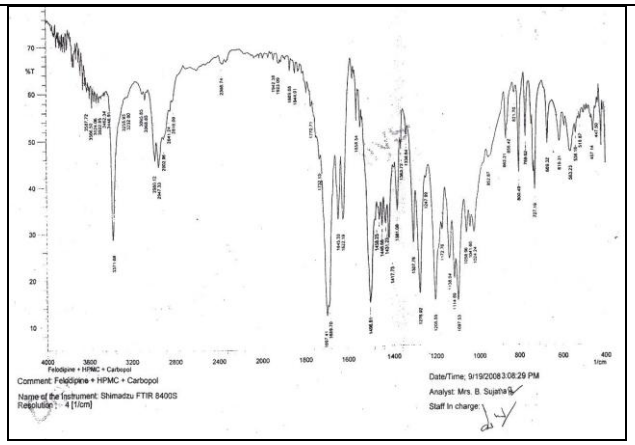
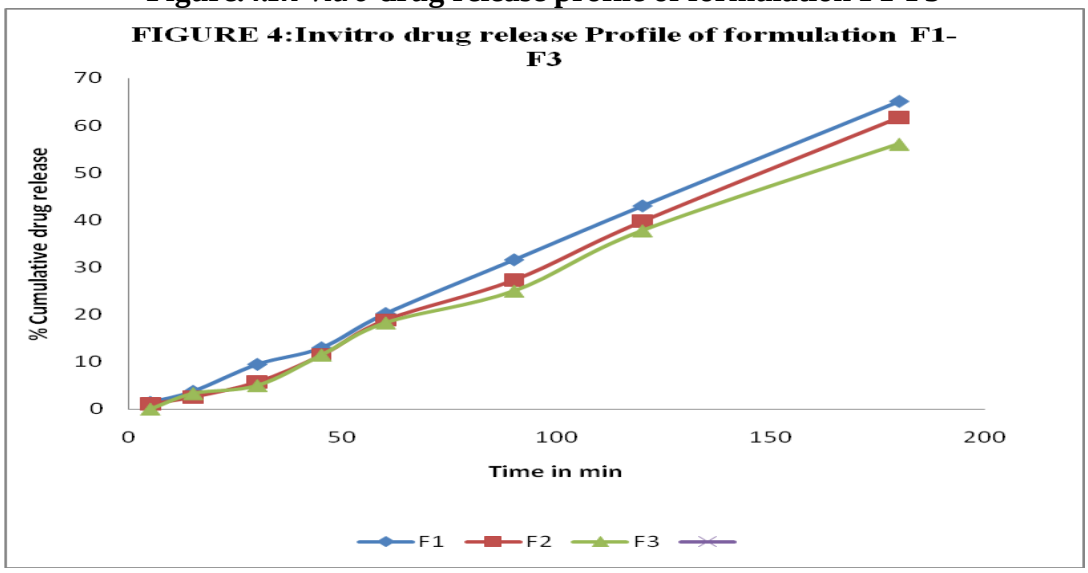


D

Figure.3.FTIR Compatibility study - IR Spectrum of Felodipine(A) HPMC(B) Carbopol (C) Felodipine, HPMC, Carbopol (D)

Figure.4.*In-vitro* drug release profile of formulation F1-F3



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