Research Article

Buccal Films Containing Felodipine: *In Vitro and Ex Vivo* Evaluation

K.Haritha, Nelluri.K.D.Devi*, A.L.Durga, V.Himaja, P.Mounika, V.N.Vyshnavi
KVSR Siddhartha College of Pharmaceutical Sciences, Andhra Pradesh, Vijayawada, India.
***Corresponding author's E-mail:** nelluriss@rediffmail.com

Received: 22-10-2018; **Revised:** 25-11-2018; **Accepted:** 08-12-2018.

ABSTRACT

As reported in the literature, Felodipine has poor bioavailability, which undergoes hepatic first pass metabolism. Hence, the aim of present work is to enhance safety and efficacy of drug molecule by formulating in a convenient dosage form for administering to achieve better patient compliance. One such approach is formulating buccal films. In the present work eight formulations (F1-F8) of soluble Felodipine buccal films were prepared by using hydrophilic polymers in different combinations and proportions. The prepared formulations were evaluated for thickness, moisture content, swelling index, weight variation, content uniformity, folding endurance, physical appearance, surface texture, in-vitro drug release and *ex-vivo* permeation. Among eight formulations (F1-F8) F8 is the best formulation, which releases 88% in 3hrs and it can be used to prolong the release.

Keywords: Buccal Films, Hydrophilic Polymers, First Pass Metabolism, Poor Bioavailability.

INTRODUCTION

Buccal drug delivery is an alternate route for oral route of administration to overcome the disadvantages like hepatic first pass metabolism, instability in acidic environment. In buccal delivery the drug directly enters in to systemic circulation, which avoids hepatic first pass metabolism[1]. The others advantages of buccal route of administration is ensuring ease of administration and possible to terminate delivery when required[2].

Mucoadhesive drug delivery system is defined as drug delivery systems, which shows bioadhesion property by using hydrophilic polymers. The hydrophilic polymer hydrates and shows adhesive property[3]. Hence by using hydrophilic polymers drug targeting to a particular region of body for extended period of time is possible. Buccal films are small, flat and are intended to be held between cheek pouch and teeth[4].

Felodipine is chemically 3-ethyl-5-methyl-4-(2,3-dichloro phenyl)-2,6-dimethyl-1,4-dihydro pyridine-3,5-dicarboxylate[5]. Felodipine is a calcium channel blocker, which is used in treatment of mild to moderate hypertension[6]. The Felodipine is completely absorbed by gastro intestinal tract but affected extensive by hepatic first pass metabolism through the portal circulation results in a low systemic availability is 15%, but not affected by food[7].

Felodipine is formulated in buccal films to enhance the bioavailability by bypassing hepatic first pass metabolism.

MATERIALS AND METHODS

Materials

Pure drug gift sample of Felodipine was from Orchid healthcare Ltd. All other ingredients HPMC E15, PEG 400, Starch, L-HPC, Methocel E4, EC used were of pharmaceutical grade.

Methods

Preparation of Buccal Films

Buccal films are prepared by Solvent Casting Technique. Required quantity of ethanol was taken and 50mg of ethyl cellulose was dissolved in ethanol by stirring and poured in to the bangle by placing it on glass plate and dried it.5mg of felodipine is dissolved in the ethanol by stirring. The other ingredients (film formers) are dissolved in the water and stirred until it dissolves. The contents of step 2 and step 3 were mixed until homogenous mixture was formed and poured it in to the bangle which is placed on the dried ethyl cellulose membrane and dried completely in room temperature or in oven.

Evaluation of Buccal Films[8-10]

Construction of Standard Graph of Felodipine

Felodipine powder equivalent to 5mg of the drug was accurately weighed by using single pan balance and it was dissolved in methanol placed in volumetric flask. Then, the volume was made up to the mark with phosphate buffer of pH 6.8. Then the solution of Felodipine was subsequently diluted with the same buffer and prepared 0, 2, 4, 6, 8 & 10µg/ml concentration and measured the absorbance by spectrophotometer at 362nm using phosphate buffer of pH 6.8 as blank.

Thickness Measurement

Films of each formulation were taken and the thickness of the film was measured using Thickness tester at different places. The average film thicknesses are computed.

Folding Endurance

Folding endurance was determined by repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking was computed as the folding endurance value.

Surface Texture

The surface texture of the films was evaluated by pressing the film with finger.

Table 1: Formulations of Felodipine Buccal Films

Contents	F1	F2	F3	F4	F5	F6	F7	F8
HPMC E15	50	50	-	-	50	100	-	-
PEG 400	50	-	-	-	-	-	50	100
Starch	-	-	50	50	-	-	50	-
L-HPC	10	10	60	10	60	10	10	10
Methocel E4	10	60	10	60	10	10	10	10
Glyerine	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9
Drug	5	5	5	5	5	5	5	5
EC	25	25	25	25	25	25	25	25
Water	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Ethanol	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total (mg)	152.9	152.9	152.9	152.9	152.9	152.9	152.9	152.9

Surface pH

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film. The procedure was performed in triplicate and average with standard deviation was reported.

Moisture absorption

All the films of equal weight were initially weighed. They were placed in dessicator containing saturated Aluminium chloride and the 79.5% relative humidity was maintained, after three days all films were taken out and they were weighed again. Average value was noted by using following formula:

%Moisture absorption = Final weight-Initial weight /Initial weight *100

Moisture loss

All the films of equal size were initially weighed. They are placed in the desiccator containing saturated Calcium chloride and internal humidity was maintained. After three days, all films were taken out and they were weighed again. The average value was noted by using following formula

%Moisture loss = Initial weight – Final weight /Initial weight*100

Swelling Index

Each films of size (1cmx1cm) were cut and their initial weight wasnoted. Films were allowed to swell for 5min in 20ml of distilled water. Films were than taken out, dried and weighed. Percentage of swelling was noted using the following formula:

%Swelling Index (SI) = Final weight-Initial weight/Initial weight x100

Drug Content Determination

Drug content uniformity was determined by taking film area of 1.5 cm^2 from each formulation and it was placed in 100 ml of volumetric flask contained some amount of phosphate buffer of pH 6.8 and then the volume is made upto the mark using same buffer. It was kept aside for 6 hours. The content of (drug) Felodipine was calculated using standard graph.

In vitro Dissolution Studies

The dissolution study was carried out using modified diffusion cell. Freshly prepared egg membrane was positioned between the donor and receptor compartments. Egg membrane was tied to one end of an open-ended cylinder, which acts as a donor compartment. The film should be placed in such a way that it should be stick on the egg membrane. The receptor compartment was filled with pH 6.8 phosphate buffer. The assembly was maintained at 37±1°C and stirred magnetically. Samples were withdrawn at definite

time intervals and analyzed using UV Spectrophotometer at 362nm.The results were expressed as mean of three determinations.

Ex-vivo studies

An *ex-vivo*permeation study of Felodipine was carried out using a fresh sheep buccal mucosa using modified diffusion cell at 37 ± 1°C. Fresh sheep bucal mucosa was positioned between the donor and receptor compartments. Sheep buccal mucosa was tied to one end of an open-ended cylinder, which acts as a donor compartment. The film should be placed in such a way that it should be stuck on the mucous membrane. The receptor compartment was filled with pH 6.8 phosphate buffer. The assembly was maintained at 37°C and stirred magnetically. Samples were withdrawn at definite time intervals and analyzed using UV Spectrophotometer at 362nm.

RESULTS AND DISCUSSION

Pre formulation Studies

Organoleptic Properties: Color: White, Odor: Odorless, Taste: Tasteless, Appearance: Crystalline powder. Melting point values of sample was found to be in range of 145^{0}C. The official melting point range for Felodipine is between 142-145°C. Hence, results were complied the limits specified in I.P.

Solubility Study

Table 2: The Solubility of Felodipine in various Solvents

Name of solvent	Solubility
DMSO	Highly Soluble
Ethanol	Soluble
Water	Slightly soluble

FT-IR Spectrophotometry

The pure drug and its physical mixture were subjected to IRand evaluated for interaction between the drug and the utilizedpolymer. The IR spectra of pure drug, Drug+ HPMC E15, Drug+Methacel E4, Drug + L-HPC, Drug + PEG 400 overlay are shown in figure 1 and 2 respectively. The figure 1 showed that the IR spectrum of pure drug and its characteristic peaks at :3370.00 cm^{-1} for N-H stretch, 1534 cm^{-1} for C-H aliphatic stretch , 1688.14 cm^{-1} for C=O stretch of ester, 1019.40 cm^{-1} for C-O-C stretch, 1615.00 N-H(Bending) respectively. The IR spectrum of physical mixture (drug + HPMC E15) shows characteristic peaks observed at :3370.00 cm^{-1} for N-H stretch, 1534.00 cm^{-1} for C-H aliphatic stretch ,1688.14 cm^{-1} for C=O stretch of ester, 1019.40 cm^{-1} for C-O-C stretch, 1615.00 for N-H(Bending) respectively which clearly indicates that there was no interaction between drug and HPMC E15. The IR spectrum of physical mixture of the drug and polymer (Methacel E4) were observed at :3370.00 cm^{-1} for N-H stretch, 1534.00 cm^{-1} for C-H aliphatic stretch ,1688.14 cm^{-1} for C=O stretch of ester, 1019.40 cm^{-1} for C-O-C stretch,1615.00 for N-H bending respectively which indicates that there was no possible interaction between drug and Methacel. In case of IR spectra of drug and L-HPC the following characteristic peaks were noticed at :3370.00cm^{-1} for N-H stretch, 1534.00 cm^{-1} for C-H aliphatic stretch, 1688.14 cm $^{-1}$ for C=O stretch of ester, 1019.40 cm^{-1} for C-O-C stretch,1615.00 for N-H bending respectively. The results indicated there was no possible interaction between drug and L-HPC. In case of IR spectra of drug and PEG 400, the following characteristic peaks were noticed at :3370.00 cm^{-1} for N-H stretch, 1534.00 cm^{-1} for C-H aliphatic stretch, 1688.14 cm^{-1} for C=O stretch of ester, 1019.40 cm^{-1} for C-O-C stretch,1615.00 for N-H bending respectively. The results indicated there was no possible interaction between drug and PEG 400. Hence, there was no positive evidence for the interaction between drug and the utilized buccoadhesive material. The results showed that the usefulness of the utilized material (HPMC E15, Methacel E4, L-HPC, PEG 400,) for preparation of various mucoadhesive buccal films contained Felodipine.

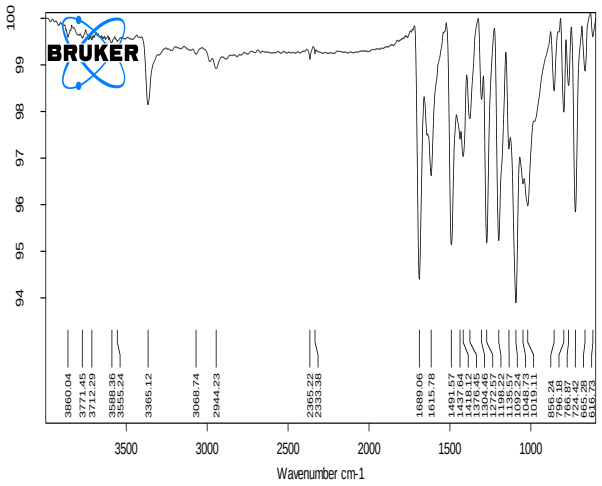

Figure 1: FT-IR STUDIES OF PURE DRUG FELODIPINE

Overley of Drug and Polymers

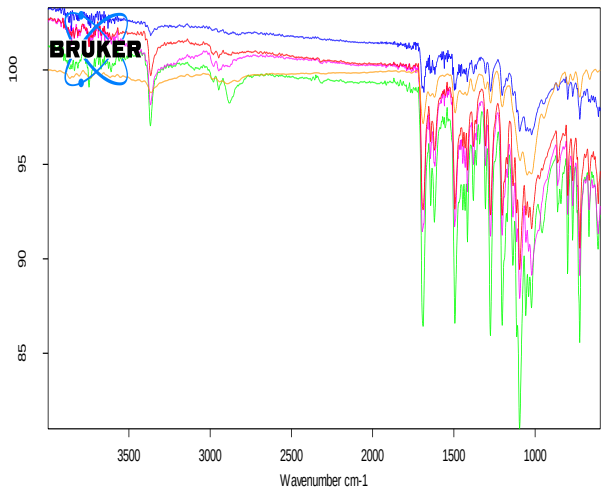

Figure 2: Overlay of Drug and Polymers used

Table 3: FT-IR Studies Streaching Values

S. no.	Wave number (cm^{-1})	Functional group	Peak observed at						Interaction
			Drug	Drug + HPMC E15	Drug+ METHACEL E4	Drug+ L-HPC	Drug+ STARCH	Drug + PEG	
1	3300-3500	N-H(S)	3365.1	3363	3363	3364	3365	3365	NO
2	2850-3000	C-H(S)	2944	2891	2831	2945	2942	2881	No
3	1670-1820	C=0(S)	1615	1689	1688	1689	1689	1690	No
4	1000-1300	C-O-C(S)	1019	1022	1020	1019	1018	1025	No
5	1600.00	N-H(B)	1615	1619	1616	1617	1617	1618	No

Construction of Standard Graph of Felodipine

Table 4: Calibration Values of Felodipine

Concentration(µg)	Absorbance
0	0
2	0.041
4	0.075
6	0.098
8	0.12
10	0.15

Standard graph for Felodipine

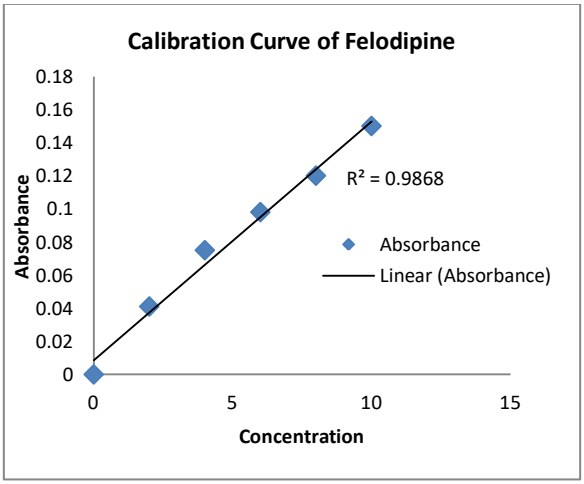

Figure 3: Standard graph for Felodipine

Thickness Measurement

The thickness of Felodipine films was measured and results are shown in Table No 5. The thickness of the various films varies from 221.03 to 241.16µm due to increase in polymer concentration.

Folding Endurance

The folding endurance of the films was measured manually and they were folded between 212 to 232 times without breaking or cracking. The ranking orders of the folding endurance of various buccal films are as follows: F8> F7 > F1> F6> F2 > F5> F4>F3. Among various polymers, HPMC E15 and PEG 400 contained films has shown highest folding endurance. The results are shown in **Table 5.**

Surface Texture

The surface texture of all the films was examined and they were found to be flexible with smooth surface texture. The results are shown in Table 5.

Surface pH

The surface pH of all the films is determined. All the films exhibited almost uniformity in their surface pH values and thefollowing range of pH was observed: 6.22 to 6.82 which indicated its compatibility with buccal pH. The results are shown in Table: 5.

Moisture absorption

The films were tested for moisture absorption and the results are shown in Table: 5. The result shows in between 7.66 to 11.72% with low SD.

Moisture loss

The films were tested for moisture loss and the results are shown in Table 5. The result shows in between 11.17 and 34.23% with low SD.

Swelling Index

The swelling index was determined for all the formulations. The results are between 57.47 to 80.06 %. The results are shown in Table 5. the order of swelling index is F8>F1>F6>F7>F5>F2>F3>F4.

Drug Content Determination

The drug content was estimated for all the formulations using standard method. The drug content of all the films was found to be uniform with low SD values, which indicates that the drug was distributed uniformly in all the films. The results are shown in Table 5.

Table 5: Evaluation Parameters of Felodipine Buccal films

Formulation	Thickness(µm)	Folding endurance	Texture	Surface pH	% Moisture Absorption	% Moisture Loss	Swelling Index	Drug content
F1	232.82±1.23	225.6±1.699	Smooth	6.56±0.008	9.19±1.23	12.46±1.699	77.12±0.001247	98.27%±0.001247
F2	226.93±1.64	215±2.449	Smooth	6.22±0.012	11.50±1.64	29.43±2.449	55.98±0.00816	97.85%±0.000816
F3	221.03±1.21	212.6±1.247	Smooth	6.63±0.020	10.56±1.21	34.23±1.247	51.87±0.01633	99.06%±0.001633
F4	221.59±1.14	213.6±2.494	Smooth	6.47±0.008	8.59±1.14	22.32±2.494	48.68±0.001247	98.41%±0.001247
F5	224.86±0.53	214.6±2.867	Smooth	6.82±0.012	11.72±0.53	32.43±2.867	57.47±0.00816	97.76%±0.000816
F6	229.77±0.32	217.6±2.054	Smooth	6.31±0.016	9.97±0.32	23.41±2.054	65.46±0.001247	99.78%±0.001247
F7	237.53±0.40	226.6±1.247	Smooth	6.46±0.016	7.66±0.40	11.17±1.247	61.72±0.017	98.83%±0.0017
F8	241.16±0.73	232.6±2.054	Smooth	6.82±0.012	8.77±1.19	21.52±1.5	80.96±0.00816	99.76%±0.000816

In vitro Dissolution Studies

The films were subjected to *in-vitro* release studies. The release of the drug from films was dependent on the nature and proportion of the polymer. *In-vitro* release studies were carried out using USP Type II dissolution apparatus in phosphate buffer of pH 6.8.

In Vitro Release Studies for Buccal Film Formulations of Felodipine

The percentage release of drug from all formulation F1 to F8 is as follows: 91.65, 98.33, 99.12, 99.82, 96.63, 92.32, 95.15 and 88.47 at the end of 180mins respectively. About 88-100 % of drug release was observed from all formulation at the end of 180mins from all the formulation F1-F8 respectively (Table 6). Among various formulations F8 has released minimum amount of drug and F4 has released maximum amount of drug within 180mins. The order of retardation time for different films was as follows F8 > F1 > F6 > F7 > F5 > F2 > F3 > F4. Hence among 8 formulations F8 has shown slow release and F4 has shown fast release. The cumulative % drug profile was plotted and shows the drug release of 8 formulations (Figure 4).

Table 6: In Vitro Release Studies for Felodipine Buccal films

S. No	Time	Cumulative % Drug Release							
		F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	5	28	31	34	32	27	33	29	23
3	10	49.5	54	55	53	45	56	51	39
4	20	59	59	62	62	56	61	55	46
5	30	66	68	72	70	69	69.1	60.6	51
6	40	71.6	75	78	77	76	72	65.5	56
7	50	75	78	83	80	78	77	71	63
8	60	78	83	89	88	84	83	74	68
9	90	82	90	91	93	91	87	79	75
10	120	86	93	94	95	93	89	84	79
11	150	89	96	97	96	95	91	91	86.3
12	180	91	98	99	99.82	96	92	95	88

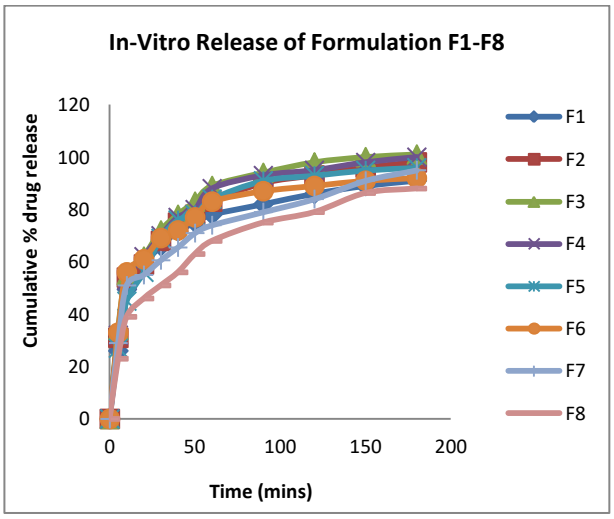

Figure 4: Cumulative % Drug Release Profile of Formulation F1-F8

Kinetics of Drug Release

To understand the order and mechanism of drug release from buccal films the data was subjected to various kinetic equations and plotted according to zero order and first order equations. The kinetic values obtained from different plots are listed in Table 7. The data was subjected to first order kinetics by plotting Cumulative % drug remained vs. time in min. Fairly linear plots were obtained for all formulation (F1 to F8) with regression value between 0.8975 to 0.9808 indicated that the rate of drug release was followed first order kinetics. (Table 7) Further the data was fitted with zero order equation and showed linear plots with their high regression co-efficient values 0.56942 to 0.9203 (Table 7).

Table 7: Kinetics of Drug Release of Formulations

Code	Zero Order R^2	First Order R^2	Best Fit
F1	0.6014	0.8975	First Order
F2	0.5694	0.9751	First Order
F3	0.612	0.9845	First Order
F4	0.616	0.9808	First order
F5	0.9203	0.9389	First Order
F6	0.6448	0.9219	First Order
F7	0.6812	0.9536	First Order
F8	0.7539	0.9521	First Order

Ex-vivo Permeation Studies

The ex-vivo drug release studies were done to understand the permeation of drug through buccal mucosa. The results were shown in Table 8. The ex-vivo studies were done for optimized formulation F8. F8 releases 85% of loaded drug which can be used for prolonged release.

Table 8: *Ex- vivo* release studies of formulation F8

S.No	Time (mins)	Cumulative % Release of F8
1	0	0
2	5	16
3	10	26
4	20	47
5	30	49
6	40	55
7	50	62
8	60	68
9	90	73
10	120	79

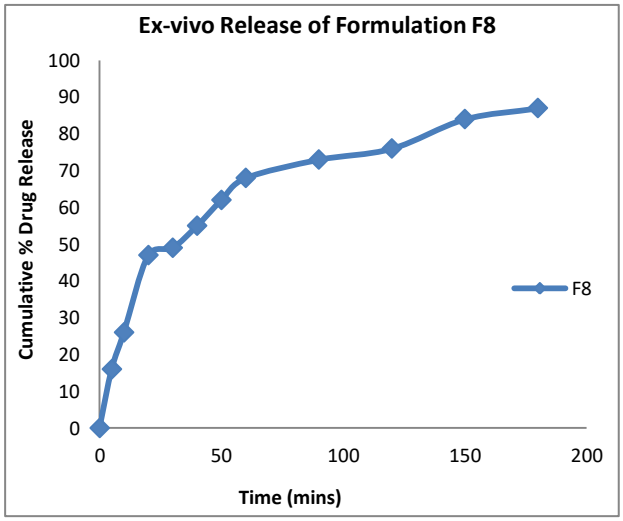

Figure 5: *Ex- vivo* release studies of formulation F8

CONCLUSION

Among the various routes of administration for novel drug delivery systems, buccal route of drug administration may be promising approach to overcome the problems such as hepatic first pass metabolism, reduction of bioavailability, frequent dosing. The selected drug Felodipine is widely used to treatment of hypertension. Secondly it undergoes first pass metabolism thus bioavailability is reduced to 18% only. Buccal films of Felodipine using polymers like HPMC E15, L-HPC, Starch, Methocel E4 and PEG400 in various proportions and combinations showed satisfactory physicochemical and drug release characteristics. The proportional amounts of various hydrophilic polymers in various formulations have influence on drug release. Results of buccal films show minimum 28% of drug release in loaded dose of 5mg and the drug release is prolonged to 3hrs. Hence, buccal films of Felodipine can be proved to be the best alternative to conventional formulations.

Acknowledgement: The authors are very much thankful to Management of KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada for their support and constant encouragement.

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Source of Support: Nil, **Conflict of Interest:** None.