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Research Article

DESIGN AND DEVELOPMENT OF FELODIPINE BUCCAL MUCOADHESIVE PATCHES

UPENDRA KULKARNI,* SIDDARTH S. DESAI

RMES's college of Pharmacy, Gulbarga, Karnataka

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ABSTRACT

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration. The mucosa has a rich blood supply and provides rapid absorption for drugs. Felodipine is a calcium channel blocker. Because of poor bioavailability of Felodipine by oral route, there is need to increase its bioavailability by formulating into a buccal dosage form. A number of buccal mucoadhesive patches of felodipine were prepared by casting method using polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (PVA) as polymer. Glycerin and propylene glycol were used as plasticizers, while the solvent was water. The films were evaluated on the basis of their release characteristic, percentage swelling and drug content uniformity . Stability study revealed that the percent drug content decreased in various patches was ranging from 1.15 to 1.90.

Key words: Felodipine, PVP, PVA, Buccal Patch, *In-vitro* release.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming the disadvantage associated with the later mode of dosing. Problems like first pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering drug via buccal route.[1] Moreover, the oral cavity is easily accessible for self medication and can be promptly terminated in case of toxicity just by removing the dosage form from buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally via this route.[2-5]

The most important goal in mucoadhesion consists of drug targeting, controlled and sustained releasing, increasing of residence time and bioavailability and decrease of adverse effect.[6-9]

Felodipine is a dihydropyridine derivative, that is chemically described as ethyl methyl 1-4-(2,3,dichlorophenyl)1-4-dihydro-2,6-dimethyl pyridine-3,5-dicarboxylate. Felodipine is almost completely absorbed from the gastrointestinal tract after oral doses but undergoes extensive first pass metabolism, with a bioavailability of about 15%. It is extensively metabolized in the gut and the liver and is excreted almost entirely as metabolites, about 70% of a dose being excreted in urine and remainder in faeces.[10-13].

In order to overcome such first pass metabolism and poor bioavailability, the drug is selected as suitable candidate for bio adhesive buccal drug delivery.

The aim of the present research investigation was to develop a new bioadhesive patches for buccal drug delivery of felodipine by using mucoadhesive polymer like PVP and PVA.

MATERIAL AND METHODS

Felodipine is a gift sample from CIPLA LTD, Bangalore, (India). PVP, PVA, glycerin, propylene glycol and sodium lauryl sulphate (SLS) were procured from S.D. Fine chemicals, Mumbai (India). And all other chemicals and regents used were of analytical grade.

Preparation of buccal mucoadhesive patches

In this study total 6 patches of different composition of polymers were prepared by casting method. Exactly 600mg of PVA was weighed and dissolved in 6 ml of water. The beaker-containing polymer was kept on magnetic stirrer for 15 minutes for formation of polymer solution at suitable temperature. 10 mg of felodipine was weighed and added to the polymer solution, and stirred the dispersion. Then one drop (0.0294 g) of glycerin was added and mixed thoroughly. The glass mould of size 5 x 3 cm^2 was placed over a flat surface. The whole solution was poured into the glass mould. The mould was kept in hot air oven for 12 hours for drying. Then the film was removed from the mould and preserved in butter paper and kept in desiccator. (F1) Similarly film F4 was prepared by adding 1drop of propylene glycol as plasticizer. Formulation F2 and F3 were prepared by adding 1% and 5% PVP using glycerin as plasticizer. F5 and F6 were prepared by using same procedure but propylene glycol was used ad plasticizer.

Evaluation of buccal patches

Physical Characteristics Study

Swelling studies of the films[14]

a) Weight increase due to swelling: A drug-loaded patch of 1 x 1 cm^2 was weighed on a pre weighed cover slip. It was kept into a petri dish and 50 ml of phosphate buffer, pH 6.5 containing 0.1% SLS was added. After every 10 min, the slip was removed and weighed upto 60 min. the difference between the initial and final weight gives the weight increase due to absorption of water and swelling of patch.

Drug content uniformity of patches

The patches were tested for the content uniformity. A patch of size 1 × 1 cm^2 was cut and placed in a 100 ml volumetric flask (A grade) and 100 ml pH 6.5 phosphate buffer containing 0.1% SLS solution was added. The contents were kept for 24 hours to dissolve the film completely. After making proper dilution to the above solution, the absorbance of the solution was measured against the corresponding blank solution at 362 nm in UV visible spectrophotometer.

In-vitro release studies of felodipine patches

A patch of 1 x 1 cm^2 size was cut and attached to a glass slide with a few drops of phosphate buffer (pH 6.5) containing 0.1% SLS. This slide was kept at an angle of 45^o in a 250 ml beaker containing 100 ml of phosphate buffer (pH 6.5) solution containing 0.1% SLS. The beaker was kept in circulating water bath in which the temperature was maintained at 37 $\pm$ 2^0 c. A non-agitated system was selected to eliminate any effect of turbulence on the release rate. Samples were withdrawn periodically after removing the slide from the beaker. The solution was stirred with a glass rod and 5 ml of sample was withdrawn using a graduated pipette, whose tip was attached to a tube with glass wool (as a filter). The slide was quickly reintroduced into the beaker. 5 ml of the buffer was replaced immediately and the beaker was kept covered with a petri dish to prevent evaporation of the fluid. The samples were taken after every 15 min up to 90 minutes and analyzed for drug content at 362 nm. The release studies were conducted for three times and average was determined.[15]

Ageing: Optimized medicated patches were subjected to stability testing. Patches were placed in a glass beaker lined with aluminium foil and kept in a humidity chamber maintained at 40 $\pm$ 2^oC and 75 $\pm$ 5% RH for 30 days. Changes in the appearance and drug content of

the stored patches were investigated after storage. The data presented were the mean of three determinations.

FT-IR analysis

The IR spectrum of the pure drug felodipine used in the present study shows characteristic absorption bands in the following IR region (Figure 1 to 6).

IR (KBR) cm^{-1}

3370(NH Stretching)
3069(Aromatic CH stretching)
2840, 2948(Ch stretching of CH_2 and CH_3 Groups)
1700, 1688 (C=O stretching)
1644 (NH Bending)
1621, 1495, 1460 (C = C ring stretching)
1099 (C O C stretching)
727, 801 (Substituted benzene ring)
564 (Cl stretching)

The polymer PVP used in present study shows the characteristic absorption bands in the following IR region

Broad peak at 3424 to 3481 may be due to the hydrogen bonded OH groups. 2895 to 2955 CH stretching. 1290 CH bending.

The polymer PVA used in the present study shows the characteristic absorption bands in the following IR region.

The broad peak at 3447(OH Hydrogen bonded), the peaks at 2694, 2740, 2884, 2948(CH stretching), 1342(CH bending) and 963(C-O).

The IR spectrum of felodipine with PVP shows the characteristic absorption bands in the following IR region.

It is quite interesting to note that, the spectrum contains very broad peaks in the range 3200 to 3500 and a very sharp peak almost merged with the broad peak at 3370 indicating the presence of OH of PVP and NH of Felodipine. Further it has the aromatic CH peak from 3050 and CH stretching of PVP in the range 2836 to 2978.The spectrum shows the presence of carbonyl group of drug at 1700 and 1688, NH bending 1643 and C=C ring stretching at 1617, 1496 and 1443.Since all the major peaks of the pure drug and PVP are present without any change in their positions in the spectrum of felodipine with PVP mixture. It may be concluded that the drug and polymer have retained their identity without losing their properties and not going in to a chemical interaction with each other. Thus the conclusion from the IR spectra of the drug and formulation is that there is no interaction between drug and polymer. Similarly the IR spectra of Felodipine with PVA reveal that the pure drug Felodipine has not gone into the interaction with PVA.

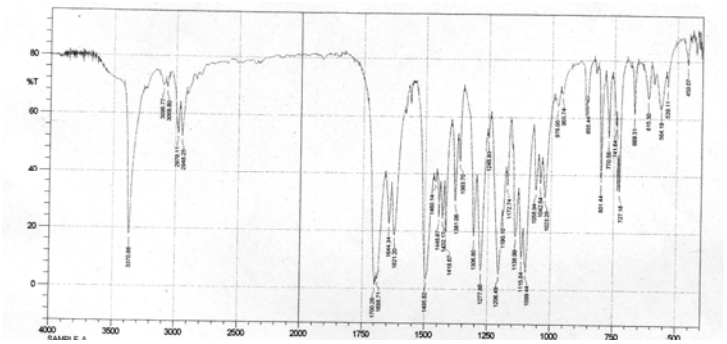

Fig. 1: FTIR spectrum of Felodipine

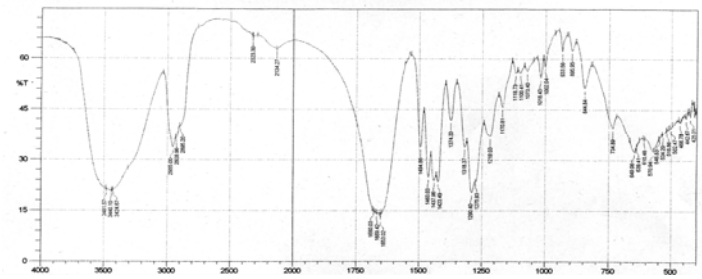

Fig. 2: FTIR spectrum of PVP

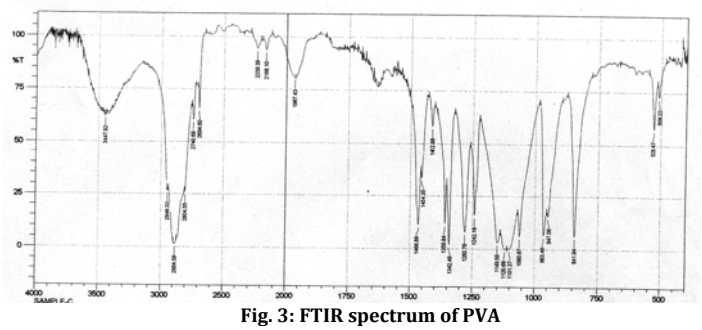

Fig. 3: FTIR spectrum of PVA

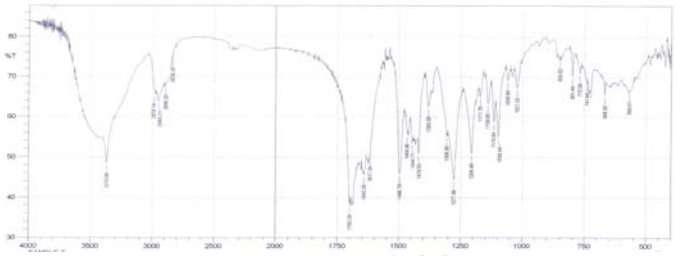

Fig. 4: FTIR spectrum of Felodipine + PVP

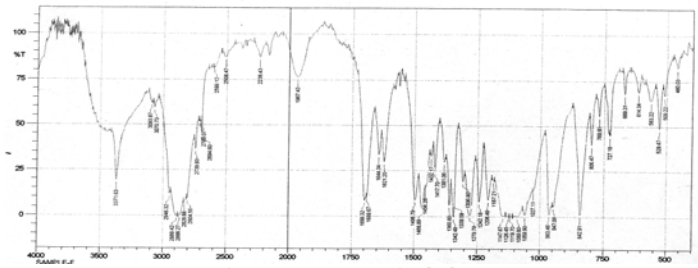

Fig. 5: FTIR spectrum of Felodipine + PVA

RESULTS AND DISCUSSION

Physical characteristics of patches

The patches were translucent, having good strength, and visually smooth surfaced. The drug and polymer distribution was uniform.

Swelling studies of the patches: The swelling of the drug loaded patches of size 1 x 1 cm^2 was studied up to 60 minutes in case of change in weight and 90 minutes in case of change in area. The swelling of the patches were observed in phosphate buffer solution (pH 6.6) containing 0.1% SLS. The data for increase in weight due to swelling are given in Tables 3 to 8 for patches F1 to F6, respectively. Swelling was more pronounced in patch F2 and F5, which contains PVP in small concentration along with PVA. Patches F1 and F4 showed less swelling (weight basis), may be due to the absence of PVP.

Table 1: Swelling studies Felodipine patches-change in weight

Formulations	Time (min)	Patch weight, F1 (mg) AM ± SD	Increase in weight (mg) AM ± SD	Percent increase in weight AM ± SD
	0	35.667 ± 0.5774	00.000 ± 0.000	0.000 ± 0.0000
	10	58.333 ± 0.5774	22.666 ± 0.577	63.551 ± 2.3179
	20	67.333 ± 1.5275	31.666 ± 2.081	88.785 ± 7.3043
F1	30	79.667 ± 1.1547	44.000 ± 1.000	123.36 ± 3.4323
	40	84.667 ± 1.1547	49.000 ± 1.000	137.38 ± 3.5717
	50	94.667 ± 1.1547	59.000 ± 1.000	165.42 ± 3.7860
	60	100.00 ± 1.0000	64.333 ± 1.5275	180.37 ± 7.1694
	0	39.333 ± 0.5774	00.000 ± 0.0000	00.000 ± 0.000
	10	63.667 ± 1.5275	24.333 ± 1.1547	61.864 ± 2.623
	20	76.000 ± 1.7321	36.666 ± 2.0816	93.220 ± 6.305
F2	30	85.667 ± 1.5275	46.333 ± 2.0816	117.79 ± 6.929
	40	98.333 ± 0.5774	59.000 ± 0.0000	150.00 ± 2.183
	50	111.67 ± 2.5166	72.333 ± 2.5166	183.89 ± 7.258
	60	121.00 ± 3.000	81.667 ± 3.0550	207.62 ± 8.900
	0	52.70 + 0.580	0.000 + 0.000	00.000 + 0.000
	10	75.30 + 3.060	22.67 + 3.215	43.038 + 6.263
	20	92.30 + 1.530	39.67 + 2.082	75.316 + 4.786
F3	30	116.3 + 2.080	63.67 + 1.528	120.88 + 1.708
	40	134.0 + 2.642	81.33 + 2.082	154.43 + 2.354
	50	146.3 + 1.526	93.67 + 1.155	177.84 + 2.073
	60	156.7 + 1.527	104.0 + 1.000	197.46 + 1.079
	0	36.30 + 0.5774	0.00 + 0.000	00.000 + 0.000
	10	57.30 + 1.5275	21.0 + 1.000	57.798 + 1.999
	20	67.70 + 0.5774	31.3 + 1.547	86.238 + 3.998
F4	30	79.67 + 4.5092	43.3 + 4.041	119.26 + 9.374
	40	82.33 + 3.2146	46.0 + 3.605	126.605 + 11.802
	50	93.70 + 4.5092	57.3 + 4.041	157.79 + 11.553
	60	103.3 + 1.1547	67.0 + 1.000	184.40 + 1.447
	0	39.33 + 0.577	0.000 + 0.000	00.00 + 0.000
	10	61.00 + 1.732	21.66 + 1.527	55.08 + 3.846
	20	72.00 + 1.000	32.67 + 1.527	83.050 + 5.0149
F5	30	83.66 + 1.527	44.33 + 1.527	112.71 + 4.5169
	40	96.00 + 1.000	56.66 + 0.577	144.06 + 1.875
	50	108.7 + 3.511	69.33 + 3.055	176.67 + 6.0749
	60	119.3 + 1.527	80.00 + 1.000	203.38 + 1.499
	0	52.67 ± 0.577	0.000 ±0.000	00.00 ± 0.0000
	10	76.00 ± 1.000	23.33 ± 0.577	44.30 ± 0.9454
	20	93.00 ± 4.587	40.33 ± 4.163	76.58 ± 7.3391
F6	30	107.40 ± 4.3590	54.33 ± 3.786	103.16 ± 6.1065
	40	119.61 ± 1.1547	67.00 ± 1.000	127.21 ± 2.3515
	50	135.33 ± 0.5774	82.66 ± 0.577	156.96 ± 2.4706
	60	155.00± 1.000	102.33 ± 0.577	194.30 ± 1.8506

Table 2: Content uniformity of Felodipine patches

Patch code	Amount of drug present (mg)* AM+SD	% of drug present AM+SD
F1	4.5729 + 0.0115	91.45 + 0.2318
F2	4.4190 + 0.0505	88.38 + 1.0106
F3	4.5394 + 0.0231	90.78 + 0.4637
F4	4.6331 + 0.0418	92.66 + 0.8360
F5	4.4859 + 0.0200	89.71 + 0.4016

Content uniformity of Felodipine patches

The content uniformity tests are commonly employed in order to make sure about the uniform dispersion of drug in patches. The drug content was analyzed at 320nm. Corresponding blanks were used for the estimation of drug. The results were expressed as AM ± SD and reported in Table 2.

The results indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 88.38 to 92.66%.

***In–vitro* release studies**

In-vitro release studies of Felodipine patches were carried out in phosphate buffer (pH 6.6). The release data of Felodipine patch were given in Tables 3 for patches F1 to F6.

A perusal to data indicated that the release of Felodipine patch was slower in patches F1 & F4 may be due to the single polymer PVA (absence of PVP), when compared to other patches. The faster release of drug was observed when the concentration of PVP increased (F6>F3>F5>F2).

Table 3: *In-vitro* release of Felodipine patches

Formulations	Time (min)	Cumulative drug released (mg) AM+ S.D	% of drug released	% of drug remain unreleased	log% of drug remain unreleased
F1	0	0.000 + 0.0000	00.00	100.00	2.0000
	15	2.036 + 0.0803	44.0723	55.9276	1.7476
	30	2.419 + 0.0880	52.3609	47.6390	1.6779
	45	2.635 + 0.0411	57.0421	42.9579	1.6330
	60	2.856 ± 0.0187	61.8317	38.1682	1.5817
F2	0	0.000 + 0.000	00.00	100.00	2.0000
	15	1.8562 + 0.0722	40.4406	59.3823	1.7736
	30	2.3900 + 0.1679	52.0697	47.7024	1.6785
	45	2.9265 + 0.0635	63.7591	35.9617	1.5558
	60	3.2632 ± 0.1258	71.0957	28.5931	1.4562
F3	0	0.0000 + 0.000	00.00	100.00	2.0000
	15	1.7102 + 0.080	38.0908	61.8715	1.7914
	30	2.6437 + 0.051	58.8808	41.1284	1.6141
	45	2.9858 + 0.032	66.5000	33.6302	1.5267
	60	3.4055 ± 0.099	75.8484	24.2019	1.3838
F4	0	0.000 + 0.000	00.00	100.00	2.0000
	15	2.1970 + 0.2364	47.9706	52.0293	1.7162
	30	2.5074 + 0.1633	54.7476	45.2523	1.6556
	45	2.7277 + 0.1311	59.5572	40.4427	1.6068
	60	2.9731 ± 0.1482	64.9149	35.0850	1.5451
F5	0	0.0000 + 0.0000	00.00	100.00	2.0000
	15	1.9746 + 0.0122	44.0780	52.9219	1.7475
	30	2.4160 + 0.0402	53.9286	46.0713	1.6634
	45	2.8933 + 0.0142	64.5828	35.4171	1.5492
	60	3.2481 ± 0.0970	72.5029	27.4970	1.4392
F6	0	0.0000 + 0.0000	00.00	100.00	2.0000
	15	1.7418 + 0.0733	38.6218	61.2922	1.7874
	30	2.7456 + 0.0698	60.8800	38.9846	1.5908
	45	3.1396 + 0.0374	69.6156	30.2296	1.4804
	60	3.6738 ± 0.0511	81.4605	18.3584	1.2638

Ageing

All patches were placed in humidity chamber at 37 ± 2 °C and 75 ± 5 % RH for four weeks. Patches were withdrawn every week and analyzed for their drug content. The percentage of drug present in the patches was determined spectrophotometrically . Percentage decrease in drug content in all the patches were also calculated. The drug loss is less though the patches were stored for one month. Percent decrease of drug content was more in patch F2 and it was least in patch F3. Further there is a need of accelerated stability testing of these dosage forms to determine their shelf life. The patches were also observed for their appearance and texture. These properties did not change in all the patches during the period of study.

In-vitro release studies of Felodipine buccal patches showed almost all the drug was released in 90 minutes. The release of Felodipine patch followed first order. The release mechanism of Felodipine patch from buccal patches was diffusion rate limited which confirmed Higuchi's model. The films were found to be stable for one month of stability studies.

Table 4: Percentage of drug present in Felodipine patches F1 to F6

Time (weeks)	F1	F2	F3	F4	F5	F6
0	87.25	88.95	89.00	87.95	86.85	88.65
1	87.17	88.75	88.90	87.75	86.75	88.55
2	86.44	88.00	88.65	87.55	86.58	88.35
3	86.02	87.54	88.30	87.15	86.15	88.18
4	85.85	87.25	88.00	86.85	85.75	87.45

Table 5: Percentage of drug loss in Felodipine patches of F1 to F6 after one month storage.

Patch Code	% of drug decreased
F1	1.60
F2	1.91
F3	1.12
F4	1.25
F5	1.27
F6	1.35

CONCLUSION

1. Suitable analytical method based on UV spectrophotometry was developed for Felodipine patch.
2. Results of buccal absorption test were encouraging i.e. 25.54% of the administered dose (5 mg) of Felodipine patch was absorbed within 5 minutes.
3. The prepared films exhibited satisfactory characteristics regarding to integrity, flexibility, dispersion of drug and other quality control parameters. Glycerin and propylene glycol (plasticizer) were included in the formulations.
4. The in-vitro release of Felodipine patch from patches F1 to F6 were in the range of 71.68 to 97.27 in 90 minutes.

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