ORIGINAL ARTICLE

Formulation and *In Vitro*, *In Vivo* Evaluation of Mucoadhesive Buccal Tablet of Felodipine

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Abstract

Aim: This study aims to formulate and evaluate the mucoadhesive buccal tablets of felodipine (FD) by direct compression to improve the drug release and subsequently oral bioavailability. **Materials and Methods:** The pure drug FD and excipient were obtained from manufacturing industries. The powder blend formulation studies, moisture absorption study, residence time, *ex vivo* permeation, and *in vivo* drug release were studied. **Results and Discussion:** The results for powder flow properties was found to be within the limits, moisture absorption study was between 20.21% and 34.05% v/w residence time 7.45 ± 0.10 (h) *ex vivo* permeation 97.83 ± 0.52% and *in vivo* drug release was extended till 24 h and area under the curve 880.59 mg/h/l with an Tmax at 8 h. **Conclusion:** The region in which it will remain in contact were perfectly done with appropriate evaluation techniques (Residence time), the moisture absorption study was carried out to check how much moisture the tablet can absorbed to release the drug and was found satisfactory. The *ex vivo* permeation study was performed by Franz diffusion cell to check the drug permeation through buccal mucosa. The *in vivo* studies were performed on New Zealand rabbits and can be concluded that the drug release from the formulated F6 was better than the marketed application programing interface.

Key words: Buccal tablet, *Ex vivo*, Felodipine, *In vivo*, Mucoadhesive

INTRODUCTION

The oral route of drug administration is the most popular option which enables easy, and better patient compliance without difficulties. Selecting the drug candidate[1] for the oral route is very important otherwise it may lead to first-pass effect, gastrointestinal enzymatic degradation, and slow onset of action.[2] To overcome the above drawback the buccoadhesive drug delivery and sublingual drug delivery could be better alternatives. In comparison to the sublingual mucosa, buccal mucosa is less permeable and does not elicit a quick commencement of absorption; hence, it is more suitable for formulations that are designed for prolonged release action. The buccal route, which is a non-invasive administration method, can be used to target systemic distribution of orally ineffective medications.[3]

First-pass metabolism in the liver and pre-systemic clearance in the gastrointestinal tract are avoided because the buccal mucosa is adequately supplied with both vascular and lymphatic drainage.[4] Figure 1 depicts the method of buccal medication administration. Buccal drug delivery is a potential field for further investigation, with the goal of systemic distribution of orally ineffective medications as well as a realistic and appealing option for non-invasive delivery of powerful peptide and protein therapeutic molecules. Buccal drug delivery is a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules.[5] As the buccal tablets may overcome the bioavailability problems, the drug candidate felodipine (FD) was selected for this research, belongs to an antihypertensive drug of BCS II. FD absolute bioavailability is 15%, the steady state is reached after 5 days and a daily dose of 2.5–10 mg day. Due to close contact with buccal mucosathe drug penetration will be rapid, bypasses hepatic

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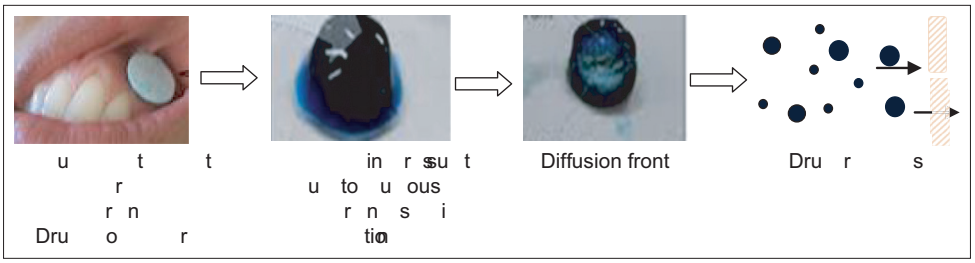

Figure 1: Mechanism of Buccal Drug Delivery

metabolism *via* cytochrome P450 3A4 and may increases bioavailability.[6] The FD has further log *P* = 4.46 and pKa of 5.07 which makes it a suitable for oral mucosal drug delivery system. Further the polymer hydroxy propyl methyl cellulose (HPMC) K4M, Carbopol 934P and sodium carboxymethyl cellulose (Na-CMC) causes the suitable surface property by wetting and strong mucosal adhesion on mucus tissues the buccal tablets were prepared.

MATERIALS AND METHODS

Drug and chemicals

FD and Aspartame were obtained as a gift sample from Dr. Reddy's laboratories Ltd. Hyderabad. India. PVP-K30, Na-CMC was purchased from Sigma-Aldrich chem., Pvt., Ltd., India. HPMC K4M, cyclodextrins, and Ethyl cellulose were procured from SD Fine Chemicals. Pvt. Ltd., Mumbai. India. Mannitol has purchased from Finar chemicals. Ltd., Mumbai, and magnesium stearate was obtained from Himedia Laboratories and all other chemicals used are of analytical grade. The animal approval for ethical committee of Vaagdevi institute of pharmaceutical science, Warangal has approved the animal work with the proposal no 1663/PO/Re/S/2012/CPCSEA.

Evaluation methods

Flow properties of blend

The flow properties of formulated FD buccal tablet were characterized by measuring

a. Angle of repose
b. Bulk density (BD)
c. Tapped density (TD)
d. Carr's compressibility index
e. Hausner's ratio.

Angle of repose[7,8]

The angle of repose is the three-dimensional angle obtained by a cone-like pile of material created by various processes (relative to the horizontal base). The technique is known as the funnel height approach. In the funnel height technique, the funnel is attached to the burette stand a graph paper was kept on a level horizontal surface and a funnel was attached with its tip at a set height (2 cm). The granules or tablet blend was gently poured through the funnel until the conical pile's peak just touched the funnel's tip. The standard limits for angle of repose are tabulated in Table 1.

$$\text{Angle of repose } (\theta) = \tan\text{-}1(h/r)$$

Where, h = height of the powder pile, r = radius of pile circle

BD[5]

A measuring cylinder is used to determine the BD. 50 mg of the blend is poured in the measuring cylinder, including the inter-particulate void volume, BD is calculated. It is expressed in g/ml.

And is given by

$$BD = M/Vo$$

Where, M = mass of the powder (weight taken in g), Vo = Void volume (Untapped Volume in ml).

TD

TD is determined by tapping the measuring cylinder until the reading does not change generally 100 taps. It is expressed in g/ml.

And is given by

$$TD = M/Vf$$

Where M = mass of the powder (weight taken in g), Vf = Tapped Volume (Final bulk volume after tapped in ml).

Compressibility index (Carr's index)[6]

This property is also known as percent compressibility, indirectly related to the flow rate, cohesiveness and particle size. Compressibility is the ability of powder to decrease in volume under pressure, is obtained from density determinations. The compressibility index of the powder was determined by Carr's compressibility index. It is simple, fast and accurate method of predicting powder flow characteristics. The standard limits are tabulated in Table 2. Compressibility Index was determined by measuring the initial volume (Vo) and final volume (Vf) after complete tapings of powder sample in a measuring cylinder.

Compressibility index (CI) =(Vo–Vf)/Vo × 100 Alternatively

Compressibility index may be calculated using measured values for BD and TD as follows.

$$\text{Compressibility index} = 100 \times \{(TD-BD)/TD\}$$

Hausner ratio[9]

Hausner's found that the ratio of TD/BD was related to inter particle friction as such, and could be used to predict powder flow properties. He showed that the powder with low inter particle friction had ratio of approximately 1.2, whereas morecohesive less free flowing powders have Hausner's ratio >1.6. Hausner's ratio <1.25 indicates good flow. The standard limits for hausner ration are tabulated in Table 3. It is the ratio of TD to the BD.

$$\text{Hausner ratio} = TD/BD$$

Moisture absorption study

Dissolve Agar (5% w/v) in hot water and transferred it into petri dishes and allowed to solidify. To eliminate moisture, six FD buccal tablets from each formulation were kept in a vacuum oven overnight before the testing.[10] They were then placed on the surface of the agar and incubated at 37 ± 2°C for 1 h. Then, the tablets were removed and weighed and the percentage of moisture absorption.

Was calculated using following formula:
% Moisture Absorption = Final weight–initial weight × 100/ initial weight

Table 1: Angle of repose values (as per USP)

Angle of repose	Nature of flow
<25	Excellent
25–30	Good
30–40	Passable
>40	Very poor

Table 2: Carr's index value (as per USP)

Carr's index	Flow character
5–15	Excellent
12–16	Good
18–21	Fair to passable
2–35	Poor
33–38	Very poor
>40	Very very poor

Table 3: Hausner ratio (as per USP)

Hausner ratio	Flow character
1.00–1.11	Excellent
1.12–1.18	Good
1.19–1.25	Fair
1.26–1.34	Passable
1.35–1.45	Poor
1.46–1.59	Very poor
>1.60	Very very poor

Residence time

For this studied a modified USP disintegration apparatus was used. The disintegration medium was 800 mL of PB (pH 6.8) maintained at 37°C. In this experiment, a glass slide was attached vertically to the apparatus and porcine buccal mucosa was tied. The hydrated tablet was using PB (pH 6.8) and for 30 s, and it was in direct touch with porcine buccal mucosa. After that, it was submerged in a disintegration medium. The time of displacement of was noted.[11,12]

Ex vivo permeation

FD *Ex vivo* permeation study of buccal tablets through; porcine buccal mucosa was performed using Franz diffusion cell- diffusion area of 4.53 cm^2 and the receptor compartment volume –16 mL at 37°C ± 0.2°C and rpm. -50. Magnetic stirrer helped to maintain the temperature and rpm.[12] We got porcine buccal mucosa from a local slaughterhouse and used it within one hour of slaughter. On collection, tissue was placed in Krebs buffer at 4°C. Surgical scissors were used to remove the epithelium from the underlying connective tissues, and the epithelium was clamped between the donor and receiver chambers of the Franz-type diffusion cell. After the buccal membrane was equilibrated for 30 min with Krebs buffer solution between both the chambers, the receiver chamber was filled with fresh PB (pH 6.8) solution. The EM buccal tablet was placed in donor chamber and wetted with 1 mL of PB (pH 6.8). By extracting 0.5 mL aliquots of the drug that had permeated through the membrane, the quantity of drug that had permeated the membrane was determined (were collected from the receiver chamber at determined time intervals and filtered through a filter paper and the medium of the same volume (0.5 mL), which was pre-warmed at 37°C, was then replaced into the receiver chamber. By measuring the absorbance of the drug at 212 nm using an ultraviolet-visible spectrophotometer, the amount of permeation was determined.[13]

In vivo drug release

In vivo studies were carried out in white New Zealand rabbits were taken with a mean weight of 1.98 ± 0.14 kg. The animals were fasted overnight and kept in individual cages before the study and the study animals were anesthetized by giving xylazine 4 mg/kg and ketamine 100 mg/kg intradermal injection upon the introduction of anesthesia, a drop of water was placed on the surface of the tablet, the tablet was applied to the oral cavity by pressing for 30 s, ensure that the tablet was placed carefully in between the check and gingiva to prevent the animal from spitting out. Blood samples of 0.5 ml

were withdrawn from the ear vein of a rabbit using a gauze needle at a regular time interval of 0.5 h, 1 h, 2 h, 4 h, 8 h, 10 h, 12 h, 16 h, 20 h and 24 h. Collected blood samples were taken in heparinized tubes and shaken well their samples were centrifuged at 3000 rpm for 15 min to separate the plasma. The clear supernatant plasma layer was collected in an Eppendorf tube and stored immediately at –20°C until analysis.[10,14]

Formulation

Solubility of FD by kneading method

Calculated amount of FD and cyclodextrins were weighed and transferred to a mortar, and done kneading for 45 min, during the process, a small volume of methanol: water (1:1) solution was added to the mixture to maintain suitable consistency. The final product was dried at 40°C for 48 h and then grounded to powder by passed through sieve No 100 and stored in a sealed glass vial. Direct compression was used to prepare FD Buccal tablets. Before direct compression, all the ingredients were screened through sieve no.100. FD was mixed manually with different ratios of HPMC K4M, Carbopol 934, Na CMC (adhesive polymer), mannitol and aspartame (Sweetening agent).

Blend was mixed with Magnesium stearate and Talc (lubricant) for 3–5 min before being compressed into tablets using a 6 mm flat-faced punch. CEMACH's 16 station rotary tablet-punching machine was used to compress the tablets. Table 4 shows the composition of the bioadhesive buccal tablet formulations of FD.

RESULTS AND DISCUSSION

Flow properties of blend

The powder flow properties such as angle of repose, BD, TD, Hausner's ratio, and Carr's index were performed using the formula to check if the power flow of our blend lies within the standard range. The results of flow properties of blend are shown in Table 5.

Moisture absorption study

The Table 6 below demonstrates how moisture absorption varies depending on the polymer ratio. F1 and F2 are less susceptible to moisture absorption without chitosan. It can be seen that the moisture absorption is also less with the F3 and F4 due to the absence of Carbopol, whereas F6 has the highest moisture absorption due to the highest polymer ratio. The graphical representation of the same is shown in Figure 2.

Residence time

From the Table 7, it can be seen that the F6 has the highest residence time it can be concluded that increase in polymer concentration the better. The graphical representation of the same is shown in Figure 3.

Ex vivo permeation

From the *ex vivo* studies using Franz diffusion cellwith porcine buccal mucosa, it can be concluded that FD buccal tablets permeation through the porcine buccal mucosa revealed that the drug was released from the formulation and permeated through the buccal membrane and hence could possibly permeate through the human buccal membrane. The results were shown in Table 8 and the graphical representation is shown in Figure 4, indicated that the drug permeation was slow and steady.

In vivo drug release

From the result of bulk flow, moisture absorbance, and residence study, it can be concluded that F6 formulation

Table 4: Composition of buccal tablets of felodipine

Properties	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
API	Felodipine	5	5	5	5	5	5	5	5
Solubility enhancer	Cyclodextrins	5	5	5	5	5	5	5	5
Mucoadhesive polymer	Carbopol 934	12.5	25	12.5	25	12.5	25	12.5	25
	HPMC K100M	37.5	18.75	18.75	37.5				
Binding agent	Na CMC					37.5	18.75	18.75	37.5
Lubricant	Mg stearate	2	2	2	2	2	2	2	2
	Talc	1	1	1	1	1	1	1	1
Sweeting agent	Mannitol	28	23	25.5	18	20.5	8	15.5	12
	Aspartame	1	1	1	1	1	1	1	1
	Total	100	100	100	100	100	100	100	100

Na-CMC: Sodium carboxymethyl cellulose, HPMC: Hydroxy propyl methyl cellulose

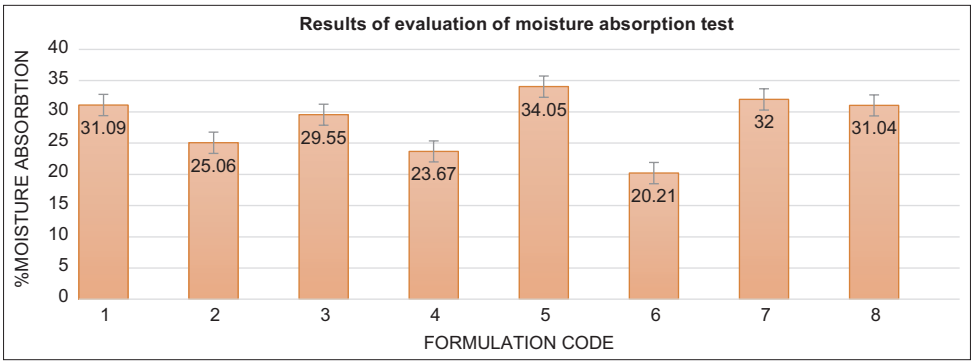

Figure 2: Graphical representation of moisture absorption study

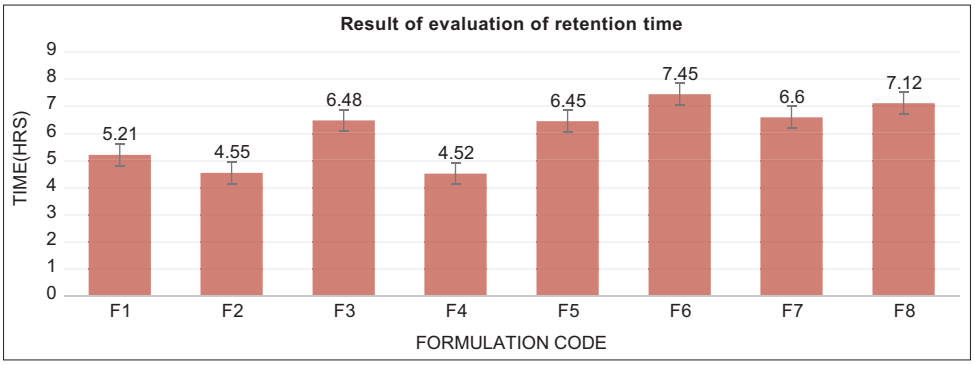

Figure 3: Graphical representation of retention time study

Table 5: Results of flow properties of blend

Formulation code	Angle of repose (θ)	Bulk density (g/cm³)	Tapped density (g/cm³)	Hausner's ratio	Carr's compressibility index (%)
F1	30°5'±0.1	0.63±0.04	0.74±0.04	1.17	17.46
F2	37°9'±0.25	0.56±0.06	0.65±0.06	1.16	16.70
F3	38°9'±0.35	0.59±0.02	0.68±0.02	1.15	15.25
F4	21°4'±0.25	0.66±0.06	0.76±0.06	1.15	13.15
F5	22°1'±0.1	0.64±0.06	0.75±0.06	1.17	14.66
F6	21°7'±0.1	0.56±0.06	0.65±0.06	1.16	16.70
F7	34°7'±0.1	0.59±0.04	0.69±0.04	1.16	14.49
F8	25°6'0.05	0.58±0.03	0.67±0.03	1.15	13.45

Table 6: Results of moisture absorption study

Formulation code	Moisture absorption (%)
F1	31.09±1.02
F2	25.06±1.36
F3	29.55±1.62
F4	23.67±1.48
F5	34.05±0.86
F6	20.21±1.31
F7	32.00±0.75
F8	31.04±1.37

Table 7: Residence time

Formulation code	Retention time
F1	5 h 21 min
F2	4 h 55 min
F3	6 h 48 min
F4	4 h 52 min
F5	6 h 45 min
F6	7h 45 min
F7	6 h 6 min
F8	7 h 12 min

gave the best result. Hence, *in vivo* studies were carried out for formulation F6 and the observed results are tabulated is Table 9. From the Figure 5, the area under the curve (AUC) of F6 was found to be 880.59 mg/h/l and tmax at 8 h, and for application programming interface AUC was found to be 450.0 mg/h/l and Tmax at 6 h.

Table 8: *Ex vivo* permeation

Time	Drug release %							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	10.27±0.26	09.29±0.22	15.17±0.20	10.77±0.30	14.17±0.20	10.34±0.10	12.17±0.20	09.17±0.20
2	23.38±0.17	18.10±0.06	20.22±0.28	27.88±0.24	26.02±0.20	22.25±0.20	25.02±0.18	20.22±0.18
3	40.04±0.28	25.03±0.12	31.21±0.12	34.65±0.34	31.11±0.11	34.52±0.11	33.01±0.09	29.01±0.09
4	46.57±0.09	33.83±0.20	40.37±0.13	50.34±0.36	44.07±0.26	46.96±0.54	39.37±0.20	34.87±0.20
5	57.11±0.05	54.09±0.15	54.33±0.14	60.71±0.68	57.23±0.10	57.98±0.67	45.23±0.11	57.23±0.10
6	70.96±0.53	62.08±0.19	68.58±0.15	63.25±0.37	69.58±0.05	68.62±0.10	60.68±0.14	66.58±0.15
7	76.28±0.11	68.46±0.20	76.94±0.26	69.54±0.24	75.24±0.16	73.84±1.04	72.20±0.12	70.24±0.16
8	78.06±0.65	72.38±0.23	86.43±0.11	75.06±0.20	81.32±0.10	88.60±0.98	78.46±0.10	76.43±0.11

Table 9: *In vivo* drug release

Time (h)	Rabbit	Rabbit
	Average	API
0.5	6.44±2.4	11±0.14
1	12.6±2.7	36.9±2.5
2	17.84±3.1	60.73±1.64
4	41.65±2.7	76.21±1.71
6	69.99±1.9	94.04±0.56
8	97.99±1.8	69.37±0.17
10	83.92±2.4	38±1.44
12	62.90±2.5	6.7±1.76
16	41.08±2.4	0
20	30.20±2.6	0
24	6.37±1.8	0

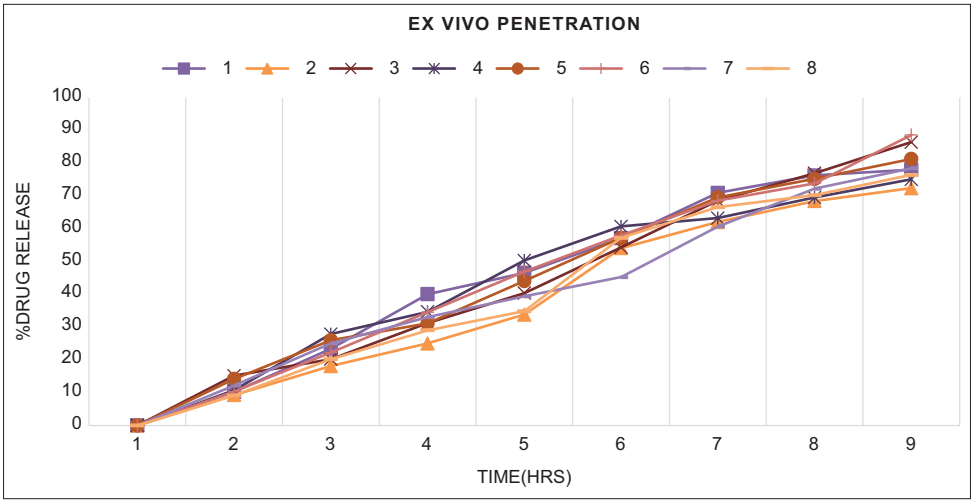

Figure 4: Graphical representation of *ex vivo* permeation

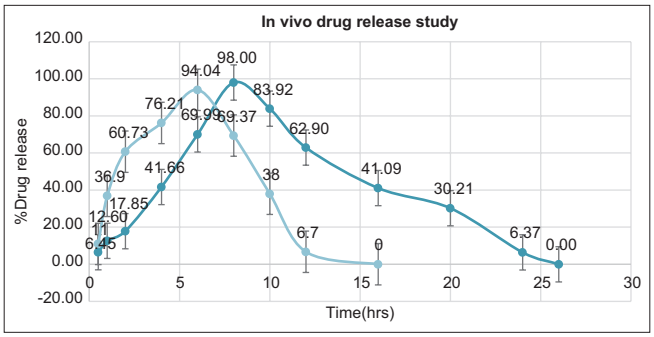

Figure 5: Graphical representation of *in vivo* drug release

CONCLUSION

In the novel drug delivery system, buccal tablets produced a sizable account in many variables. The present research consolidated the information impairs the process of constructing concrete association between these parameters with appropriate polymer selection. The results of all the physical characterization of all formulations (F1-F8) were found to be satisfactory. The results of the study show that therapeutic levels of enalapril can be delivered through buccal cavity. It is concluded form the powder flow property, residential time, *ex vivo* permeation, and *in vivo* drug release that the formulation F6 is the most promising ratio of polymers that has been used.

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