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Research Article

Formulation And *Invitro, In Vivo* Evaluation Of Mucoadhesive Buccal Tablet Of Enalapril Maleate

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Abstract: The buccal area of the mouth mucosal cavity provides an adorable route of administration for systemic and local medication distribution. Among the several transmucosal locations accessible, the mucosa of the buccal cavity was determined to be the most convenient and easily approachable site for the administration of therapeutic drugs as retentive dose forms delivery. The objective of the current research is based on to improve the bioavailability and efficacy of the Enalapril maleate (EM) a commonly used antihypertensive drug through buccal mucosal. The pure drug EM and excipient polymers such as, hydroxypropyl methylcellulose (HPMC K100), Carbopol 934p, Chitosan and polyvinyl pyrrolidone (PVP K30) were obtained from manufacturing industries. EM buccal tablets were prepared using direct compression. The powder blend formulation studies such as Bulk density, tapped density, Hausner ratio, Carr's index and angle of repose were carried out, moisture absorption study was performed by using 5%W/V agar, residence time was carried out using porcine buccal mucosa, *ex vivo* permeation was performed using Franz diffusion cell and *in vivo* drug release for API and formulated tablets were studies using rabbits. The result of our study showed that the powder flow properties were found to be within the limits, moisture absorption study was 67.63%, residence time till 8.15 hrs, *ex vivo* permeation 99.12% and *in vivo* drug release was extended till 24 hrs. The bioregion 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 API.

Key words: Enalapril maleate, buccal delivery system, BSC class III, hypertension, polymers

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1. INTRODUCTION

Drug delivery system (DDS) is a tool that permits the introduction of a drug substance within the body and progresses its efficacy and safety by regulating its rate, time, and site of drug release within the body.[1] DDS embraces the administration of the active/inactive therapeutic product, which releases the active moiety of the product, by the successive transport across the biological membranes to the target site of action.[2] There are various routes of delivering the drug into the systemic circulation such as, ocular, nasal, oral, buccal, sublingual, pulmonary, transdermal, and vaginal/anal[3]. However, the oral cavity has been cited as one of the best sites for the delivery of drugs, either mucosal or transmucosal can be achieved through this route. The oral mucosal surface, usually being rich in blood supply, enhances drug bioavailability, thereby enabling rapid drug transport into the systemic circulation.[4] Hence, it is an alternate route of delivery of drugs over both injectables and enteral methods. A Schematic diagram of how the drug absorption takes place via buccal route is shown in figure 1. Mucoadhesive delivery systems (MDDS) is a concept from the early 1980, it has gained considerable interest in pharmaceutical technology. The delivery of drugs through buccal mucosa (inside of the cheeks) of the oral cavity between upper gingiva (gums) is called buccal drug delivery system (BDDS). The mucosa of the oral cavity consists of (1) mucus layer, (2) epithelium, (3) connective tissue and (4) smooth muscle layer. The mechanisms involved in BDDS are drug adhering to the mucous membrane, swelling and diffusion. BDDS targets to treat local & systemic conditions. BDDS give an extended time of contact at the attached site, upgrade the patient compliance, improve the therapeutic performance of drug, high drug loading capacity, excellent accessibility, painless administration, avoids first pass metabolism and lay a lower financial burden when contrasted with the other dose structures.[5] There are few disadvantages of BDDS such as; if the BDDS adhere too firmly to the mucosa membrane it required much force to extract the formulation after use, which could cause mucosa injury and few patient suffer unpleasant feeling. The aim of the study is to formulate, and evaluate the mucoadhesive buccal tablets of EM by direct compression to improve the drug release and subsequently oral bioavailability. During formulation of the buccal tablets various factors were taken into consideration such as molecular weight of the polymer, pH of the polymer, concentration of the polymer, flexibility of the polymer chain, swelling factor and stereochemistry of the polymers.[6] The objective of the study is to formulate and evaluate the formulation for its power flow properties (Bulk density, tapped density, Hausner ratio, Carr's index and angle of repose), moisture absorption study, residence time, *ex vivo* permeation and *in vivo* drug release.The buccal delivery system will help to overcome the bioavailability problems of EM belongs to an antihypertensive drug of BCS III. Its absolute bioavailability is 40%, $t_{1/2}$ in the range of 11-14 hrs and a daily dose of 2.5 to 40 mg / day. Due to close contact with buccal mucosa the drug penetration will be rapid, bypasses first pass metabolism and increases bioavailability, the EM has further log P value of 2.45 and pKa of 3 which makes it a suitable for oral mucosal drug delivery system.[5,6] Enalaprilat, the active metabolite of enalapril, inhibits ACE. Inhibition of ACE decreases levels of angiotensin II, leading to less vasoconstriction and decreased blood pressure[7].

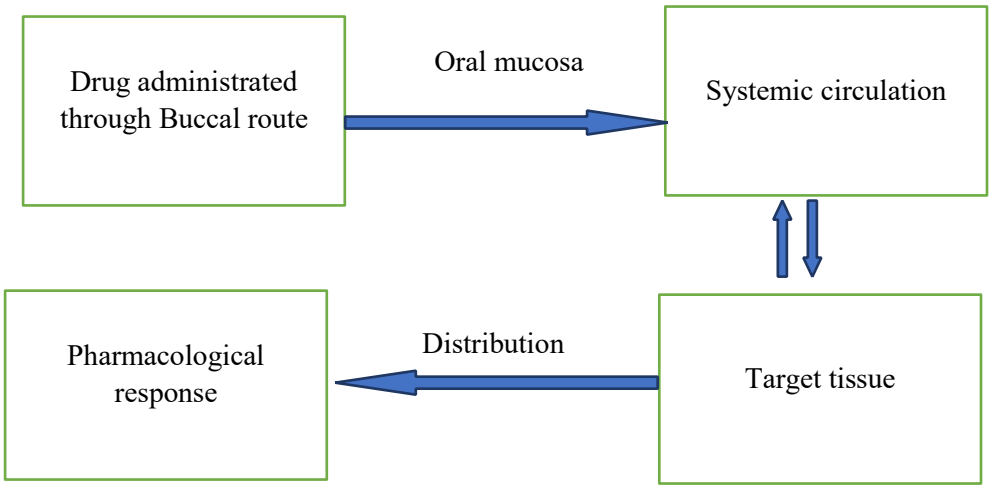

Fig 1. Schematic diagram of drug absorption via buccal route

2. MATERIALS AND METHODS

EM and Aspartame were obtained as a gift sample from Dr. Reddy's Laboratories Ltd. Hyderabad. India. PVP-K30, Chitosan are gift samples from Hetero laboratories, Hyderabad. HPMC K100M and Ethylcellulose were procured from SD Fine Chemicals. Pvt. Ltd. Mumbai. India. Mannitol has been purchased from Finar chemicals. Ltd. Mumbai and magnesium stearate was obtained from Himedia Laboratories and all other chemicals used are of analytical grade. For Ethical Committee Approval for Animals, the animal approval for the ethical committee was obtained from Vaagdevi institute of pharmaceutical science no.: 1663/PO/Re/S/2012/CPCSEA. The animal was maintained as per Helinski declaration for animal maintenance.

2. 1 Formulation of EM buccal tablets

Each tablet contains 20 mg of EM before direct compression; EM was mixed manually with Carbopol 934p, HPMC K-100M, Chitosan, PVP K-30, mannitol and aspartame were screened through sieve no 60 and mixed for 10 min. The backing layer (EC) was compressed using an 8.0mm flat faced punch on a tablet compression machine. After mixing the blend with magnesium stearate for 3-5 min, the tablets were compressed using 8mm flat-faced punches, with a sixteen station CEMACH rotary tablet-punching machine.

Composition of the prepared mucoadhesive buccal tablet formulations of EM were given in table 1.

Table 1 Composition of buccal tablets of Enalapril Maleate

Properties	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
API	Enalapril maleate	20	20	20	20	20	20	20	20
mucoadhesive polymer	Carbopol 934	5	10			5	10	10	5
	HPMC K100M	20	20	20	20	20	20	20	20
	Chitosan	---	---	7.5	15	7.5	15	7.5	15
Binding agent	PVP K-30	30	30	30	30	30	30	30	30
Lubricant	Mg stearate	1	1	1	1	1	1	1	1
Sweetening agent	Mannitol	33	28	30.5	23	25.5	13	20.5	18
	Aspartame	1	1	1	1	1	1	1	1
Backing membrane	Ethyl cellulose	50	50	50	50	50	50	50	50
	Total	160	160	160	160	160	160	160	160

2. 2 Pre formulation studies of EM powder blend

Before direct compression, all the ingredients were screened through sieve no 60. EM was mixed manually with different ratios of polymers such as Carbopol 934p, HPMC K-100M and Chitosan, to this PVP K-30 (binder), mannitol (diluent) and aspartame (sweetening agent) were mixed for 10 min. The above blend was mixed with magnesium stearate (lubricant) for 3-5 min.

2. 3 Evaluation of EM powder blend before compression

2.3.1 Bulk density5

Bulk density is determined by a constant mass method using a measuring cylinder. The bulk density of powder is the ratio of the mass of an untapped powder sample to its volume, including the contribution of the inter-particulate void volume.It is expressed in gm/ml and is given by

$$\text{Bulk density} = M/Vo$$

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

2.3.2 Tapped density

Tapped density is the ratio between mass of powder blend and its volume after tapping. Tapped volume is measured by tapping the measuring cylinder till there is no change of reading. It is expressed in gm/ml and is given by

$$\text{Tapped density} = M/Vf$$

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

2.3.3 Hausner ratio

Hausner ratio is an indirect index to predict powder flow. It is calculated by the following formula.

Hausner ratio = Tapped density (ρT)/Bulk density (ρB)

2.3.4 Compressibility index (Carr's index)

Compressibility index (Carr's index) is an indirect parameter to assume flow property of powder. Compressibility index determined by measuring the initial volume (Vo) and final volume (Vf) after complete tapings of powder sample in a measuring cylinder.

$$\text{Compressibility index (CI)} = (Vo - Vf)/Vo \times 100$$

2. 4 Angle of repose[6]

The angle of repose is the three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by different methods. The method is the fixed height method. In the fixed funnel, the method employs a funnel that was secured with its tip at a given height (2 cm), above the graph paper that was placed on a flat horizontal surface. Granules or tablet blends were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. The angle of repose is calculating using formula.

$$\theta = \tan^{-1}(h/r)$$

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

2. 5 Evaluation of EM buccal tablets

2. 6 Moisture absorption study[7]:

Agar (5% w/v) was dissolved in hot water and was transferred into a petri dish and allowed to solidify. Six EM buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture. They were then placed on the surface of the agar and incubated at 37 ± 2 °C for one hr. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

% Moisture Absorption = Final weight – Initial weight x 100/ Initial Weight

2. 7 Residence time[8]:

The residence time was tested using a modified USP disintegration apparatus. The disintegration medium was 800 mL of PB (pH 6.8) maintained at 37 °C. The porcine buccal mucosa was tied to the surface of a glass slide vertically attached to the apparatus. The tablet was hydrated using PB (pH 6.8) and was placed in intimate contact with the porcine buccal mucosa for 30 sec. It was then immersed in the disintegration medium, time of displacement of the tablet from the mucosal surface was noted.

2. 8 *Ex vivo* permeation[9]

Ex vivo permeation study of EM buccal tablets through the porcine buccal mucosa obtained from local slaughter house was performed using Franz diffusion cell with a diffusion area of 4.53 cm^2 and the receptor compartment volume of 16 mL at 37 °C ± 0.2 °C and 50 rpm. This temperature and rpm were maintained by using a magnetic stirrer. The tissue was placed in Krebs buffer at 4°C until experiments started. The EM buccal tablet was placed in the donor chamber and wetted with 1 mL of PB (pH 6.8). The amount of drug permeated through the membrane was determined by removing aliquots (0.5 mL) from the receiver chamber at predetermined 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 a UV-visible spectrophotometer, the amount of permeation was determined.

2. 9 In vivo drug release[10]

In vivo studies were carried out in white New Zealand rabbits in individual cages before the study and were anesthetized by xylazine 4 mg/kg and ketamine 100 mg/kg intradermal injection upon the introduction of anaesthesia, a drop of water was placed on the surface of the tablet, the tablet was applied to the oral cavity by pressing for 30 sec. Blood samples of 0.5 ml were withdrawn in regular time interval of 0.5 hr, 1 hr, 2 hr, 4 hr, 8 hr, 10 hr, 12 hr, 16 hr, 20 hr and 24 hr was obtained after centrifuged at 4500 rpm for 15 min and the analysis were carried out. A set of 4 rabbits were induced with formulated drugs and 1 rabbit was induced with API.

3. STATISTICAL ANALYSIS:

The statistical analysis was performed using Microsoft excel software 2010. The average of the four rabbits was calculated using the formula , Avg±∑N=4. The AUC (Area Under the Curve was calculated using the formula , Area=$(Y_1+Y_O/2)(X_1-X_O)$.

4. RESULTS AND DISCUSSION:

4.1 Flow properties of blend

The table 2 below shows the result of powder flow properties such as bulk density, tapped density, Hausner's ratio Carr's index and angle of repose which were performed using the formula to check the were the powder flow of the blend lies within the standard range. The limits of repose angle (°) are good (25-30), excellent (31-35), fair (36-40), passable (41-45), poor (46-55), very poor (56-65) and very very poor > 66. The flow property of the prepared blend was 21.7.±0.1 and was good.

Table 2. Results of flow properties of blend

Formulation Code	Angle of repose(θ)	Bulk density(g/cm^3)	Tapped density(g/cm^3)	Hausner's ratio	Carr's compressibility index (%)
F1	25.6±0.05	0.58±0.01	0.67 ±0.01	1.15	13.45
F2	37.9±0.25	0.66±0.06	0.76 ±0.06	1.15	13.15
F3	22.1±0.1	0.69±0.02	0.76 ±0.02	1.10	10.00
F4	21.4±0.25	0.64±0.06	0.75 ±0.06	1.17	14.66
F5	30.5±0.1	0.59±0.04	0.69 ±0.04	1.16	14.49
F6	21.7.±0.1	0.59± 0.04	0.69 ± 0.04	1.16	14.49
F7	38.9±0.35	0.66±0.02	0.75 ±0.02	1.13	1200
F8	34.7'±0.1	0.58±0.03	0.67 ±0.03	1.15	13.45

4.2 Moisture absorption study and Residence time

Based on the moisture absorption studies for the buccal tablet, one can determine the integrity after absorbing moisture[7]. The table 3 and 4 below shows the moisture absorption and retention time which varies depending on the polymer ratio. F1 and F2 are less susceptible to moisture absorption without Chitosan, and can be seen that the moisture absorption and retention time is also less with the F3 and F4 due to the absence of Carbopol,

whereas F6 has the highest moisture absorption and retention time due to the highest polymer ratio. Retention time helps one to understand how much min the drug can stay in contact with the buccal cavity.

Table 3. Results of moisture absorption study & retention time

Formulation Code	Moisture absorption (%)	Retention time (Min)
F1	12.09±1.22	5 hrs 41 min
F2	16.72± 1.57	5 hrs 55 min
F3	11.06±1.36	5 hrs 38 min
F4	13.00±1.36	5 hrs 52 min
F5	54.87±0.24	6 hrs 55 min
F6	**67.63**±1.22	**8 hrs 15 min**
F7	53.76±0.23	6 hrs 20 min
F8	60.57±1.25	7 hrs 50 min

± *SD*

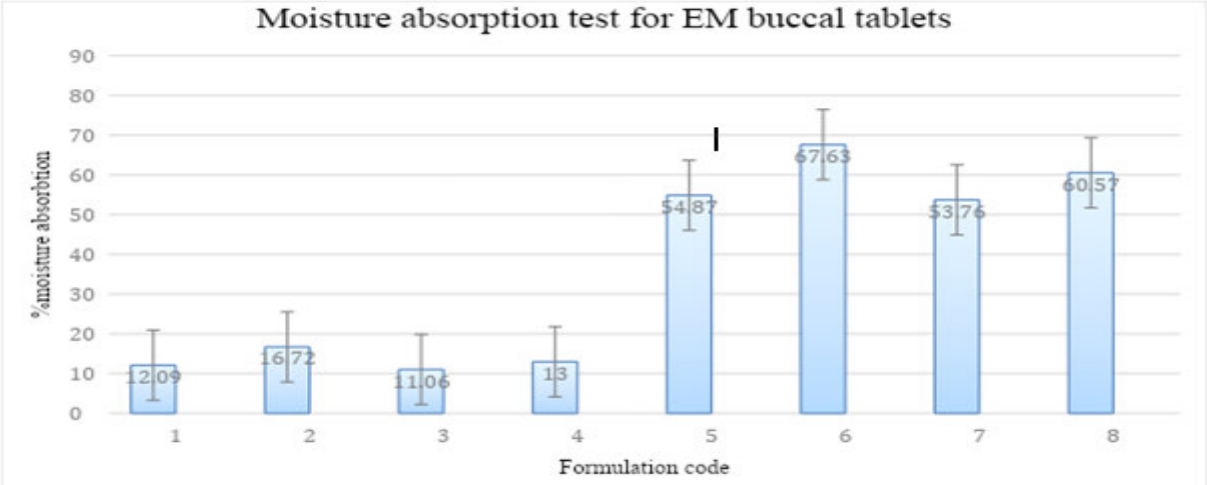

Fig 2. Graphical representation of moisture absorption

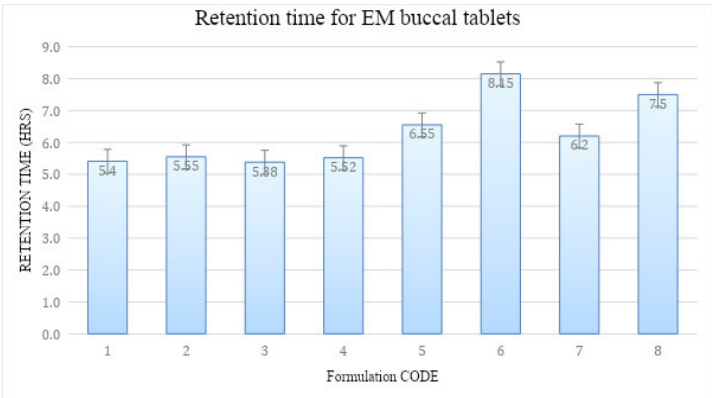

Fig 3. Graphical representation of retention time

4.3 Ex vivo permeation study:

The ex vivo permeation study shows the feasibility of this route of administration for a drug candidate. Porcine buccal mucosa has been extensively used as an *ex vivo* model to study the permeability in the buccal route by using the Franz diffusion cell. A mucosal tissue thickness of about 500 µm is recommended for *in vitro* transbuccal permeation studies since the epithelium remained the major permeability barrier for all diffusants at this thickness. The *ex vivo* permeation study using Franz diffusion cell showed that the EM buccal tablets were 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 4 and figure 4, indicating that the drug permeation was slow and steady.

Table 4. Results of ex vivo permeation study

Time	Drug release %							
	F1	F2	F3	F4	F5	F6	F7	F8
1	09.17±0.20	09.29±0.22	10.27±0.26	10.77±0.30	12.17±0.20	15.58±0.10	14.17±0.20	15.17±0.20
2	20.22±0.18	18.10±0.06	23.38±0.17	27.88±0.24	25.02±0.18	30.93±0.24	26.02±0.20	20.22±0.28
3	29.01±0.09	25.03±0.12	40.04±0.28	34.65±0.34	33.01±0.09	46.81±0.25	31.11±0.11	31.21±0.12
4	34.87±0.20	33.83±0.20	46.57±0.09	50.34±0.36	39.37±0.20	68.73±0.47	44.07±0.26	40.37±0.13
5	57.23±0.10	54.09±0.15	57.11±0.05	60.71±0.68	45.23±0.11	76.02±0.11	57.23±0.10	54.33±0.14
6	66.58±0.15	62.08±0.19	70.96±0.53	63.25±0.37	60.68±0.14	82.45±0.22	69.58±0.05	68.58±0.15
7	70.24±0.16	68.46±0.20	76.28±0.11	69.54±0.24	72.20±0.12	88.76±0.26	75.24±0.16	76.94±0.26
8	76.43±0.11	72.38±0.23	78.06±0.65	75.06±0.20	78.46±0.10	99.12±0.19	81.32±0.10	86.43±0.11

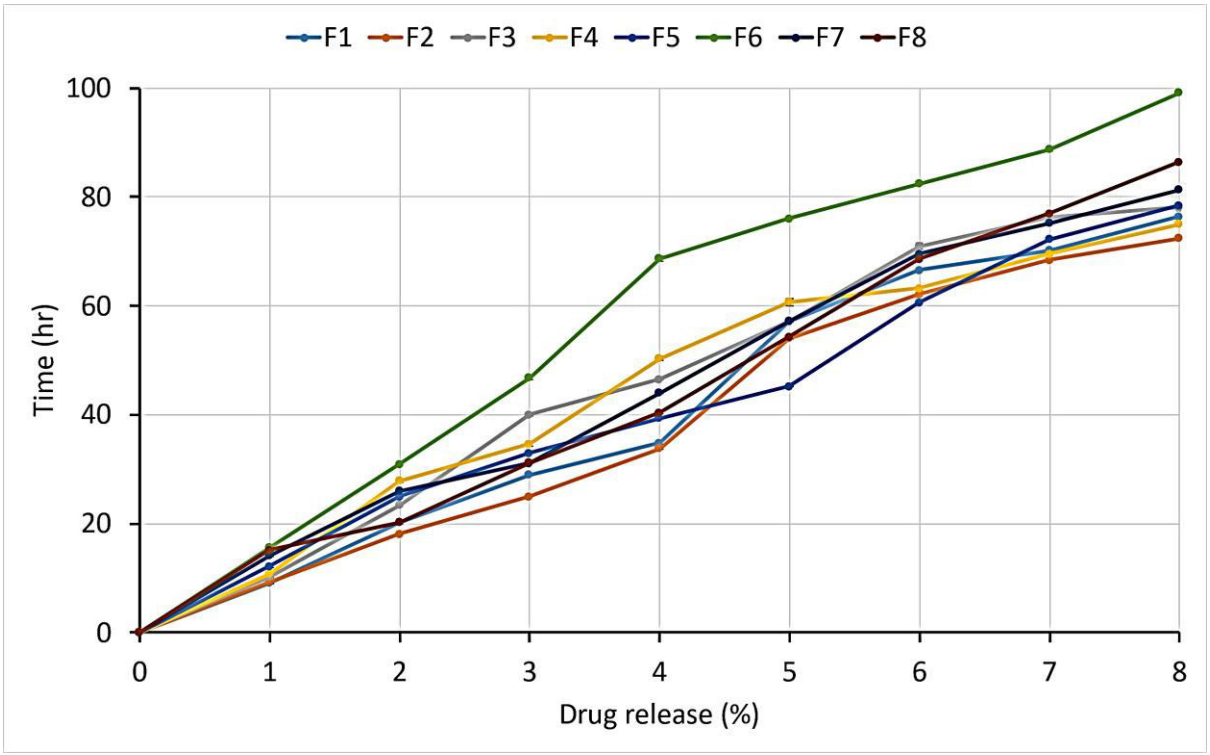

Fig 4. Results of ex vivo permeation

4.4 *In vivo* drug release

From the result of bulk flow, moisture absorbance, *ex vivo* permeation study and residence study it can be concluded that F6 formulation gave the best result. Hence *in vivo* studies were carried out for formulation F6. A set of 4 rabbits were taken and the formulated buccal tablet was placed in the buccal cavity of the rabbit and for 1 rabbit API i.e EM was placed in the buccal cavity. Through this *in vivo* study the drug release, AUC and T_{max} were also calculated. The time taken for the drug to get absorbed till elimination of the drug was noted in table 5 and, the graphical representation of the same is shown in figure 5.

Table 5. Results of in vivo drug release

Time (hrs)	Rabbit	Rabbit
	F6	API
0.5	9.0±1.04	15±1.20
1	13.90±1.50	32.4±0.23
2	25.54±3.42	56.98±1.34
4	51.05±1.58	76.21±0.14
6	99.32±0.71	98.05±0.19
8	83.92±5.08	69.37±0.86
10	64.24±3.00	28.33±0.91
12	38.33±6.81	6.7±1.54
16	27.79±1.52	0
20	6.37±1.02	0
24	0	0

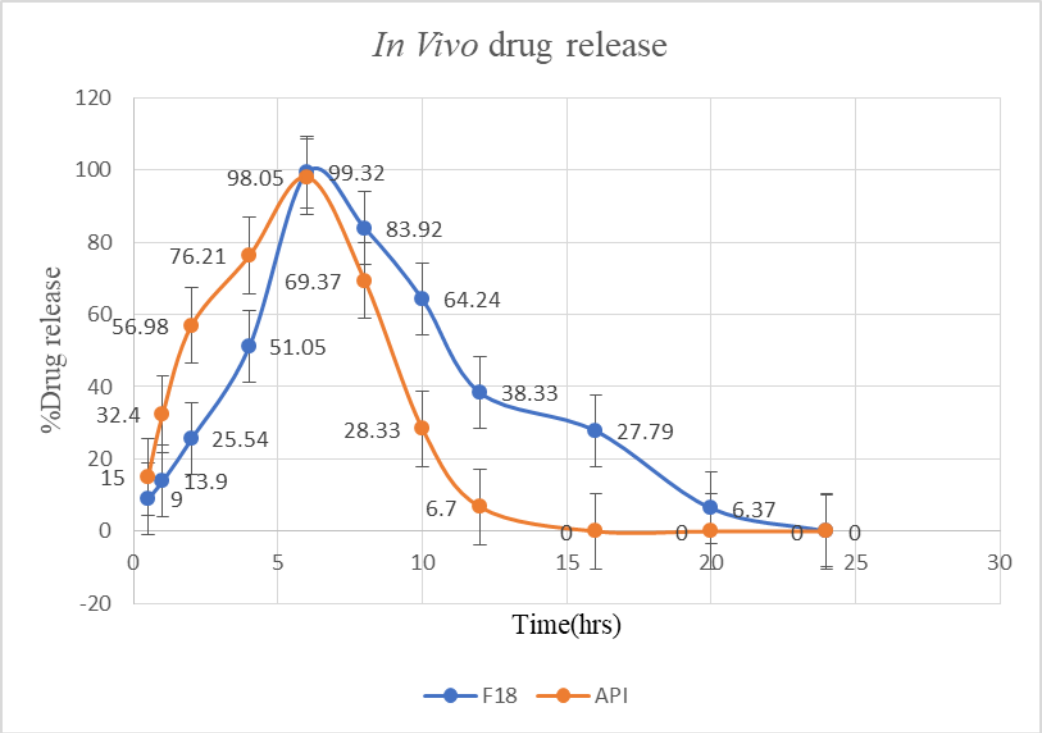

Fig 5. In vivo drug release

From the graph, the AUC of EM buccal tablet F6 was calculated and was found to be 892.66 mg.hrs/litre and T_{max} was 6hr. and for API AUC was calculated and was found to be to be 677.54 mg.hrs/litre and Tmax was 6hr.

5. CONCLUSION

In the current research, the region in which it will remain in contact was perfectly done with appropriate evaluation techniques (Residence time), the moisture absorption study was carried out to check how much moisture the tablet can absorb 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 porcine buccal mucosa and was found to have drug permeation till 8hrs and Ajay Semalty *et al,* [24] formulated Enalapril maleate film found to have permeation till 10 hrs were as the study done by Dilip kumar *et.al* [25] formulated buccal tablets showed permeation till 8hr similar to the current study. 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 API. The results of the study show that therapeutic levels of enalapril can be delivered through buccal cavity. It was concluded from 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.

6. AUTHORS CONTRIBUTION STATEMENT

Joan Vijetha R contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript and Balamurugan K contributed to discuss the methodology and to correct the manuscript.

7. ACKNOWLEDGEMENTS

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8. CONFLICT OF INTEREST

Conflict of interest declared none

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