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Formulation and Evaluation of Mucoadhesive Buccal Tablets of Pravastatin

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ABSTRACT

The present study involves the formulation and evaluation of buccal tablets of Pravastatin, an antihyperlipidemic drug which has high first pass metabolism, So buccal drug delivery has been considered an alternative to the oral dosing for compound subjected to degradation in the gastrointestinal tract or to first pass metabolism. An attempt has been made to developed mucoadhesive buccal tablets comprising of drug containing mucoadhesive layers and drug free backing layer ethyl cellulose of to release the drug for extended period of time with reduction in dosing frequency, dose related side effects and improve bioavailability of drug. Tablets of Pravastatin were prepared by direct compression using mucoadhesive polymers Carbopol 943-P HPMC K4M and Sodium CMC. Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, swelling index, surface pH, bioadhesive strength, in vitro drug release, *ex vivo* drug permeation and FTIR studies. The modified in vitro assembly was used to measure the bioadhesive strength of tablets with fresh goat buccal mucosa as model tissue. In order to determine the mode of release, the data was subjected to Krosmeyer and Peppas diffusion model. All the formulations followed Fickian release mechanism. Tablet containing Carbopol 934P & Na CMC in the ratio of 1:1 had maximum *in vitro* drug release for 6 hrs.

Keywords: Buccal tablets, Mucoadhesive, Pravastatin

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INTRODUCTION

Mucoadhesion has become an interesting topic for research over the last two decades, for its potential to optimize localized drug delivery, by retaining dosage forms at the site of action or systemic delivery, by retaining a formulation in intimate contact with the absorption site[1]. The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. On the first case, the aim is to achieve a site specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation[2]. Unlike oral drug delivery, which presents a hostile environment for drugs, especially proteins and polypeptides, due to acid hydrolysis and the hepatic first-pass effect, the mucosal lining of buccal tissues provides a much milder environment for drug absorption[3]. Other routes, such as nasal, ocular, pulmonary, rectal, and vaginal drug administration, have provided excellent opportunities for the delivery of a variety of compounds[4].

Pravastatin is a HMG CoA reductase inhibitor used to lower cholesterol(LDL) and triglycerides (type of fat) in the blood. It is incompletely absorbed following oral administration and undergoes extensive first pass metabolism resulting low bioavailability (17%). The physicochemical properties of Pravastatin, its low half-life (1.5-2hrs), molecular weight (424.5g/mol) and first pass metabolism make it suitable candidate for administration by buccal route. Hence, in the present work an attempt was made to formulate mucoadhesive buccal tablet for Pravastatin using different mixtures of polymers in order to avoid extensive first pass metabolism, degradation in the stomach and prolonged effect.

MATERIALS AND METHODS:

Materials:

Pravastatin was procured from Spectrum Pharma labs, Hyderabad, India. HPMCK4M, Carbopol-940P, Sodium CMC, Mg. stearate and talc were procured from SD Fine Chemicals, Hyderabad, India. All other reagents used were of analytical grade.

Methods:

Mucoadhesive buccal tablets were formulated by direct compression method. All the ingredients of the formulation were passed through sieve no# 60 and were blended in a mortar with a pestle to obtain uniform mixing. The blended powder was then evaluated for Pre-compression parameters. The blended powder of the core was compressed on 8mm punch in a single stroke

multi station tablet punching machine and was removed. Composition of the prepared bioadhesive buccal tablet formulations of Pravastatin were given in Table 1.

Table 1. Composition of Pravastatin buccal tablets

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Pravastatin	20	20	20	20	20	20	20	20
Carbopol 940P	70	60	50	40	70	60	50	40
HPMC K4M	40	50	60	70	–	–	–	–
NaCMC	–	–	–	–	40	50	60	70
Lactose	40	40	40	40	40	40	40	40
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight(mg)	180	180	180	180	180	180	180	180

HPMC-Hydroxy Propyl Methyl Cellulose, NaCMC-Sodium Caboxy Methyl Cellulose, Mg. Stearate-Magnesium stearate

EVALUATION TESTS OF PRAVASTATIN BUCCAL TABLETS

Physical Evaluation:

According to the methods mentioned in monograph of Pravastatin in pharmacopeia, the Thickness, weight variation, hardness of formulations F_1 to F_8 were studied using digital micrometer, electronic balance, Pfizer hardness tester, respectively.

Content uniformity:

20 tablets were randomly selected and average weight was calculated. Tablets were powdered in a glass mortar. Powder equivalent to 10mg was weighed and dissolved in 100 ml of 6.8 pH phosphate buffer filtered and drug content analyzed spectrophotometrically in UV-Vis spectrophotometer at 239.4 nm

In vitro drug release of buccal tablets:

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the buccal tablets[5]. The dissolution medium consisted of 200ml of phosphate buffer pH 6.8. The release was performed at 37^{o}C ± 0.5^{o}C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in to the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through filter paper and analyzed after appropriate dilution by UV spectrophotometer at 239.4 nm.

In vitro Swelling studies:

The degree of swelling of mucoadhesive polymer is an important factor affecting adhesion. For

conducting the study, a tablet was weighed and placed in a Petri dish containing 5ml of phosphate buffer pH 6.8 in 6hrs, at regular intervals of time (1, 2, 4, and 6hrs), the tablet was taken carefully by using filter paper[6]. The swelling index was calculated using the following formula

$$\text{Swelling Index(S.I.)} = (Wt-Wo)/Wo \times 100$$

Where S.I. = Swelling index, Wt = Weight of tablet after swollen at time't', Wo = Weight of the initial tablet.

In vitro mucoadhesion study:

Mucoadhesive strength of the tablets was measured on a modified two-arm physical balance. The sheep buccal mucosa was used as biological membrane for the studies. The sheep buccal mucosa was obtained from the local slaughter house and was used within 3hrs of procurement[7]. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37 ^{0}C.

The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH6.8. The left pan of physical balance was removed. To the left arm of balance, a thick thread of suitable length was hung. To the free end of thread attach a glass stopper of circular base (diameter 2.5cm).A clean 250ml beaker was placed below the glass stopper. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass beaker was tightly fitted into a glass beaker filled with phosphate buffer pH6.8 at 37± 0.5 ^{0}C), so that it just touches the mucosal surface. The buccal tablet was suck to the lower side of a rubber stopper. The two sides of the balance were made equal before the study, by keeping a 5gm weight on the right hand pan. A weight of 5gm was removed from the right hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 1min contact time. Mucoadhesive strength was assessed in terms of weight (gm) required to detach the tablet from the membrane. The mean value of three trials was taken for each buccal tablet.

$$\text{Force of adhesion(N)} = \text{Mucoadhesive strength}/100 \times 9.81$$

Matrix erosion study:

Each tablet weighed (W1) were immersed in a phosphate buffer pH 6.8 for pre determined time (1, 2, 4, and 6hrs). After immersion of the tablets were wiped off by the excess of surface water by the use of filter paper[6]. The swollen tablets were dried at 60^{o}C for 24hr in an oven and kept in a dessicator for 48 hr prior to be reweighed (W2). The matrix erosion of the tablet was calculated by using the formula given in the equation i.e.

$$\text{Matrix Erosion}(\%) = (W_1-W_2)/w_1 \times 100$$

Surface pH Study

The bioadhesive tablet was allowed to swell by keeping it in contact with 1 ml of distilled water for 2 hr at room temperature. The pH was measured by bringing the pH-meter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1 min[8].

Accelerated Stability studies:

The optimized formulation was subjected to stability studies at 40^0C±75% RH for period of three months. Each tablet was individually wrapped in aluminium foil and packed in ambered coloured bottle and put at above specified condition in a stability chamber for three months[8]. For every one month tablets were analyzed for the hardness, friability, thickness, drug content and *in vitro* drug release. The results are obtained within the limits.

RESULTS AND DISCUSSION

Physicochemical properties:

The hardness of prepared buccal tablets was found to be in the range of 4.33 Kg/cm^2 to 5.73Kg/cm^2 .The thickness was found to be 3.15 mm to 3.30 mm with RSD of 0.5 to 1.2%. The friability of all tablets was less than 1% i.e., with in the limit. The percentage deviation from mean weights of all the formulations of tablets was found to be within the prescribed limits. The drug content ranged from 97.53 to 99.15% with RSD values 0.318-0.115%. The low values in standard deviation indicates uniform drug content in all the formulations prepared as observed from table given table 2:

Table 2. Physico-chemical parameters of Pravastatin buccal tablets.

Formulation Code	Weight variation(mg)	Thickness (mm)	Hardness(Kg/cm^2)	Friability(%)	Drug content (%)
F1	179.0±2.0	3.17±0.04	4.33±0.05	0.61±0.01	97.53±0.318
F2	178.5±1.8	3.15±0.03	5.43±0.05	0.65±0.03	99.62±0.152
F3	180.0±1.2	3.20±0.05	4.43±0.11	0.68±0.06	99.56±0.225
F4	179.0±1.9	3.17±0.01	5.83±0.05	0.69±0.07	99.49±0.3
F5	180.5±1.2	3.15±0.03	4.53±0.05	0.72±0.05	99.85±0.115
F6	178.0±1.7	3.15±0.04	4.06±0.05	0.63±0.04	99.82±0.115
F7	178.5±1.3	3.17±0.04	5.03±0.05	0.74±0.02	98.51±0.040
F8	179.7±1.5	3.30±0.03	5.73±0.05	0.77±0.02	99.12±0.115

Each value represents the mean ±SD (*n* =3).

***In vitro* drug release of buccal tablets**

In vitro drug release studies revealed that the release of Pravastatin from different formulations varied according to the type and ratios of the matrix forming polymers. The formulations F1, F2, F3, and F4 containing drug carbopol 940p and HPMC K4M polymers were ranging from 86.15% to 78.95 % and F5, F6, F7, and F8 containing drug carbopol 940P and Na CMC 88.55% to

98.15% . The formulation F5 containing carbopol 940p and Na CMC in the ratios showed highest 98.15% drug release in 6hrs. The dissolution profiles of tablet were influenced by type of polymer used. Dissolution profiles of formulations containing different Carbopol: HPMC K4M polymer ratios i.e., F1, F2, F3 and F4 showed that as the concentration of HPMC K4M increased in the formulation the release rate decreased. This property was due to hydrophilic and swellable nature of HPMC K4M as supported by swelling studies. From the same data it was observed that as the concentration of secondary polymer Na CMC decreased and increase of carbopol concentration in formulation the release rate of Pravastatin also increased due to erosion.

Table 3: In-vitro drug release profiles of formulations F1-F4

Time(hr)	Cumulative % drug release			
	F1	F2	F3	F4
0.5	7.24±0.45	6.58±0.67	7.40±0.20	9.23±0.24
1	24.89±0.21	20.47±0.26	18.51±0.22	19.55±0.52
2	38.96±0.12	32.25±0.22	29.74±0.11	29.99±0.34
3	49.95±0.96	44.15±0.84	41.10±0.25	40.54±0.46
4	61.42±0.77	56.19±0.75	53.35±0.21	51.20±0.17
5	74.43±0.84	71.82±0.77	66.30±0.24	62.57±0.41
6	86.15±0.54	81.05±0.98	80.76±0.15	78.95±0.17

Table 4: in-vitro drug release profiles of formulations F5-F8

Time(hr)	Cumulative % drug release			
	F5	F6	F7	F8
0.5	10.44±0.20	10.35±0.35	11.35±0.35	9.68±0.17
1	23.59±0.21	23.80±0.26	24.16±0.55	21.54±0.20
2	38.90±0.22	37.40±0.12	37.10±0.40	33.54±0.52
3	53.36±0.84	51.15±0.96	50.19±0.34	45.66±0.12
4	69.41±0.46	65.04±0.46	63.42±0.21	57.91±0.75
5	85.03±0.54	81.29±0.24	76.79±0.17	70.29±0.77
6	98.15±0.15	95.00±0.17	92.05±0.98	88.55±0.54

Each value represents the mean ± SD (n=3)

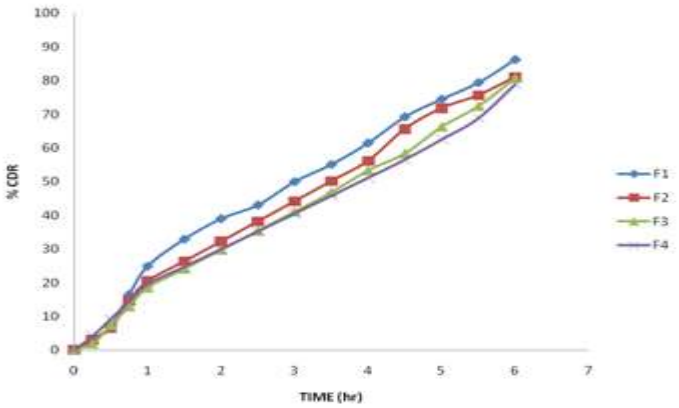

Figure: 1. Comparative invitro drug release profiles of F1-F4 forulations

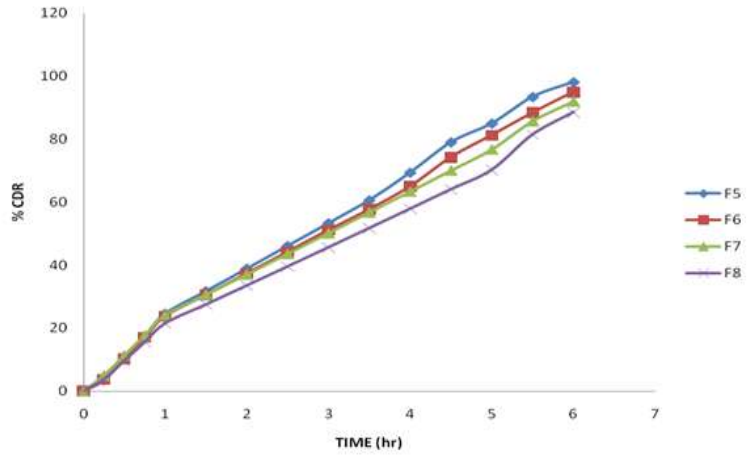

Figure: 2. Comparative invitro drug release profiles of F5-F8 forulations

The formulations with NaCMC (F5, F6, F7 and F8) showed high release of drug due to erosion i.e., 85.18% to 98.15%. Among all these formulation F5 showed 98.15% drug release in 6hr and was selected as best formulation. The results were shown in the in the Table 3 and 4. The comparison of cumulative percent drug release of all formulations was shown in Figure 1 & 2.

Swelling Studies of buccal tablets

The swelling studies were conducted for all formulations i.e., F1 to F8 and the results were shown in Table.5. All the formulations were hydrated generally by keeping the tablets in contact with phosphate buffer pH 6.8 for 1h to 6h.The highest hydration (swelling) i.e.,47.2-70.3 % was observed with the formulation F1. This may be due to quick hydration of polymers (carbopol and HPMC). The swelling rate of tablets increased in the case of formulation FH1 containing carbopol 940p and HPMC (table.5 shows the results)

Measurement of bioadhesion strength

The *in vitro* mucoadhesive strength study was performed and the results are shown in Table 5. On the modified physical balance and measure the force required to detach the tablet. The mucoadhesive characteristics were affected by the concentration of the mucoadhesive polymers. Increase in concentration of polymer increases mucoadhesive strength of formulation. The formulation (F1, F2, F3, and F4) with HPMC K4M and carbopol 940p showed the mucoadhesive strength of 12.27g 14.49g, 15.852g, and 21.64g respectively. The formulations (F5, F6, F7 and F8) with Carbopol: NaCMC showed the bio adhesive strength of 23.21g, 21.43g, 19.76 and 18.916g respectively. Results are shown table 5 and in figure 3.

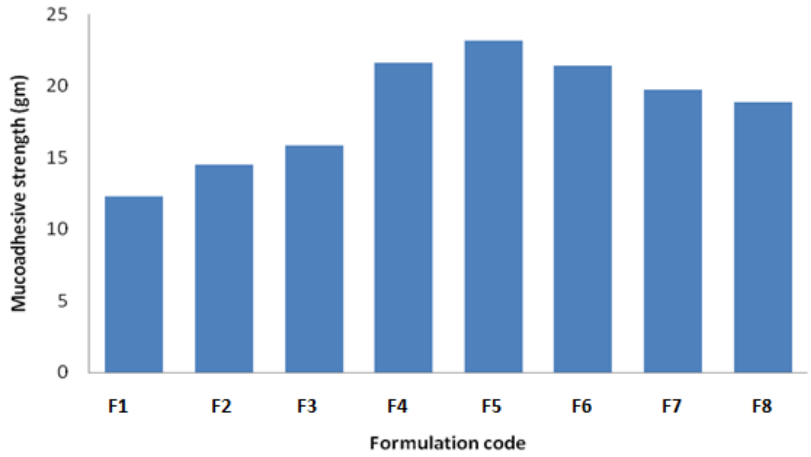

Figure 3. Bioadhesion strength profile of F1-F8 formulations

Matrix erosion study:

The mucoadhesive polymers used are hygroscopic and retain large amount of water. Tablets containing Na CMC as secondary polymer F5 to F8 showed the matrix erosion 8.45, 9.86, 9.5, and 10.45 respectively. This is because the presence of water that balanced the weight loss due to erosion and was more evident for this group, as it showed higher hydration rate. For this reason no matrix erosion was reported for F5 to F8. The matrix erosion of the tablets from each formulation (F5 to F8) was evaluated and the results are provided in Table 5.

Table 5. The Bioadhesive strength, Residence time, Surface pH and Matrix erosion values of Pravastatin buccal tablets.

Formulation Code	Bioadhesion Strength (gm)	Ex-vivo residence time(hr)	Surface p^H	Matrix erosion (%)	Swelling Index (%)
F1	12.27±0.11	5.22±0.12	4.55±0.01	10.85 ±0.17	68.2± 0.21
F2	14.49 ± 0.07	4.55±0.15	4.48±0.13	10.55 ± 0.22	67.3± 0.19
F3	15.85±0.06	5.32±0.19	5.63±0.33	9.43 ± 0.21	65.8± 0.22
F4	21.64±0.06	6.21±0.16	5.41±0.29	9.12 ± 0.10	54.9± 0.18
F5	23.21±0.03	5.45±0.25	6.89±0.15	8.45 ± 0.18	50.3± 0.10
F6	21.43±0.09	6.42±0.10	5.99±0.22	9.86 ± 0.22	57.7± 0.22
F7	19.76±0.08	4.23±0.13	6.01±0.11	9.5 ± 0.19	65.4± 0.21
F8	18.91±0.05	6.33±0.17	5.21±0.25	10.45 ± 0.15	70.3± 0.17

Each value represents the Mean ±SD (*n* =3).

Surface P^H study

As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. Surface pH of the formulations F1 to, F8 was found to be 4.55 ± 0.01, 5.21 ± 0.25 respectively. Especially the surface pH of F5 was found to be 6.89+0.15. This pH is near to the neutral, so the formulation (F5) does not cause any irritation on the mucosa. Surface pH values for all the formulations shown in Table 5.

Release kinetics and mechanism

The *in vitro* drug release data were fit to different equations and kinetic models to explain the drug release profiles. The coefficient of correlation of each of the kinetics was calculated and compared. The *in vitro* drug release profile of the optimized formulation of Mucoadhesive buccal tablets i.e, F5 fit to Higuchi model. They best fit to zero order behavior. The data was further treated as per Korsmeyer's equation. The slope (n) values obtained by this equation indicated that the drug released by Non- Fickian diffusion predominated with the optimized formulation.

Table 6. Release kinetics and mechanism of drug release of optimized(F5) formulation

Formulation code	Mathematical models(Kinetics)				
	Zero order	First order	Higuchi model	Peppas model	
	r^2	r^2	r^2	n value	r^2
F5	0.988	0.879	0.959	0.926	0.989

Accelerated Stability study of Pravastatin buccal tablets

The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40^0C $\pm$ 75 % RH on optimized formulation. The formulation was found to be stable, with no significant change in the weight variation, thickness, friability, hardness, swelling index, surface pH, matrix erosion, mucoadhesive strength, drug content and *in vitro* drug release pattern.

CONCLUSION

Pravastatin mucoadhesive buccal tablets could be formulated using the drug, Carbopol 940p and HPMC K4M, Na CMC with their proportions. It can be seen that by increasing the concentration of Carbopol 940p and decreased concentration of Na CMC in the formulation, the drug release rate from the tablets was found to be Increased. and with the concentration mucoadhesive strength was also increased. But when the concentration of HPMC K4M increased and Carbopol decreased the drug release rate was found to be decreased. From the formulations F1, F2, F3,F4,F5,F6,F7 and F8 the formulation F5 was selected as optimized formulation because it showed maximum release and the other properties such as swelling index was also low, mucoadhesion force shown good.

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