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Formulation of Buccal bioadhesive Tablet of Diltiazem Hydrochloride and its Evalution

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Abstract: Buccal bioadesive tablet containing diltiazem hydrochloride was prepared for treatment of hypertension. Carbopol 974 and hydroxy propyl methyl cellulose K4M were used in combination as a bioadesive polymer. The tablets were assessed for release using a model drug as diltiazem hydrochloride by using in vitro dissolution method. The tablets have shown the significant release of model drug which shows good effect of drug by avoiding first pass metabolism of diltiazem hydrochloride. The tablets were evaluated by using various parameters as weight variation, tablet hardness, drug content, bioadhesion force and swelling index.
Key words: Diltiazem hydrochloride, carbopol 974P, hydroxy propyl methyl cellulose K4M, buccal bioadesive tablet.

1. Introduction:

Buccal drug delivery has been proposed as an alternative to per-oral and parenteral administration of drug.[i] Buccal drug delivery have rendered this route of administration useful for a variety of drugs. Buccal drug delivery system has gained an increased attention due to several advantages over peroral administration such as the drug is not subjected to the destructive acidic environment of the stomach, avoiding hepatic first pass effect, enhanced bioavailability of drugs that are offered by mucosa which is relatively permeable with a rich blood supply.[ii] At present much effort is being channeled into the study of a class of polymeric compounds with apparent mucoadhesive properties. Mucoadhesion been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the buccal mucosa. Formulations includes tablets, patches, tapes, films, semisolids (ointments and gels) and powders.[iii] A mucoadhesive drug delivery system has desirable features such as localization of the dosage form in specified regions to improve and enhance bioavailability of drugs, promotion of intimate contact of the formulation with the underlying surface to allow modification of tissue permeability for absorption of macromolecules, e.g: peptides and proteins, prolonged residence time of the dosage form to permit once-a-day dosing.[iv]. Diltiazem hydrochloride is selected as a drug due to its high first pass metabolism, half life of 3 to 5 hrs and log P 2.79.

2. Materials and method:

2.1 Materials:

Diltiazem hydrochloride was obtained from Nicholas Piramal, Mumbai, carbopol 974P hydroxy propyl methyl cellulose K4M, citric acid and sodium saccharine was procured from Research lab fine chemical industries Mumbai. Evaluation was done on equipments available in laboratory at Appasaheb Birnale College of Pharmacy, Sangli.

2.2 Method:

2.2.1 Selection of polymer Composition:

Carbopol 974P and HPMC K4M are used in buccal formulation. By using different concentration of carbopol 974P and HPMC K4M, placebo tablets were prepared. 2^2 factorial design were applied to two polymer concentration as shown in table

Table 1: Design Matrix for the formulations of placebo by using 2^2 factorial design.

X1	X2	HPMC	Carbopol
+	-	8	7.5
+	+	12	7.5
-	-	8	15
-	+	12	15

2.2.2 Formulation of medicated Tablets:

A 3^2 full factorial design was constructed where amount of HPMC K4M(X_1) and carbopol(X_2) were selected as the independent variables. The levels of two were selected on the basis of the preliminary studies which showed an optimum result for bioadhesion and swelling index. The time required for drug release at 3h, bioadhesion force (F) and studies were selected as response variables.

A statistical model incorporating attractive and polynomial terms used was to evaluate the response

$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$

Where Y is dependent variable, b_0 is the arithmetic mean response of the 9 runs and b_1 is the estimated coefficient for the factor X_1. The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1 X_2) shows how the response changes when two factor are changed simultaneously. The polynomial terms (X_1, X_2) are included to investigate nonlinearity.

2.2.3 Preparation of diltiazem hydrochloride Tablet:

The tablets were prepared by direct compression method as follows:

1. Diltiazem hydrochloride tablets were prepared by direct compression techniques.
2. Drug and the excipients were homogeneously blended. 150 mg of the powder blend was pre-compressed on 6 station tablet punching machine at a pressure of 0.5 ton to form a single layered flat beveled tablets of 8 mm diameter.
3. Further, 10 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons to get a bilayer tablet.
4. Each tablet contained total weight of 160 mg. The prepared formulation was evaluated for parameters like weight variation test, tablet hardness, friability, tablet thickness,*in vitro* dissolution study, *in vitro* bioadhesion force study, study swelling index, in situ diffusion study.

3. Evaluation:

3.1 Tablet thickness and diameter: [v, vi]

Thickness and diameter of a tablet were measured using vernier calipers. Three tablet from each batch were used and average value was calculated.

3.2 Weight variation test): [v, VI]

20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight.

3.3 Tablet hardness: [v, VI]

The hardness was tested using Monsanto tester. The force is measured in kilograms.

3.4 Uniformity of Content: [vii]

Five tablets from each batch were powdered individually and a quantity equivalent to 10 mg of diltiazem hydrochloride was accurately weighed and extracted with a suitable volume of methanol. Each extract was suitably diluted and analyzed spectrophotometrically at 236 nm. Spectrophotometric analysis of formulation excipients using highest concentration employed in the formulation, indicated no interference at 236 nm in methanol.

Table 2: Formulation of diltiazem hydrochloride.

Formulation	**Formulations and quantity (mg)**								
Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Drug	30	30	30	30	30	30	30	30	30
Carbopol 974P	7.5	11.25	15	7.5	11.25	15	7.5	11.25	15
HPMC K4M	8	8	8	10	10	10	12	12	12
Avicel	30	30	30	30	30	30	30	30	30
Sodium Saccharin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Citric acid	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Lactose	71.2	67.45	63.7	69.2	65.45	61.7	67.2	63.45	59.7
Ethyl cellulose	10	10	10	10	10	10	10	10	10
Total	160	160	160	160	160	160	160	160	160

3.5 In-vitro dissolution studies: [VI]

In vitro drug release of the samples was carried out using USP – type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of 6.8 phosphate buffer was placed into the dissolution flask, for whole study maintaining the temperature of 37 ± 0.5 °C at 50 rpm. One tablet was placed in each dissolution flask. The apparatus was allowed to run for 3 hours. Aliquots (5 ml) of the solution were collected by the auto sampler from the dissolution apparatus at each 30 min for 3 hrs and were replaced with fresh dissolution medium. Absorbance of this solution was measured at 236 nm. Cumulative percent drug release was calculated using an equation obtained from standard curve. Release studies were performed in triplicate. Analysis was done using 'PCP Disso V-3' soft ware, India.

3.6 Bioadhesive Force:

The bioadhesive forces of all the prepared formulation were determined using the mucoadhesive force measuring device. The bioadhesive strength of the mucoadhesive polymer under study was determined by measuring the force required to detach the formulation from a mucin disc using the measuring device. Initially, the mucin discs were prepared by compression of crude porcine mucin (250 mg) by a multistation rotary punch disc machine (FLUIDPACK MINIPRESS) using a flat-faced punch of 8 mm diameter. The mucin disc was fixed to the glass vial using α-cyanoacrylate adhesive. Then this glass vial was connected to the right arm of the balance in inverted position. The mucin disc was hydrated with distilled water prior to bioadhesion testing. Each tablets were placed on the lower vial, lower vial was then elevated till the surface of the tablet came in contact with the mucin disc. Both the tablet and the hydrated mucin disc were left in contact for 2 min using a preload of 10 g to establish the contact between them and allow the formation of an adhesive bond. The preload time and force were kept constant for all the tested formulations. After completion of the preload time, water was allowed to drip from a glass bottle through an infusion set into a preweighed plastic jar placed on the left pan of the balance at a constant rate of 30 drops per minute. The addition of water was stopped when the mucin disc was detached from the tested sample, the filled plastic jar was reweighed, and the weight of water required to detach the tested sample from the mucin disc was calculated by difference. The results were the mean of three runs.

The Bioadhesive Force can be calculated as per formula given below:

$$F = 0.00981\ {}^{W}/_{2}$$

W = Amount of Water

3.7 Swelling index: [viii]

Tablets were weighed individually (designated as w_1) and placed separately in petridishes containing phosphate buffer 6.8 pH. At regular intervals (0.5, 1, 2, 3, 4 h), samples were removed from the petridish and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (w_2). The swelling index of each system was calculated using the following formula:

$$\text{Swelling Index} = \frac{w_2 - w_1}{w_1} \times 100$$

4. Results:

Table 3: Weight variation, thickness, diameter, hardness, drug content:

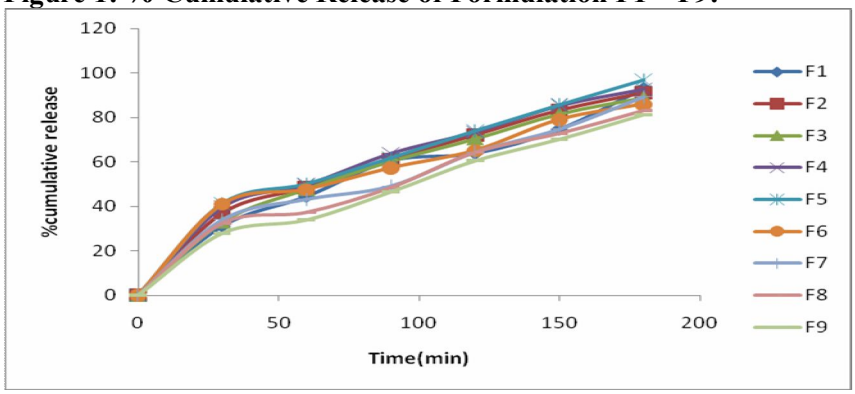
Formulation batches	Weight uniformity (mg)	Thickness (mm) ± Sd	Diameter (mm)	Hardness (Kg/cm^2)	Drug content (%)
F1	160.85	1.4±0.01	8	4-5	98.41
F2	160.49	1.5±0.02	8	4-5	99.70
F3	159.2	1.4±0.02	8	4-5	99.65
F4	160.5	1.4±0.02	8	4-5	100.47
F5	161.4	1.5±0.02	8	4-5	99.21
F6	161.9	1.6±0.02	8	4-5	101.32
F7	161.7	1.4±0.03	8	4-5	99.35
F8	162.6	1.5±0.02	8	4-5	101.31
F9	163.6	1.6±0.03	8	4-5	98.20

4.1 In-vitro dissolution studies:

Table 4: % Cumulative Release of Formulation F1 – F9:

		% Cumulative Release								
Sr.No	Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	30	34.5	36.9	32.9	39.6	41.2	41.0	33.9	32.4	27.8
3	60	44.5	48.5	47.7	49.8	50.1	47.6	43.1	37.3	33.8
4	90	60.6	61.2	60.2	63.8	61.8	57.2	49.1	48.5	46.4
5	120	63.9	72.2	70.2	73.5	74.0	65.1	64.3	64.4	60.4
6	150	74.8	83.3	81.4	85.4	85.7	79	74.6	72.9	70.1
7	180	97.2	92.2	86.4	94.1	95.1	83.4	91.3	85.0	81.2

Figure 1: % Cumulative Release of Formulation F1 – F9:

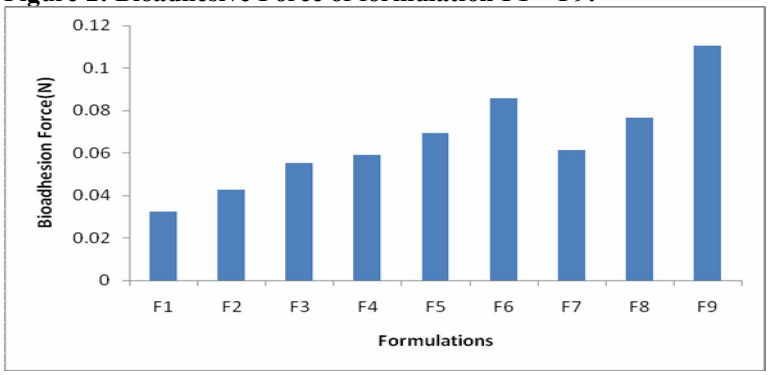


4.2 Bioadhesive Force:

Table 5: Bioadhesive Force of formulation F1 – F9:

Formulation	Bioadhesion Force (N)
F1	0.0325±0.011
F2	0.0426±0.009
F3	0.0551±0.015
F4	0.0591±0.014
F5	0.06925±0.016
F6	0.0859±0.021
F7	0.0613±0.013
F8	0.0765±0.02
F9	0.1104±0.01

Figure 2: Bioadhesive Force of formulation F1 – F9:

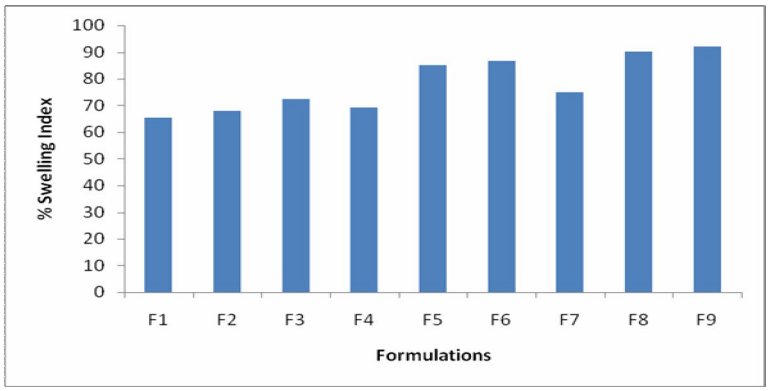


4.3 Swelling index:

Table 6: Swelling index of formulation F1 – F9:

Formulation	%Swelling index
F1	65.34
F2	68
F3	72.34
F4	69.24
F5	85.12
F6	86.72
F7	74.83
F8	90.26
F9	92

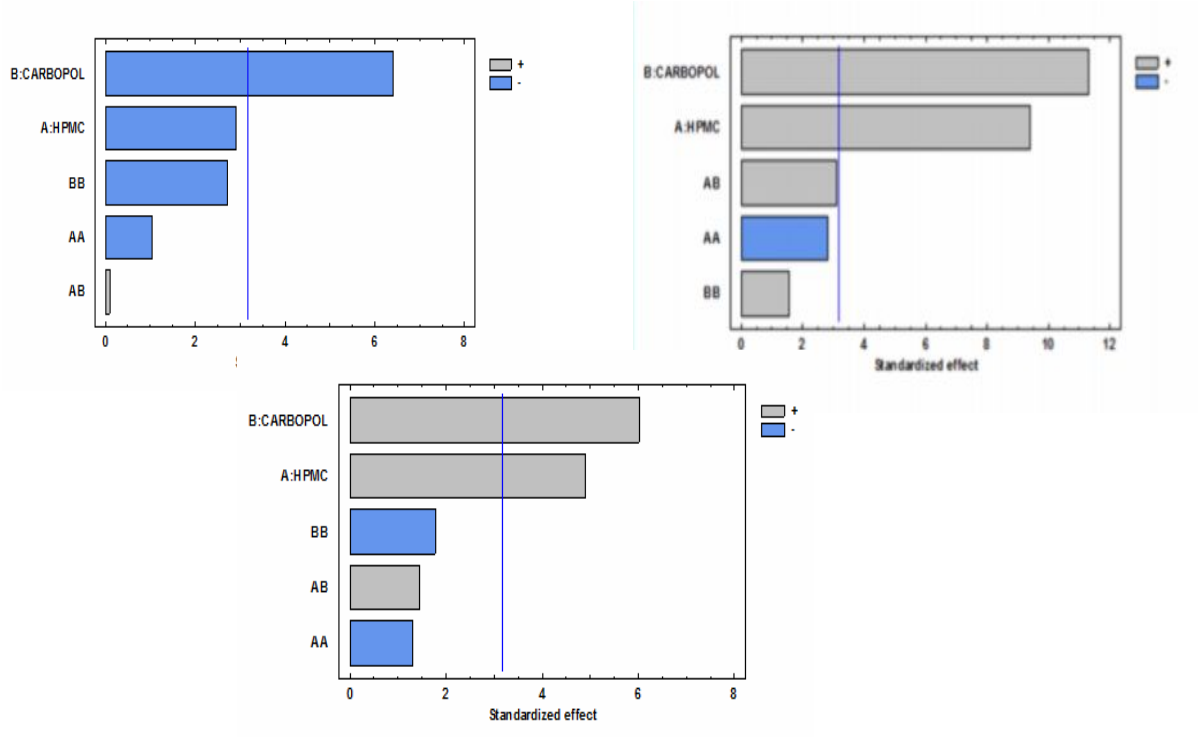
Figure 3: Swelling index of formulation F1 – F9:



4.4 Optimization Study:

Table 7: Design Matrix for the formulations of diltiazem hydrochloride by using 3^2 factorial design:

Formulation	Independent Variables		Actual Values		Response Variables		
	X_1	X_2	X_1	X_2	Y_1-Rel_{3h} (%)	Y_2-F (g)	Y_3-%S
F 1	-1	-1	8	7.5	97.11	0.0325	65.24
F 2	-1	0	8	11.25	92.91	0.0426	68
F 3	-1	1	8	15	86.63	0.0551	72.34
F 4	0	-1	10	7.5	94.12	0.0597	69.85
F 5	0	0	10	11.25	95.18	0.0692	85.12
F 6	0	1	10	15	83.89	0.0853	86.72
F 7	1	-1	12	7.5	91.41	0.0713	74.83
F 8	1	0	12	11.25	89.86	0.0765	90.26
F 9	1	1	12	15	81.30	0.1104	92



Pareto Charts: Figure 4 (Left): Drug Release, Figure5 (Right): Bioadhesion Force, Figure 6 (Below): Swelling Index.

5. Discussion:

5.1 Weight variation:

In weight variation test, the pharmacopoeial limit for percentage deviation for the entire tablet more than 130 but less than 324 mg is 7.5%. The average percent deviation of all the tablet formulation was found to be within the above limit and hence all the formulation passed the test for uniformity of weight as per the official requirements. [vi]

5.2 Tablet thickness and diameter:

Thickness of the formulation F_1 to F_9 was found to be 1.4±0.01to 1.6±0.03 and diameter of all formulation was found to be 8mm.

5.3 Tablet hardness:

The hardness of tablets was observed to be 4-5 kg/cm^2.

5.4 Uniformity of Content:

Drug content values were found in between 98.20 to 101.32%.

5.5 In-vitro dissolution studies:

The percent cumulative release of formulation was found between 81- 97%. The difference in drug release might be attributed to difference in polymer concentration. As the polymer concentration increases drug release decreases, this is due to increased diffusional path length. The overall rate of drug release tends to decrease with increase in polymer amount. This may be attributed to the fact that with an increase in hydrogel concentration, the viscosity of the gel layer around the tablet tends to limit further the release of active ingredient. Carbopol affects drug release significantly than HPMC; the presence of carbopol in the formulation decreases the drug release, which may be attributed due to increased imbibitions of water into polymer. Similarly, increase in the swelling of carbopol which holds the water inside the matrix and thus decreases the release of drug from the dosage form. [ix] In the formulation F_1 drug release is maximum due to lowest polymer concentration. As the carbopol concentration in the formulation F_8 and F_9 increases, drug release decreases.

5.6 Bioadhesion force:

Concentration of carbopol affects the bioadhesion force significantly. It was observed that concentration of HPMC also increases the bioadhesion force to a small extent. Hence it is attributed that formulation F_1 had the lowest bioadhesion force and bioadhesion

force of formulation F_9 was highest. This may be due to increases in the concentration of carbopol and HPMC. It seems that increase in overall carbopol ratio leads to more adhesion sites and subsequently stronger force is observed. The combination of two polymer shows highest adhesion strength this is because carbopol absorbs water and entraps in HPMC network in addition intermolecular complexation between two polymers would be effective. [x]

5.7 Swelling index:

The swelling index is the parameters which are used to study the swelling ability of the polymer. The swelling index is affected considerably by the polymer concentration. As the polymer is increased the swelling index is increased, this might be due to increased absorption of the water in the polymeric matrix. Both the polymer are of hydrophilic nature having ability to hold water within it.

5.8 Optimization study:

Factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interactions. A 2-factor experiment each at 3 levels requires 9 experiments. This technique was applied to quantify the influence of formulation parameters on the drug release, bioadhesion force and swelling index. The independent variables were carbopol concentration and HPMC concentration. Preliminary experiments were performed to confirm the operational formulation range that would successfully give bioadhesion and swelling that the runs could be conducted at the operational units dictated by the factorial design. Qualitative estimates of the influence of the individual variables could be made by inspection of the data in Table 2. However, it would be difficult visually to make predictions as to whether the interactions actually existed between the variables, or which single variable had the most dominant effect. The standardized Pareto Chart shown contains a bar for each effect, sorted from most significant to least significant. The length of each bar is proportional to the standardized effect, which is equal to the magnitude of the t-statistic that would be used to test the statistical significance of that effect. A vertical line is drawn at the location of the 0.05 critical values for Student's t. Any bars that extend to the right of that line indicate effects that are statistically significant at the 5% significance level. From all the magnitude carbopol concentration was found to affect significantly to all the responses. Results revealed that drug release in formulations was decreased linearly as the carbopol concentration is increased. Further bioadhesion force and swelling was increased as Carbopol and HPMC concentration increases. In formulation F_1 and F_2, the drug release was found to be good but bioadhesion force and swelling was lowest. The formulation F_6, F_7, F_8 and F_9 showed retarded drug release as both polymer concentration increases but bioadhesion was maximum. In formulation F_3, F_4 bioadhesion and swelling was increased but formulation F_5 shows optimum drug release and good bioadhesion force and swelling index as compared to formulation F_3 and F_4. So from the above study we can concede that formulation F_5 showed optimized results, hence can be considered as optimized one.

6. Conclusion:

The study suggests that the buccoadhesive tablet of diltiazem hydrochloride was prepared using carbopol and HPMC providing regulated release up to 3 h. The tablet demonstrated ample bioadhesive strength. The factorial optimization technique yields results with a high degree of prediction and realization. Formulation F_5 were found to be the best formulations to achieve the aim of this study. The study can, therefore enable the formulator to reach and quantify the optimum, decreasing experimentation during formulation.

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Refrences:

i. Shojael H., Buccal mucosa as rout for systemic drug delivery - A review. J. Pharm.Sci., 1998, 1:15-30.

ii. Swarbrick J., .Boylan j., Encyclopedia of Pharmaceutical Technology, Vol 2, Marcel Dekkar, New York, 1990, 189-211.

iii. Rathbone M., Ponchel G., Ghazali F., Oral mucosal drug delivery, Vol.74, Marcel Dekker, New York, 1996, 221-274.

iv. Vincent H., Lee L., Peptide and Protein drug delivery, Advances in Parenteral sciences/4, Marcel Dekker, New York, 1990, 42-43.

v. Lachman L., Herbert A., Lieberman, Joseph L. Kanig, The Theory and Practice of Industrial Pharmacy: Third Edition: Varghese Publication House, p.171-194.

vi. Indian Pharmacopoeia, Govt. of India, Ministry of Health and Family Welfare, 4th ed., The Controller of Publication, Delhi, Vol. 1, 1996 , p. 522-533.

vii. Singh B., Ahuja N., Development of controlled-released mucoadhesive hydrophilic matrices of diltiazem hydrochloride, Drug Dev. Ind. Pharm, 2002, 28:431-442.
viii. Desai K., Kumar T., Preparation and evaluation of novel buccal adhesive system, AAPS Pharm. Sci. Tech., 2004, 5(3): 35.
ix. Kshirsagar.R.V,Jain.V,Wattamwar.S, Effect Of Different Viscosity Grade HPMC Polymers On Gastroretentive Drug Delivery Of Metformin HCL, Int Journal of Applied Pharmaceutics, 2009, 1; 44-50.
x. Mohammadi.S.S,Najafi.R.B,Yousefi.G., Fomulation and in vitro evaluation of Predinisolone buccoadhesive tablets.II Farmaco , 2005, 60; 339 - 344.

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