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Formulation and evaluation of Mucoadhesive Buccal tablets of Valsartan

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Abstract:
The main aim of this work was to formulate and study mucoadhesive buccal tablets of Valsartan using various suitable bioadhesive polymers such as CP 934, HPMC K4M, and Na CMC. A backing layer of ethyl cellulose was used which is impermeable in nature. Six formulations of Valsartan were prepared by direct compression method. The prepared tablets were characterized by swelling studies, % matrix erosion, surface pH, bioadhesive properties, *In-vitro* drug dissolution and *In-vitro* diffusion studies. It was found that swelling index was proportional to CP and Na CMC content. As the Na CMC content increases the swelling index also increased. The surface pH of all formulations was found to be satisfactory, and values were in between the range of 5-7 pH, hence no irritation to buccal cavity is assumed. Tablets containing CP: HPMC in the ratio 1:3 has shown maximum percentage of *In-vitro* drug release as well as *In-vivo* diffusion through buccal mucosa. The drug release was found to be zero order release. The formulation F3 was considered as the optimized formulation based on satisfactory bioadhesive strength, *In-vitro* dissolution drug release of 59.69 ± 0.95%, *In-vitro* drug diffusion of 43.66 ± 0.68% for 8 h.

Keywords: Valsartan, Mucoadhesive Buccal Tablets,HPMC K4M, Carbopol 934.

INTRODUCTION

1.1 ORAL MUCOADHESIVE DRUG DELIVERY:-[1,2,3,4]

Oral route of administration of drugs is most preferred to the patient and the clinician also. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of many drugs. Due to this other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery offer's distinct advantages over per oral administration for systemic drug delivery. Further oral transmucosal drug delivery bypasses first-pass effects in the GI tract and liver and avoids GI side effects.[1]

PERMEATION BARIERS ACROSS BUCCAL MUCOSA

The main barriers that govern the permeation across the buccal mucosa are

- **Membrane coating granules**
- **Mucus**
- **Saliva**
- **Basement membrane**

THE BIOADHESIVE DOSAGE FORMS

The bioadhesive dosage forms gave new research field. These dosage formulations are mainly available for local therapeutic use, for systemic therapeutic use. These forms have adhesion properties on a mucosa for a sufficient time to produce a therapeutic effect. Bioadhesion is the property of a biological or synthetic material to adhere to a biological tissue

for a given time. The bioadhesion mechanism is used to solve bioavailability problems resulting from a too short stay of the pharmaceutical form at the absorption site.[4]

Bioadhesive tablets can adhere to the buccal mucosa, and the drug is released upon hydration of the device, forming a hydrogel. Bioadhesive tablets are usually prepared by direct compression. A double layer tablets, consisting of core drug layer and impermeable backing ethyl cellulose layer. The two buccal adhesive tablets commercially available in UK are "buccastem" (Prochlor perazine maleale) and "Suscard Buccal" (glyceryl trinitrate).[5]

MATERIALS:

List of materials used

S. no	Materials	Source
1	Valsartan	Gift sample from Ranbaxy Pvt. Ltd
2	Carbopol 934	Central drug house, New Delhi
3	HPMC K4M	Yarrow Chem. Chemical Products. Bombay
4	Na CMC	NR Chem. Mumbai
5	D. Mannitol	Merck. Mumbai
6	Magnesium Stearate	Rolex
7	Talc	Karnataka fine chem. Bangalore
8	Ethyl cellulose	Central drug house, New Delhi
10	Sodium dihydrogen ortho phosphate	Karnataka fine chem. Bangalore
11	Disodium hydrogen ortho phosphate	Karnataka fine chem. Bangalore

METHODOLOGY:

1. Standard plot of Valsartan in 6.8 pH:

Valsartan dissolved in 50 ml of phosphate buffer to produce primary stock solution having a concentration of 1 mg/ml. 10 ml of primary stock further diluted to 100 ml to produce secondary stock solution having concentration of 100 µg/ml. 0.5-3 ml aliquots of the secondary stock were further diluted to 10 ml to produce standard solutions having concentrations of 5-30 µg/ml. The absorbance of the solutions was measured at 250 nm using double beam UV-Visible spectrophotometer. The plot of absorbance vs. concentration (µg/ml) was plotted and data was subjected to linear regression analysis. [17]

2. Preparation of mucoadhesive tablets:

Tablets were prepared by direct compression technique. The ingredients of core layer of different combinations were accurately weighed and mixed in a glass mortar and pestle for 30 min to obtain uniform mixture. The mixture was passed through 60 µm mesh. Then core layer of the above blend (110 mg) was compressed at minimum compaction force in 9 mm punches of single stroke tableting machine. The upper punch was raised without disturbing the core tablet and impermeable backing layer Ethyl cellulose of 40 mg was weighed and added on core tablet and again compressed at a compaction force of 5-7 kg/cm^2. **(19, 20, 22, 23, 24)**

1. Evaluation parameters: (30, 31)

a. Bulk density for powder:

Calculated based on following formula

$$\text{Bulk density } (\rho_0) = \frac{M}{V_0}$$

Where,

M = mass of powder taken

V_0= apparent untapped volume

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b. Tapped density:

Calculated based on following formula

$$\text{Tapped density } (\rho_t) = \frac{M}{V_f}$$

Where, M = Weight of sample powder taken

V_f = Tapped volume

c. Hardness:

The hardness of five tablets was measured using Pfizer hardness tester. It is expressed in kg/cm^2.

d. Thickness and diameter:

Thickness and diameter of the prepared tablets were evaluated with the help of vernier calipers and screw gauge.

e. Friability:

The friability of the tablets was determined using Roche friabilator. 20 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min. After 4 min the tablets were weighed again. The friability was then calculated using the formula,

$$\text{Friability (\%)} = \frac{\textit{Initial weight} - \textit{Final weight}}{\textit{Initial weight}} \times 100$$

f. Weight variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the percentage shown in table 9 and none deviate by more than twice the percentage ± 7.5

g. Drug content estimation:

Three tablets were crushed into powder, the quantity of powder equivalent to average weight of formulation was weighed and taken in a volumetric flask dissolved in 15 ml of methanol, the solution is filtered through whatman filter paper, from this 1 ml of solution is withdrawn and diluted to 10 ml. Again from this, 1 ml of solution is withdrawn and diluted to 10 ml, absorbance is taken at 250 nm and % drug content is calculated by the formula,

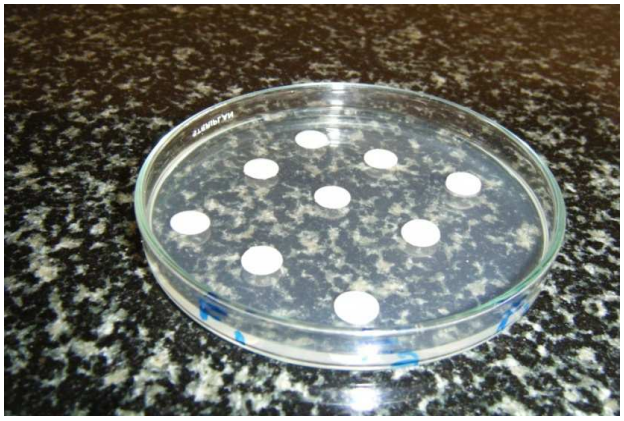
$$\text{Drug content} = \frac{\text{Absorbance}}{\text{Slope}} \times \text{Dose} \times \text{Dilution factor} \times \frac{1}{1000}$$

$$\text{\% Drug Content} = \frac{\text{Drug content}}{\text{Dose of the formulation}} \times 100$$

h. % swelling study:

Buccal tablets were weighed individually (W1) and placed separately in 2 % agar gel plates with the core facing the gel surface and incubated at 37 ± 0.1°C. The tablets were removed from the petridish and excess surface water removed carefully using filter paper. The swollen tablet was then reweighed (W2) and the swelling index was calculated using following formula. [27]

$$\text{\% Swelling index} = \frac{\text{Final weight (W2)} - \text{Initial weight (W1)}}{\text{Initial weight (W1)}} \times 100$$



i. Matrix erosion:

Tablets initial weight was noted down (W1). Swollen tablets were dried at 60 °C for 24 h in an oven and kept in desecator for 48 h and reweighed (W3). % matrix erosion were calculated using following formula, [21]

$$\text{\% Matrix erosion} = \frac{\text{W1-W3}}{\text{W3}} \times 100$$

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j. Surface pH study:

Surface pH studies were carried out in order to investigate the possibility of any side effects. This has to be studied as the alkaline or acidic pH irritates buccal mucosa. The tablet was allowed to swell by keeping in contact with 1ml distilled water in a petridish for 2 h at room temperature. The pH was identified by bringing the electrode into contact with tablet surface and allowing the surface to equilibrate for 1 min. [18]

k. Ex-vivo mucoadhesive time:

The *Ex-vivo* mucoadhesion time was examined after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 mL of the phosphate buffer pH 6.8 and kept at 37 ± 1°C. After 2 min, a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 h. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time. [18]

***l. Ex- vivo* mucoadhesive strength**

A modified balance method was used for determining the mucoadhesion strength. Fresh sheep buccal mucosa was obtained from the local slaughter house and used within 2 h of slaughter. The buccal mucosa was separated by removing the under lying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8. The fresh buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was attached to flat end of beaker with the help of cyanoacrylate gum, a watch glass attached to thin chains at equal distance forms the left hand pan. To the lower side of the watch glass the tablet was adhered just above the mucosa. The right pan consists of empty beaker, both the pans are balanced by adding suitable weights, then a 5 gm weight is removed from right hand pan, which lowered the left hand pan making tablet to come in contact with buccal mucosa. The balance was allowed in this position for 3 min. Then water was gradually added to the right hand pan until tablet detaches from the buccal mucosa. The weight required to detach the tablet from the mucosal surface gave the measure of mucoadhesive strength. Experiments were carried out triplicate and the averages of them are noted down.[18]

m. In-vitro drug release:

The USP type II dissolution apparatus was used to study the release of drug from buccal tablets. The dissolution medium consists of 900 ml of phosphate buffer pH 6.8. The release was performed at 37 ± 0.5°C, at a rotating speed of

50 rpm. The impermeable layer of the tablet was attached to a glass slide with instant adhesive. The slide was put in the bottom of the dissolution vessel, so that the tablet remained on the upper side of the slide. Dissolution was carried out and samples of 5 ml, at each time intervals were withdrawn at pre determined time intervals and replaced with fresh medium. The samples were filtered through whatman filter paper and were analyzed spectrophotometrically at 250 nm against phosphate buffer pH 6.8 as blank. [20, 23]

n. *In-vitro* buccal diffusion studies:

In-vitro buccal permeation study was carried out through sheep buccal mucosa using frans diffusion apparatus. Sheep buccal mucosa was obtained from the local slaughter house and stored in phosphate pH 6.8, used within 2 h of slaughter. The mucosa was separated from underlying connective tissues with surgical scissors and clamped in between donor and receptor compartment of diffusion cell. Buccal tablet was placed with the core facing the mucosa. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 6.8 and hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. 1 ml of sample of sample was withdrawn at regular intervals of time and analyzed UV spectrophotometrically. [20, 32, 33]

o. Pharmacokinetic modeling of drug dissolution profile: [34, 35, 36]

In order to examine the release mechanism of drug from the tablets, the *In-vitro* drug release data of best buccoadhesive tablet formulation of Valsartan were subjected to following release models

- Zero order,
- First order,
- Higuchi
- Peppas models.

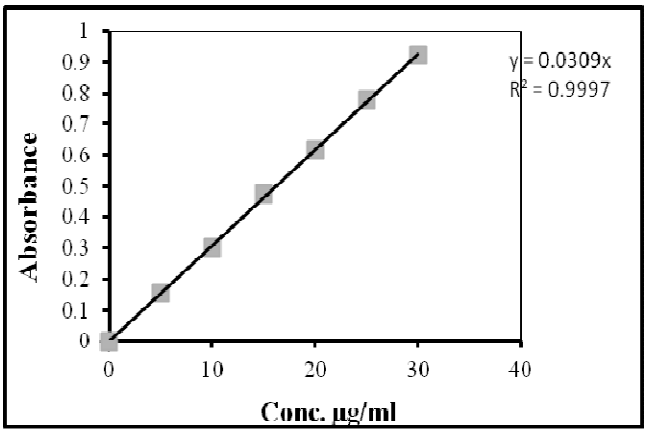
p. Stability studies:

Stability studies for 2 months were carried out for the best formulation; the best formulation is kept under two different conditions like at 30 ± 2°C & 65 ± 5 % RH and other at 40 ± 2°C & 75 ± 5 % RH. After 30 days first month stability studies were carried out for important parameters like dissolution, diffusion, swelling index, matrix erosion, mucoadhesive strength, diameter, thickness, drug content. The same study is repeated after completion of 60 days.

RESULTS:

1. Calibration curve of Valsartan in phosphate buffer pH 6.8

Sl. no.	Conc. µg/ml	Absorbance Mean ±SD
1	0	0
2	5	0.157±0.02
3	10	0.301±0.03
4	15	0.474±0.01
5	20	0.616±0.02
6	25	0.777±0.03
7	30	0.923±0.03



Standard graph of Valsartan in phosphate buffer pH 6.8

2. Formulation chart:

Sl. No	Ingredients.	Formulation (mg)					
		F1	F2	F3	F4	F5	F6
1	Valsartan	15	15	15	15	15	15
2	Carbopol 934	40	23.7	20	40	23.7	20
3	HPMC K4M	40	56.3	60	-	-	-
4	Na CMC	-	-	-	40	56.3	60
6	D. Mannitol	13	13	13	13	13	13
7	Magnesium Stearate	1	1	1	1	1	1
8	Talc	1	1	1	1	1	1
9	Backing layer Ethyl cellulose	40	40	40	40	40	40
10	Total weight	150	150	150	150	150	150

3. Preformulation study:

Formulation	Angle of repose (°)	Bulk density (gm/mol)	% Compressibility
F1	22.98±0.98	0.250	17.32
F2	25.43±1.34	0.266	21.41
F3	34.02±0.57	0.305	16.67
F4	33.28±0.70	0.273	21.43
F5	33.67±1.26	0.298	15.38
F6	36.41±0.76	0.322	16.67

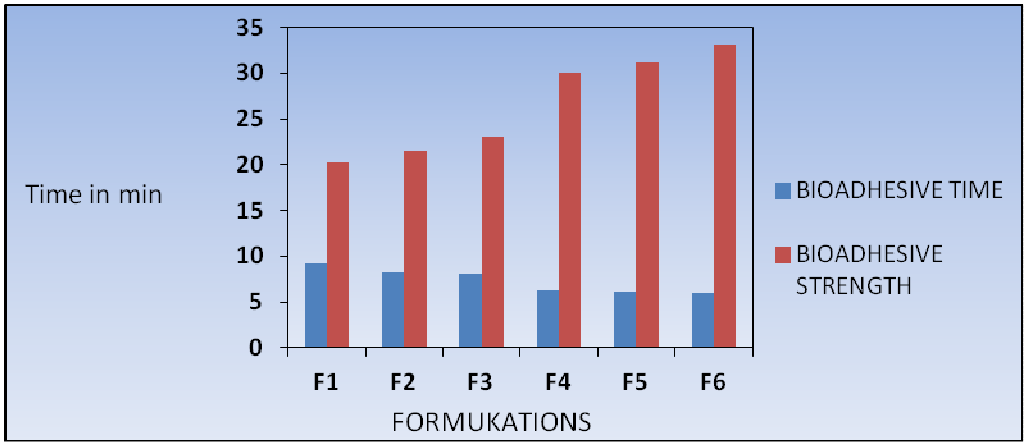
4. Evaluation of tablets:

a. Physicochemical parameters:

Formulation	Diameter (cm)	Hardness kg/cm²	Thickness (mm)	Weight variation (mg)	Friability (% loss)
F1	9	5.60±0.51	2.62±0.05	151.6±1.18	0.166
F2	9	5.43±0.40	2.72±0.04	151.4±1.00	0.230
F3	9	5.33±0.25	2.72±0.04	148.6±1.10	0.043
F4	9	5.66±0.32	3.00±0.00	149.7±0.96	0.190
F5	9	5.33±0.25	2.94±0.05	149.7±1.06	0.066
F6	9	5.20±0.20	2.76±0.05	151.2±1.16	0.063

b. Bioadhesive parameters:

Formulation	Bioadhesive time (h)	Bioadhesion strength (gm)
F1	9.20±0.03	20.26±0.12
F2	8.25±0.07	21.51±0.27
F3	8.15±0.04	23.04±0.11
F4	6.32±0.03	29.97±0.16
F5	6.10±0.07	31.13±0.03
F6	6.02±0.03	33.09±0.03



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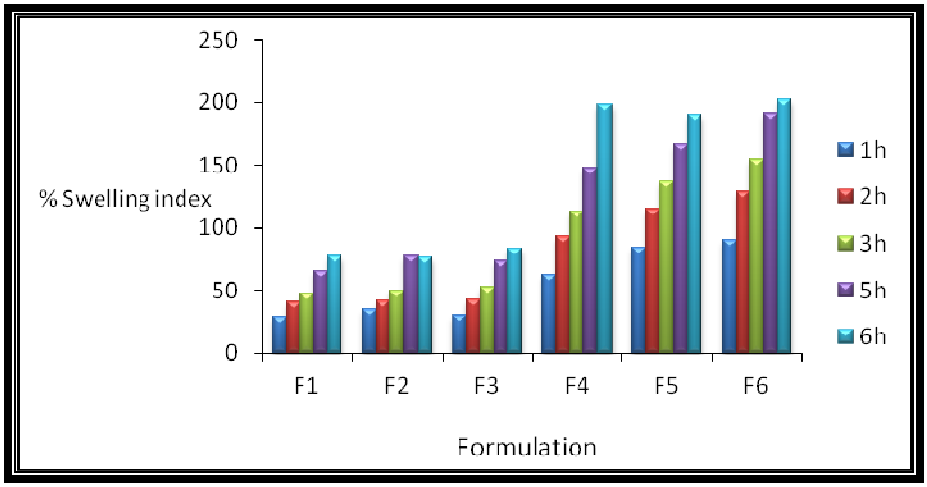
c. Content uniformity:

Formulation	Amount of drug present (mg)	% Drug content
F1	14.36±0.11	95.76±0.76
F2	14.05±0.24	93.69±1.63
F3	14.66±0.27	97.81±1.82
F4	14.68±0.22	97.95±1.47
F5	14.42±0.06	96.14±0.38
F6	13.99±0.26	93.33±1.73

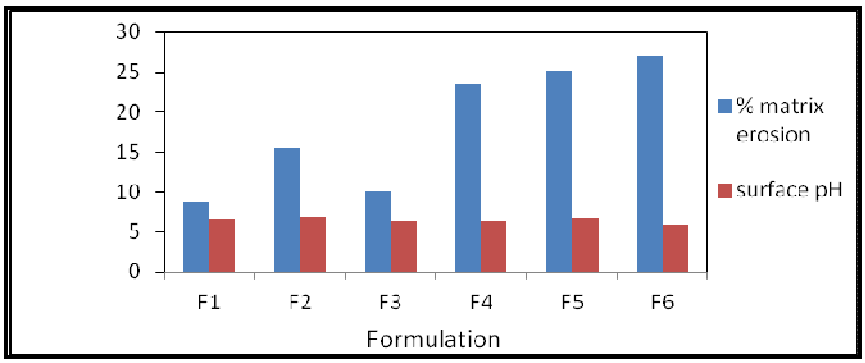
d. % Swelling index of the developed buccal tablets

% SWELLING INDEX					
Formulation	1h	2h	3h	5h	6h
F1	28.99	40.58	47.48	65.04	77.50
F2	35.03	41.71	49.40	77.56	76.65
F3	30.01	42.68	52.92	73.63	83.35
F4	62.75	93.27	113.11	147.61	198.15
F5	84.72	115.47	136.86	166.41	190.61
F6	90.42	128.97	154.49	191.48	201.88



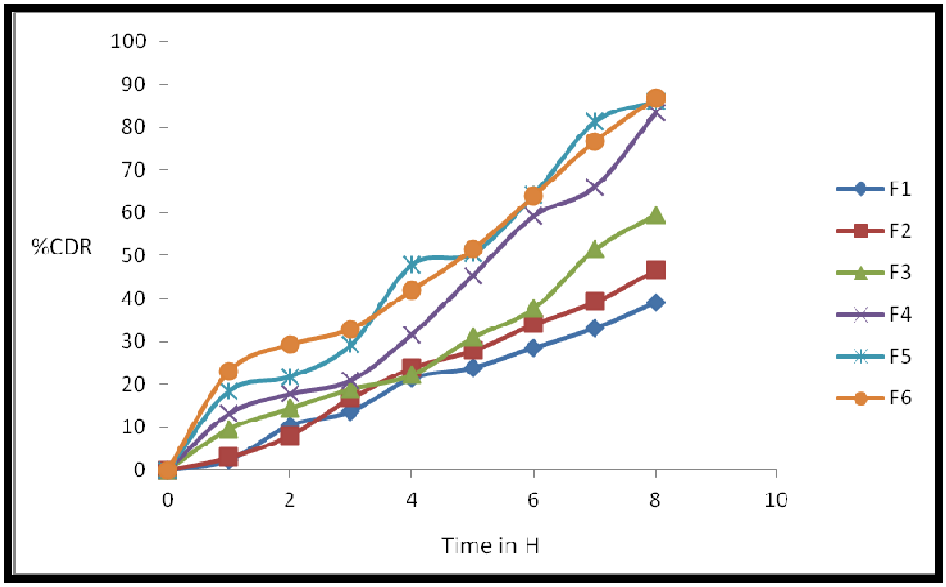
e. % matrix erosion and surface pH study:

Formulation	% Matrix erosion	Surface pH
F1	08.80±0.14	6.45±0.21
F2	15.55±0.06	6.87±0.11
F3	10.11±0.04	6.35±0.22
F4	23.52±0.11	6.40±0.17
F5	25.16±0.07	6.82±0.005
F6	27.03±0.06	5.90±0.10



***f. In-vitro* dissolution studies.**

Time (h)	% Cumulative Drug Release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	2.35 ± 1.21	2.923 ± 1.26	9.590 ± 1.58	13.09 ± 1.48	18.43 ± 0.77	22.94 ± 0.69
2	10.42 ± 0.11	8.010 ± 1.31	14.37 ± 2.38	17.81 ± 0.91	21.82 ± 1.05	29.26 ± 0.88
3	13.68 ± 2.20	16.72 ± 0.54	18.96 ± 0.28	20.94 ± 0.42	29.15 ± 0.16	32.91 ± 0.38
4	21.44 ± 1.54	23.80 ± 0.25	22.23 ± 1.95	31.64 ± 0.72	47.87 ± 0.97	41.91 ± 1.07
5	23.88 ± 0.32	27.83 ± 0.85	30.96 ± 2.01	45.41 ± 1.64	50.53 ± 1.05	51.43 ± 1.30
6	28.55 ± 1.54	34.03 ± 0.17	37.79 ± 0.95	59.31 ± 1.03	64.32 ± 0.57	63.88 ± 1.50
7	33.16 ± 0.55	39.21 ± 0.48	51.50 ± 0.43	66.12 ± 0.77	81.23 ± 0.47	76.67 ± 1.30
8	39.11 ± 1.16	46.69 ± 0.45	59.69 ± 0.95	83.45 ± 0.61	86.02 ± 1.21	86.67 ± 0.63



g. Drug release kinetic studies of 6 formulations:

Formulation	Regression value (R^2)			
	Zero order	Higuchi	Peppas	First order
F1	0.9917	0.9569	0.9070	0.9900
F2	0.9936	0.9861	0.8880	0.9852
F3	0.9699	0.9494	0.8505	0.9204
F4	0.9741	0.9293	0.8470	0.8673
F5	0.9825	0.9365	0.9011	0.9082
F6	0.9770	0.9247	0.9201	0.8946

Conclusion:

The best polymer composite was selected from the various ratios of the polymers. The best polymer ratio was found to be Carbopol 934, HPMC K4M in the ratio 1:3. The mucoadhesive strength of buccal tablets increases as the concentration of secondary polymer increases. The above polymer composite had shown satisfactory results in the parameters such as thickness, hardness, drug content, swelling index, matrix erosion, mucoadhesive strength, *in-vitro* dissolution and *In-vitro* diffusion.

The satisfactory formulation shows a zero order drug release profile depending on the regression value and shown a satisfactory dissolution profile. Slow, controlled and maximum release of Valsartan over a period of 8 h was obtained from buccal tablets F3 formulation containing Carbopol 934P, HPMC K4M.

Further work is to be carried out in order to determine its efficacy and safety by long term pharmacokinetic and pharmacodynamic studies in human beings.

Summary:

- UV Spectroscopic method was developed for the determination of Valsartan in phosphate buffer pH 6.8 at 250nm and in methanol at 250 nm.
- FTIR spectrum of pure drug and drug-polymer mixture revealed no chemical interaction.
- The prepared formulations were evaluated for the precompression parameters such as angle of repose, bulk density, % compressibility, post compression parameters such as weight variation, thickness, diameter, hardness, friability, drug content, swelling index, matrix erosion, surface pH, bioadhesive properties such as bioadhesive time, bioadhesive strength, and drug release studies like In-vitro dissolution and invitro diffusion studies.
- The stability studies were carried out for the most satisfactory formulation F9 and that showed no major change in physicho chemical parameters, mucoadhesive strength, swelling index, matrix erosion, hardness, drug content, and In-vitro dissolution profile.
- The best In-vitro drug release profile was achieved by formulation F6 and maximum diffusion profile was achieved by the same formulation within the period of 8 h.

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