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Design of a Novel Buccoadhesive System for Unidirectional Release of Valsartan

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ABSTRACT:

The present work deals with the formulation of buccal drug delivery system for management of hypertension containing valsartan as API. A sustained release (6 hours) buccoadhesive dosage forms, namely, unidirectional release mucoadhesive film is formulated. The in-vitro preliminary dissolution studies revealed that HPMC K4M and Methylcellulose 400cps are excellent film forming polymer and hydrophilic PVP K-30 as mucoadhesive agent based on separability, solubility in the ethanol solvent system, film forming property, flexibility and physical appearance of film. The bilayered film was designed with ethyl cellulose as backing membrane and the drug incorporated in mucoadhesive layer. A 3^2 full factorial design approach was employed to build the quality into formulation and thus showed the predictive drug release characteristics. Results of multiple regression analysis revealed that the independent variables significantly affected the dependent variables. The optimized bilayered film batch exhibited Surface pH 6.88, Swelling index 4.2 %, Tensile strength 118g/cm², 91.64% drug release in 6 hours, Ex vivo muco adhesion time 320 minutes and also releases the drug in unidirectional fashion towards the mucosa till 6 hours.

Key words: Valsartan, 3^2 full factorial design, buccal drug delivery, Unidirectional Release

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INTRODUCTION:

Buccal drug delivery leads direct access to the systemic circulation through the internal jugular vein thus bypasses drugs from the hepatic first pass metabolism leading to high bioavailability. Buccal route is an attractive route of administration for systemic drug delivery. Buccal bioadhesive films, releasing drugs in the oral cavity at a slow and predetermined rate, provide distinct advantages over traditional dosage forms for treatment of many diseases. For a drug of short to intermediate half- life (5 to 9 hours), dosage regimen can be fixed by giving the drug approximately at every half- life or more frequently. Drug having low solubility and relatively shorter half- life suggests its suitability for sustain release formulation.^[1]

Valsartan is selected as a model drug here, is a potent and specific competitive antagonist of Angiotensin-II –AT1 receptor. It is used orally for the treatment of hypertension. It is a “class-II” drug according to Biopharmaceutics Classification System (BCS), possessing low solubility and high permeability absorption characteristics. It has a low bioavailability of 23%, because of its poor absorption in lower gastrointestinal tract. Valsartan has a short elimination half- life. The initial phase $t_{1/2\alpha}$ is < 1 hour while the terminal phase $t_{1/2\beta}$ is 5-9 hours. It undergoes little or no hepatic metabolism but mainly conjugated to bile for excretion. Therefore, it is selected as a

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suitable drug for the design of buccoadhesive films with a view to improve its oral bioavailability and increase its drug effectiveness by formulating it in a sustained release dosage form. Valsartan is rapidly absorbed after oral administration. Peak plasma levels is achieved 2-4 h after oral administration and then decline with a terminal half-life reported in various studies in the range of 5–9 h. A peak plasma concentration (C_{max}) of 1.64 mg/L occurred after oral administration of a single 80 mg dose of valsartan. [2, 3, 4]

The product currently marketed is conventional tablet and capsule. The released drug absorption is altered by pH of medium, the presence of food, and the body's physiological factors, all of which can cause fluctuation in amount of drug absorbed. Also fluctuation in plasma drug concentration leads to exaggerated side effects, this all limitations can be minimized by adopting a sustained release formulation.

Recently, oral buccoadhesive films have been developed which allow for sustained release of drug from the dosage form. Once the film is placed in contact with the buccal mucosa, the release of API occurs slowly from it. This release is controlled by the amount of film former and solubility of the drug. Rational of research is a) Valsartan has shorter half-life so it is advantageous to administer it in modified release dosage form. b) Avoidance of first pass metabolism leads to increase in bioavailability. c) No chance of dose dumping and prevention of rapid termination of effect. d) Fluctuation in pH does not affect the release in case of films compared to marketed products. e) Fluctuation in plasma drug concentration leads to exaggerated adverse effects; it can be minimized by adopting sustained release system. f) Minimize patient to patient variability in drug action.

2. Materials and methods:

2.1 Materials

2.1.1 Materials used in formulation of oral buccoadhesive film

Valsartan was supplied by Torrent Pharmaceuticals Pvt Ltd, Ahmedabad, Gujarat, India. Hydroxypropyl methylcellulose K4M, USP, Polyvinyl Pyrrolidone K-90 (PVP K-90), USP and Ethyl cellulose were supplied from Signet Chemical Corporation Pvt. Ltd, Mumbai, India. Polyvinyl Alcohol (PVA), USP (Molecular Weight:1,25,000) was supplied by Laser Chemicals, Gujarat, India.

Polyethylene glycol- 400(PEG-400), BP was supplied from Burgoyne Burbidges And Co Pvt Ltd, Mumbai, India.

2.2 Methods

2.2.1 Calculation of the dose for film of valsartan

Oral dose of valsartan is 40 mg. Now, film of 2 cm × 2 cm dimension (4 cm^2) is to be administered which should contain 40 mg of valsartan. But the mould i.e. glass plate for casting of film has 63.585 cm^2 area. So total amount of valsartan required to be added in the film casting solution is 635.85 mg.

2.2.2 Preparation method of bilayered films [5]

Bilayered films were prepared by a casting/ solvent evaporation technique. The backing membrane was prepared by dissolving ethyl cellulose (2%) in mixture of acetone and isopropyl alcohol (65:35), and 10 % dry weight of polymer of dibutylphthalate as plasticizer. The plasticized ethyl cellulose solution was poured in to 7 cm diameter petriplate and solvent was allowed to evaporate at controlled rate by covering the mould with inverted glass funnel, to avoid blistering effect on dried films. This film act as backing membrane. The mucoadhesive composition containing APIs was prepared using different combinations of polymers by dissolving in 70% ethanol:water solvent system and after complete dissolution was over, the drug solution in solvent was added to it. 10% PEG 400 was added as plasticizer. This polymeric solution containing APIs was poured into plate containing a backing membrane of ethylcellulose solution and dried at temp of 40° for overnight; the dried films were kept in desiccators till further use. The films were cut into $2 \text{ cm} \times 2 \text{ cm}$ (4 cm^2) and evaluated.

Backing membrane	2% Ethylcellulose (Acetone : Isopropyl alcohol = 65:35 solvent)
Mucoadhesive layer	Drugs, HPMC K4M , PVP K-30, Methylcellulose- 400 cps (Ethanol-water solvent system)

In this work, a 3^2 full factorial design was applied to find out the optimum combination of independent variables HPMC K4M content and Methylcellulose 400cps content in order to obtain predicted drug release at 2,4 and 6 hours.

Table 1: Independent variables and levels selected for them.

Levels	Low	Medium	High
Variables	-1	0	+1
X ₁ : HPMC K4M Content	1%	3%	5%
X ₂ : Methylcellulose 400cps Content	2%	5%	8%

Table 2: composition of batch as per factorial design

Ingredients	BATCH								
	A1	A2	A3	A4	A5	A6	A7	A8	A9
Valsartan (mg)	63	63	63	63	63	63	63	63	63
PVP K-30 (mg)	5	5	5	5	5	5	5	5	5
HPMC K4M (%)	1	3	5	1	3	5	1	3	5
Methylcellulose 400cps (%)	2	2	2	5	5	5	8	8	8
PEG-400 (%)	10	10	10	10	10	10	10	10	10
Ethanol:water (q.s)ml	20	20	20	20	20	20	20	20	20

Table 3: Desirability range for the response variables

Response variables	Constraints
Y ₁ : Cumulative % drug released in 2 hours	15 % ≤ Y ₁ ≤ 30%
Y ₂ : Cumulative % drug released in 4 hours	50 % ≤ Y ₂ ≤ 65%
Y ₃ : Cumulative % drug released in 6 hours	80 % ≤ Y ₃ ≤ 95%

3 EVALUATION OF BUCCAL FILM^[5, 6, 7, 8, 9]

3.1 SWELLING STUDY

Buccal Films (2 cm x 2 cm) were weighed individually (designated as W1) and placed separately in 2% agar gel plates, incubated at 37 ± 1 °C, and examined for any physical changes. At regular 1-hour time intervals until 6 hours, patches were removed from the gel plates and excess surface water was removed carefully using the filter paper. The swollen patches were then reweighed

(W2) and the swelling index (SI) was calculated using the following formula:

$$SI = (W2 - W1) / W1 * 100$$

The experiments were performed in triplicate, and average values were reported.

3.2 SURFACE pH

Each film (2 cm x 2 cm) was allowed to swell by keeping it in contact with 1 ml of Phosphate buffer pH 6.8 for 2 hours at room temperature, and the pH was noted by bringing the electrode into contact with the surface of the patch and allowing it to equilibrate for 1 minute. The experiments were performed in triplicate, and average values were reported.

3.3 FOLDING ENDURANCE

A film strip of 2 cm x 2 cm was cut evenly and repeatedly folded and unfolded at the same place till it broke. The number of times, the film could be folded at the same place, without breaking was recorded as the value of folding endurance. The experiments were performed in triplicate, and average values were reported. This tells about the mechanical property of the film to some extent i.e. one can know qualitatively which batch shows good resistance to the stress applied. Higher is the folding endurance, better is the film.

3.4 CONTENT UNIFORMITY OF THE FILMS

Drug content uniformity was determined by dissolving the film by homogenization in 100 mL of an isotonic phosphate buffer (pH 6.8) for 8 h under occasional shaking. The 5 mL solution was taken and diluted with isotonic phosphate buffer pH 6.8 up to 20mL, and the resulting solution was filtered through a 0.45 mm Whatman filter paper. The drug content was then determined after proper dilution at 250 nm using a UV spectrophotometer (Shimadzu, SPD-10 A VP, Japan). The experiments were carried out in triplicate and average values were reported. The filtrate is analyzed UV spectrometrically at 250 nm using a blank film solution as reference sample.

3.5 IN VITRO DRUG RELEASE

The USP XXIII (23) rotating paddle method was used to study drug release from the buccal films; The film dosage form was cut into a circle with an area of 4 cm² and

ethylcellulose backing layer was attached to a 4cm diameter weight using double adhesive tape or instant adhesive (cyanoacrylate adhesive) and placed at the bottom of the dissolution vessel so that the film dosage form faced upright, 200 ml of phosphate buffer (pH 6.8) was used as the dissolution medium, at 37.0 ± 0.5 -C, and a rotation speed of 50 rpm was used. Samples (10 ml) were withdrawn at 1, 2,3,4,5 and 6 hours and replaced with fresh medium. The samples were filtered through 0.45- μ m Whatman filter paper and analyzed spectrophotometrically at 250 nm. The experiments were performed in triplicate, and average values were reported.

3.6 THICKNESS OF FILM

Three films of each formulation were taken and the film thickness was measured using micrometer screw gauge at three different places and the mean value was calculated.

3.7 TENSILE STRENGTH

It was measured using a lab made instrument consisting of an aluminium wire passed over two pulley. At the one extreme of the wire a basket was tied which accommodates the weight and on the other extreme provision for tying of the film was made. Both the sides were made equal before measurement. The film was tied and weights were added on the other side. The amount of weight at the time of film breakage is recorded as tensile strength.

Other method: Measured using Universal testing machine (Shimadzu AG100kNG and software: Winsoft tensile and compression testing) according to standard of ASTM at SICART, Vallabhvidyanagar, India. Instruments made up of two jaws: upper jaw (grip II, movable) and lower jaw (Grip I, fixed). Load cell of upper jaw was connected with the software. Software used to set film parameters like gauge length (mm), width (mm), thickness (mm), speed (mm/min), and initial load. Film was fixed between two jaws and then instrument was run. Tensile strength was measured and results were display on software.

3.8 EX VIVO ADHESION TIME

The *ex vivo* adhesion time was evaluated ($n = 3$) after application of the patches onto mucin solution (30%v/v) and was fixed in the inner side of the beaker, above 2.5

cm from the bottom, with cyanoacrylate glue. One side of each film was wetted with one drop of isotonic phosphate buffer pH 6.8 and pasted to the mucin solution by applying a light force with a fingertip for 30 seconds, filled with 200 mL of phosphate buffer pH 6.8, kept at 37 ± 1 °C. After 2 minutes, a 50 rpm stirring rate to simulate the buccal cavity environment, and film adhesion was monitored up to 6 h. The time required for the patch to detach from the mucin was recorded as the mucoadhesion time.

4. Result and Discussion:

In the preliminary study, the excipients and their levels were selected based on separability, solubility in the ethanol solvent system, film forming property, flexibility and physical appearance of film. The invitro preliminary dissolution studies revealed that HPMC K4M and Methylcellulose 400cps are excellent film forming polymer and hydrophilic PVP K-30 as mucoadhesive agent. The bilayered film was designed with ethylcellulose as backing membrane and the drug incorporated in mucoadhesive layer.

A 3^2 full factorial design approach was employed to build the quality into formulation and thus showed the predictive drug release characteristics. The combined effect of two formulation independent variables i.e. HPMC K4M content (X_1) and Methyl cellulose Content (X_2) were investigated. Results of multiple regression analysis revealed that the independent variables significantly affected the dependent variables.

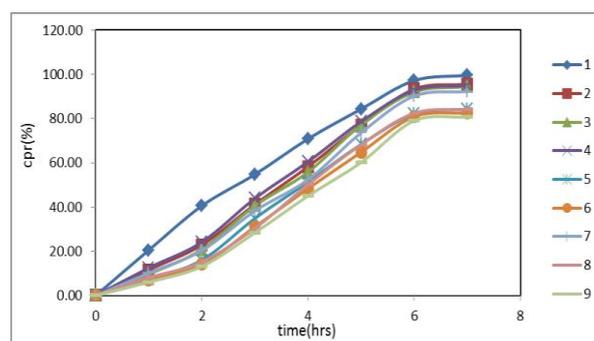


Figure 1 :Comparison of in-vitro dissolution profile of batches A1 to A9

Table 4: Release at 2, 4 and 6 hours of drug for batches A1 – A9.

Batch code	X ₁	X ₂	Y ₁	Y ₂	Y ₃
A1	-1	-1	40.59	70.85	97.24
A2	0	-1	22.91	58.28	93.41
A3	1	-1	20.90	55.87	92.02
A4	-1	0	24.18	60.52	92.86
A5	0	0	16.04	51.33	82.05
A6	1	0	14.07	48.35	80.91
A7	-1	1	20.38	52.43	90.24
A8	0	1	15.16	50.17	82.48
A9	1	1	13.17	45.05	79.06

Table 5: Evaluation Results of the designed batches

Batc h	Folding Endurance	Surface pH	Swelling index	Drug content uniformity	Tensile strength (kg/cm ²)
A1	170	6.52±0.21	4.5	99.12±0.51	8±0.6
A2	>200	6.82±0.11	2.2	97.18±0.14	5±0.2
A3	>200	6.92±0.10	3.5	99.0±0.62	7±0.4
A4	>200	6.62±0.18	1.7	100.45±0.43	6±3.3
A5	155	6.77±0.19	3.5	99.62±0.21	7±0.9
A6	140	6.42±0.13	5.5	99.65±0.20	11±0.3
A7	>200	6.32±0.21	3	99.72±0.23	10±2.5
A8	165	6.97±0.10	4.8	98.90±1.11	9±0.6
A9	150	6.84±0.29	5	98.19±1.11	10±2.2

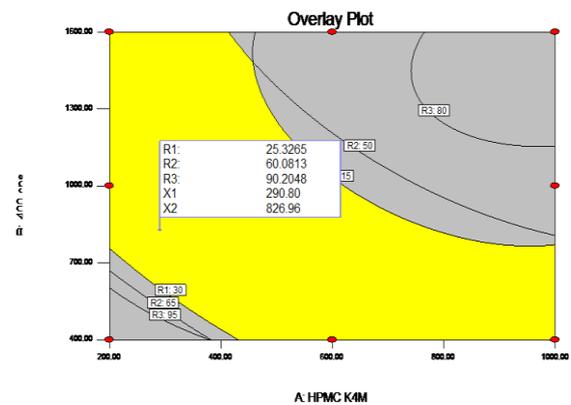
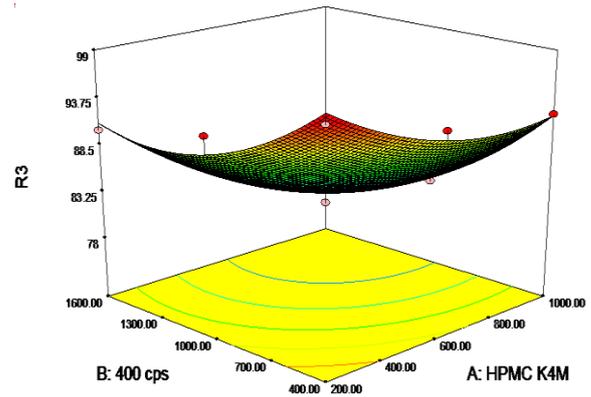
The selection of regression coefficients was done on the basis of P value (< 0.05)

Table 6: Reduced model

$Y_1 = 15.31 - 6.168 X_1 - 5.948 X_2$
$Y_2 = 51.89 - 5.75 X_1 - 6.22 X_2$
$Y_3 = 83.45 - 4.725 X_1 - 5.15 X_2$

The reduced models developed for all responses gave us nearly same values as the experimental values. So, the reduced models can be named as valid reduced model equations for the given full factorial design.

This Contour plot shows the effect of concentration of HPMC K4M(X1) and concentration of MC 400cps (X2) on Percent of drug release in 6 hours (Y3). All the responses showed non-linear relationship with the HPMC K4M content and Methylcellulose (400 cps) content. So to obtain all the predicted results in one formulation, overlay plot was drawn and the optimized region was identified.



4.1 PREPARATION OF CHECKPOINT BATCH

Table 7: Composition of Optimized Formulation: Check point batch

Variables	Quantity (%)	Response variables	Predicted %
X ₁ : HPMC K4M Content	1.45	Y ₁ : Cumulative % drug released in 2 hr	25.33
X ₂ : Methylcellulose (400 cps) Content	4.13	Y ₂ : Cumulative % drug released in 4 hr	60.08
		Y ₃ : Cumulative % drug released in 6 hr	90.20

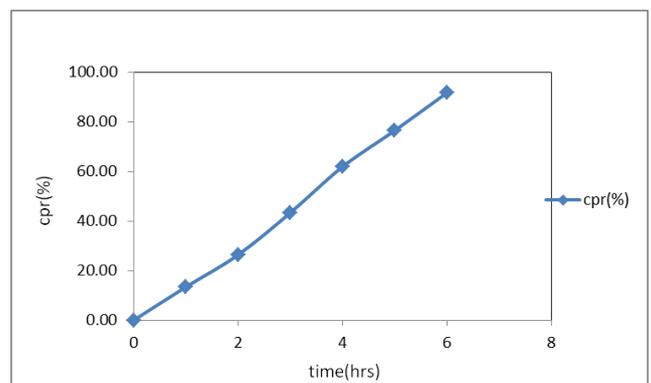


Figure 2: In – vitro release of Optimized Batch C1

4.2 VALIDATION OF THE MODEL

Table 8: Comparison between the Experimental and Predicted Values for the check point batch

Check point Batch	Response	Predicted	Observed	Constraints (%)	Residuals	Predicted error (%)
C1	Y1	25.33	26.34	15-30	-1.01	3.987
	Y2	60.08	61.82	50-65	-1.74	2.896
	Y3	90.20	91.64	80-95	-1.44	1.596

$$\text{Predicted error (\%)} = \frac{(\text{observed value} - \text{predicted value})}{\text{predicted value}} \times 100$$

The results show a good relationship between the experimental and predicted values, which confirms the practicability of the model. Hence, it may be concluded that required product characteristics could be obtained by systematic approach to the formulation development study.

4.3 DEVELOPMENT OF OPTIMIZED FORMULA

Table 9: Formula of optimized batch on the basis of overlay plot

SR.NO	INGREDIENTS	Quantity (%)	Quantity (Actual)	USE
1	Ethylcellulose (Acetone : Isopropyl alcohol = 65:35 as solvent)	2	400 mg	Backing layer
2.	Valsartan	0.2	40 mg	Antihypertensive agent
3.	HPMC K4M	1.45	290 mg	Film former, mucoadhesive polymer
4.	Methylcellulose (400cps)	4.13	826.96 mg	Film former, release retardant
5.	PVP K-30	1	200 mg	Mucoadhesive polymer
6.	PEG400 (% of polymer concentration)	10	10%	Plasticizer
7.	Ethanol (70%) : Water	qs	q.s 20 ml	Solvent system

4.4 EVALUATION RESULTS OF OPTIMIZED BATCH

Table 10: Evaluation of optimized batch

SR.NO	PARAMETERS	RESULTS
1	Folding Endurance	>200
2	Surface pH	6.88±0.18
3	Swelling Index	4.2 ±0.56 %
4	Drug Content Uniformity	99.1 ± 0.72 %
5	Thickness of film	0.42 ±0.5mm
6	Tensile Strength	0.118Kg/cm ²
7	Ex vivo mucoadhesion time	320 minutes

The optimized bilayered film batch exhibited Surface pH 6.88, Swelling index 4.2 % ,Tensile strength 118g/cm², 91.64% drug release in 6 hours, Exvivomucoadhesion time 320 minutes and also releases the drug in unidirectional fashion towards the mucosa till 6 hours. Thus, ultimately we formulated buccoadheivealsartan films with better drug delivery. Improved bioavailability and reduced dosing leads achievement of improved patient compliance. The overall result of the study indicates that such buccoadheive system is an excellent drug delivery system for delivery of valsartan. It may improve the patient compliance due to its conveniency as well as its acceptability with respect to mechanical property and solubility characteristics. In Conclusion, The optimized mucoadhesive buccal dosage forms is expected to provide clinicians with a new choice of an economical, safe and more bioavailable formulation in the management of hypertension.

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