AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and Evaluation of Mucoadhesive Buccal Patch of An Antihypertensive Drug

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ABSTRACT

Perindopril is an angiotensin converting enzyme inhibitor. The bioavailability of Perindopril following oral administration is 20 % due to high hepatic first pass metabolism. When administered orally, frequent dosing is needed due to its short biological half-life (0.8 to 1hr). sobuccal patches are one of the better option for perindopril administration. 9 Formulations were prepared using 3^2 full factorial designs by solvent-casting technique to explore the effects of sodium alginate and carbopol 934 (as independent variables) on drug release, mucoadhesive strength and retention time (as dependent variables). The prepared buccal patches were also evaluated for, weight uniformity, patch thickness, folding endurance, surface pH, swelling studies, % moisture content,% drug content, tensile strength, drug release studies, mucoadhesive strength, retention time. The ex-vivo permeation studies were carried out across excised sheep buccal mucosa using modified Franz diffusion cell. Patches exhibited drug release in the range of 70.37to 96.62% in 8 hrs. Drug release from patches followed zero order and higuchi release model and the mechanism of the drug release was due to swelling and erosion of hydrophilic polymers. The formulation was optimized with desirable drug release, mucoadhesive strength and retention time by applying computer software Design Expert 8.0.7.1. Ex-vivo drug release values for the cumulative amount of the drug permeated across the sheep buccal mucosa from optimized formulation was 76.76%. The experimented values were in good agreement with expected values for the optimized formulation which demonstrate the feasibility of the model in the development of buccal patches.

Keywords: Perindopril, Mucoadhesion, Factorial design

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Received 10 March 2013, Accepted 29 March 2013

Please cite this article in press as: Zala PR. *et al.*, Formulation and Evaluation of Mucoadhesive Buccal Patch of An Antihypertensive Drug. American Journal of PharmTech Research 2013.

INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit the oral administration of certain classes of drugs. Consequently, other absorptive mucosa is considered as potential sites for drug administration. Transmucosal routes of drug delivery after distinct advantages over peroral administration for systematic drug delivery. These advantages include possible by pass of first pass effect, avoidance of pre-systemic elimination within the G.I. tract, and depending on the particular drugs, a better enzymatic flora for drug absorption. The potential irritation and the irreversible damage to the ciliary action of the nasal dosage form as well as the large intra and inter subject variability in mucus secretion in the nasal mucosa, could significantly affect drug absorption from this site. Even though the rectal, vaginal and ocular mucosa all offer certain advantages butthe poor patient acceptability associated with these sites render them reserved for local application rather than systemic drug administration. The oral cavity on the other hand is highly acceptable by patients, the mucosa is relatively permeable with a rich blood supply. The oral mucosal drug delivery systems can be localized easily and well accepted by patients. The total surface of the oral cavity is about 100 cm. The mucosal membranes of the oral cavity can be divided into five regions such as the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingival), palatal mucosa, and the lining of the lips. These oral mucosal regions are different from each other in terms of anatomy, permeability to drug, and their ability to retain a system for a desired length of time. Although the buccal mucosa is less permeable than the sublingual mucosa and it does not yield a rapid onset of action as seen with sublingual delivery, mucosa of the buccal area has an expanse of smooth and relatively immobile surface, which is suitable for placement of retentive system. These characteristics make the buccal mucosa a more appropriate site for prolonged systemic delivery of drugs[1]. Perindopril is an angiotensin converting enzyme inhibitor and is used in the treatment of hypertension and congestive cardiac failure. The bioavailability of Perindopril following oral administration is very low. Perindopril is absorbed rapidly on oral administration. When administered orally, frequent dosing is needed due to its short biological half-life (0.8 to 1hr). Secondly drug undergoes high hepatic first pass metabolism (Bioavailability is reduced to 20 %).[1]

MATERIALS AND METHODS

Materials

Perindopril was gifted by Zydus research Centre, Ahmedabad. Sodium alginate, carbopol 934 was purchased from Yarrow chem. Ltd (Mumbai). All chemicals used were of analytical grade .sheep buccal mucosa is obtained from local slaughter house.

Design of Experiments[2,3]

Table 1: Actual and coded values1

Factors	Actual values			Coded values		
	Low level	Medium level	High level	Low level	Medium level	High level
X_1- Con. Of Sodium alginate	400	450	500	-1	0	+1
X_2- Con. Of Carbopol 934	50	100	150	-1	0	+1

Based on evaluation of prototype formulation, two polymers were found to be having predominant effect on mucoadhesive strength and drug release. A 3^2 Full Factorial design was employed to study the effect of two independent variables(X1= sodium alginate(mg) and X2=carbopol(mg)) in three different concentrations on the dependent variables like drug release,mucoadhesive strength, retention time. For sodium alginate 400, 450, 500 mg and for carbopol 50, 100, 150 mg were decided as the levels to be studied for the factors. Buccal films F1-F9 were prepared by varying the levels of the independent variables as required by the experimental design and factors levels were suitably coded. The amount of the remaining excipients was kept constant.

Methods

Evaluation of Mucoadhesive Buccal patches

Physical evaluation [3]

All the buccal patches were visually inspected for clarity, flexibility and surface texture.

Weight uniformity[4]

For evaluation of patch weight three patches of $1\times1cm^2$were cut from three different positions of the petridish and each weighed individually on a digital balance.

Thickness uniformity [5]

1 cm^2patch were subjected to measurement of thickness. For evaluation of thickness, three patches of $1\times1cm^2$each formulation was taken & the patches thickness was measured by using micrometer screw gage.

Folding endurance[6]

Three patches of each formulation of size $1\times1cm^2$ were cut by using sharp blade. Folding

endurance was determined by repeatedly folding a small strip of patch at the same place till it broke. The number of times, the patch could be folded at the same place without breaking, gave the value of folding endurance.

Surface pH[7]

The surface pH of the patches was determined in order to investigate the possibility of any side effects, in-vivo. An acidic or alkaline pH may cause irritation to the buccal mucosa; it was our attempt to keep the surface pH as close to neutral as possible. For the determination of surface pH three patches of 1×1cm^{2}of each formulation were kept in contact with 1ml of distilled water for 2hrs, in petri dish. Excess of water was drained and the pH was noted by bringing the electrode near the surface of the formulation and allowing it to equilibrate for one min.

Swelling index[8]

For the determination of swelling index the pre-weighed three patches of 1×1cm^{2}of each formulation were placed in a petridish(containing 10 ml of water).After particular interval patches was removed and wiped with tissue paper and weighed.

Formula of Swelling Index

$$S.I. = \frac{W2\text{-}W1}{W1} \times 100$$

Where-

S.I. - swelling index

W1- weight of buccal patch before dipping into beaker

W2- weight of buccal patch after dipping in beaker & wiped

% Moisture content[2]

The buccal patches were kept in Petridish in desiccator containing $CaCl_2$powder for 24 hrs. The initial and final weight of patch is recorded. Moisture content values were calculated using the formula.

$$\text{Moisture content \%} = \frac{\text{initial wt.} - \text{final wt.}}{\text{final wt.}} \times 100$$

% Drug content[9]

Three patches of 1×1cm^{2}of each formulation were taken in separate 10ml volumetric flask. 10 ml of phosphate buffer pH6.8 was added and continuously stirred for 24 hr. The solution were filtered, diluted suitably and analyzed at 215 nm in a U.V. spectrometer. The average of drug

contents of three patches was taken as final reading.

Tensile strength[10]

Tensile strength of the patch was determined with JAMCO tensiometer (Mfg by PONCO MACHINE TOOLS, Ahmedabad). The sensitivity of the machine was 1 g. It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (2.5 × 1 cm^2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in g. Tensile strength is expressed as follows:

$$\text{Tensile strength} = \frac{\text{Tensile load at break}}{\text{Cross section area}}$$

In-vitro diffusion study [5]

in vitro skin permeation studies were performed by using a modified franz diffusion cell with a a receptor compartment capacity of 200 ml. the dialysis membrane was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were cut into size of 1×1 cm^2 and placed over the drug release membrane and the receptor compartment of the diffusion cell was filled with phosphate buffer pH 6.8. the whole assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm, the temperature was maintained at 37 ± 0.5˚C. The samples of 5 ml were withdrawn at time interval of 1 hrs upto 8 hrs and analyzed for drug content spectrophotometrically at 215 nm against blank. The receptor phase was replenished with an equal volume of phosphate buffer pH 6.8 at each time of sample withdrawal. The cumulative amounts of drug permeated were plotted against time.

Ex vivo permeation study[5]

Ex vivo permeation studies are carried out in modified franz diffusion cells. The patch kept on buccalepithelium. The lower side of donor compartment completely closed tied with buccal mucosa of sheep. The patch attached to mucosa should remain inside the donor compartment. Phosphate buffer of 6.8 pH added in donor chamber.

The mouth of receptor compartment is kept fixed within donor compartment. The receptor compartment of the apparatus has phosphate buffer pH 6.8 in it and magnetic bead.The receptor compartment is kept on magnetic stirrer kept on 50 rpm speed and 37^0c temperature .The sample of 5 ml withdrawn at the time interval of 1 hr up to 8 hrs and replaced with equal volume of fresh

diffusion medium. The withdrawn sample determined by UV-VIS Spectrophotometer for amount of perindopril. (Research proposal no.NRV-03/2012.)

Mucoadhesive strength[10]

The mucoadhesive strength of mucoadhesive buccal patch is measured by a modified two arm balance using sheep buccal mucosa. Sheep buccal mucosa is tied to open end of beaker and pH 6.8 buffer is added into the beaker upto upper surface of the mucosa. The patch is attached to lower side of pan with adhesive. The buccal mucosa and patch should be remaining in contact. Weight is added into another arm by. The addition of weight is stopped when buccal patch is detached from buccal mucosa. Weight required to detach the system from buccal mucosa is noted and it's called mucoadhesive strength and it's unit is gm.

$$\text{Force of Adhesion} = \frac{\text{Mucoadhesive strength}}{1000} \times 9.81$$

Retention .time[2]

The retention time is determined using modified Disintegration apparatus. The disintegration medium 900 ml of phosphate buffer pH 6.8 maintained at 37^0 C. The segment of buccal mucosa of sheep was glued to the surface of glass slab, which was then vertically attached to the apparatus. Patch was hydrated on one surface using pH 6.8 Phosphate buffer. The hydrated surface was brought into contact with the mucosal membrane & allowed the apparatus to move up & down. The time required for complete detachment of the patch from surface was recorded.

Optimization

The computation for optimized formulation was carried using software, DESIGN EXPERT 8.0.7.1 (STAT-EASE). The response parameters considered for optimization were drug release at the end of 8 hrs, Mucoadhesive strength, Retention time.

For the optimization, goal was set for dependent (response) and independent variable (factor). Constraints set for response and factor are shown in table

Table 2: Constraints

Name	Goal	Lower Limit	Upper Limit
X1- Cocentration of Sodium algimate	In the range	400	500
X2- Cocantration of Carbopol 934	In the range	50	150
% drug release	Maximum	70.37	96.62
Mucoadhesive strength (gm)	In the range	8.97	20.73
Retension time (min)	In the range	135	350

RESULT AND DISCUSSION

Table 3: Formulation table of Perindopril buccal Patches

Formulation	Drug (mg)	sodium alginate (mg)	carbopol(mg)	PG %	Distilled water (ml)
F1	77	400	50	30	15
F2	77	450	100	30	15
F3	77	500	150	30	15
F4	77	400	50	30	15
F5	77	450	100	30	15
F6	77	500	150	30	15
F7	77	400	50	30	15
F8	77	450	100	30	15
F9	77	500	150	30	15

Preparations of Buccal Patches.

The Perindopril patches were formulated by solvent casting method, by dissolving weighed quantity of drug in required volume of distilled water in a beaker. The polymer was added to another beaker and dissolved by keeping the beaker on thermostatically controlled magnetic stirrer which is maintained at 37±0.5ºC and at low speed. Then this polymer solution was added to beaker containing Perindopril. Keep The required quantity of plasticizer is added drop wise to the beaker while stirring is continued. The solution was poured into enumerated flat petridish. Funnel was kept inverted over the petridish for slow evaporation of solvent and to prevent cracking of patch. The patches were allowed to dry overnight at room temperature. Then the Patches were cut into 1×1 $cm^2$and packed in an aluminum foil and stored in desiccators for further use. Blank buccal patches were also prepared for each formulation without drug.

Table 4: Average Weight, Patch Thickness, Folding endurance, Surface pH, % Moisture content,% Drug content, Tensile strength of Perindopril buccal patches:

code	Average Weight (mg)	Patch Thickness (mm)	Folding endurance	Surface pH	% Moisture content	% Drug content	Tensile strength gm/cm^2
F1	27.67±0.577	0.165±0.0071	220±6.11	6.62±0.0252	5.87±1.995	97.27±0.468	70.57±0.42
F2	31±1	0.193±0.0058	235±3.51	6.74±0.0586	4.20±1.773	97.81±0.405	79.45±0.53
F3	35±1	0.217±0.0058	244±4.51	6.83±0.0681	6.61±1.696	96.33±0.468	85.81±0.67
F4	31.33±0.577	0.187±0.0058	258±1	6.45±0.0651	6.19±0.110	97.54±0.231	74.54±0.42
F5	35.67±0.577	0.220±0.0100	264±3	6.57±0.0208	3.73±1.582	95.65±0.616	82.50±0.75
F6	40.33±1.528	0.263±0.0058	276±2.08	6.85±0.0252	6.73±1.501	96.87±0.842	90.45±0.87
F7	35.33±0.577	0.233±0.0058	287±3.79	6.58±0.0351	4.77±1.628	94.57±0.805	81.04±0.89
F8	40±1	0.267±0.0058	299±2.08	6.55±0.0666	5.06±2.596	96.19±0.405	86.21±0.65
F9	45.33±0.577	0.293±0.0058	311±6.66	6.75±0.0252	5.88±1.246	97.81±0.405	94.76±0.42

- **Physical appearance**

All the prepared patches were observed physically and they were found to be transparent, smooth, uniform and flexible. No defects such as cracking were observed.

- **Weight uniformity:**

The weight uniformity of patches was between 27.67 to 45.33 mg suggestive of minimal deviation

- **Patch Thickness:**

The thickness of the patches varied from 0.165 to 0.293 mm.

- **Folding Endurance:**

The folding endurance was found to be in the range of 220 to 311. This data revealed that the patches did not break and had good mechanical strength along with flexibility and maintained their integrity with buccal mucosa folding when applied.

- **Surface pH**

Surface pH was found to be in the range 6.45 to 6.85 which indicates that buccal patches have neutral pH which will not be irritating to buccal mucosa.

- **% Moisture content:**

The moisture content was found to be in the range 3.73 to 6.61%.The low moisture content in the formulations resulted in stability of patches and not giving a completely dried and brittle film.

- **%Drug content:**

The drug content was in the range of 94.57 to 97.81%, which revealed that the drug content was almost uniform in all the patches with low standard deviation values.

- **Tensile strength:**

The tensile strength was found to be in the range of 70.57±0.42 to94.76±0.42gm/cm^{2}The tensile strength measures the ability of a patch to withstand rupture.

Table 5: Swelling Index of Perindopril buccal patches

Codes	Swelling Index (Time in hours)				
	1	2	3	4	5
F1	12.04±1.96	21.65±3.25	40.96±1.80	51.81±1.79	66.27±1.82
F2	13.01±3.07	40.29±5.76	51.11±2.51	66.31±1.64	76.06±2.36
F3	14.95±1.5	39.26±2.85	55.16±2.21	67.3±1.10	81.30±1.78
F4	9.62±2.92	31.17±1.13	51.58±1.57	60.22±0.97	69.87±2.07
F5	12.14±1.52	33.62±2.35	58.86±2.04	67.27±1.94	82.22±1.92
F6	9.15±1.27	42.56±3.57	67.31±1.08	75.82±1.58	85.02±2.31
F7	16.99±2.87	37.75±2.02	59.44±3.02	68.89±2.04	83.97±1.53
F8	19.84±2.52	41.32±1.26	62.80±0.53	76.04±1.30	86.87±1.62
F9	20.58±1	45.59±3.34	70.60±4.53	80.88±1.18	88.97±0.14

- **Swelling study**

Swelling study results were found to be in the range 66.27% to 88.97%.

Table 6: % CDR after 8 hrs. Mucoadhesive strength, Force of adhesion (N), Retention time of Perindopril buccal patches:

Formulation Codes	% CDR after 8 hrs	Mucoadhesive strength (gm)	Force of adhesion (N)	Retention time (min)
F1	96.62±0.780	8.97±0.252	0.088±0.0025	135
F2	84.12±0.781	14.73±0.252	0.145±0.0025	225
F3	75.71±1.030	17.77±0.379	0.174±0.0037	275
F4	95.21±0.801	10.47±0.751	0.103±0.0074	170
F5	81.69±1.283	15.70±0.624	0.154±0.0061	245
F6	71.43±2.118	19.13±0.404	0.188±0.0040	300
F7	86.87±0.808	12.47±0.321	0.122±0.0032	200
F8	78.95±0.295	16.50±0.436	0.162±0.0043	260
F9	70.37±0.604	20.73±0.252	0.203±0.0025	350

- **Mucoadhesive strength**

The mucoadhesive strength was in the range of 8.97 to 20.73 gms, which revealed that the buccal patches having higher degree of mucoadhesion and which will not easily detached from buccal mucosa.

- **Retention time**

The retention time was in the range of 135 to 350 min. which revealed that the buccal patches will not easily detached from buccal mucosa.

Release kinetic models

It was found that the release of Perindopril from the buccal patch followed zero-order kinetics. The coefficient of determination (R^2) was found to be much closer to 1 for zero order equation. This suggests that the drug permeation from buccal patches, possibly owing to swelling of hydrophilic polymer and also follows higuchi model for the release of drug from a homogeneous polymer matrix type delivery system that depends mostly on diffusion characteristics.

Table 7: Kinetic release parameters for Perindopril buccal patches

Formulation	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Korsmeyer-Peppas (R^2)	(n)
F1	0.919	0.965	0.963	0.811	0.084
F2	0.958	0.986	0.967	0.842	0.092
F3	0.988	0.984	0.931	0.889	0.114
F4	0.933	0.958	0.961	0.824	0.089
F5	0.969	0.975	0.959	0.865	0.095
F6	0.991	0.965	0.919	0.91	0.116
F7	0.943	0.987	0.97	0.813	0.089
F8	0.988	0.978	0.947	0.869	0.107
F9	0.991	0.965	0.889	0.917	0.131

Response 1:% Drug Release at the end of 8 hrs.

The F-value of 48.87 indicates that the Mathematical model for Rel 8 h was significant(R-Squared 0.9879). The factors A, B, AB, A^2 andB^2were found to have a significant infiuence on the drug release. The polynomeal equation generated for the Rel 8h is represented in this equation.

% Drug Release =+81.81-10.53 * A-3.71 * B+1.60 * A * B+1.45 * A^2-0.34 * B^2

The negative influence of the Concentration of Sodium alginate and Carbopol 934 on the Release at 8 hours is clearly evident from the one factor plot and the mathematical model generated. The negative influence of the Concentration of Sodium alginate and Carbopol 934 on the Release at 8 hours was noticeable from the 3D plot and also from contour plots.

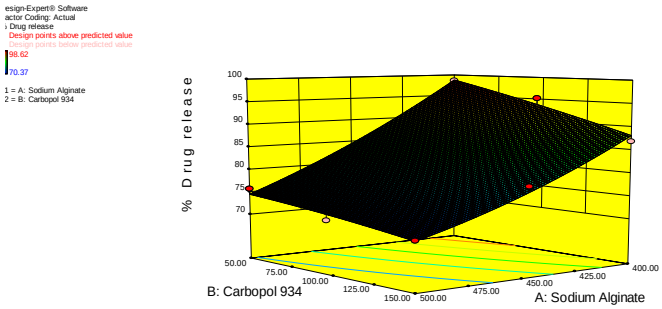

Figure 1: 3D Response surface plot showing the effect of concentration of Sodium alginate and Carbopol on Drug Release(8hrs)

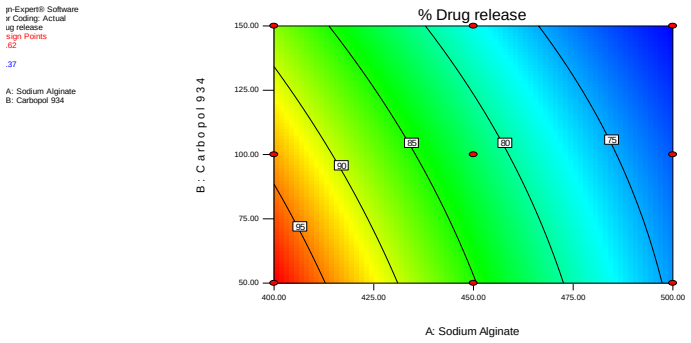

Figure 2: Contour plot showing the effect of concentration of Sodium alginate and Carbopol on Drug Release(8hrs)

Response 2:Mucoadhesive strength (gm)

The F-value of 95.46 indicates that the polynomial model for Mucoadhesive strength was significant (R-Squared 0.9938). The factors A, and B were found to have a significant infiuence on the Mucoadhesive strength. The polynomial equation generated for the responseMucoadhesive strength is represented in this equation.

Mucoadhesive strength =+15.59+4.30 * A+1.38 * B-0.15 * A * B-0.73 * A^2+0.083B^2

Concentration of Sodium alginate and Carbopol 934 were found to have a significant influence on Mucoadhesive strength which is evident from Mathematical model generated. The positive influence of Concentration of Sodium alginate and Carbopol 934 on Mucoadhesive strength was noticeable from the 3D plot and contour plot. The 3D plot and contour plots revealed the fact that as the concentration of Carbopol 934 increased Mucoadhesive strength was found to increase but Sodium alginate less affect on Mucoadhesivestrength.

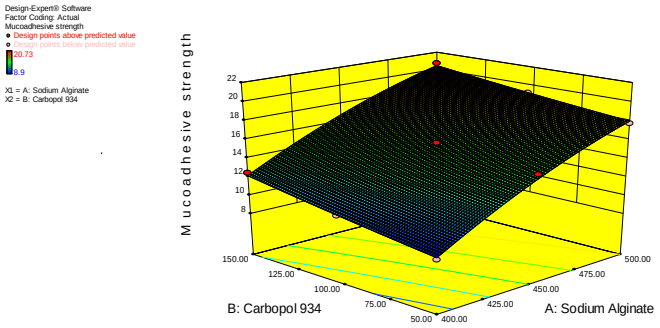

Figure 3: 3D Response surface plot showing the effect of concentration of Sodium alginate and Carbopol on Mucoadhesive strength

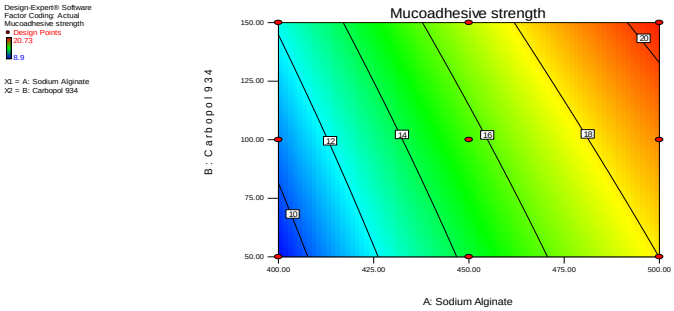

Figure 4: Contour plot showing the effect of concentration of Sodium alginate and Carbopol on Mucoadhesive strength

Response 3 : Retention Time (min)

The F-value of 40.83 indicates that the polynomial model for Retention Time was significant (R-Squared 0.9855). The factors A, and B were found to have a significant infiuence on theRetention Time. The polynomial equation generated forRetention Time is represented in this equation.

Retention Time = =+241.67+70.00 * A+29.17 * B+2.50 * A * B-5.00 * A^2+2.50 * B^2

The Concentration of Sodium alginate and Carbopol 934 were found to have a significant influence on Retention time.The positive influence of Concentration of Sodium alginate and

Carbopol 934 on Retention timewas noticeable from the 3D plot and contour plot. The 3D plot and contour plots revealed the fact that as the concentration of Carbopol 934 increased Retention time was found to increase but Sodium alginate less affect on Retention time.

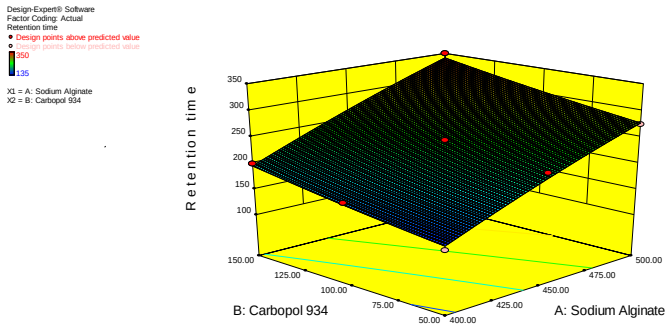

Figure 5: 3D Response surface plot showing the effect of concentration of Sodium alginate and Carbopol on Retention Time

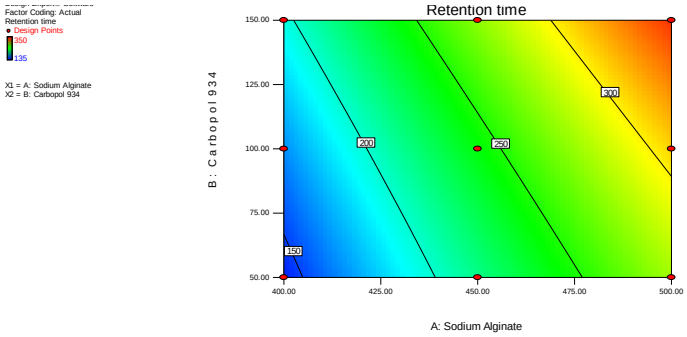

Figure 6: Contour plot showing the effect of concentration of Sodium alginate and Carbopol on Retention Time

Optimized formulation

Table 8: Compositions of theOptimized Formulation

Ingredients	Quantity(mg)
Concentration of Sodium alginate	435
Concentration of Carbopol 934	105

Evaluation of optimized formulation:

The optimized formulation were evaluated for different responses parameters like % Drug release, and Mucoadhesive Srength,Retention Time.

Table 9: Observed values and predicted values of optimized formulation

Responses	Observed	Predicted
% Drug release after 8h	79.64±2.062	81.94
Mucoadhesive strength (gm)	16.17	15.27
Retention time (min)	250	248.54

Table 10: Difussion data of Optimized formulation

Time (hrs)	% CDR In-vitro drug release	% CDR ex vivo drug release
1	14.02±1.344	12.5
2	23.23±1.835	20.17
3	39.24±1.288	38.03
4	50.74±1.293	49.41
5	57.04±1.058	55.69
6	62.01±1.020	62.51
7	69.20±0.595	71.4
8	79.64±2.062	76.76

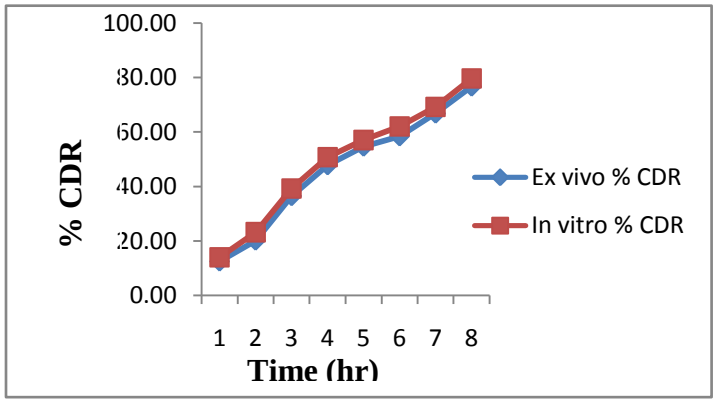

Figure 7: Optimized formulation

Ex vivo drug permeation of Perindopril buccal patch using porcine mucosa showed 12.5% To 76.76%during 8 hours. The correlation between *In vitro* drug release and *Ex vivo* drug permeation through sheep buccal mucosa with a correlation coefficient from 0 .9744to 0.9739.

Stability Protocol

Stability studies were carried out on the optimized formulation. Patches of optimized formulation were first wrapped in aluminum foil then placed in stability chamber at 40 ^{o}C, 75% $\pm$ 5% relative humidity for 1 month. Patches was evaluated for physical characteristics; mucoadhesive properties, and in vitro drug release. Results obtained were compared with data obtained for zero time.

Table 11: % Drug release of optimized Perindopril patch before and after one month.

Time (hrs)	% Drug Release at zero month	% Drug Release after one month
1	14.02±1.344	12.5
2	23.23±1.835	21.5
3	39.24±1.288	37.25
4	50.74±1.293	49
5	57.04±1.058	55.86
6	62.01±1.020	60.28
7	69.20±0.595	67.68
8	79.64±2.062	77.34

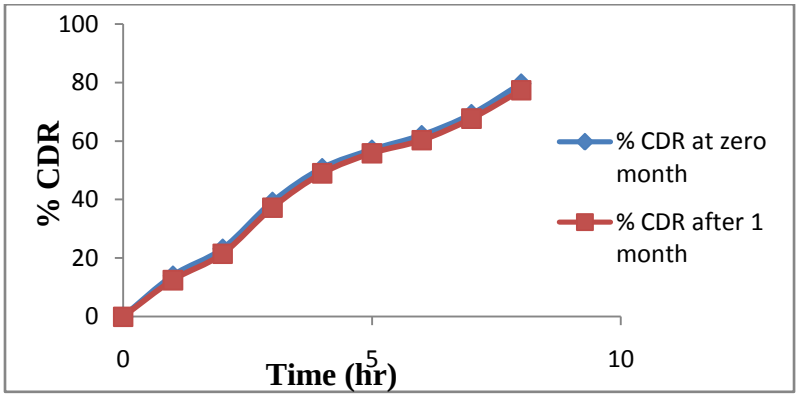

Figure 8: In vitro Drug Release profiles

CONCLUSION

In this work, an attempt was made to formulate and evaluate controlled release buccal Perindopril patches using statistical optimization technique. The Perindopril buccal patches were formulated by solvent casting technique employing Factorial design 3^2. The factors investigated included were concentration of Sodium alginate and Carbopol 934 as indepependent factors and % drug release, Mucoadhesive strength, and retention time as dependent factors. The software used was DESIGN-EXPERT VERSION 8.0.7.1 (STAT-EASE INC) demo version software. The response parameters were analyzed by ANOVA and mathematical models for each response parameters were generated using MLRA. The optimized formulation developed by setting constraints on dependent and independent variables. The optimized formulation developed was and evaluated for the response parameters. The experimental values were compared with those of predictor values by mathematical model. The actual response values were in accordance with those obtained from the predictor equation.

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