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FORMULATION, OPTIMIZATION AND EVALUATION OF SIMVASTATIN BUCCAL PATCH FOR LOCAL TREATMENT OF PERIODONTITIS

[1]Ashwini R. Madgulkar, [1]Mangesh R. Bhalekar, [1]Sayali S. More* and [1]Shraddha K. Pardeshi

[1]Department of Pharmaceutics, AISSMS College of Pharmacy, Pune-411001, India.

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***Corresponding Author**
Sayali S. More
Department of Pharmaceutics, AISSMS College of Pharmacy, Pune-411001, India.

ABSTRACT

The aim and objective of this study was to develop mucoadhesive buccal patch of Simvastatin for the local treatment of periodontitis. Simvastatin has short biological half-life (3 h), high first-pass metabolism and poor oral bioavailability (5%), hence an ideal candidate for buccal (local) delivery system. Simvastatin patch was developed by using mucoadhesive polymer as Chitosan and HPMC K4M as hydrophilic in nature. Propylene glycol 40% of total polymer weight was used as plastisizer. Patch was prepared by solvent casting method. Prepared patches were evaluated using different test such as weight uniformity, thickness, pH, swelling index, folding endurance, *In-vitro* drug release and permeation studies. The formula was optimized using DOE 3^2 factorial design and was checked for the effect of Chitosan and HPMC K4M on Folding endurance, % Drug release, Mucoadhesion. It was found that as the concentration of Chitosan and HPMC K4M increases there is decrease in drug release and increase in folding endurance and Mucoadhesion property.

KEYWORDS: Simvastatin, Buccal patch, Periodontitis, Chitosan, HPMC K4M, Mucoadhesion.

INTRODUCTION

Periodontitis means "inflammation around the tooth" - it is a serious gum infection that damages the soft tissue and bone that supports the tooth. It is the infection which affect the *Periodontium* (it is a tissue around the tooth and which supports the tooth). With Periodontitis

alveolar bone is slowly and progressively lost. Dental plaque if not removed with brushing it hardens and forms tartar/calculus. Plaque can gradually and progressively damage the tissues around the teeth if not removed it leads to gingivitis (inflammation of gums). Lack of proper care can lead to formation of pockets between teeth and gums (bacteria starts to grow in these pockets leading to further damage of nerve and connective tissue). Further these bacteria starts damaging soft tissue and bone that supports the tooth ultimately leading to tooth loss. Treatment to Periodontitis include oral and local therapy but oral treatment has low bioavailability and hence local treatment such as patch / films, gels, strips, fibers are preferred.[1]

Simvastatin besides being statins i.e. lipid lowering agent has been reported to aid bone regeneration and has anti-inflammatory property for Periodontitis therapy. It has certain disadvantages like short biological half-life (3 h), high first-pass metabolism and poor oral bioavailability (5%) hence, it can be considered ideal candidate for local treatment of Periodontitis.[2,3]

In the present study Chitosan and HPMC K4M were used to develop a film containing Simvastatin for local treatment of periodontitis.

MATERIAL AND METHOD

Material

Simvastatin was received as gift sample from Astron Research limited, Ahmedabad. Solvents used were of analytical grade. All other chemicals and excipients were procured from local sources and were of analytical grade.

Method

Preparation of mucoadhesive buccal patch

Mucoadhesive layer containing drug[4]

Mucoadhesive layer containing Simvastatin was prepared by the solvent casting technique; Propylene glycol was used as plasticizer, and Chitosan and HPMCK4M as Mucoadhesive and hydrophilic polymer (Table 1). The formula was optimized using a 3^2 full factorial design (Design Expert, Version 11, Stat-Ease Inc., Minneapolis, MN, USA). Chitosan and HPMC K4M were used as polymer in different concentration as shown in Table 1.

Chitosan was dissolved in 1% glacial acetic acid by continuous stirring using magnetic stirrer and was kept overnight to get clear solution. Simvastatin was dissolved in ethanol and HPMC K4M was added to it. Both solutions were mixed, and Propylene glycol was added with stirring till uniform solution. This solution was kept overnight to get rid of entrapped air, poured on petri plate previously greased with silicon oil and was allowed to dry to allow uniform drying at room temperature (Table 2).

Backing layer[5]

Ethyl Cellulose (5% w/v) was dissolved in a mixture of Acetone and Isopropyl alcohol (6:4) to this propylene glycol (40% w/w of polymer) was added as the plasticizer. This solution was sprayed on one side of Simvastatin patch by Pharma R and D Coater keeping parameters as spraying rate 1 ml/min, RPM 1 minute and Pressure between 0-5 kg/cm^2. This sprayed patch was then allowed to dry. After drying patches were wrapped in aluminium foil and kept in dessicator till further studies.

CHARACTERIZATION OF SIMVASTATIN

Calibration of drug by HPLC method[6]

Calibration of Simvastatin in phosphate buffer pH 6.8 was performed by HPLC method. The stock solution of drug 1000 µg/ml was prepared in phosphate buffer pH 6.8. Further dilutions 2, 4, 6, 8, 10, 12, 14 µg/ml were prepared and analyzed using HPLC (Agilent technologies pvt. Ltd.). Mobile phase used was Acetonitrile:Methanol:Water (50:40:10) having λmax of 238 nm, flow rate of 1ml/min and retention time as 4.6 minutes.

Drug-polymer compatibility study[2]

The physicochemical interactions between Simvastatin and excipients used in the formulation of buccal patch (Chitosan, HPMC K4M and Propylene glycol) were studied using Fourier transform infrared spectroscopy (FTIR). Drug and excipients (1:1) were stored in hermetically sealed glass vials at 40°, 75% RH for one month. The infrared spectra were recorded in the FTIR (Schimadzu, Japan) instrument in the wave length region between 4400 and 600 cm^{-1} by KBr pellet method. The spectra obtained for drug, polymer and physical mixture of drug and polymer were compared and checked for any interaction.

Experimental design and statistical analysis

In this study, a 3^2 full factorial design was employed to optimize the formulation of patches. In order to optimize formulations, the amount of Chitosan and HPMC K4M was chosen as

independent variables whereas responses chosen were Drug release, Folding endurance and Mucoadhesion force.

Analysis of data

The data obtained by experimental design was evaluated using Design expert 11.0 software. 3D response surfaces curves were constructed to study the effect of two independent variables alone and in combination on drug release, folding endurance and mucoadhesion (Table 1). All the responses, observed were simultaneously fitted to quadratic models and were evaluated in terms of statistical parameters to get optimized batch of formulation. The experimental values of the responses were quantitatively compared with that of the predicted values by calculating residual and linear plots.

Table 1: Independent variable and their selection for formulation of patch.

Variables			Levels		
			-1	0	+1
A		Concentration of Chitosan (mg)	400	600	800
B		Concentration of HPMC K4M (mg)	100	200	300
Responses			**Goals**		
Y1		Drug release	In range		
Y2		Folding endurance	Maximum		
Y3		Mucoadhesive force	Maximum		

Table 2: The 3^2 factorial design of composition of patches containing Simvastatin.

Batch code	Simvastatin (mg/cm^2)	Chitosan (mg)	HPMC K4M (mg)	Propylene glycol (ml)
F1	2.5	400	100	0.19
F2	2.5	600	100	0.26
F3	2.5	800	100	0.34
F4	2.5	400	200	0.23
F5	2.5	600	200	0.30
F6	2.5	800	200	0.38
F7	2.5	400	300	0.26
F8	2.5	600	300	0.34
F9	2.5	800	300	0.42

EVALUATION OF SIMVASTATIN PATCHES

Weight uniformity[2]

The individual weight of 3 patches (1 cm^2) from each batch was determined using an electrical balance. The results were expressed as mean and standard deviation.

Thickness uniformity[3]

Patch thickness was measured at 5 different points i.e. one at the centre and four at different corners using the Vernier Caliper (Aerospace). The results were expressed as mean and standard deviation.

pH of patch[7]

The films (1 cm^2) were soaked in 5ml of distilled water for 1h at room temperature. The surface pH was recorded by mounting the electrode on the surface of the swollen film and allowing it to equilibrate for 1 minute. The experiment was performed in triplicate. The results were expressed as mean and standard deviation.

Folding endurance[8]

Folding endurance was determined by repeatedly folding the film at the same place till it breaks or folded up to 300 times without breaking. The results were expressed as mean and standard.

Swelling index[9]

Polymers have a tendency to absorb water and swell. Thus, swelling index study was performed to study the hydration characteristics of the film. 1 cm^2 patches were weighed separately (initial weight= W1) and placed in petri plates containing 5 ml phosphate buffer pH 6.8 and allowed to swell. The swollen films were weighed individually after 90 minutes (Final weight = W2). Swelling index of each system was calculated using the following formula:

$$\text{Swelling index} = \frac{(W2-W1)}{W1} \text{ X } 100 \qquad \text{..... (1)}$$

Drug content[10]

The medicated patch (4 cm^2) containing 10mg of Simvastatin was dissolved in 50 ml Ethanol. The solution was suitably diluted with with mobile phase [Acetonitrile:Methanol:water (50:40:10)] to get the final concentration 10 µg/ml .This solution was analyzed by HPLC . The experiment was performed in triplicate and the drug content was expressed as percentage using following equation:

$$\% \text{ Drug content} = \frac{\text{Experimental drug content}}{\text{Theoretical drug content}} \text{ x } 100 \qquad \text{..... (2)}$$

In vitro Mucoadhesion test[11]

The Mucoadhesion force of the patches was measured using Texture Analyzer (CT3 Texture Analyzer, Make-Brookfield Engineering Labs, Inc., Model Texture Pro CT V1.4 Build 17) equipped with a 5 g load cell. The measurement of Mucoadhesive force was done on excised goat buccal mucosa which was procured from slaughter house. Buccal mucosa was tied to the probe. The patch was placed between two circular discs which was wetted with phosphate buffer pH 6.8 before the study. The upper circular disc had a cavity of 12.7 mm diameter through which the mucosal membrane was exposed to the probe. The probe and circular cavity were aligned to ensure that film comes into direct contact with exposed surface of mucosal membrane. The probe with the skin was lowered at a speed of 1.0 mm/s and skin was kept in contact with the patch for 10.0 seconds with 5 g load and trigger value of 50 after which the probe was taken back at the speed of 1 mm/s. Data collection and calculations were performed using Texture- Pro CT V1.3 Build 14 software. The adhesive force and adhesiveness were used to evaluate the Mucoadhesive strength of film.

In vitro Mucoadhesion time[9]

The *In vitro* residence time of Simvastatin films was evaluated by assessing the time required for the films to detach from goat buccal muocsa. this test was performed for optimized patch (F9). The test was carried in disintegration apparatus using 500 ml phosphate buffer pH 6.8 maintained at 37°. The goat buccal mucosa was fixed by tying with thread while mucosal side facing up on the surface of a glass slide. The mucosa was moistened with phosphate buffer solution (pH 6.8). The film (1 cm^2) was wetted with the same buffer and was pasted to the goat buccal mucosa by applying a light force with fingertip for one minute and was allowed to move up and down so that the patch was completely immersed in and out of buffer solution. The time taken by the patch to detach from the mucosal surface was recorded and the averages of three reading was recorded.

In vitro drug release[2]

The drug release from patch was studied using USP type II paddle apparatus. The dissolution medium consisted of 250 ml phosphate buffer pH 6.8 containing 0.15% sodium dodecyl sulfate. The later was included to ensure sink conditions. The release studies were performed at 37±0.5°, at a stirring rate of 50 rpm. Buccal patch (4 cm^2) which contains 10 mg Simvastatin was glued to watch glass with cynoacrylate adhesive from one side to ensure unidirectional drug release. The watch glass was placed in bottom of the vessel so that the

patch remain on the upper side of the watch glass. Samples (5 ml) were withdrawn after 1 h interval upto 6 h and replaced with equal volume of fresh dissolution medium to maintain sink condition. The samples were filtered and suitably diluted with mobile phase which was analyzed by HPLC.

***In vitro* diffusion studies**[5]

Drug diffusion studies were carried out by using Franz diffusion. Goat buccal mucosa procured from slaughter house was mounted on a diffusion cell in between the donar and receptor compartment. The buccal patch (3.14 cm^2) F9 (optimized batch) was fixed on the buccal mucosa. Receptor compartment was filled with Methanolic:Phosphate buffer 7.4 (3:7). The fluid was maintained at 37±2° and stirred continuously at 50±2 rpm. Aliquots of 1ml were collected at predetermined intervals for 6 h and suitably diluted, filtered through 0.22 µm filter and analyzed by HPLC. Same Methanolic:Phosphate buffer pH 7.4 (3:7) 1 ml was replaced in the receptor medium to maintain the sink condition

Percentage moisture absorption[3]

Formulated patch (F9) was weighed (W1) and exposed to 84% relative humidity using saturated solution of potassium chloride in desiccators until a constant weight (W2) is achieved. % moisture uptake was calculated by following formula:

x 100 .....(3)

Percentage moisture content[3]

Weighed formulated patch (F9) (W1) were placed in dessicator containing calcium chloride at room temperature for a period of 24 hours. Patch was then weighed again (W2). % moisture content was calculated using following formula:

$$\% \text{ moisture content} = \frac{W1-W2}{W2} \times 100 \qquad .....(4)$$

RESULT AND DISCUSSION

Charachterization of drug

Calibration of Simvastatin by HPLC

Calibration curve of Simvastatin in phosphate buffer pH 6.8 was established using HPLC having parameters as λmax 238 nm, flow rate 1 ml/min and retention time of 4.6 minutes. Linearity in the range of 2-10 µg/ml was evaluated using five concentration levels with three

replicate at each level. A linear regression equation was obtained (y=131228x-42102) with a regression coefficient (R^2) of 0.9997 (fig. 1).

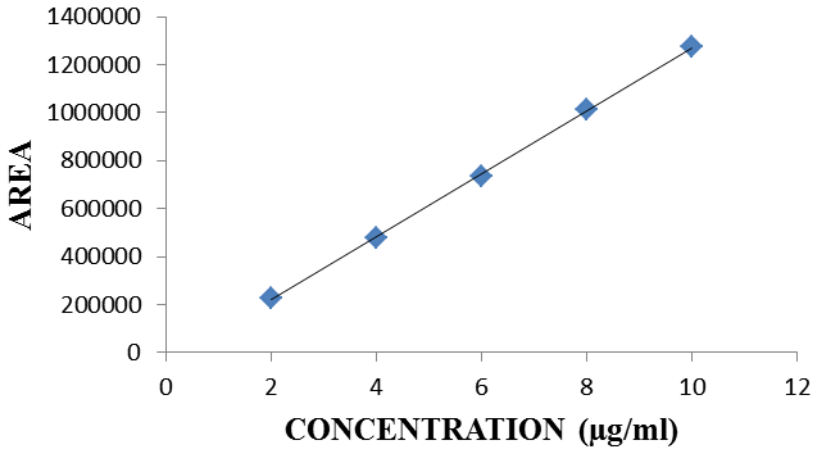

Fig. 1: Calibration of Simvastatin in Phosphate buffer pH 6.8.

Drug-Polymer Compatability

This test was carried out to check the interaction of drug and polymer. The FTIR spectral analysis of Simvastatin showed the principal peaks were observed at wave numbers 3530.10, 3047.18, 2930.37, 1729.97, and 1701.26 cm^{-1} confirming the purity of the drug. In the FTIR spectra of the physical mixture of Simvastatin, HPMC K4M, Propylene glycol the major peaks of Simvastatin were observed at wave numbers 3515.90, 3060.82, 2933.18, and 1719.66 cm^{-1}. By compairing the graph of both Simvastatin and its physical mixture it was observed that all the peaks lie in their appropriate range. No new peaks were observed which indicated there is no interaction between drug and other excipients (fig. 2).

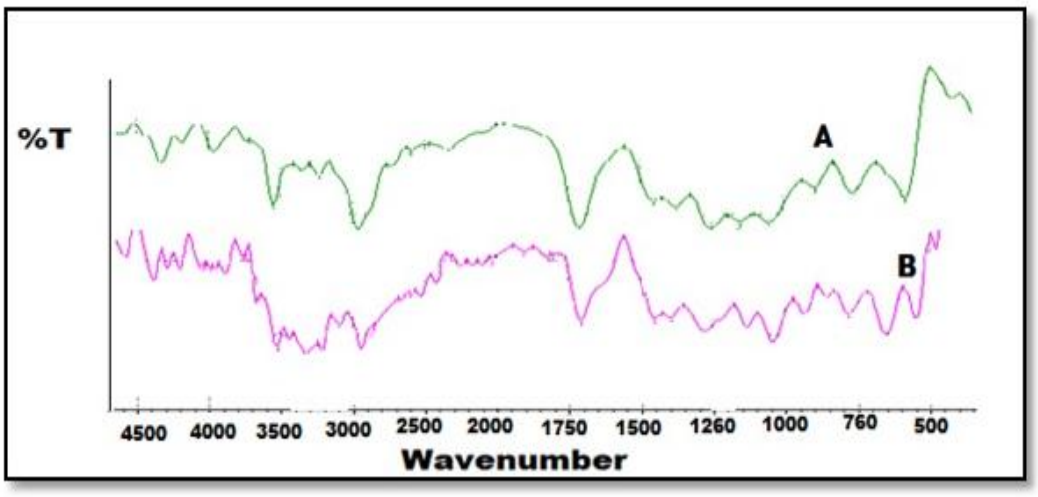

Fig. 2: FTIR spectra A) Simvastatin and B) Physical mixture.

EVALUATION OF PATCHES

Weight uniformity

The weight of patches of 1 cm^2 ranged from between 12.4±0.05 to 28.2±0.01. Results revealed increase in weight was consistent with polymer concentration (Table 4).

Thickness of uniformity

Prepared patches were smooth, uniform and flexible. Thickness of patches was found to be between 0.08±0.01 to 0.2±0.04 mm. Each batch showed uniformity of thickness of patch (Table 4).

pH of patch

The Surface pH of the prepared buccal patch was determined to check possible irritation potential of the film. Surface pH of all the patches was found to be in the range 6.51±0.4 to 6.84±0.1 which is close to oral cavity pH 5-7.5. This indicates that no irritation will occur on application of the patches (Table 4).

Folding endurance

Folding endurance measures the ability of the patch to withstand the mechanical rupture which should be minimum 300, all the patches were found to be in the range of 354-392, Thus indicating adequate strength of patches (Table 4).

$$\text{Folding endurance} = 377.96 + 9.67A + 8167B - 2.25AB - 1.37A2 - 3.37B2 \quad \text{..... (5)}$$

The above equation shows quantitative effect of independant variable on the folding endurance of the patch. The value of co-relation R^2 was found to be 0.8808.

As per the equation 5 it can be inferred that both polymers Chitosan and HPMC K4M has positive effect leading to the conclusion that as the concentration of the polymers will increase the folding endurance will also increase thus making the patch less flexible (fig. 3).

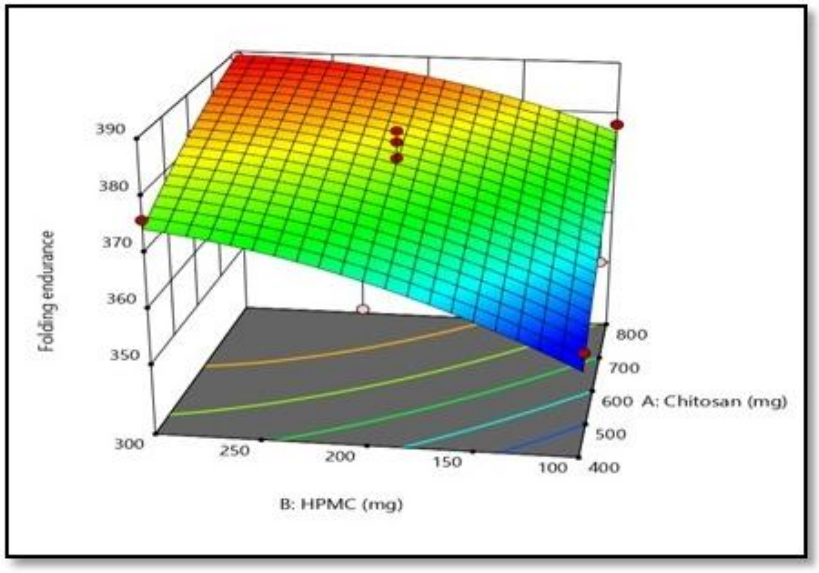

Fig. 3: Response surface plots showing effect of Chitosan and HPMC K4M on folding endurance of buccal patch.

Swelling Index[14]

Swelling Index studies are carried out to study the ability of polymer to absorb water. As HPMC K4M is hydrophilic polymer it has tendency to absorb water as its concentration in formulation goes on increasing. Fig. 4 Indicates swelling index of F1 to F9 of which F9 having higher concentration of HPMC K4M has shown higher Swelling index (Table 5). Since, swelling of patch may lead to its early detachment less swelling is preferred. F1 shows less swelling index among all patches indicating less concentration of HPMC K4M leads to less Swelling index value.

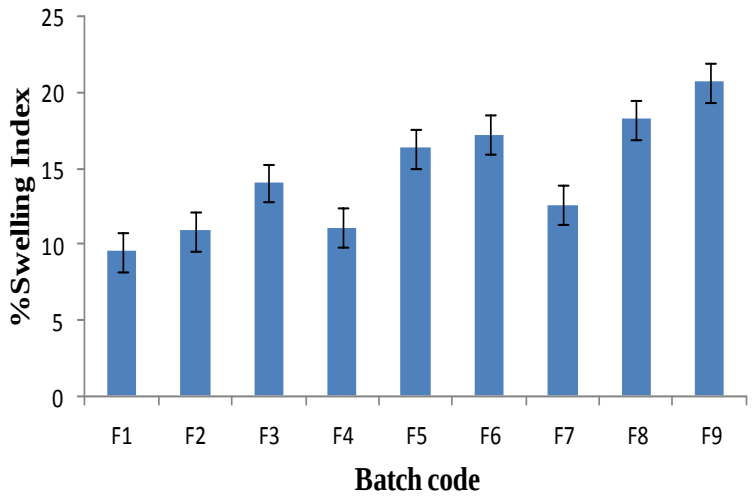

Fig. 4: Swelling index of patches in phosphate buffer pH 6.8.

% Drug content

% Drug content of all the patches was found to be in between 96.42±0.03 and 99.21±0.16. Maximum drug content was found to be in F3 batch. Values of drug content are reported in (Table 5).

***In-vitro* Mucoadhesion test**[13]

This test was performed in order to check the mucoadhesion property of the patch i.e. Adhesiveness and Adhesive (mucoadhesive) force. It was performed on goat buccal mucosa obtained from slaughter house. Chitosan being mucoadhesive in nature patch shows good mucoadhesive property. F9 showed maximum Adhesive force and Adhesiveness. Table 5 indicates mucoadhesive properties of patches F1-F9.

$$\text{Mucoadhesion force} = 19.99 + 3.78\,A + 3.35\,B + 1.90\,AB + 0.8062\,A2 + 0.3863\,B2 \quad \text{..... (6)}$$

The above equation 6 shows quantitative effect of independant variable on Mucoadhesion force of the patch. The value of co-relation R^2 was found to be 0.8999.

As the viscosity of polymer gel increases adhesive force increases, a synergistic action of both polymers may have enhanced adhesion. Since both polymers imparts mucoadhesion property its increase in concentration have increased mucoadhesion property of patch. As per the equation it can be inferred that both polymers Chitosan and HPMC K4M has positive effect leading to the conclusion that as the concentration of the polymers will increase the mucoadhesive force will also increase from the equation it can also be observed that Chitosan imparts more mucoadhesive property as compared to HPMC K4M (fig. 5).

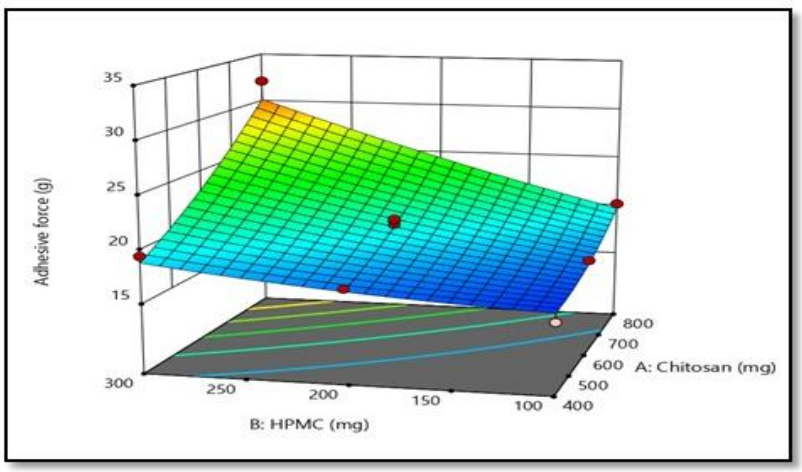

Fig. 5: Response surface plots showing effect of Chitosan and HPMC K4M on Mucoadhesive force of buccal patch.

In vitro Mucoadhesion time[14]

Even if a patch has sufficient mucoadhesive force the dilution due to biological fluids and the mechanical movements in buccal cavity may lead to its early detachment. To verify this *in vitro* Mucoadhesion (residence) time test was performed determined in USP disintegration apparatus. The mucoadhesioin time varied between 16 hours 20 minutes. Chitosan being mucoadhesive shows positive effect on mucoadhesion time i.e. as the concentration of chitosan increases mucoadhesion also increases but HPMC K4M has hydrophilic property and thus promotes detachment of patch from mucosa. Unless patch has adequate residence time with the buccal mucosa therapeutic level of drug cannot be achieved.

In vitro drug release[15]

In-Vitro cumulative % drug release of all the formulations F1-F9 are represented graphically in figure and % release at end of 6th h is shown in table 20. Highest but sustained release of drug is preferred from such formulations so that diffusion can take place (Table 3) (fig. 6).

Table 3: *In-vitro* drug release of formulation (f1-f9).

Batch code	F1	F2	F3	F4	F5	F6	F7	F8	F9
% Drug release at 6th hour	65.51	58.47	48.59	59.68	53.84	44.26	51.27	48.74	39.09

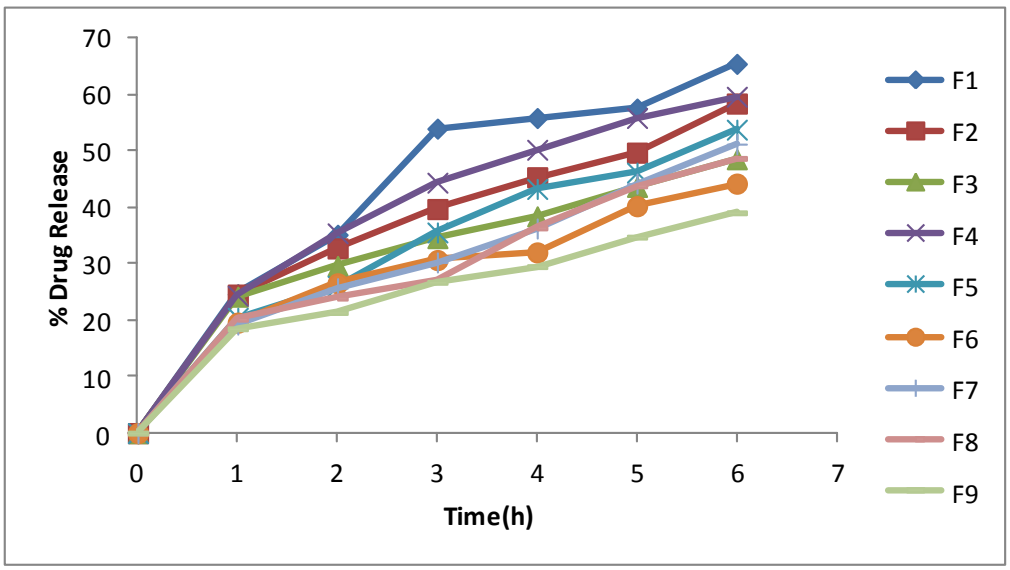

Fig. 6: In-vitro drug release of formulations (F1-F9).

$$\%\,\text{Drug release} = 55.28 - 8.92A - 7.17B + 0.7825AB - 0.2225A2 + 0.4225B2 \quad \text{..... (7)}$$

The above equation shows quantitative effect of independant variable on the % drug release of the patch. The value of co-relation R^2 was found to be 0.9440.

As per the equation 7 it can be inferred that both polymers Chitosan and HPMC K4M has negative effect on drug release leading to the conclusion that as the concentration of the polymers will increase drug release will decrease making the patch more prolonged and controlled release formulation. Chitosan has significant negative effect on drug release as compared to HPMC K4M (fig. 7).

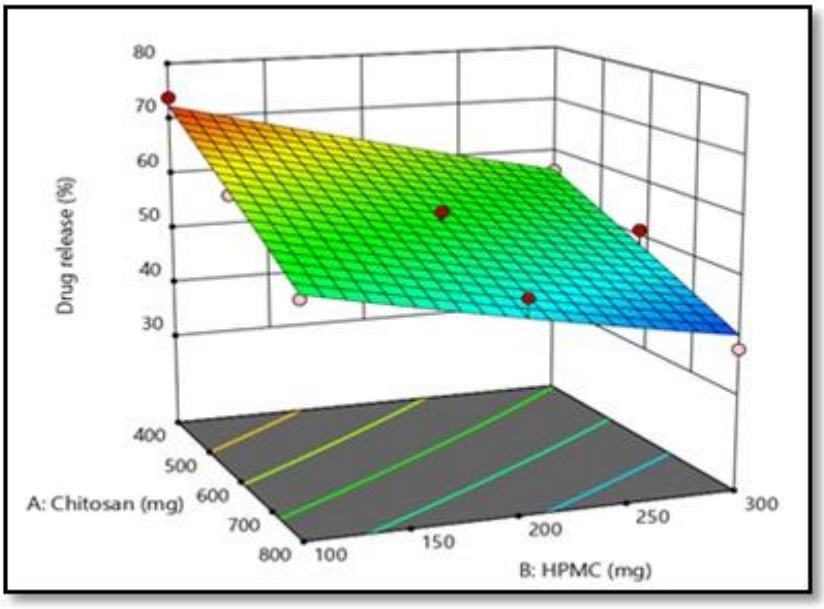

Fig. 7: Response surface plots showing effect of Chitosan and HPMCK4M on % drug release of buccal patch.

In vitro diffusion studies[15]

Considering all the parameters F9 was chosen as optimized batch from design expert software. *In vitro* studies were carried out for optimized batch (F9). Goat buccal mucosa was procured from slaughter house. Methanolic Phosphate buffer pH 7.4 (Methanol:Phophate buffer pH 7.4 in the ratio 3:7) was used as media for diffusion studies. Flux of F9 patch was found to be 1.40 mg/hr/cm^2.

Percentage moisture absorption

Percentage moisture absorption of F9 patch was found to be 1.59±0.063 indicating low moisture absorption. Moisture absorption increase as the concentration of hydrophilic polymer increases. Low moisture absorption protects the formulation from microbial contamination and also bulkiness.

Percentage moisture loss

Percentage moisture loss of F9 patch was found to be 2.27±0.183**.** Moisture absorption increase as the concentration of hydrophilic polymer increases. Patch should contain appropriate moisture to avoid microbial contamination and its bulkiness.

Table 4: Thickness, Weight, Folding Endurance, pH.

Batch Code	Thickness (mm)	Weight (mg)	Folding Endurance	pH
F1	0.08±0.01	12.5±0.2	354	6.51±0.4
F2	0.12±0.02	17.9±0.05	372	6.63±0.07
F3	0.15±0.03	19.5±0.4	377	6.57±0.2
F4	0.09±0.04	13.6±0.1	373	6.55±0.6
F5	0.16±0.01	18.9±0.1	392	6.84±0.5
F6	0.13±0.01	20.6±0.02	387	6.74±0.1
F7	0.10±0.01	15.2±0.02	378	6.61±0.9
F8	0.13±0.07	19.2±0.5	395	6.83±0.4
F9	0.20±0.04	28.3±0.01	392	6.77±0.1

Table 5: % Assay, % Swelling Index Adhesive Force.

Batch Code	Assay %	Swelling Index %	Adhesive Force (g)
F1	97.37±0.05	9.52±0.14	15.1
F2	98.41±0.42	10.9±0.08	17.4
F3	99.21±0.16	14.09±0.06	20.19
F4	96.42±0.03	11.13±0.07	17.25
F5	98.19±0.32	16.33±0.0.04	20.6
F6	99.03±0.01	17.27±0.02	22.16
F7	98.13±0.08	12.62±0.06	19.46
F8	99.01±0.06	18.24±0.06	21.17
F9	98.71±0.03	20.69±0.02	32.15

Table 6: Results of Optimized Batch F9.

Thickness (mm)	Weight (mg)	pH	Folding endurance	Swelling Index %	Assay %	Mucoadhesion time (minute)	Adhesive Force (g)
0.20±0.04	28.3±0.01	6.77±0.1	392	20.69±0.02	98.71±0.03	259	32.15

CONCLUSION

DOE was used to establish design space for the development of the formulation with desired attributes using 3^2 factorial design. Chitosan is mucoadhesive polymer and HPMC K4M is hydrophilic polymer which has adhesion property and retards the drug release. Hence the combination of a mucoadhesive and release retarding polymers patch was prepared. Based on response surface it was observed that F9 formulation containing Chitosan and HPMC K4M 800 mg and 300 mg respectively was the best formulation of buccal patch. F9 was choosen as

optimized batch which showed prolonged drug release from formulation and having maximum mucoadhesion property.

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