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Research Article

Mucoadhesive Bilayered Patches for Administration of Sumatriptan Succinate

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Abstract. The purpose of this study was to develop and optimize formulations of mucoadhesive bilayered buccal patches of sumatriptan succinate using chitosan as the base matrix. The patches were prepared by the solvent casting method. Gelatin and polyvinyl pyrrolidone (PVP) K30 were incorporated into the patches, to improve the film properties of the patches. The patches were found to be smooth in appearance, uniform in thickness, weight, and drug content; showed good mucoadhesive strength; and good folding endurance. A 3^2 full factorial design was employed to study the effect of independent variables viz. levels of chitosan and PVP K30, which significantly influenced characteristics like swelling index, *in-vitro* mucoadhesive strength, *in vitro* drug release, and *in-vitro* residence time. Different penetration enhancers were tried to improve the permeation of sumatriptan succinate through buccal mucosa. Formulation containing 3% dimethyl sulfoxide showed good permeation of sumatriptan succinate through mucosa. Histopathological studies revealed no buccal mucosal damage. It can be concluded that buccal route can be one of the alternatives available for administration of sumatriptan succinate.

KEY WORDS: bioadhesive; buccal patches; chitosan; sumatriptan succinate; 3^2 factorial design.

INTRODUCTION

Sumatriptan succinate is 3-[2-(dimethyl amino) ethyl]-*N*-methyl-1H-indole-5-methane sulfonamide succinate. It is 5-HT_1receptor agonist used in the treatment of migraine. It is administered orally, in doses of 25, 50 or 100 mg as a single dose, nasally in doses of 10 mg or 20 mg and also subcutaneously, as two 6-mg doses over 24 h (1). However, a substantial proportion of patients suffer from severe nausea or vomiting during their migraine attack, and also low oral bioavailability (15%) due to high first-pass metabolism, may make oral treatment unsatisfactory (2). Nasal route and subcutaneous route have their own limitations, like lower retention time for nasal solution (3) and inability of self administration for injectables respectively.

This justifies a need to develop an effective formulation, which allows the drug to directly enter the systemic circulation bypassing the first-pass metabolism, thereby increasing bioavailability of sumatriptan succinate. Buccal route is one such alternative.

Buccal route of drug delivery provides direct access to the systemic circulation through the internal jugular vein bypassing the first pass metabolism leading to high bioavailability (4). Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy drug withdrawal, facility to include permeation enhancer/enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release systems for local or systemic actions make buccal adhesive drug delivery system as promising option for continued research (5).

In the present study, mucoadhesive bilayered buccal patch of sumatriptan succinate for buccal administration was developed and optimized aiming at studying various formulation variables and its effect on patch properties. Also attempts were made to improve buccal penetration of the drug. Bilayered design of the patch was selected to obtain unidirectional release of the drug, greater surface area of contact, and administer the bitter drug without taste masking (6).

For development of mucoadhesive, bilayered buccal patches of sumatriptan succinate, chitosan was used as base matrix polymer (7,8). Because of the properties such as hydrophobicity, low water permeability, drug impermeability, and moderate flexibility, ethyl cellulose was used as a backing layer polymer (8).

The concept of administration of sumatriptan succinate via buccal route, by formulating the mucoadhesive bilayered buccal patches has not been fully explored so far. Hence results of present investigation would help to establish the suitability of buccal route for administration of sumatriptan succinate and influence of matrix polymers like chitosan and PVP K-30 on the physicochemical properties of buccal patches of sumatriptan succinate.

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MATERIALS AND METHODS

Materials

Sumatriptan succinate and chitosan with molecular weight 514.87 kDa and degree of deacetylation 94% were received as gift samples from Elder Pharmaceuticals, Mumbai, India and Indian Institute of Fisheries, Cochin, India respectively. Ethyl cellulose (10 cps), gelatin, polyvinyl pyrrolidone K30, dimethyl sulfoxide and polysorbate 80 (Tween 80) were purchased from Research Lab-Fine Chem, Mumbai, India. Transcutol was obtained as gift sample from Colorcon India Ltd.

Methods

Preparation of Mucoadhesive Bilayered Buccal Patches (8,9)

Backing Layer. For preparing a formulation a glass Petri plate of 9 cm diameter was used as a casting surface. Initially, backing membrane of ethyl cellulose was fabricated by slowly pouring a solution containing 500 mg of ethyl cellulose and 2% dibutyl phthalate in 10 ml acetone to the glass Petri plate and air drying for 1 h.

Mucoadhesive Layer Containing Drug. Initially, 2.5% *w/v* chitosan was dissolved in 10 ml of 2% *v/v* lactic acid under constant stirring till clear solution was obtained. Then to this solution, 2% *w/v* gelatin, 1% *w/v* PVP K30, 5% *v/v* glycerin and 0.1 *w/v* sodium saccharine were added by stirring with magnetic stirrer. Then sufficient amount of sumatriptan succinate was added with stirring so as to have 10 mg of drug per patch of 2 cm diameter. The resultant clear solution was then poured on the preformed backing layer of ethyl cellulose and allowed to dry undisturbed for 4 h at 60°C in the oven. The dried bilayered patch was cut into discs of 2 cm diameter.

Optimization of Formulation (10)

A 3^2 randomized full factorial design was used in this study. Two factors were evaluated, each at three levels, and experimental trials were performed on all nine possible combinations (Table I). The amount of chitosan (X_1) and the amount of PVP K30 (X_2) were selected as independent variables. The mucoadhesive strength and *in-vitro* residence time were selected as dependent variables.

Regression polynomials for the individual dependant variables (mucoadhesive strength and *in-vitro* residence time) were calculated with the help of Design Expert 7.1 software and applied to approximate the response surface and contour plots. The general model as shown below was generated,

$$y = \alpha_0 + \alpha_1 x_1 + \alpha_2 x_2 + \alpha_3 x_1 x_2 + \alpha_4 x_2^2 + \alpha_5 x_1 x_2^2 + \alpha_6 x_1^3 x_2^2 + \alpha_7 x_1^3 x_2 + \alpha_8 x_1 x_2^3 + \alpha_9 x_1^4 + \alpha_{10} x_2^4 \quad (1)$$

α_1 is estimated coefficient for the factor X_1, similarly X_2 is estimated coefficient for the factor X_2that is α_1 .... α_{10} are regression coefficients of the independent variable (X_1, X_2) The main effects (X_1, and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1, and X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity.

Weight and Thickness of the Patch (11)

Assessment of weight and patch thickness was done on ten patches. Patches were directly weighed on analytical balance and patch thickness was determined by optical microscopy by taking transverse sections from different points within a patch and observing under ×100 magnification. The mean and standard deviation were calculated.

Content Uniformity

For determination of content uniformity of the patches ten patches were taken. Drug extracted in water from each patch was analyzed by UV spectrophotometer at λmax of 282 nm after appropriate dilutions. The mean and standard deviation were calculated

Surface pH (11)

Buccal patch was left to swell for 15 min on the surface of 2% *w/v* agar plate. The surface pH was measured by means of pH paper placed on the surface of the swollen patch.

Table I. Optimization of Buccal Patches of Sumatriptan Succinate

Formulations	Drug per patch (mg)	Chitosan % *w/v* X_1	Gelatin % *w/v* X_2	PVP % *w/v*	Glycerin % *v/v*	Sodium saccharine % *w/v*	Lactic acid 2% solution (ml)
F-1	10	3.5	2.0	0.5	5.0	0.1	100
F-2	10	1.5	2.0	1.5	5.0	0.1	100
F-3	10	2.5	2.0	1.5	5.0	0.1	100
F-4	10	3.5	2.0	1.5	5.0	0.1	100
F-5	10	1.5	2.0	1.0	5.0	0.1	100
F-6	10	3.5	2.0	1.0	5.0	0.1	100
F-7	10	1.5	2.0	0.5	5.0	0.1	100
F-8	10	2.5	2.0	0.5	5.0	0.1	100
F-9	10	2.5	2.0	1.5	5.0	0.1	100

Swelling Studies (12)

After weighing the patch (W_1), it was immersed in pH 6.8 phosphate buffer solution maintained at 37°C. The weight at end of 120 min was reported (W_2). The swelling index was determined from the formula,

$$\text{Swelling Index} = (W_2 - W_1)/W_1 \times 100 \quad (2)$$

The experiment was carried out for three patches.

In-Vitro Drug Release Studies (13)

USP apparatus type II (VEEGO USP Dissolution apparatus,) was used to study drug release from patch formulation under sink conditions at 37°C and 50 rpm. A single patch was placed in 500 ml dissolution media containing pH 7.4-phosphate buffer**.** A patch was applied on glass slide in such a way that mucoadhesive layer of the patch was in contact with dissolution media and non-adhesive backing layer was fixed on the slide with the help of two-sided adhesive tape. Samples (5 ml) were withdrawn at suitable time intervals and replaced with fresh dissolution medium. The amount of sumatriptan succinate was determined by UV spectrophotometer at 282 nm (Shimadzu 1602 Japan**)** with the help of standard curve of drug (range 1–80 µg/ml and $y=0.0099x$; $r^2=0.9993$ in phosphate buffer pH 7.4). A test on placebo was performed to eliminate interference of the ingredients of the patch. The test was performed on six patches.

Drug Release From Backing Layer (14)

For determination of drug release from the backing layer, Franz diffusion cell was used. A bilayered buccal patch was placed between donor and receptor compartment. The complete unit was maintained at 37°C, donor compartment (3 ml) was filled with simulated saliva pH 6.8 (sodium chloride 4.5 g, potassium chloride 0.3 g, sodium sulfate 0.3 g, ammonium acetate 0.4 g, urea 0.2 g, lactic acid 3 g and distilled water up to 1,000 ml, adjusting pH of solution to 6.8 by 1 M NaOH solution) and receptor compartment (21 ml) contained phosphate buffer pH 7.4 with synchronous stirring. At predetermined interval 2 ml sample was removed from donor compartment and analyzed at 282 nm by UV spectrophotometric analysis to check release of drug from the backing layer of the patch.

In-Vitro Bioadhesion (15)

Bioadhesion studies were carried out using the bioadhesion test apparatus working on the principle of double beam physical balance. The porcine buccal mucosa excised and washed, was tied tightly with the mucosal side upwards, using a thread over the protrusion in the Teflon block. This block was then placed into the glass container, which was then filled with simulated saliva (pH 6.8) kept at 37±1°C, such that the saliva just reaches the surface of mucosal membrane and keeps it moist. This was then kept below left hand setup of the balance. The patch was then stuck with a little moisture, on to the lower surface of other Teflon cylinder suspended from the left hand side of the balance and was brought in contact with the mucosa placed on block by removing 5 g weight from the right pan of the balance. The balance was kept in this position for 3 min and then slowly weights were added on the right pan, till the patch separated from the mucosal surface. The excess weight on the pan i.e. total weight minus 5 g is force required to separate the patch from mucosa. This gave the mucoadhesive strength of the patch in 'g'. The test was performed on six patches.

In-Vitro Residence Time (11)

The *in-vitro* residence time was performed after application of patch on freshly cut porcine mucosa. The porcine buccal was fixed on the glass slide with cyanoacrylate glue. The slide was tied to the disintegration apparatus and suspended in the beaker filled with 800 ml simulated saliva pH 6.8. The slide was allowed to reciprocate in the medium by switching on the motor. Experiment was continued till the patch got detached or eroded from the mucosa. The test was performed on six patches.

Permeation Studies (16)

Diffusion studies were carried out, to evaluate the permeability of drug across the porcine buccal mucosal membrane (15), by using glass surface Franz diffusion cell. Porcine buccal mucosa was obtained from local slaughterhouse (R.K. Pork, Mumbai, India) and used within 2 h of slaughter. The tissue was stored in phosphate buffered saline (PBS) pH 7.4 solution upon collection. The epithelium was separated from underlying connective tissues with surgical

Table II. Physicochemical Characteristics of Formulation from F-1 to F-9

Formulation	Diameter (cm)	Thickness (micron) mean±SD	Weight (mg) mean±SD	Content uniformity per patch (mg)	Mucoadhesive strength (g)	*In-vitro* residence time (min)
F-1	2	235.4±0.85	55.28±0.05	10.2±0.34	16.52	125
F-2	2	224.0±0.75	52.57±0.25	9.8±0.54	04.60	23
F-3	2	205.8±0.75	47.77±0.16	9.9±0.24	06.41	93
F-4	2	243.5±0.75	57.34±0.37	10.8±0.57	14.58	165
F-5	2	211.5±0.85	50.35±0.22	10.5±0.53	05.64	30
F-6	2	256.4±0.85	60.20±0.06	10.2±0.60	16.44	146
F-7	2	198.0±0.75	45.60±0.19	10.6±0.53	04.48	32
F-8	2	234.5±0.92	55.51±0.24	10.2±0.59	06.49	87
F-9	2	214.8±0.85	50.31±0.17	10.7±0.43	05.49	89

Table III. Response 1—Mucoadhesvie Strength; Analysis of variance (ANOVA) for Selected Factorial Model

Source	Sum of Squares	*df*	Mean square	*F* value	*p* value Prob>*F*	
Model	219.24	5	43.84	774.04	<0.0001	Significant
X_1-chitosan	179.52	1	179.52	3,169.02	<0.0001	
X_2-PVP K-30	1.33	1	1.33	23.52	0.0160	
X_1 X_2	1.00	1	1.06	18.85	0.0225	
X_1^2	36.03	1	36.03	636.08	0.0001	
X_2^2	1.28	1	1.28	22.72	0.0175	
Residual	0.16	3	0.05			
Cor total	219.41	8				

scissors and clamped in between donor and receiver chambers of the diffusion cells for permeation studies. Receptor compartment contained 21 ml of pH 7.4 phosphate buffer while donor compartment was filled with 3 ml simulated saliva of pH 6.8. The patch was placed on the mucosal surface in donor compartment and 2 ml aliquots were removed at time intervals of 15, 30, 45, 60, 75, 90, 105, 120 min from the receptor compartment while the solution was being stirred continuously using magnetic stirrer, replacing it with fresh 2 ml medium each time. The experiment was carried out at 37°C. The amount of drug permeated was assayed using HPLC method of analysis with the help of standard curve of drug (y=85,244x; r^2=0.9986, range 5–80 μg/ml and mobile phase, phosphate buffer pH 3: methanol 80:20). The apparatus used for HPLC analysis was Jasco 200 plus system equipped with a UV detector. Computerized data acquisition and treatment were performed with the Borwin Chromatography Software. Chromatographic conditions applied were flow rate 1.0 ml/min and mobile phase phosphate buffer pH 3: methanol (80:20) separation was carried out at 25°C temperature on a 250 mm×4.0 mm, reverse-phase column packed with 5 μ C18 silica particles (Kromasil C18). Absorbance was measured at 282 nm. The graph of % drug permeated *v/s* time was plotted, and flux, permeability coefficient and enhancement ratio was determined according to method described by Lalla *et al.* (16). The experiments were performed in triplicate, and average values were reported.

Histopathological Evaluation of Buccal Mucosa (17)

Histopathological evaluation of tissue incubated in phosphate buffer saline solution pH 6.8 was compared with that treated with buccal patch for 2 h. The tissue was fixed with 10% formalin, routinely processed and embedded in paraffin. Paraffin sections were cut on glass slides and stained with hematoxylin and eosin. A pathologist blinded to the study to detect any damage to tissue at Haffkins Research Centre, Mumbai, India examined sections on light microscope.

Mechanical Properties of the Patch

Folding Endurance Test (11). The number of times the film could be folded at the same place till it broke gave the value of the folding endurance.

Tensile Strength and Elongation at Break (18). Prolific Tensile tester determined tensile strength and Elongation at break. The equipment equipped with a 5 kg load cell, and patch strip dimension of 15×2.5 cm and free of air bubbles or

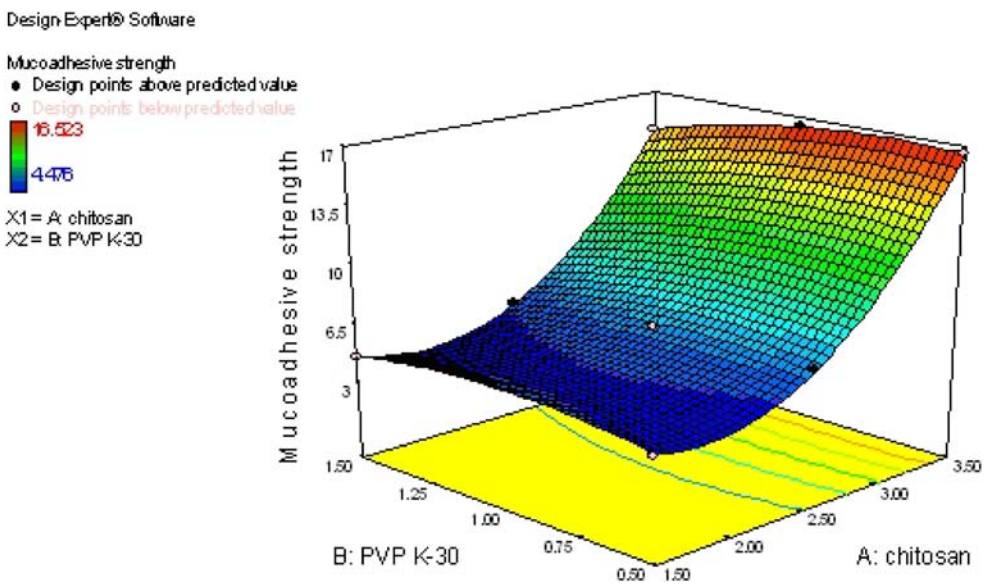

Fig. 1. Surface response plot for mucoadhesive strength

Table IV. Response 2—*In-vitro* Residence Time; Analysis of Variance (ANOVA) for Selected Factorial Model

Source	Sum of squares	*df*	Mean square	*F* Value	*p* value Prob>*F*	
Model	21,256.86	3	7,085.62	386.82	<0.0001	Significant
X_1-chitosan	20,455.18	1	20,455.18	1,116.71	<0.0001	
X_2-PVP K-30	185.14	1	185.14	10.10	0.0246	
X_1 X_2	616.52	1	616.52	33.65	0.0021	
Residual	91.58	5	18.31			
Cor total	21,348.45	8				

physical imperfections, was held between two clamps positioned at a distance of 3 cm. The force and elongation was measured when film broke. For this study four patches were tested. The following Eqs. 3 and 4 were used to calculate the mechanical properties of the patches,

$$\text{Tensile strength} = \frac{\text{Force at break(N)}}{\text{Initial cross sectional area of sample(mm}^2\text{)}} \quad (3)$$

$$\text{Elongation at break} = \frac{\text{Increase in length(mm)}}{\text{Original length (mm)}} \times \frac{100}{\text{Cross setional area(mm}^2\text{)}} \quad (4)$$

RESULTS AND DISCUSSIONS

Physicochemical Characteristics of the Patches

Physicochemical characteristics of the patches are shown in Table II. Based on the quantities of the polymers, chitosan and PVP K-30, ranging from 1.5% *w/v* to 3.5% *w/v* and 0.5% *w/v* to 1.5% *w/v* respectively, the thickness of different formulation was found to be varying. The surface pH of all formulations ranged from 6 to 7 and hence no mucosal irritation was expected. The results of content uniformity confirmed uniformity of drug content in the patch. The patches of all formulation have good flexibility, strength, transparency, and smooth surface.

Optimization of Formulation

The model *F*-value of 774.0444 implied that the model was significant. There was only a 0.01% chance that a "Model *F*-value" this large could occur due to noise. Values of "Prob>*F*" less than 0.05 indicate model terms are significant. In this case X_1, X_2, X_1^2, X_2^2 were significant model terms. Values greater than 0.1 indicate the model terms are not significant (Table III).

The final models for mucoadhesive strength was as follows,

$$\text{Mucoadhesive strength} = +6.67 + 5.47X_1 - 0.47X_2 - 0.52X_1X_2 + 4.24X_1^2 - 0.80X_2^2 \quad (5)$$

(R^2=0.9992). As seen from Fig. 1, the surface response plot revealed that a corresponding increase in the mucoadhesive

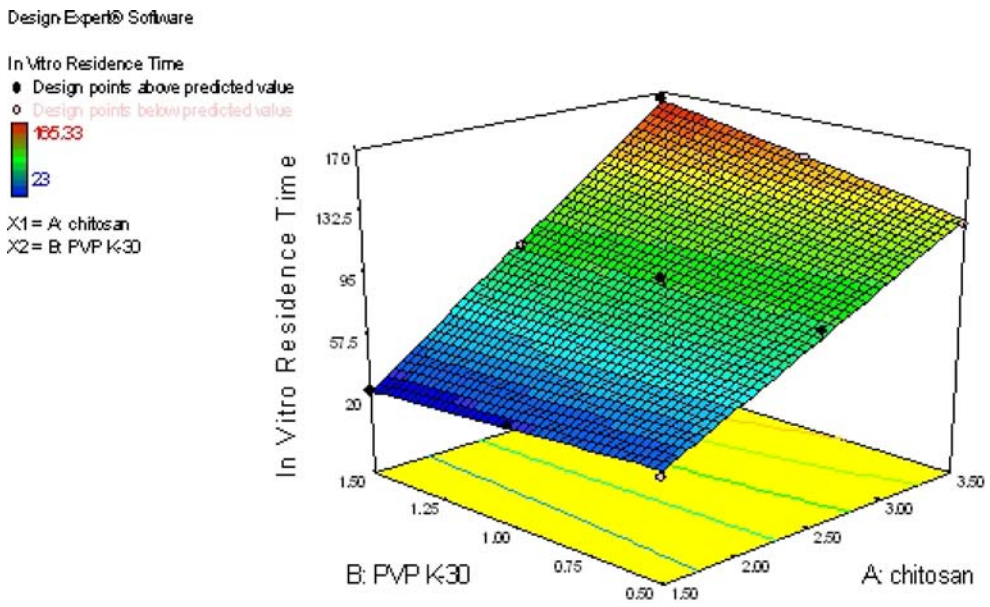

Fig. 2. Surface response plot for *in-vitro* residence time

strength of patches was observed with increase in concentration of chitosan. This may be due to contact of the polymers with glycoprotein rich mucous wound fluid, thus causing amine groups in the structure to combine with the negative charge groups (carboxyl, sulfate, etc) on the tissue surface; this property may be enhanced by increasing the chitosan concentration in the patch (19)

The results also indicated that the effect of concentration of chitosan was more significant than the effect of concentration of PVP K30. Moreover, PVP K30 had a negative effect on mucoadhesive strength; that is, as the concentration of PVP K30 increased the mucoadhesive strength decreased.

As seen from Table IV, the Model *F*-value of 386.83 implied the model was significant.Values of "Prob>*F*"indicated that X_1, X_2, X_1, X_2 were significant model terms.

The final models *in-vitro* residence time was as follows,

$$\textit{In Vitro}\ \text{Residence Time} = -7.08361 + 33.55833X_1 - 50.69500X_2 + 24.83000X_1X_2 \quad (6)$$

(R^2=0.9957) The *in-vitro* residence time with porcine buccal mucosa in simulated saliva (pH 6.8) varied from 32 to 165 min. The results also indicated that the effect of concentration of chitosan was more significant than the effect of concentration of PVP K30 (Fig. 2). Patches containing low proportion of chitosan, formed gel very fast and got eroded rapidly. Moreover, PVP K30 had a negative effect on *in-vitro* residence time; that is, as the concentration of PVP K30 increased *in-vitro* residence time decreased.

It was concluded that the desired patches with mucoadhesive strength in the range 10–20 g and *in-vitro* residence time in the range 120–150 min could be obtained by using chitosan amount in the range 2.99% to 3.5% *w/v* and PVP K30 amount in the range 0.5% to 1.1% *w/v*. Therefore formulation containing 3.5% *w/v* of chitosan and 1% *w/v* of PVP K30 was selected as optimized formulation (F-6).

Swelling Study

Figure 3 depicts the degree of swelling of formulations F-1 to F-9 in simulated saliva solution of pH 6.8. Swelling of patches was started within 5 min due to presence of soluble excipients, PVP K-30 and Gelatin. Maximum increase in swelling was observed at 30 min. Increase in chitosan and PVP K-30 led to increase in the extent of swelling of the patches. In case of formulations F-2, F-5, and F-7, erosion of patches was observed at 30 min. As the proportion of chitosan was increased in the formulation, erosion of the patches slowed down. Thus *in-vitro* residence time of the formulations containing higher proportion of chitosan (F-1, F-4, and F-6) was found to be more than formulations containing lower amount of chitosan (F-2, F-5, and F-7).

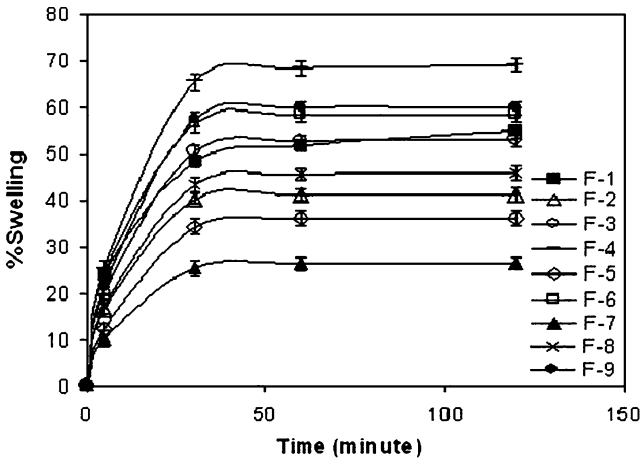

Fig. 3. Swelling behavior in simulated saliva (pH6.8)

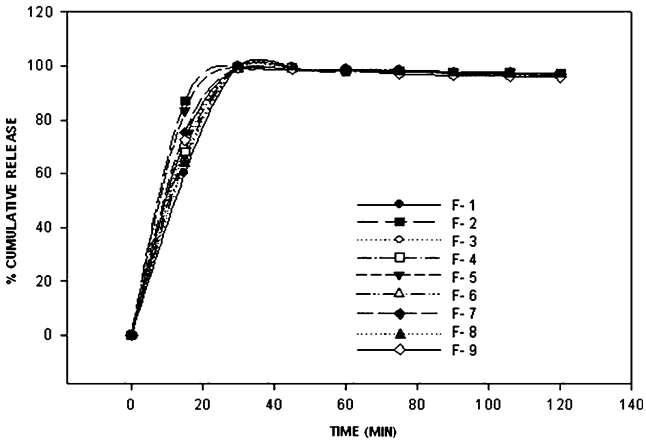

Fig. 4. *In-vitro* drug release study of buccal patches (F-1 to F-9)

The drug release appeared to increase with an increasing amount of the hydrophilic polymer PVP K30. The increase in the drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water-soluble drug sumatriptan succinate. Moreover, the hydrophilic polymer PVPK30 would dissolve creating more pores and channels for the drug to diffuse out of the patches (20) but as concentration of chitosan increased, drug release was decreased, this could be due to the extensive swelling of the chitosan, which created a thick gel barrier, making drug diffusion more difficult. The drug release was found to increase with increasing concentrations of PVP K30 and decreasing concentrations of chitosan. The dissolution profile for the different formulations was as shown in Fig. 4 with the complete release observed in 30 min.

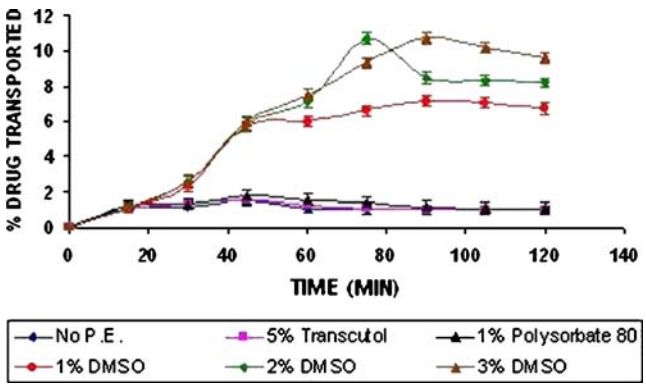

Fig. 5. Comparison of permeation of sumatriptan succinate through porcine mucosa in presence of different penetration enhancer

Table V. Permeation of Sumatriptan Succinate through Porcine Buccal Mucosa in Presence of Different Penetration Enhancer

Formulations containing	Permeability coefficients, mg cm/min	Flux, mg/cm^2 min	Enhancement ratio	Statistical significance Student *T* test
No penetration enhancer	0.003	0.010	–	–
Transcutol 5%	0.003	0.010	0.939	$P>0.05$
Polysorbate 80 1%	0.003	0.011	1.090	$P<0.05$
DMSO 1%	0.059	0.196	18.727	$P<0.05$
DMSO 2%	0.075	0.251	23.969	$P<0.05$
DMSO 3%	0.090	0.301	28.696	$P<0.05$

To evaluate the performance of backing membrane in avoiding release of sumatriptan succinate, a study was conducted using Franz diffusion cell. Results of study showed that no drug was released in 120 min in the donor compartment of diffusion cell. This indicated that ethyl cellulose membrane was impermeable to sumatriptan succinate and the swelling of mucoadhesive layer did not change integrity of backing layer. Hence patch was found to be efficient for unidirectional release of sumatriptan succinate through buccal mucosa.

The formulation having the best mucoadhesive strength, *in-vitro* residence time more than 120 min and desired drug release (F-6) was subjected to permeation studies through the buccal mucosa to find out the extent of drug permeability in terms of permeation coefficient and flux.

Permeation Studies

Sumatriptan succinate being hydrophilic with Log *P* value of 0.93 (Drug bank. Available at http://redpoll.pharmacy.ulbera.cyibin/getCard.Cgi?CARD=APRD00379.txt.) exhibits low permeability through buccal mucosa and there is a need to enhance its buccal permeation with help of penetration enhancer (21) that causes perturbation and dissolution of paracellular fluid, enhancing its paracellular transport (22). Based on this fact, different penetration enhancers (transcutol (23), polysorbate 80 (24), and DMSO (25) were tried to improve buccal penetration of sumatriptan succinate through buccal mucosa.

Figure 5 gives comparison of permeation of sumatriptan succinate through porcine buccal mucosa for formulations containing different penetration enhancer. The permeability coefficient was calculated from the graph. These results are listed in Table V.

Table VI. Evaluation of Final Optimized Formulation

Parameter	Results
Weight (mg)	60.20±0.06
Thickness (micron)	256.43±0.85
Content uniformity (mg)	10.20±0.67
Surface pH	6–7
Swelling index (%)	0.69±1.34
Drug release (%)	98.76±1.45
Mucoadhesive strength (g)	16.67±0.38
In-vitro residence time (min)	146.66±1.07

Results of the trials with 5% transcutol and 1% polysorbate 80 showed not much improvement in the permeation of sumatriptan succinate as compared to trials with DMSO. DMSO increased the permeability of drug significantly with level 3% showing the best results.

When penetration enhancer is added, it is very unlikely that low concentrations of penetration enhancers would influence the physicochemical properties of patch such as mucoadhesive strength, *in-vitro* residence time, and drug release. The formulation optimized for the amount of penetration enhancer was still subjected to physiochemical characterization (Table VI) to confirm that penetration enhancer did not adversely affect the other physicochemical characteristics.

Histopathological Evaluation of Buccal Mucosa

The microscopic observations indicated that the final formulation containing 3%DMSO had no significant effect on the microscopic structure of mucosa. As shown in Fig. 6, no cell necrosis was observed. Cellular membrane was intact and no damage was observed to the treated porcine buccal mucosa. Thus, formulation containing 3% DMSO appeared to be safe with respect to buccal administration.

Mechanical Properties of the Patch

To check the tensile strength, flexibility and elasticity of the patches, folding endurance test tensile test and elongation

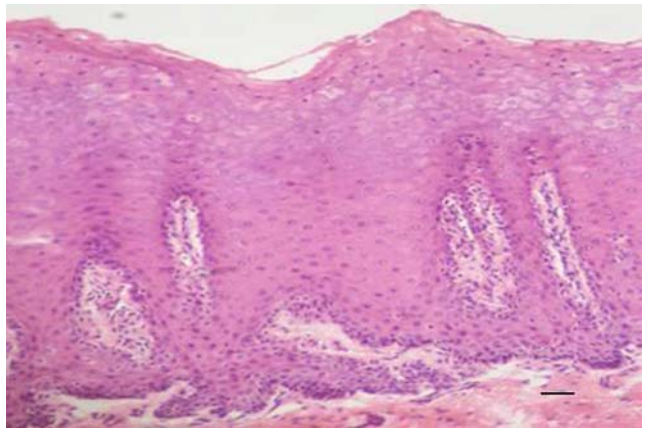

Fig. 6. Histopathological evaluation of sections of porcine buccal mucosa treated with patch containing 3% DMSO (1 cm *bar* represents 100 μm)

at break were performed. The recorded folding test for patch of the optimized formulation (F-6) was 219 times. Tensile strength of the patch of the formulation was found to be 0.4133 N/mm^2 and elongation at break of 3.072% mm^2. These values indicated that patch prepared by using optimized formula would have sufficient strength, flexibility and elasticity while handling, packing and transport.

CONCLUSION

It may be concluded that buccal route is one of the alternatives available for administration of sumatriptan succinate. However use of penetration enhancer is necessary to achieve permeation of drug through buccal mucosa. The results showed that mucoadhesive bilayered buccal patch containing 3.5% *w*/*v* chitosan, 1% PVP K-30 and 3% DMSO produced buccal patches having good mucoadhesive strength, 98% drug release over 2 h and 12% permeation of the drug through buccal mucosa without causing any tissue damage.

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