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Research Article

BUCCAL DELIVERY OF PRAVASTATIN-FORMULATION DEVELOPMENT AND EVALUATION

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Abstract

The purpose of the present study was to develop and systematically evaluate the in vitro and ex vivo performances of bioadhesive buccal patches of Pravastatin sodium using the hydrophobic polymer Eudragit RSPO as the base matrix by solvent casting technique. The hydrophilic polymers Hydroxypropyl methyl cellulose and Sodium carboxy methyl cellulose were incorporated into the patches to improve the bioadhesive properties and to modify the rate of drug release. The formulations were evaluated for various physicomechanical properties, ex vivo mucoadhesive strength, residence time and in vitro drug release. The invitro drug release of optimized formulation was found to be non-fickian exhibiting zero-order release. Permeation enhancers, sodium lauryl sulphate (SLS) and dimethyl sulfoxide (DMSO) were incorporated into the formulations to increase drug permeation across the buccal mucosa and SLS1% was found to better enhance the permeability of Pravastatin sodium.

Key Words: Pravastatin, Buiccal delivery, Eudragit, Permeation, DMSO.

Introduction

Increasing interest in novel drug delivery systems has lead to the incidence of several substantial alternatives to oral conventional delivery of therapeutic agents, out of which transmucosal devices have gained a tremendous importance (Suneela et al, 2007). The ease with which certain compounds can be absorbed across the oral mucosa and the convenience of this route as a means of systemic drug delivery has led to development of a number of therapeutic substances for oral or buccal administration (Squier, 1991). The buccal mucosa is well vascularized enabling easy access to the systemic circulation via the internal jugular vein, thus bypassing the pre-systemic metabolism in the liver or

degradation in the gastrointestinal tract of susceptible drugs (Charde et al, 2008). Also, other advantages such as excellent accessibility, low enzymatic activity, 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 drug delivery system a promising option for research (Hoogstrate, 1998). However, there are certain limitations associated with conventional buccal drug delivery, such as the low flux, which results in low drug bioavailability and lack of dosage from retention at the site of absorption. Consequently, buccal delivery necessitates the use of mucoadhesive polymers as these dosage forms should ideally adhere to the mucosa and withstand salivation, tongue movement and swallowing for a significant period of time. Also, these systems provide the possibility of holding the active ingredients and release them in a controlled manner over relatively prolonged periods (Nafee et al, 2004).

The permeation of hydrophilic drug through membrane is a major limiting factor for the development of bioadhesive buccal delivery systems. Incorporation of permeation enhancers to the buccal formulation is essential in this context. These substances reduce the barrier properties of the buccal epithelium and hence, facilitate the drug permeation through buccal mucosa.

Pravastatin Sodium, designated chemically as [1S-[1α(βS*,δS*), 2 α,6 α,8β(R*),8a α]]- 1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthalene- heptanoic acid monosodium salt is a HMG- CoA reductase inhibitor antilipemic agent (Li et al, 2009). The systemic bioavailability of Pravastatin is about 17 % indicating extensive presystemic metabolism in the liver. The main metabolite of Pravastatin, a 3α-hydroxy isomeric compound (SQ 31 906), has approximately one-tenth to one-fortieth of the HMG-CoA reductase inhibitory activity of Pravastatin, i.e. the enzyme inhibition is mainly attributable to the parent drug. Also, the drug is reported to be unstable in acidic pH (Otter, 1998). Hence, buccal route can be exploited to be one better alternative for the effective delivery of the drug to systemic circulation. In addition, the properties of the compound like a low molecular weight of 446.52, an octanol/water partition co-efficient of 1.44, its low daily dose of 10-40 mg and short half-life (1.5-2.7 hours) justifies the suitability for its administration by the buccal route.

In the present study, bioadhesive controlled release patches were developed for buccal delivery of Pravastatin Sodium using hydrophobic polymer Eudragit RSPO as a base matrix. Hydrophilic polymers like Hydroxypropyl methyl

cellulose (HPMC E15), sodium carboxy methyl cellulose (SCMC) were incorporated to improve the mucoadhesive properties and to modify the rate of drug release.

Materials and Methods

Materials

Pravastatin sodium is a gift sample from Medreich Ltd (Bangalore, India). Hydroxypropyl methyl cellulose E15 (HPMC E15), sodium carboxymethyl cellulose (SCMC) are gift samples from Suven Life Sciences (Hyderabad, India). Eudragit RSPO was received as a gift sample from Aurobindo Pharmaceuticals (Hyderabad, India). Propylene Glycol, sodium lauryl sulfate, dimethyl sulfoxide were purchased from Finar chemicals Ltd (Ahmedabad, India).

Methods

Ex vivo Drug permeation studies

Ex vivo permeation study of Pravastatin sodium through porcine buccal mucosa was performed using Franz diffusion assembly, at 37±0.2ºC and 50 rpm. The temperature and revolutions were maintained using a magnetic stirrer (Remi Equipments Ltd., Mumbai, India). Porcine buccal mucosa was procured from local slaughter house and used within 2 hours of slaughter. The tissue was stored in isotonic phosphate buffer, pH 7.4 at 4ºC upon collection (Kulkarni et al, 2009).

The majority of the underlying connective tissue was removed with the help of a scalpel blade and then the remaining buccal mucosa was carefully trimmed with a pair of surgical scissors. This membrane was allowed to equilibrate for 1 hour to conserve its elasticity. After this, the membrane was carefully mounted between the two compartments of Franz diffusion cell with an area of 2.26 cm^2 and a receptor compartment volume of 20 ml containing pH 6.8 phosphate buffer solutions.

The donor chamber was charged with a 4 ml (2.5 mg/ml) of drug solution. Aliquots of 3 ml were collected at predetermined intervals for a period of 6 h from the receptor chamber, which was replaced with an equivalent volume of prewarmed buffer. The collected samples were analyzed at 239 nm using a UV spectrophotometer (T60, Analytical Technologies Ltd, India) to determine the amount of drug permeated through the buccal mucosa. The experiment was performed in triplicate (n=3) and mean values the cumulative amount of drug permeated were plotted against time. The flux (J) and the permeability coefficient (P) were calculated using the following equations.

$$J = \frac{dQ}{dt.A} \quad (1)$$

$$P = (dQ/dt)/\Delta C.A \quad (2)$$

Where J is flux ($mgh^{-1}cm^{-2}$); P is permeability coefficient ($cm\ h^{-1}$); dQ/dt is the slope obtained from the steady-state portion of the curve; ΔC is the concentration difference across the mucosa and A is the effective area of diffusion (cm^2) (Vishnu et al, 2007; Shanker et al, 2009).

Fabrication of bioadhesive buccal patches

The buccal patches were prepared by solvent casting method (Vishnu et al, 2007; Wong et al, 1999) using ERSPO, HPMC E 15 and SCMC (table 1). The polymeric mixtures were added to the solvent mixture (ethanol: water=1:1)with high agitation on a cyclomixer and kept for swelling for 6 hours, 30% w/v of propylene glycol was added as plasticizer, and then drug solution was added after 1 hour. The obtained mixture was cast into an anumbra petri dish and allowed to dry for 24 hours at room temperature, till a flexible film was formed. These films were packed in aluminum foil and stored in desiccators. Each patch of diameter 1.6 cm contained 10 mg of Pravastatin sodium.

Table-1: Composition of Pravastatin sodium buccal patches.

Formulation	Pravastatin Sodium	ERSPO	HPMC	SCMC	PG (ml)	Ethanol: water 1:1 (ml)	SLS 1% (mg)	DMSO 3% (ml)
F1	192.3	1153.8	-	-	0.34	20	-	-
F2	192.3	769.2	384.6	-	0.34	20	-	-
F3	192.3	576.9	576.9	-	0.34	20	-	-
F4	192.3	384.6	769.2	-	0.34	20	-	-
F5	192.3	769.2	-	384.6	0.34	20	-	-
F6	192.3	576.9	-	576.9	0.34	20	-	-
F7	192.3	384.6	-	769.2	0.34	20	-	-
F8	192.3	576.9	576.9	-	0.34	20	11.53	-
F9	192.3	576.9	576.9	-	0.34	20	-	0.034
F10	192.3	769.2	-	384.6	0.34	20	11.53	-
F11	192.3	769.2	-	384.6	0.34	20	-	0.034

Physico-mechanical characterization

Weight and Thickness of the Patch

Assessment of weight and patch thickness was done on ten patches. Patches were directly weighed on electronic balance (Shimadzu, AUX*220, Japan) and patch thickness was determined by measuring at different points using a screw guage. The mean and standard deviation were calculated.

Content Uniformity

Drug content was determined the homogenization of the wafer in 100 ml of pH 6.8 phosphate buffer for 4-6 h until the patch was completely dissolved in the solvent and the resulting solution was filtered through Whatmann filter paper No.1. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 239 nm against phosphate buffer as blank. The experiment was performed in triplicate and average values were reported.

Folding Endurance: The flexibility of patches can be measured quantitatively in terms of as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

Surface pH determination: The surface pH was determined in order to predict the possible irritative effects of each formulation on the mucosa. Each patch was placed in petri plate and allowed to swell in contact with 2 ml of phosphate buffer, pH 6.8 for 2 hours at room temperature, and the pH was recorded with the aid of a digital pH meter. Experiments were performed in triplicate and average values were reported (Nafee et al, 2004).

Moisture Absorption Studies

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture.

5% w/v agar was dissolved in hot water, transferred into petriplates and allowed to solidify. Three patches from each formulation were selected, laminated on one side with water impermeable backing membrane. They were placed on the agar plates, incubated at 37±1ºC, and examined for any physical changes. At regular 1-hour intervals until 6 hours,

patches were removed from the plates, excess surface water was removed carefully using a filter paper and were reweighed and the weight at the end of 6 h was recorded.

$$\%\text{Moisture absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Content

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating the moisture loss using the formula:

$$\text{Moisture Content (\%)} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Measurement of bioadhesive strength

Bioadhesive strength of the patches was measured using a modified physical balance. The instrumental setup broadly composed of a modified physical balance, in which both the pans are replaced by glass pans suspended by copper wire. At the right side, a glass beaker of 50 ml was placed in inverted position in order to fix the model mucosal membrane. The porcine cheek pouch, excised and washed was fixed to the glass beaker. The mucoadhesive patch of 2.26 cm^2 was fixed to the bottom of right pan using cyanoacrylate adhesive. The exposed patch surface was moistened with 1 ml of pH 6.8 phosphate buffer for 1 min. for initial hydration and swelling. A preload of 5 gm was placed over the right pan and kept undisturbed for 5 min. to establish the adhesion between patch and the mucosal tissue. Then, the preload was removed and then the weights were slowly added onto the left pan in increments of 0.1 gm, until the patch detaches from the mucosal membrane. The weight required to detach the patch from the mucosa gives the measure of the bioadhesive strength of the mucoadhesive patch. After each measurement the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before taking reading (Shanker et al, 2009).

The following parameters were calculated from mucoadhesive strength:

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength (gm)}}{1000} \times 9.81$$

$$\text{Bond strength } (Nm^{-2}) = \frac{\text{Force of adhesion}}{\text{Surface area}}$$

Ex vivo residence time

The ex vivo residence time was determined using a modified USP disintegration apparatus. The patch was hydrated from one surface and applied on the porcine buccal mucosa which 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 phosphate buffer, pH 6.8, maintained at 37ºC. The slide was allowed to reciprocate in the medium until the patch got detached or eroded from the mucosa. The time required for the erosion or detachment was recorded as a mean of triplicate determinations (Patel et al, 2007 b).

In vitro Drug Release study

The in vitro permeation studies from the patches were performed using Franz Diffusion cell. The drug containing film was kept between donor and receptor compartments, separated from these compartments by dialysis membrane. The receptor compartment (30 mL) was filled with phosphate buffer, pH 6.8. The experiment was performed at 37±0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. 3 ml of sample was collected from the receptor compartment at appropriate time intervals up to 6 h and replaced with phosphate buffer pH 6.8. Analysis was carried out using UV-Visible Spectrophotometer at 239 nm against phosphate buffer pH 6.8 as reference (Adhikari et al, 2010).

Ex vivo permeation studies

Ex vivo permeation study of Pravastatin sodium from buccal patches through porcine buccal mucosa was performed using Franz diffusion assembly, at 37±0.2ºC and 50 rpm. The temperature and revolutions were maintained using a magnetic stirrer (Remi Equipments Ltd., Mumbai, India). Porcine buccal mucosa was procured from local slaughter house and used within 2 hours of slaughter. The tissue was stored in isotonic phosphate buffer, pH 7.4 at 4ºC upon collection (Kulkarni et al, 2009). The majority of the underlying connective tissue was removed with the help of a

scalpel blade and then the remaining buccal mucosa was carefully trimmed with a pair of surgical scissors. This membrane was allowed to equilibrate for 1 hour to conserve its elasticity. After this, the membrane was carefully mounted between the two compartments of Franz diffusion cell with an area of 2.26 cm^2 and a receptor compartment volume of 20 ml containing pH 6.8 phosphate buffer solution.

The patch was placed by occlusion on the buccal mucosal surface and was wetted with 1ml of phosphate buffer. The amount of drug permeated through the membrane was determined by removing 3 mL aliquots from the receptor compartment, and by replacing the same volume of buffer at regular intervals for a period of 6h. Then the samples were analyzed by using UV-Visible spectrophotometer at λmax of 239 nm. The experiment was performed in triplicate (n=3) and mean value was used to calculate the flux (J) and the permeability coefficient (P).

The target flux was calculated using the following equation.

$$J_{Target} = \frac{C_{SS.}\, Cl_T .BW}{A}$$

'A' represents the surface area of the patch (i.e. 2.26cm^2), 'BW' the standard human body weight of 60 kg, 'Css' the Pravastatin concentration at the therapeutic level (27.4ng/ml) and the 'Cl_T' the total clearance (13.5ml/min/kg), the calculated target flux value of Pravastatin was 0.66 mg/hr/cm^2 (Singhvi et al, 1990).

Results and Discussion

Ex vivo drug permeation

The cumulative amount of Pravastatin penetrated through the buccal mucosa indicates that Pravastatin exhibits permeation of 75.76%. This could be because, Pravastatin, being hydrophilic with a log P value of 1.44, exhibits slightly low permeability through buccal mucosa. The values of flux and permeability coefficient were found to be 0.613 mg/hr/cm^2 and 0.0613 cm h^{-1} respectively which were not in accordance with the required flux for the drug (0.66 mg/hr/ cm^2). These results specify the need of a penetration enhancer to achieve higher permeability.

Physico-mechanical characterization

The physicomechanical evaluation (table 2) indicates that the weight variation of the formulated buccal patches varied between 79.4±1.45 (F11) and 87.5±3.02 (F7). The thickness of patches varied between 0.32±0.04 (F1) and 0.48±0.02

mm (F4). Thickness increased with increase in the polymer concentration both of HPMC and SCMC. The values of folding endurance revealed that all the formulations were sufficiently flexible, with the highest being 142±10 folds in case of F4 and lowest being 95±15 folds in case of F1. The drug content in all the formulations was in the range of 98.41%±0.42% (F1) to 101.05%±0.15% (F6). This indicates uniform dispersion of drug throughout the film in all formulations.

Table-2: Physico-mechanical properties of Pravastatin buccal patches.

Formulation	Weight (mg)	Thickness (mm)	Folding endurance	Drug Content (%)	Surface pH
F1	82.6±2.53	0.32±0.04	95±15	98.41±0.42	6.67±0.03
F2	82.4±3.25	0.38±0.06	122±10	99.42±0.39	6.45±0.02
F3	81.5±2.44	0.42±0.04	135±18	99.97±0.28	6.56±0.01
F4	84.7±0.75	0.48±0.02	142±10	100.42±0.06	6.44±0.02
F5	80.6±2.53	0.39±0.04	108±8	97.5±0.24	6.62±0.02
F6	79.5±2.65	0.43±0.07	118±15	101.05±0.15	6.78±0.01
F7	87.5±3.02	0.45±0.02	132±14	100.92±0.10	6.74±0.02
F8	78.8±2.82	0.42±0.06	128±12	99.38±0.08	6.66±0.04
F9	79.2±2.26	0.42±0.04	126±10	102.42±0.06	6.71±0.07
F10	82.5±1.16	0.39±0.04	110±10	99.28±0.10	6.74±0.02
F11	79.4±1.45	0.40±0.02	107±12	100.52±0.06	6.62±0.04

Moisture absorption and moisture content determination

The results of moisture absorption and moisture content studies of buccal patches are presented in table 3. Results show that there were differences in moisture absorption of ERSPO and Hydrophilic polymers HPMC and SCMC. The percentage moisture absorbed was observed to be 55.73%±4.81% in case of formulation with ERSPO alone (F1), and varied from 76.07%±4.62% (F2) to 91.66%±4.35% (F4) in case of formulations with ERSPO: HPMC and from 82.22%±5.26% (F5) to 95.75%±6.95% (F7) in case of formulations with ERSPO:SCMC. This must be due to more hydrophilicity of SCMC as

compared to HPMC E15. The moisture absorption capacity also increased with increase in the polymer content in all the formulations.

The moisture content of the formulations ranged between 2.33%±0.92% (F1) and 4.21%±1.04% (F4). The moisture content was found to increase with increase in the concentration of hydrophilic polymer. The small moisture content in the formulation helps them to remain stable over the time and from being in a completely dried state which renders them brittle.

Table-3: Moisture absorption (%) and Moisture content (%) of Pravastatin buccal patches, mean ± S.D (n=3).

Formulation	Moisture absorbed (%)	Moisture Content (%)
F1	55.73±4.81	2.33±0.92
F2	76.07±4.62	3.06±1.08
F3	81.50±8.84	3.23±0.92
F4	91.66±4.35	4.21±1.04
F5	82.22±5.26	3.36±1.44
F6	84.62±3.37	3.58±1.52
F7	95.75±6.95	4.02±0.87
F8	83.47±5.43	3.15±1.50
F9	82.72±2.18	3.36±1.02
F10	94.45±4.45	2.62±0.42
F11	91.42±3.83	2.48±0.76

Measurement of bioadhesive strength and ex vivo residence time

Mucoadhesive strength of the patches may be due to chemical bonding or it could be due to the physical entanglement of swelled polymer with mucin thereby producing stronger mucoadhesion. It is in turn affected by various factors like biological membrane used in the study, molecular mass, swelling rate of polymers present in the formulation (Shojaei et al, 1998. Pramod Kumar et al 2006). The measurement of the mucoadhesivity of patches was therefore of great importance as they are intended to remain in contact with the buccal mucosa for a prolonged period to facilitate the controlled release of Pravastatin Sodium.

The values of mucoadhesive strength, force of adhesion and bond strength of the formulated patches are listed in the table 4. The mucoadhesion behavior seemed to be dependent on the kind of mucoadhesive polymer used in the formulation. ERSPO films showed less mucoadhesion than that of the films containing combination of polymers Patches

containing hydrophilic polymers showed satisfactory mucoadhesion properties as can be studied from the results. The mucoadhesive strength and force of adhesion increased with increasing content of the hydrophilic, bioadhesive polymers in the formulation. From the results obtained, it can be seen that the SCMC showed better adhesion properties than HPMC. This can be attributed to higher swelling nature due to hydration, viscosity and hence higher bioadhesion (Pramod kumar T.M et al, 2006) of SCMC than less viscous HPMC E15.

Hence, the addition of hydrophilic polymers was considered suitable for the formulation of buccal mucoadhesive eudragit patches of Pravastatin Sodium.

The ex vivo retention time is one of the important physical parameter of buccal mucoadhesive tablets. This test reflects the adhesive capacity of polymers used in formulations. In case of formulations containing ERSPO: HPMC, the retention time was more when compared to formulations containing ERSPO, due to higher mucoadhesive nature of HPMC E15. With the increasing concentrations of polymers in formulations, the retention time also increased from 4.5±0.2 hrs to 6.2±0.4 hrs. F3 showed an optimum retention time of 5.8±0.4 hrs.

Among the formulations containing ERSPO: SCMC, the retention time decreased with increase in the concentration of SCMC. This can be because, SCMC is highly water soluble and forms loose mass of polymer in higher concentrations and long term exposure to aqueous environment. F5 showed a higher retention time of 6.4±1.1 hrs.

Table 4: Mucoadhesion properties and ex vivo residence time of Pravastatin buccal patches, mean ± S.D (n=3).

Formulation	Mucoadhesive strength (gm)	Force of adhesion (N)	Bond strength (Nm^{-2})	*Ex vivo* residence time (hr)
F1	14.68±1.24	0.14±0.02	637.22±4.56	3.4±1.1
F2	18.25±0.55	0.18±0.06	792.18±6.23	4.5±0.2
F3	24.06±1.35	0.24±0.02	1044.37±4.34	5.8±0.4
F4	28.98±1.29	0.28±0.03	1257.94±5.56	6.2±0.1
F5	22.11±0.67	0.22±0.01	959.73±7.06	6.4±1.1
F6	25.08±1.18	0.25±0.10	1088.65±2.18	5.7±0.2
F7	27.5±0.75	0.27±0.06	1193.69±4.28	5.3±1.2
F8	23.69±0.54	0.21±0.06	950.18±6.86	5.8±0.6
F9	24.26±1.24	0.24±0.07	1066.08±5.26	6.1±0.2
F10	22.96±1.19	0.26±0.05	1170.25±7.12	6.2±0.4
F11	21.86±1.19	0.25±0.05	1168.35±7.12	6.1±0.4

In vitro drug release

The *invitro* drug release pattern from Pravastatin patches is shown in fig. 2a, 2b. All the formulations showed slow, sustained release of drug over a period of 6 hrs. From the results obtained from the present study, the drug release from the Eudragit patches could be modified by the addition of hydrophilic polymers. The increase in rate of 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. Moreover, the hydrophilic polymers would leach out, creating more pores and channels for the drug to diffuse out of the patches (Wong et al, 1999).

In case of patches containing HPMC, the drug release increases substantially with increase in HPMC concentration to certain extent. This was duly due to the low viscosity and relatively high hydrophilicity of the polymer. The formulation F3 (ERSPO: HPMC= 3:3) was considered to be the best with a drug release of 98.63±2.54% in 6 hrs.

In case of patches containing SCMC, it can be evidenced that with an increase in the SCMC concentration in the formulation, an increase in the rate of drug release was observed only at lower concentrations. This could be due to the extensive swelling of the high viscous polymer, which created a thick gel barrier for drug diffusion (Wong et al, 1999). Hence, from the observations, F5 (ERSPO: SCMC = 4:2) has proved to be the best formulation among the series exhibiting a drug release of 97.74±3.32% in 6 hrs.

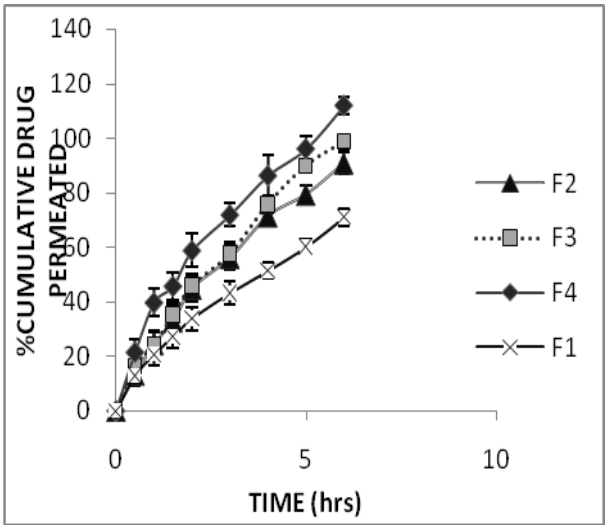

Fig.2a. In vitro release profile of Pravastatin from buccal patches F2-F4 versus F1

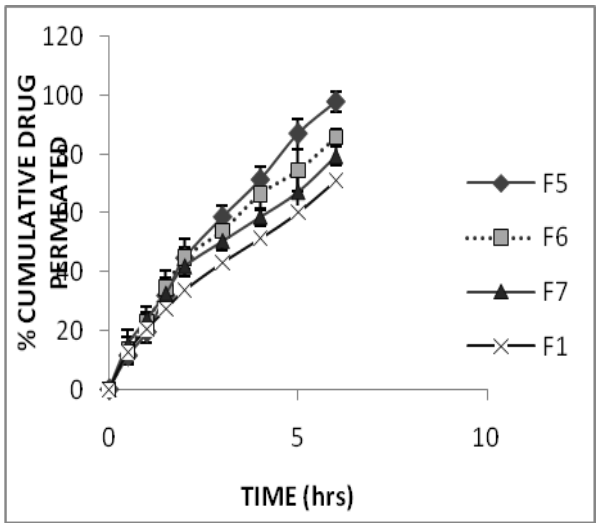

Fig.2b. In vitro release profile of Pravastatin from buccal patches F2-F4 versus F1

In order to predict and correlate the release behavior of Pravastatin from different patches, it is necessary to fit into suitable mathematical models. The in vitro release data were evaluated kinetically using mathematical models like zero-

order, first-order, Higuchi and Korsemeyer- Peppas models and R^2 were represented in table 5. When the release rates and their respective coefficients were compared, it was found that drug release from all the formulations followed zero-order release except from F4 which followed Higuchi kinetic model. The mechanism of release from all the patches was non-fickian, i.e. Korsemeyer-Peppas 'n' value ranging from 0.650 to 0.770, except F4, where n=0.505.

Table-5: Release kinetics for *in vitro* permeation of Pravastatin from buccal patches.

Formulation	Zero order	First order	Higuchi	Korsemeyer- Peppas	
	R^2	R^2	R^2	R^2	n
F1	0.988	0.974	0.979	0.996	0.676
F2	0.973	0.964	0.97	0.994	0.770
F3	0.983	0.854	0.965	0.995	0.745
F4	0.935	0.954	0.955	0.99	0.505
F5	0.985	0.867	0.954	0.993	0.709
F6	0.963	0.867	0.956	0.993	0.710
F7	0.981	0.958	0.954	0.994	0.650

Ex vivo permeation study

Based on the above results, formulations F3, F5 and F8-F11 were selected for ex vivo permeation study. The flux, permeation coefficient and cumulative drug permeated from formulation F3 were found to be 0.512 mg/hr/cm^2, 0.0512 cm hr^{-1} and 69.49%±3.25% respectively and that of F5 to be 0.483 mg/hr/cm^2, 0.0483 cm hr^{-1} and 67.49±2.87% respectively.

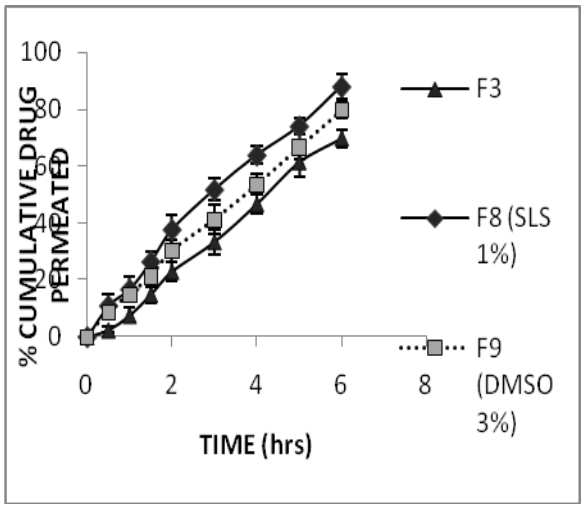

Fig.3a. Ex vivo release profile of Pravastatin from buccal patches F8-F9 versus F1

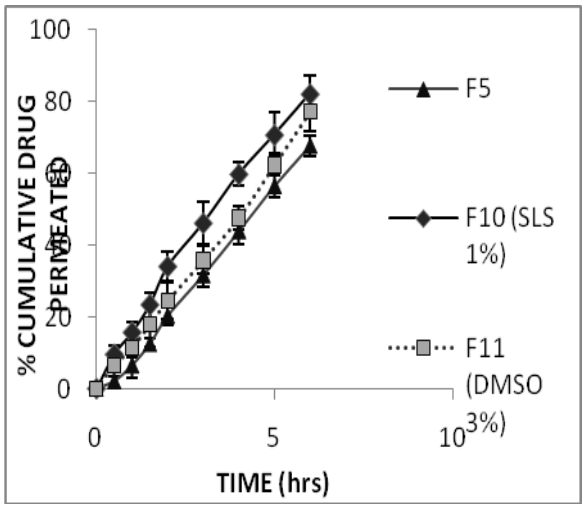

Fig.3b. Ex vivo release profile of Pravastatin from buccal patches F10-F11 versus F1

The formulations F8 and F9 containing 1% SLS and 3% DMSO have shown enhanced %drug permeation of 88.05%±4.46% and 79.84%±2.75% respectively. The %drug permeation in case of formulations F10 and F11 containing 1% SLS and 3%DMSO was found to be 82.05%±4.89% and 77.06%±5.65% respectively.

Hence, from the results, it can be inferred that 1% SLS proves better to improve the permeation of Pravastatin Sodium across the buccal mucosa, with a permeation flux of 0.68 mg/hr/cm^2 and permeability co-efficient of 0.068 cm^2/hr (in case of F8) and 0.649 mg/hr/cm^2 and permeability co-efficient of 0.0649 cm^2/hr (in case of F10). The permeation enhancement activity of SLS may be due to the perturbation and dissolution of paracellular fluid, thus enhancing the paracellular transport (Shindaye et al, 2010).

Conclusion

Development of bioadhesive buccal delivery systems was one of the potential alternatives to oral conventional administration to avoid first-pass effect and provide prolonged release. Addition of hydrophilic polymers, HPMC and SCMC to the patches formulated using ERSPO showed better improvement in bioadhesion and release properties. The release of Pravastatin from the formulations exhibited Zero-order kinetics, following non-fickian mechanism of release. The results strongly suggest that increase in the permeation was substantial on the incorporation of sodium lauryl sulphate, showing effect on paracellular transport.

References

1. Adhikari S.N, Nayak B.S, Nayak A.K, Mohanty B. (2010). Formulation and evaluation of buccal patches for delivery of Atenolol. AAPS PharmSciTech.
2. Charde S, Mudgal M, Kumar L, Saha R. (2008). Development and evaluation of buccoadhesive controlled release tablets of Lercanidipine. AAPS PharmSciTech. 9(1): 182-190.
3. Hao J, Paul Heng W.S. (2003). Buccal delivery systems. Drug development and Industrial Pharmacy. Vol. 29, no. 8, pp. 821–832.
4. Hassan N, Ahad A, Ali M, Ali J. (2010). Chemical permeation enhancers for transbuccal drug delivery. Expert Opin. Drug Deliv. *7*(1):97-112.
5. Hassan N, Ali M, Ali J. (2010). Development and evaluation of novel buccoadhesive wafers of Nimodipine for treatment of hypertension, 17(2).

6. Hoogstraate J.A.J, Wertz W.P. (1998) Drug delivery via the buccal mucosa. PSTT. Vol.1, No.7: 309-316.
7. Indian Pharmacopoeia (1996). 1, 477-480.
8. Kulkarni U, Mahalingam R, Pather S.I, Xiaoling Li, Jasti B. (2009). Porcine Buccal Mucosa as an In Vitro Model: Relative Contribution of Epithelium and Connective Tissue as Permeability Barriers. Journal of Pharmaceutical Sciences, 98(2).
9. Li et al. (2009). Stable Pharmaceutical Formulations containing Pravastatin. US patent application publication, US 2009/0292016 A1.
10. Patel V. M, Prajapati B.G, Patel M. M (2007). Effect of Hydrophilic Polymers on Buccoadhesive Eudragit Patches of Propranolol Hydrochloride Using Factorial Design. AAPS PharmSciTech, 8(2).
11. Patel V.M, Prajapati B.G, Patel H.V, Patel K.M. (2007). Mucoadhesive bilayer tablets of Propranolol Hydrochloride. AAPS PharmSciTech. 8(3); E1-E6.
12. Patel V.M, Prajapati B.G, Patel M.M. (2007). Design and characterization of chitosan-containing mucoadhesive buccal patches for propranolol hydrochloride. Acta Pharmaceutica.
13. Perioli L, Ambrogi V, Angelici F, Ricci M, Giovagnoli S, Capucella M, Rossi C. (2004). Development of mucoadhesive patches for buccal administration of ibuprofen. Journal of Controlled release, 99:73-82.
14. Perumal V.H, Lutchman D, Mackraj I, Govender T. (2008). Formulation of Monolayered films with drugs and polymers of opposing solubilities. International Journal of Pharmaceutics, 358 (2008); 184-191.
15. Pramod kumar T.M, Shivakumar H.G. (2006). Novel core in cup buccoadhesive systems and films of Terbutaline sulphate- development and in vitro evaluation. Asian journal of Pharmaceutical sciences. 1(3-4). 175-187.
16. Semalty M, Semalty A, Kumar G. (2008). Formulation and characterization of Mucoadhesive Buccal films of Glipizide. Indian J Pharm Sci. 70(1): 43-48.
17. Singhvi S.M., Pan H.Y, Morrison R.A, Willard D.A. (1990). Disposition of Pravastatin Sodium, a tissue-selective HMG- CoA reductase inhibitor, in healthy subjects. Br. J. clin. Pharmac. 29: 239-243.
18. Shanker G, Kumar C.K, Kumar V. B, Prabhakar Reddy V. (2009). AAPS PharmSciTech. 10(2): 530-539.
19. Shidhaye S.S, Saindane N.S, Sutar S, Kadam V. (2008). Mucoadhesive Bilayered Patches for Administration of Sumatriptan Succinate. AAPS PharmSciTech. 9(3): 909-916.

20. Shindaye S.S, Pritesh V.T, Dand N.M, Kadam V.J (2010). Buccal Drug Delivery of Pravastatin Sodium. AAPS PharmScitech, 11(1):416-424.
21. Sohi H, Ahuja A, Ahmad F.J, Khar R.K. (2010) Critical evaluation of permeation enhancers for oral mucosal drug delivery. Drug development and Industrial Pharmacy. 36(3): 254-282.
22. Song Y, Wang Y, Thakur R, Meidan VM, Michniak B. (2004). Mucosal drug delivery: membranes, methodologies, and applications. Crit Rev Ther Drug Carrier Syst. 2004; 21(3):195-256.
23. Squier C.A. (1991). The Permeability of Oral Mucosa. Critical Reviews in Oral Biology and Medicine, 2(1): 13—32.
24. Sudhakar Y, Kuotsu K, Bandyopadhyay A.K. (2006). Buccal bioadhesive drug delivery- A promising option for orally less efficient drugs. Journal of Controlled Release. 114: 15-40.
25. Suneela P, Urman K.L, Otaigbe J.U, Repka M.A. (2007) Stabilization of Hot-melt extrusion formulations conataining solid solutions using polymer blends. AAPS PharmaScitTech. 8(2):E1-E10.
26. Vishnu Y.V, Chandrasekhar K, Ramesh G, Madhusudan Rao Y. (2007). Development of Mucoadhesive patches for buccal administration of Carvedilol. Current Drug Delivery. 4: 27-39.
27. Weingartner O, Lütjohann D, Böhm M, Laufs U. (2010). Relationship between cholesterol synthesis and intestinal absorption is associated with cardiovascular risk. Atherosclerosis 210:362–365.
28. Yuen K.H, Wong F.C, Peh K.K (1999). Formulation and evaluation of controlled release Eudragit buccal patches. International Journal of Pharmaceutics, 178:11-22.
29. http://www.drugs.com/mmx/pravastatin-sodium.html.
30. http://www.drugbank.ca/drugs/DB00175.
31. http://www. userweb.port.ac.uk.
32. http://www. rxlist.com.

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