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Formulation and Evaluation of Timolol Buccal Patches

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ABSTRACT

The present study is concerned with formulation and evaluation of mucoadhesive buccal patches containing antihypertensive drug i.e. Timolol to avoid the first pass effect and to improve its bioavailability with reduction in dosing frequency and also dose related side effects. The patches were prepared by solvent casting technique with varying concentration of HPMC E15 as polymer and propylene glycol as the plasticizer and evaluate their physicochemical properties, *in vitro* drug release, moisture absorption, surface pH, mechanical properties, *in vitro* bio adhesion, and *ex vivo* drug permeation through porcine buccal membranes from optimized buccal patch. The physicochemical interaction between timolol and polymer was investigated by Fourier transform infrared spectroscopy. Moisture absorption, surface pH, tensile strength, elongation at break, peak detachment force and work of adhesion values of the optimized formulation F4 were found to be 124±10.59%, pH 6.61±0.28, 3.89 kg/mm^2, 14.16 mm^2, 4.92±0.06N and 0.65±0.08mJ respectively. Formulation F4 showed 68.99 ±1.67% of the drug release in *in vitro* condition and follows zero order kinetics and drug release mechanism follows non-fickian diffusion. *Ex vivo* drug permeation through porcine buccal membrane was performed and 58.52±1.59% of the drug permeated in 6 hrs with flux 0.22 mg/h/cm^2.The optimized formulation F4 with permeation enhancer tween 80 (1% v/w) showed drug release 64.47±1.63 % in 6 hrs with flux 0.33mg/h/cm^2. FTIR studies showed no evidence of interaction between the drug and polymers. Drug release from the buccal patches follows desire controlled release phenomenon as required in mucoadhesive drug delivery.

Keywords: Timolol, buccal patches, *ex vivo* permeation, bio adhesion.

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INTRODUCTION

Recently extensive efforts have been focused on targeting the delivery of drug in to a particular region of the body for an extensive period of time, not only for local drug targeting but also for the better control of systemic drug delivery. Delivery of drug through the absorptive mucosa is easily accessible in various body cavities, like the nasal, buccal, ocular, sublingual, rectal, and vaginal mucosa, offers discrete advantages over peroral administration for systemic drug delivery [1]. The main advantage of using these routes is that they avoid the first -pass effect of drug clearance. Introducing the concept of mucoadhesion into the controlled drug delivery in the early 1980's. Definition of mucoadhesive drug delivery systems are the delivery systems which utilize the bioadhesion property of some hydrophilic polymers and which become adhesive on hydration and hence can be used for drug targeting to a particular region of the body for prolonged periods of time [2]. The mucous layer is present in different parts of the body, which includes gastro intestinal tract, urogenital tract, ear, nose and eye. These are the potential sites for attachment of any bioadhesive system [3, 4].

Mucoadhesive drug delivery systems utilize the bioadhesion property of firm polymers. A material has an ability to adhere to a particular area of the body for a prolonged period of time not only for local targeting of drugs but also for maintaining the drug concentration in therapeutic level [5]. Administration of the drug through buccal route it may overcome problems such as hepatic first pass metabolism and drug degradation in the harsh gastro intestinal environment. In addition, the oral cavity is easily accessible for self-medication and be drug action quickly terminated in case of toxicity or adverse reaction by removing the dosage form from buccal cavity [6, 7]. If extended drug delivery is desired the buccal mucosa makes a more appropriate choice of site because it is less permeable than the sublingual site [8.] Timolol is a β- adrenergic antagonist and it can be used as antihypertensive, antianginal and an anti-glaucoma agent. The buccal drug delivery system is advantageous in the case of Timolol to overcome the problem of repeated dosing due to its shorter half-life (2.5-5 hrs) and bioavailability 60%. Extended release of the drug and increased bioavailability leads to the significant reduction in the dose and hence dose related side effects. Hence, in the present research an attempt was made to formulate mucoadhesive buccal patch for Timolol using different concentrations of HPMC E15 polymer in order to circumvent hepatic first pass metabolism, degradation in the gastro intestinal part and prolonged effect.

MATERIALS AND METHOD

Materials:

Timolol was a gift sample from Hetero labs, HPMC E15, Phenol red were purchased from Qualikems fine chemicals Pvt. Ltd. All other reagents used were of analytical grade.

Tissue preparation:

Porcine buccal tissue was taken from domestic pigs at the slaughter house. It was collected within 10 minutes after slaughter of the pig and tissue was stored in Krebs buffer solution pH 7.4 [sodium chloride (118 mM), potassium chloride (5.4 mM), sodium hydrogen phosphate (1 mM), magnesium sulfate (1.2 mM), calcium chloride (1.9 mM), sodium hydrogen carbonate (25 mM) and dextrose (11.1 mM)] at 4˚C. It was transported immediately to the laboratory and was mounted within 2h of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffered saline to remove any adherent material. The buccal membrane from the tissue was isolated and buccal epithelium was carefully separated from the underlying connecting tissue with surgical technique. The buccal membrane was allowed to equilibrate in receptor buffer for approximately 1hr to regain lost elasticity.

***Ex vivo* drug permeation studies through porcine buccal mucosa:**

Pig's buccal mucosa, like a composition to that of human mucosa closer than any other animal in terms of structure and composition and for that reason porcine buccal membrane was selected for drug permeation studies. *Ex vivo* drug permeation studies were performed with porcine buccal mucosa using a Franz diffusion cell. The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with an internal diameter (ID) of 2 cm (4 cm^2 area) and a volume of 18 ml of 7.4 pH phosphate buffer solution was placed in the receptor compartment. The donor compartment contained 5ml of drug solution with concentration of 1% w/v and phenol red at a concentration of 20 µg/ml. The reason for this that phenol red acts as a marker compound and is not expected to permeate through the porcine buccal membrane [9, 10]. In the receptor compartment absence of phenol red indicates the buccal membrane intactness. The entire setup was placed over magnetic stirrer and the temperature was maintained at about 37^0C at 50 rpm. Samples were collected at predetermined time intervals from receptor compartment and replaced with an equal volume of the buffer. The percent amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 295nm using a UV Spectrophotometer. After performing the experiment in triplicate (n=3), mean values were calculated [11, 12]. The cumulative amount of the

drug permeated was plotted against time. The flux (J) was calculated by using the following equation (1).

$$J = dQ/dtA \quad (1)$$

Where J is flux (mg/h/cm $^{2)}$; dQ/dt is the slope obtained from the steady-state portion of the curve; A is the area of diffusion (cm^2).

Preparation of buccal patches:

Solvent casting method was used for preparation of Buccal patches with varying ratios of HPMC E15 as polymer and propylene glycol as plasticizer. The polymer was added to 20 mL of solvent mixture (Dichloromethane (DCM): Alcohol 1:1 for HPMC E15) and allowed to stand for 6 h to swell. Propylene glycol and Timolol were dissolved in 5ml of solvent mixture and added to the polymer solution. The polymer solution was set aside for 2 hrs to remove entrapped air, poured into a petri plate, and dried at 40˚C in an oven. The developed patches were removed carefully, cut to size (each having an area of 3.14 cm^2), and stored in a desiccator. The composition of the patches is shown in Table 1. Prepared patches were subjected to weight variation, thickness variation and content uniformity.

Table 1: Formulation ingredients of Timolol buccal patches

Formulation	Timolol (mg)	HPMC E15(mg)	DCM& Methanol (1:1) (ml)	Propylene glycol (15%) (ml)
F1(1:5)	158.95	794.75	25	0.119
F2(1:7.5)	158.95	1192.12	25	0.171
F3(1:10)	158.95	1589.5	25	0.229
F4(1:12.5)	158.95	1986.87	25	0.286
F5(1:15)	158.95	2384.25	25	0.357

Note: Each patch (3.14 cm^2) contained 10mg of Timolol, 15% v/w of propylene glycol to the total polymeric weight, incorporated as plasticizer.

Moisture Absorption Studies:

The polymers used for the formulation of mucoadhesive patches are hydrophilic polymers. Moisture absorption studies were performed in accordance with the procedure described earlier [13]. 5% w/v agar in distilled water, which in hot condition was transferred into petri plates and it was allowed to solidify. Then 3 patches from each formulation were weighed and placed over the surface of the agar and left for 2 hrs at 37˚C and the patch was reweighed. The percentage of moisture absorbed was calculated using the equation 2.

$$\% \text{ Moisture absorbed} = [(\text{Final weight} - \text{Initial weight})/\text{Initial weight}] \times 100 \ldots\ldots \quad (2)$$

Surface pH Study:

To determine the surface pH of the patches the method takes on by Bottenberg et al., [14]. For this determination a glass rod was used. The mucoadhesive buccal patches were allowed to swell for 2 hrs on the surface of agar plates at room temperature, and the pH was noted down by taking the electrode in contact with the surface of the patch, allowing it to equilibrate for one minute.

Measurement of Mechanical Properties:

A microprocessor based advanced force gauze equipped with a motorized test stand (Ultra Test, Mecmesin, West Sussex, UK) is used for evaluation of mechanical properties of the patches. Strip of film having 60 x 10 mm dimensions and free from air bubbles or physical imperfections, were held between two clamps positioned at a distance of 3 cm. A cardboard was attached on the surface of the clamp to prevent the film from being cut the grooves of the clamp. At the time of measurement, the strips were pulled by the top clamp at a rate of 2.0 mm/s at a distance till the film broke. The force and elongation were measured when the films were broken. Results from film samples, which were broken at the end and not between the clamps were not included in the observations. Measurements were run in six replicates for each formulation [15]. The tensile strength and elongation at break values were calculated using equation 3&4.

Tensile strength (kg/mm^2) = [Force at break (kg)/Initial cross sectional area of the sample (mm^2)]…….. (3)

Elongation at break (% mm^{-2}) = [Increase in length (mm) × 100]/ [Original length × Cross sectional area (mm^2)]……. (4)

***In vitro* Bioadhesion Studies:**

The strength of bioadhesion of the buccal patches was determined using an ultra-test (Mecmesin, west Sussex UK) equipped with a 5-kg load cell. Obtained fresh porcine buccal mucosa from slaughterhouse was stored in simulated saliva solution (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8.00 g NaCl in 1000 ml of distilled water at P^H 6.75). The porcine buccal mucosa was held tightly to a circular stainless steel adapter with a diameter of 2.2 cm provided with the equipment. This was fixed to advanced force gauze. The prepared buccal patch was placed over another cylindrical stainless steel adaptor of same diameter and mounted on the platform of motorized test stand. Buccal patch with a backing membrane was adhered on to it using a solution of cyanoacrylate adhesive. All measurements were conducted at room temperature. 100µl of 1% mucin solution of crude mucin procured from sigma chemicals was used to moisten the porcine buccal membrane during measurement. At a speed of 0.5 mm/s the upper support was lowered until contact was made with the buccal mucosa at the predetermined force of 0.5 N for a contact time of 180 sec. The upper support was withdrawn at a speed of 0.5mm/s to detach the membrane from the patch at the end of

the contact time. Data collection and calculations were performed using the data plot software package of the instrument. Two parameters, namely the work of adhesion and peak detachment force were used to study the buccal adhesiveness of patches [16, 17]. Determination of the work of adhesion from the area under force distance curve while the peak detachment force required detaches the patch from the buccal mucosa.

***In vitro* Release Studies:**

In vitro drug release from buccal patches was studied using the USP type II dissolution apparatus. Patches were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the patch. The patch was further fixed to a 2×2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of phosphate buffer pH 6.6 at 50 rpm at a temperature of 37±0.5˚C [18, 19]. Samples of 5 ml were collected at predetermined time intervals up to 6 hrs and replaced with fresh medium and samples were analyzed using a UV-Visible Spectrophotometer at 295 nm. The drug release mechanism from the prepared buccal patches was determined by finding the best fit of the drug release data to zero order, first order, higuchi, korsmeyer- peppas plots.

***Ex vivo* permeation of Timolol through Porcine Buccal Mucosa from Buccal Patch:**

The *ex vivo* permeation of Timolol from buccal patch for the optimized formulation through porcine buccal mucosa was studied. The buccal mucosa was isolated as described in the tissue preparation section. The mucosa was placed over a Franz diffusion cell whose diameter was 2 cm. The buccal patch was placed between the buccal mucosa and the dialysis membrane, so as to secure the patch tightly from getting dislodged from the buccal membrane. Phosphate buffer pH 7.4 was placed over magnetic stirrer and the temperature was maintained at 37˚C. Samples of 1 ml were collected at predetermined time points from the receptor compartment and replaced with an equal volume of buffer [20, 21]. Estimation of drug content in the sample was done by UV- Visible spectrophotometer.

FTIR Studies:

The FTIR studies were carried out for pure drug and physical mixture of Timolol and HPMC E15. The FTIR spectra of the samples were obtained using the KBr disk method using an FTIR spectrophotometer. Samples were mixed with dry crystalline KBr in a 1:100 (sample: KBr) ratio and the pellets were prepared. A spectrum was collected for each sample within the wave number region 4,000-400 cm^{-1}.

RESULTS AND DISCUSSION

Drug Permeation Studies through Porcine Buccal Membrane:

For *ex vivo* permeation study porcine buccal mucosa has been chosen as a model because of its similarity to human buccal mucosa and its availability in large quantities from slaughterhouses. Cumulative amount of timolol permeated through the porcine buccal epithelium is shown in figure 2. The buccal mucosa could be separated successfully because no detectable levels of phenol red (marker compound) were found in the receptor compartment. The cumulative percentage amount permeated in 6 hrs was found to be 58.52 ± 1.59 % and flux was calculated 0.22 mg/h/cm^2. The permeation of drug through the porcine buccal mucosa was found to be rapid up to first 3h followed by a slow penetration in the next 3hrs.

Weight, Thickness and Drug content:

The prepared Timolol buccal patches were smooth in appearance, uniform in weight, thickness and drug content and showed no visible cracks and showing good folding endurance. The Table 2 shows the important physicochemical parameters of buccal patches of timolol. The weight of the patches ranged from 56.6±4.23 to 216.28±2.64 mg which indicates that weight of patches increased with increase in polymer concentration in the formulation. The thickness ranged from 0.15±0.014 to 0.29±0.012 mm and was found to be increased with the increase in polymer concentration. The drug content in the buccal patches was uniform showed that the drug was dispersed uniformly throughout the patches. The drug content of buccal patches was found to be in the range of 95.9±0.58 % to 99.2±0.24 %. The mean and standard deviations were calculated. All these parameters were within acceptable limits.

Surface pH study:

Surface pH of the buccal patches was determined in order to investigate the risk of any side effects *in vivo*. As an acidic or basic pH may cause irritation to the buccal mucosa, it was our attempt to keep the surface pH as close to neutral as possible. The results showed that the surface pH of all the patches ranged from 6.34±0.42 to 6.72±0.24 and found to be within an acceptable salivary pH (5.8 to 7.4). Hence, these patches may not cause any irritation to the buccal cavity.

Moisture absorption studies:

The moisture absorption studies give an indication of the relative moisture absorption capacities of polymers and the integrity of the formulations. The results of moisture absorption studies were shown in Table 2.

Table 2. Physico-Chemical properties of Timolol Buccal Patches

Formulation code	Weight variation	Thickness variation	Surface pH	Folding endurance	Drug content	%Moisture absorbed
F1	56.6±4.23	0.15±0.014	6.34±0.42	>100	95.9±0.58	85.6±12.4
F2	75.7±4.57	0.19±0.01	6.43±0.50	>100	97.6±0.57	94.5±19.43
F3	106.7±3.41	0.23±0.011	6.5±0.43	>100	98.4±0.55	111.2±11.05
F4	158.4±2.17	0.26±0.015	6.61±0.28	>100	99.4±0.25	124.3±10.59
F5	216.28±2.64	0.29±0.012	6.72±0.24	>100	99.2±0.24	136.5±10.6

Each value represents the mean ±SD (n=3)

Percentage moisture absorbed value ranged from 85.6±12.4 to 136.5±10.6%w/w. The results showed that, percentage of moisture absorption was increased with increase in polymer content of formulations.

Mechanical properties of Patches:

Apart from good bioadhesive strength, ideal buccal film should be elastic, flexible and enough strong to withstand breakage due to stress during its residence in the mouth [24]. The results of the mechanical properties, i.e. tensile strength and elongation at break are shown in Table 3. Tensile strength and elongation at break increased with the increase in the polymer content.

Table 3. Mechanical properties and *in vitro* bioadhesive studies of buccal patches

Formulation code	Mechanical Properties		*In vitro* bioadhesive studies	
	Tensile strength	Elongation at break	Peak detachment force(N)	Work of adhesion(mJ)
F1	1.85±0.35	10.06±0.021	1.56±0.09	0.25±0.05
F2	2.35±0.248	11.08±0.01	2.14±0.08	0.32±0.07
F3	3.26±0.60	13.42±0.24	3.57±0.04	0.45±0.01
F4	3.89±0.543	14.16±0.02	4.92±0.06	0.65±0.08
F5	4.14±0.53	15.56±0.03	5.79±0.07	0.74±0.04

Each value represents the mean ±SD (n=3)

***In vitro* bioadhesion studies:**

For evaluation of buccal patches, most commonly used technique is the measurement of adhesive strength results shown in Table 3. Work of adhesion is a measure of work that should be done to remove a patch from the buccal mucosa, calculated from the area under t the force distance curve. Maximum applied force at which the patch detaches from buccal mucosa is known as peak detachment force. The work of adhesion and peak detachment force for formulation F4 was 0.25±0.05mJ and 1.56±0.09N respectively.

***In vitro* drug release studies:**

The *in vitro* drug release of Timolol patches were shown in Figure 1. The results reveal that an increase in polymer concentration causes an increase in the viscosity of the polymer, therefore

decrease in drug release. This is because increasing the amount of polymer in the patches, forms a water swollen gel like state that could substantially reduce the penetration of dissolution medium into the patches and so the drug release was retarded. Formulation F1 showed maximum drug release 89.76±1.4%, whereas formulation F5 shows lowest drug release of 59.97± 1.98 %. The *in vitro* drug release data was fit into different kinetic models to explain the release kinetics of Timolol from buccal patches. The drug release kinetic models used were zero order equation, first order equation and korsemeyer –peppas models [22, 23]. The results reveals that all the formulations follows zero order kinetics (R^2 values 0.8283 for formulation F1 to 0.984 for formulation F5) when compared with R^2 values 0.8208 for formulation F1 to 0.9136 for formulation F5 of first order kinetics. On the other hand 'n' values indicated that the amount of drug released was by non fickian diffusion [23].

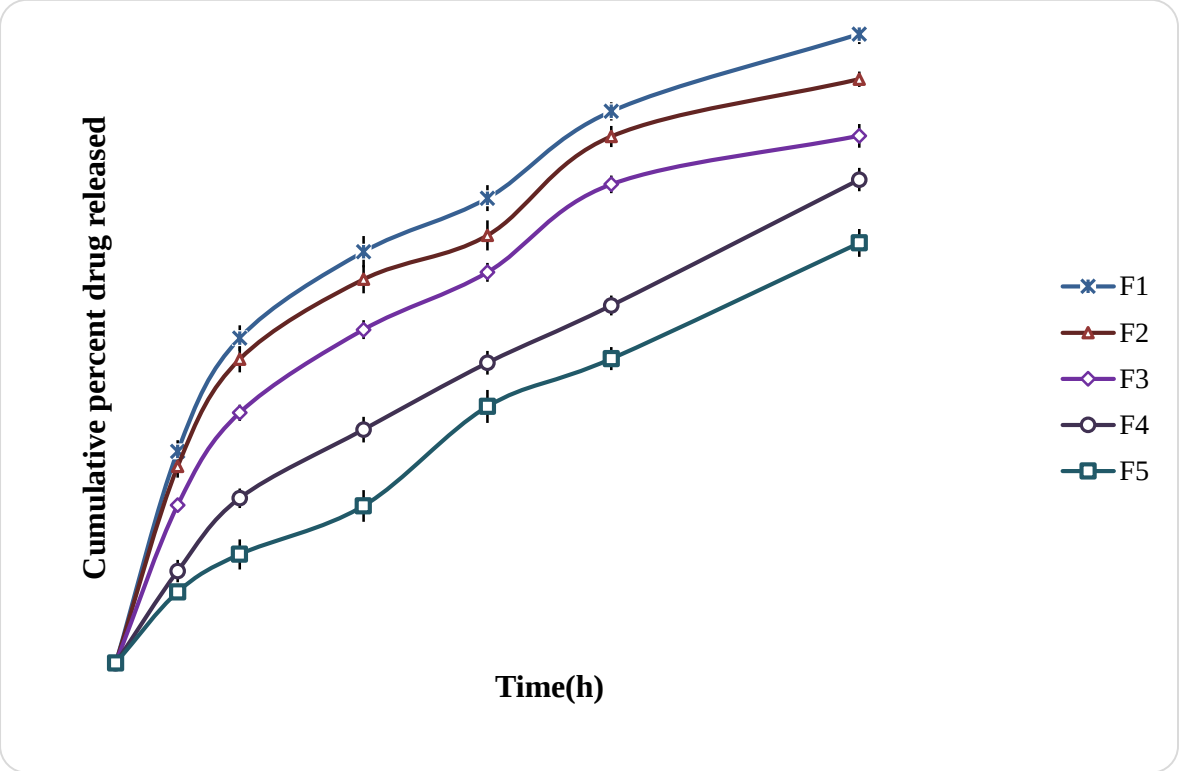

Figure 1. *In vitro* drug release studies of Timolol buccal patches

***Ex vivo* drug permeation studies:**

Ex vivo drug permeation studies were conducted for drug solution and optimized formulation. The formulation F4 was selected as optimized formulation for the *ex vivo* permeation studies due to its adequate *in vitro* drug release, its capacity to retain the structure in moisture absorption studies. The results of drug permeation from buccal patches of Timolol through the porcine buccal mucosa reveal that the drug was released from the formulation and permeated through the porcine buccal mucosa and hence could possibly permeate through the buccal membrane of humans. The results indicated

that the drug permeation is slow and steady, cumulative drug permeation was 39.94±1.46% in 6 hrs and the flux was calculated to be 0.19 mg /hr/cm^2 compared to permeation of drug from solution form shown cumulative drug permeation was 58.52 ± 1.59% in 6 h and the flux was calculated to be 0.22 mg /h/cm^2, hence to increase the drug permeation from the patches permeation enhancer tween 80 in the concentration of 1% was added to the optimized formulation which showed a result of flux 0.33 mg /hr/cm^2.Hence with the use of permeation enhancer showed a good result in increase of drug permeation. The cumulative percentage amount of Timolol that had penetrated through the buccal epithelium from buccal patch was shown in the Figure 2.

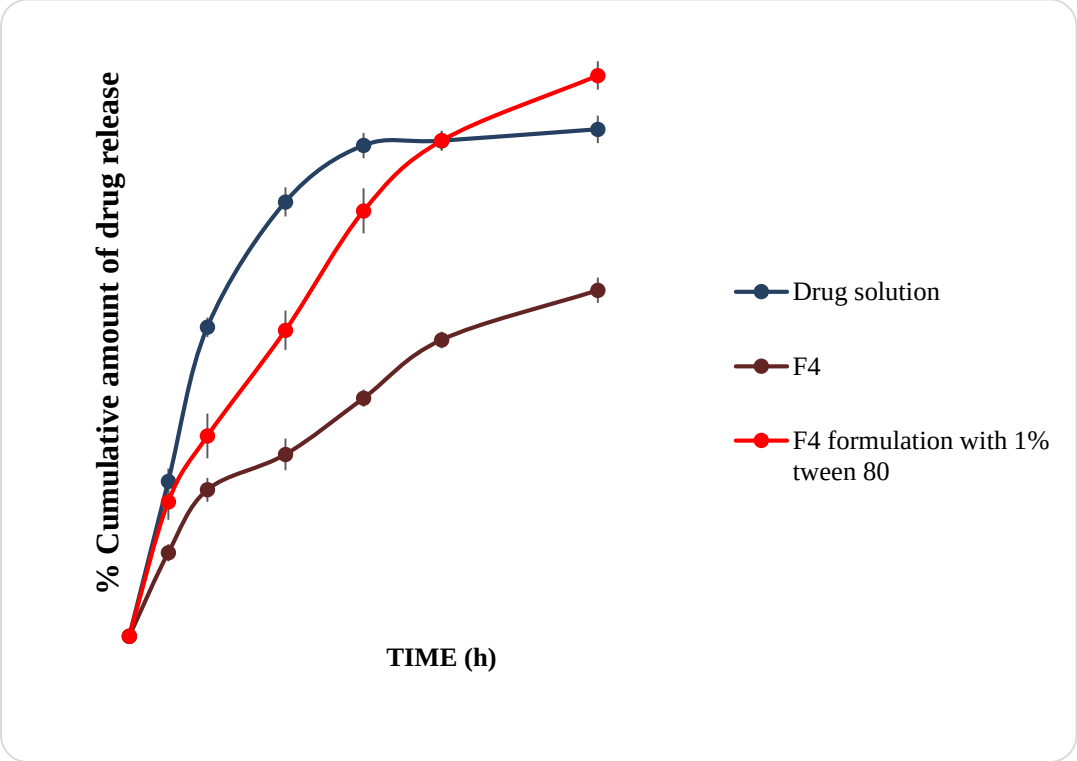

Figure 2. *Ex vivo* drug permeation of Timolol drug solution and buccal patches with and without permeation enhancer.

Drug-polymer interaction studies:

Compatibility studies were performed using Fourier Transform Infrared (FTIR) spectrophotometer. The IR spectrum of pure drug (Timolol) and physical mixtures of drug and excipients were shown in Figure 3.

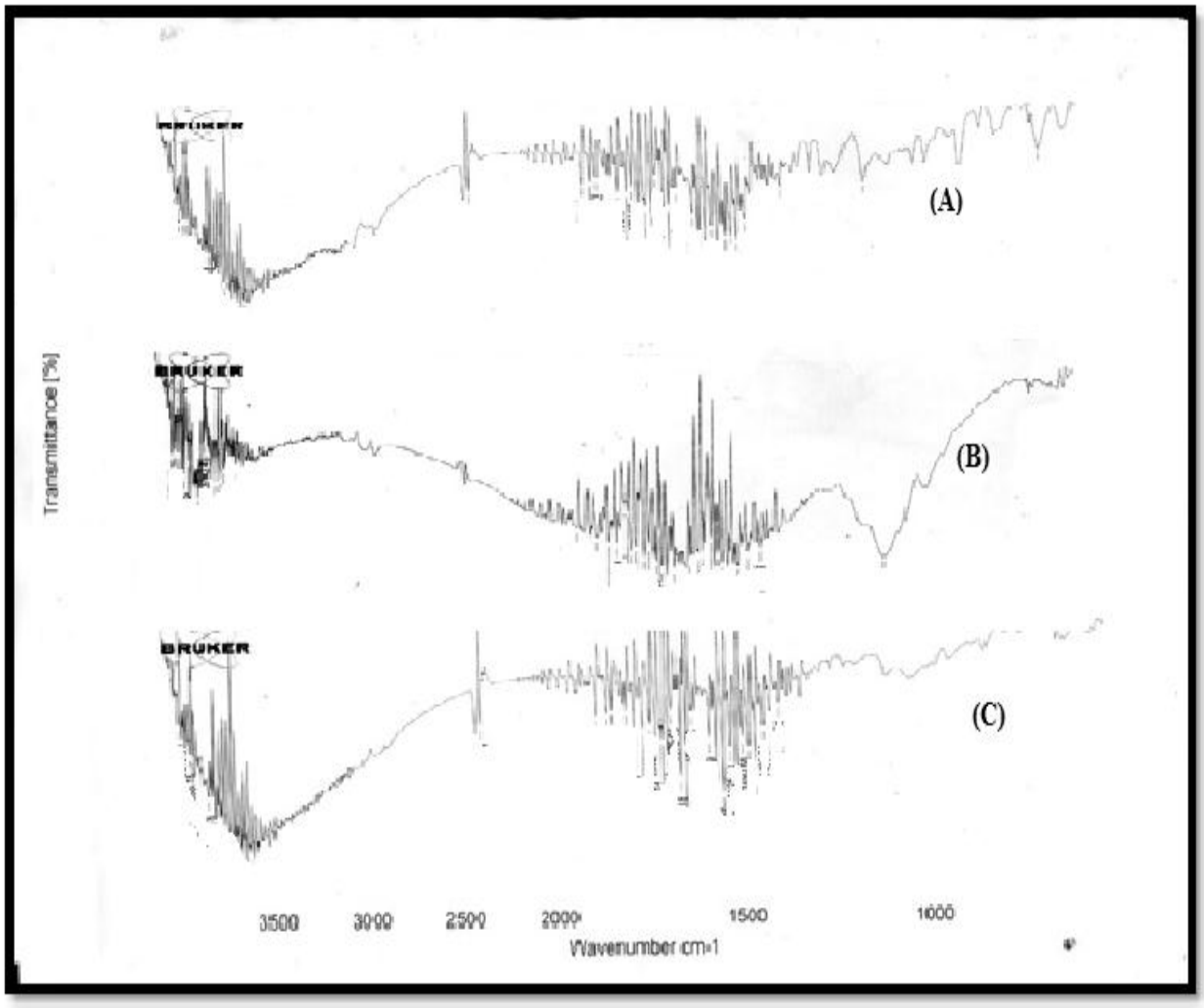

Figure 3. FTIR spectra of (A) Pure drug Timolol, (B) Pure HPMC E15 Polymer, (C) Mixture of drug and polymer

The FTIR spectral analysis of Timolol alone showed that the principal peaks were observed at wave numbers of 3431.12cm^{-1} (N-H stretching), 1193.12 cm^{-1} (C-N stretching), 2246.33cm^{-1} (N=C stretching). In the FTIR spectra of the physical mixture of Timolol and HPMC E15 were 3431.17cm^{-1}, 1234.34 cm^{-1}, 2246.36 cm^{-1} wave numbers were observed. However, some of the additional peaks were observed with physical mixtures, which could be due to the presence of polymers. The FTIR spectrum of physical mixture showed superimposition of the HPMC E15 and drug molecule. These results suggest that there is no interaction between the drug and polymers used in the present study.

CONCLUSION

The present study showed that Timolol buccal patch containing HPMC E15 in the ratio of 1:12.5 with 15%v/w of PEG-400, achieved the desired objectives of buccal drug delivery, such as

overcoming of first pass effect, extended release and frequency of administration may serve as better system for buccal delivery. The polymeric films containing Timolol were prepared and evaluated for physicochemical, *in vitro* drug release and permeation characteristics. The formulations containing HPMC E15 and permeation enhancers (Tween 80 1% v/w) were found to higher flux (0.33 mg/cm²/hr.). The mucoadhesive patches of Timolol with required flux could be prepared with suitable mechanical properties, further studies are recommended to find their therapeutic utility in humans by pharmacokinetic and pharmacodynamics studies.

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REFERENCES

1. Ananta Choudhury, Sujoy Das, Satish Dhangar, SumitKapasiya and AbhishakKanango. Development and Characterization Buccoadhesive Film of Ciprofloxacin Hydrochloride. Int j Pharm Tech Res 2010; 2 (2): 1050-1057.
2. Anuj Kumar, VikasPhatarpekar, Naveen Pathak, KumudPadhee, Minakshi Garg and Neeta Sharma, Development & Evaluation of Carvedilol Bioerodable Buccal Mucoadhesive patches. Pharmacie Globale 2011; 3(7): 1-5.
3. Sudhakar Y, Kuotsu K, Bandyopadhya AK. Buccal bioadhesive drug delivery-A promising option for orally less efficient drugs. J.Control. Rel 2006; 114:15-40.
4. Rajesh Singh Patel and S.S. Poddar. Development and Characterization of Mucoadhesive Buccal Patches of Salbutamol Sulphate. Cur Drug Del 2009; 6: 140- 144.
5. S.B.Bhanja, P.Ellaiah, S.K.Martha, P.K.Sahu, S.P.Tiwari, B.B.Panigrahi, D.Das. Design and evaluation of Timolol maleate mucoadhesive buccal tablets. Int.J.Pharm& Health Sci 2010; 1 (2): 100-108.
6. Hao Z, Jie Z and James B.S. Oral Mucosal Drug Delivery Clinical Pharmacokinetics and Therapeutic Applications. Clini Pharmacokinetics 2002; 41 (9): 661- 680.
7. Anders R, and Merkle H.P. Evaluation of laminated mucoadhesive patches for buccal drug delivery. Int. J. Pharm 1989; 9: 231-240.
8. Vamshi Vishnu Y, Chandrasekhar K, Ramesh G, Madhusudan Rao Y. Development of Mucoadhesive Patches for Buccal Administration of Carvedilol. Current Drug Delivery 2007; 4:27-39.

9. Junginger, H.E., Hoogstrate J.A. and Verhoef, J.C. Recent advances in buccal drug delivery and absorption - *in vitro* and *in vivo* studies. J. Control. Rel 1999; 62: 149-159.
10. Veuillez, F., Reig, F.F., Guy, R.H., Jacques, Y., Deshusses J. and Buri P. Permeation of a myristoylated dipeptide across the buccal mucosa: topological distribution and evaluation of tissue integrity. Int. J. Pharm 2002; 231:1-9.
11. Schurmann, W. and Turner, P. A membrane model of the human oral mucosa as derived from buccal absorption performance and physicochemical properties of the β-blocking drugs atenolol and propranolol. J. Pharm. Pharmacol 1978; 30:137-147.
12. Tucker, I. G. A method to study the kinetics of oral mucosal drug absorption from solutions. J. Pharm. Pharmacol 1988; 40:679-683.
13. Khurana, R., Ahuja A. and Khar, R. K. Development and evaluation of mucoadhesive films of miconazole nitrate. Indian J. Pharm. Sci, 2000; 60:449-453.
14. Bottenberg. P., Cleymaet. R., Muynek. C. D., Remon. J. P., Coomans D. and Slop. D. Development and testing of bioadhesive, fluoride containing slow-release tablets for oral use. J. Pharm. Pharmacol 1991; 43:457-464.
15. Peh, K. K. and Wong, C. F. Polymeric films as vehicle for buccal delivery: swelling, mechanical, and bioadhesive properties. J. Pharm. Pharm. Sci 1999; 2:53- 61.
16. Choi H, Jung J, Young C.S, Rhee C, Lee M, Han J, Park, and Kim C. Formulation and *in vivo* evaluation of omeprazole buccal adhesive tablet,J.Control. Rel 2000; 68: 405-412.
17. Wong, C. F., Yuen, K. H. and Peh, K. An *in vitro* method for buccal adhesion studies: Importance of instrument variables. Int. J. Pharm 1999; 180:47-57.
18. Madhusudan Rao Y, Jithan A.V. ed. Advances in drug delivery vol.1 2010; 139-210.
19. Chinna Reddy P, Ramesh G, Vamshi Vishnu Y, Shravan Kumar Y, Madhusudan Rao Y. Development of bilayered mucoadhesive patches for buccal delivery of felodipine: *in vitro* and *ex vivo* characterization. Curr Trends Biotech Pharm 2010; 4:673-683.
20. Chandra Sekhar K, Naidu KVS, Vamshi Vishnu Y, Ramesh G, Kishan V, Madhusudan Rao Y. Transbuccal Delivery of Chlorpheniramine Maleate from Mucoadhesive Buccal Patches. Drug Del 2008; 15:185-191.
21. Wong CF, Yuen KH, Khiangpeh K. An *in vitro* method for buccal adhesion studies: importance of instrument variables. Int.J.Pharm 1999; 180: 47-57.
22. Korsmeyer R.W, Gurny R, Doelker E, Buri P and Peppas N.A. Mechanism of solute release from porous hydro matrices and other factors may be responsible. Int. J. Pharm 1983; 15: 25-35.

23. Peppas N.A. Analysis of Fickian and non-Fickian drug matrix tablets with respect to the compression force release from polymers. Pharm Acta Helv 1985; 60: 110-111.
24. Aulton, M. E., Abdul-Razzak, M. H. and Hogan, J. E. The mechanical properties of hydroxy propyl methyl cellulose films derived from aqueous systems: the influence of solid inclusions. Drug Dev. Ind. Pharm 1981; 7:649-668.