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Research Article

Preparation of Mucoadhesive Patches for Buccal Administration of Metoprolol Succinate: *In Vitro* and *In Vivo* Drug Release and Bioadhesion

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Abstract

Purpose: *To develop mucoadhesive patches for buccal administration of metoprolol succinate and to evaluate their in vitro and in vivo bioadhesion.*
Methods: *The mucoadhesive buccal patches were prepared by solvent casting technique using two different mucoadhesive polymers. The formulations were tested for in vitro drug permeation studies, buccal absorption, in vitro drug release studies, moisture absorption as well as for in vitro and in vivo bioadhesion.*
Results: *The peak detachment force and work of adhesion for MC5 (sodium carboxymethylcellulose, i.e., Na CMC) patch were 0.87 N and 0.451 mJ respectively and the corresponding values for CH5 (chitosan) were 5.15N and 0.987 mJ. Formulation CH5 (prepared with chitosan) showed 67.1 % release, while MC5 (Na CMC) showed drug release of 81.9 % in 6 h. Basic pharmacokinetic parameters such as C_{max}, T_{max} and AUC_{total} varied statistically ($p < 0.05$) when given by the buccal route compared with that of the solution given by the oral route.*
Conclusion: *The results indicate that formulation of suitable bioadhesive buccal patches with the desired permeability is feasible. The development of bioadhesive buccal formulation for metoprolol succinate with a lower dose and few side effects may be attainable.*

Keywords: *Mucoadhesive, Buccal patches, Metoprolol succinate, Sodium carboxymethylcellulose, Chitosan, Bioavailability*

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INTRODUCTION

Rapid developments in the field of molecular biology and gene technology has resulted in a generation of many macromolecular drugs including peptides, proteins, polysaccharides and nucleic acids possessing superior pharmacological efficacy, site specificity and are devoid of untoward and toxic effects However, the main impediment for the oral delivery of these drugs is their extensive presystemic metabolism and instability in acidic environment resulting in inadequate and erratic oral absorption [1]. Parenteral route of administration is the only established route that overcomes these drawbacks. However, these formulations are costly, require repeated administration and hence show poor patient compliance,, in addition to the other hazardous effects associated with this route [2]. Over the past few decades, pharmaceutical scientists have been exploring transdermal and transmucosal routes as alternative routes to the parenteral route. Among the various transmucosal sites available, the buccal mucosa has been found to be a convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery because it has an expanse of smooth muscle which is relatively immobile, abundant vascularization, rapid recovery time after exposure to stress and the near absence of Langerhans cells. Direct access to systemic circulation through the internal jugular vein bypasses the hepatic first pass metabolism leading to high drug bioavailability. Furthermore, these dosage forms are self-administrable, low-cost and have superior patient compliance [3].

With the right dosage form design, the local environment of the mucosa can be controlled and manipulated to optimize the rate of drug dissolution and permeation. A rational approach to dosage form design requires a complete understanding of the physicochemical and biopharmaceutical properties of the drug and excipients. Advances in experimental and computational methodologies will be helpful in shortening the processing time from formulation design to clinical use [4].

Metoprolol succinate is a non-selective and β-adrenergic antagonist with no intrinsic sympatomimetic activity and is widely used to treat essential hypertension and angina pectoris. Although it is completely absorbed from the gastrointestinal tract, systemic availability is only approximately 25 – 35 % due to first-pass metabolism. Metoprolol succinate was selected as a model drug for the investigation because its oral dose is 25 mg and half life is 3-4 h. Metoprolol succinate is metabolized primarily by aromatic ring glucuronidation [5]. Its oxidative metabolites are metabolized by conjugation via glucronidation and sulfation. A suitable buccal drug delivery system should be flexible and possess good bioadhesive properties so that it can be retained in the oral cavity for the desired duration. In addition, it should release the drug in a predictable manner to elicit the required therapeutic response. The objective of this study was to prepare mucoadhesive buccal patches of metoprolol succinate and evaluate their properties.

EXPERIMENTAL

Materials

Metoprolol succinate was obtained as a gift from Aarti Pharmaceuticals, India while sodium carboxymethylcellulose and chitosan were supplied by Sigma Pvt Ltd, India. The plasticizer, propylene glycol, was purchased from Merck (Mumbai, India). All the other reagents were of analytical grade.

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Tissue preparation

Porcine buccal tissue from pigs was obtained from local slaughter house and used within 2 hours of slaughter. The tissue was stored in kerb buffer (pH 7.4) at 4 ^{o}C after collection. The epithelium was separated surgically from the underlying connective tissue and delipidized by incubation with chloroform:

methanol (2:1) at room temperature for 12 - 72 h, either before or after digestion with strong alkali or concentrated acid. The delipidized membrane was allowed to equilibrate for approximately one hour in receptor buffer (kerb buffer) to regain the lost elasticity.

In vitro drug permeation studies

The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with internal diameter of 1.0 cm with a receptor compartment volume of 20.0 ml. A solution containing 20 ml of alcohol, propylene glycol and phosphate buffer (pH 6.8) in a ratio of 40:15:45 was placed in the receptor compartment. The donor compartment (5 ml capacity) contained phenol red at a concentration of 10 µg/ml and a solution of 3 ml of phosphate buffer pH 6.8 in which 2 mg of metoprolol succinate was dissolved. Phenol red served as a marker that would not permeate the porcine buccal membrane. The entire set up was placed in a water bath stirred by a magnetic stirrer at 37 ± 1 ℃.

A sample (1 ml) was collected at predetermined time intervals from the receptor compartment and replaced with an equal volume of fresh receptor fluid [6]. The experiment was conducted in triplicate.

Production of bioadhesive films

The films were prepared by casting [7]. Aqueous solution (20 ml) of the polymer (either sodium CMC or chitosan), ranging from a polymer concentration of 1 – 6 %w/v, was prepared and left for 4 h for maximum swelling; 5 %w/v of propylene glycol (1 ml) was added as plasticizer. Metoprolol succinate solution (1 ml, 2 %w/v) was mixed with 20 ml of the polymer solution and cast in a Petri dish 30 min later. It was dried at room temperature (25 ^{o}C) for 12 h. The films were observed and checked for possible imperfections upon their removal from the Petri dish and dried in a desiccator pending evaluation. The films were examined in order to select those with the best characteristics for further evaluation.

In vitro release study

Drug release from the buccal patches was studied using USP type II dissolution test apparatus [8]. Patches (10 mm diameter) were cut, and an impermeable backing membrane on one side of the patch. The assembly for release studies was prepared by placing the patch in contiguity with cellulose acetate dialysis membrane such that the drug release from the patch diffuses through dialysis membrane. This assembly was placed in dissolution apparatus containing 500 ml of phosphate buffer (pH 6.8) and rotating at 50 rpm at 37 ± 0.5 ^{0}C. Samples (5 ml) were collected at different time intervals and diluted with phosphate buffer (pH 6.8), 2 ml of which was analysed spectrophotometrically (UV-1800, Shimadzu, Japan) at 222 nm [9]. The experiment was performed in triplicate.

Moisture uptake/Swelling index) studies

Moisture uptake gives an indication of the ability of the patches to maintain their integrity after absorption of moisture. Agar dispersion (5 %w/v) was prepared by dissolving agar in hot water [10]. The dispersion (20 ml) was transferred to a 4-inch diameter glass Petri dish and allowed to solidify. Six drug-free patches from each formulation were selected, weighed and placed in a vacuum oven(40 – 45 ^{o}C) overnight prior to the study to remove any residual moisture. Each patch was laminated on one side with a water-impermeable backing membrane of ethyl cellulose, using an adhesive, incubated at 37 ^{0}C for 1 h, and reweighed [11]. Moisture uptake was calculated as percent change in weight of the patch. The experiment was performed in triplicate.

Measurement of mechanical properties of patches

The mechanical properties of the patches were evaluated using a tensile tester fabricated in-house with stainless steel and has two clamps (one movable and the other stationary). A 50 x 10 mm patch, without any visual defect, was positioned between the two clamps, separated by a distance of 2 cm. The lower clamp was held stationary and the patch was pulled apart by the upper clamp moving at a rate of 2 mm/sec until the patch broke. The force and elongation of the film at the point the patch broke was recorded [12,13]. The tensile strength (T) and elongation (E) at break point were calculated using Eqs 1 and 2, respectively:

$T = F/A$ ..... (1)

where F is the force at break point and A is initial cross-sectional area of the test patch.

$E = (\Delta L/L) \times (100/A)$ ..... (2)

where ΔL is increase in length, L is the original length and A is the cross-sectional.

***In vitro* bioadhesive strength**

The bioadhesive strength of buccal patches was determined using modified equipment. Fresh porcine buccal mucosa obtained from a slaughter house was kept in simulated saliva (28.80 g Na_2HPO_4 and 11.45 g KH_2PO_4 in 1000 ml of distilled water at pH 6.8) [12] and secured tightly to a circular stainless steel adapter of (diameter, 2.2 cm) provided with the equipment. The test buccal patch was placed over another cylindrical stainless steel adapter of similar diameter and mounted on the platform connected to a pulley. The buccal patch was fixed to a backing membrane with a cycnoacrylate adhesive. The upper support was lowered at a speed of 0.5 mm/s until contact was made with the tissue. At the end of the contact time (10 - 15 sec), the upper support was withdrawn at a speed of 0.5mm/s to detach the membrane from the patch. During the test, 100 µl of phosphate buffer (pH 6.8) was applied to moisten the porcine buccal membrane. The test was conducted at room temperature. Peak detachment force, which is the force required to detach the buccal patch from the tissue was recorded while the work of adhesion was determined from the area under the force - distance curve [15].

***In vivo* bioadhesion studies**

Eight healthy male rabbits were used in the study. The institutional animal ethics committee (IAEC)'s permission was obtained prior to start the study. (approval no.: 3/837ac/PH/10). Initially a slight pressure was applied with a finger for one minute till the patch adhered to the buccal mucosa. The rabbits were deprived of food and drinks during the test. Residence time of the film on buccal mucosa in the oral cavity, which was taken as the time for the patch to dislodge completely from the buccal mucosa, was recorded [16].

***In vitro* permeation of metoprolol succinate**

In vitro permeation of metoprolol succinate from a buccal patch (formulation MC4) through porcine buccal membrane was studied. The buccal membrane was isolated and mounted over a Franz diffusion cell whose internal diameter was 10 mm and a buccal patch, which was fixed to a dialysis membrane made up of cellulose (molecular weight cutoff, 5000) in order to ensure that the patch does not dislodge from the membrane during the test [17,18]. The buccal patch was sandwiched between the buccal mucosa and the dialysis membrane. The whole diffusion cell assembly was agitated with the aid of a magnetic stirrer at 37 ± 0.5 ^oC. One millilter sample was withdrawn hourly and analyzed by spectrophotometrically at 222 nm.

In vivo bioavailability Study

Metoprolol succinate a cardiovascular drug may sometimes produce hypotension in normal patients that may be difficult to control and hence bioavailability studies was conducted in an animal model (rabbit). The study was approved by the institutional ethical committee. Rabbit was used because its buccal membrane closely resembles the human buccal membrane in structure and permeability. Rabbits were housed in separate cages. The rabbits selected for the study were housed in separate cages and had no medication for two weeks prior to the study. They were denied food and water during the study. The cages of rabbit were placed in 18 h light/6 h dark conditions. The test patch (MC4), containing 125 mg of the drug, was laminated on one side with a water impermeable backing layer and fixed to the buccal section of the oral cavity with the patch side. A gentle pressure was applied with a finger for 1 min to ensure good adhesion to the mucosa. The rabbits were placed on their side on a surgery table, 2 ml of blood was collected from the ear vein, centrifuged, and the serum separated was stored at – 20 ^{o}C until analysed [19]. The rabbits were moved to their cages and blood samplings continued at intervals for up to 8 h. The drug bioavailability of the patch was compared with that of a solution (0.5 ml) containing 12.5 mg of metoprolol succinate in phosphate buffer administered to the rabbits. The drug was not administered in the form of tablet because it could not be assured that the rabbits would swallow it. Relevant pharmacokinetic parameters were determined and analysed statistically.

Analysis of serum metoprolol succinate

The quantitative determination of metoprolol succinate in rabbit serum was carried out by high performance liquid chromatography (HPLC, Shimadzu, Japan, SPD-20A detector) method at room temperature [20]. Phosphate buffer (0.02M, pH 6.8)/acetonitrile (60/40, v/v) was used as mobile phase at a flow rate of 1 ml/min; the injected volume was 10 µl and the detection wavelength was set at 222 nm.

Statistical analysis

All the data were statistically analysed by Student t-test and one-way ANOVA to determine statistical difference between sets of data. A probability value of $p < 0.05$ was applied to determine significant difference. The software used was SigmaPlot 11 (Systat Software Inc).

RESULTS

Drug penetration through porcine buccal membrane

The cumulative amount of metoprolol succinate transported across the buccal epithelium is plotted against time in Fig 1. Drug permeation was rapid and linear first 4 h and then gradually slowed down thereafter.

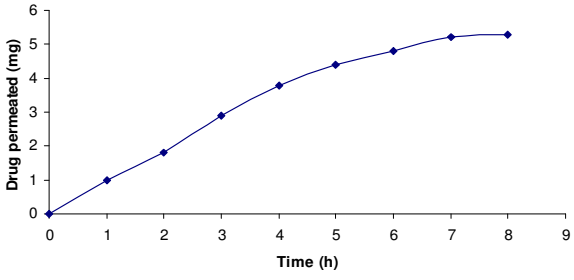

Fig 1: *In vitro* permeation of petoprolol succinate through porcine buccal mucosa

In vitro buccal absorption of metoprolol

Based on computations made, 72 % of the drug permeated through the buccal membrane in 20 min. The drug was absorbed at a rapid rate for the first 5 min, followed by a steady permeation rate.

In vitro drug release

The drug release profiles of metoprolol succinate from buccal patches are shown in Figs 2 and 3. In case of Sodium CMC (MC5) 81.92% of the drug was released when

compared with Chitosan (CH5) from which only 67.12% of drug was released. The formulation (CH5) with a drug to polymer ratio of 1:2.5 was used for the evaluation of drug release and bioadhesive properties of the patches. The best fit with the highest correlation coefficient (r^2) was shown by the Higuchi model model (r^2 = 0.997), followed by first order.

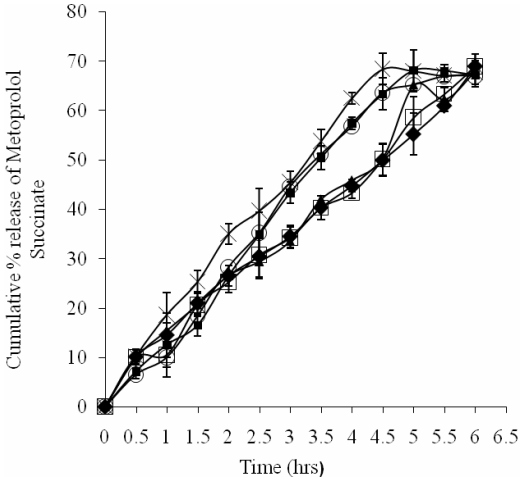

Fig 2: Drug release profile of metoprolol succinate buccal patches made with chitosan (♦ = CH-1, □ = CH-2, ▲ = CH-3, x = CH-4, ■ = CH-5, o = CH-6)

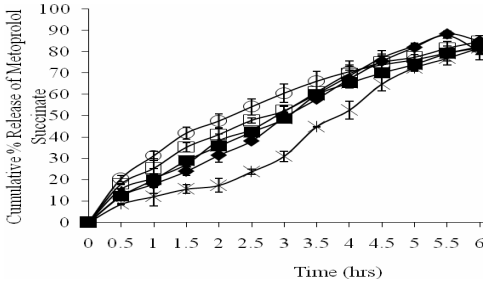

Fig 3: Drug release profile of metoprolol succinate buccal patch containing sodium CMC (♦ = MC-1, □ = MC-2, ▲ = MC-3, ■ = MC-4, ¤ = MC-5, o = MC-6)

Moisture uptake

The results of moisture absorption studies are presented in Table 1. Moisture uptake ranged from about 72.3 to 154.1 %w/w for patched made with sodium CMC and 61.9 to 98.2 %w/w for those made with chitosan.

Mechanical properties of films

The results of the mechanical properties (tensile strength and elongation at break) are presented in Table 1. Statistically significant differences were observed among the elongation data ($p < 0.05$).

In vitro bioadhesion

The results of the *in vitro* bioadhesion of patches MC5 and CH5 indicate that he peak detachment force and work of adhesion of the former were 0.87 ± 0.31 N and 0.45 ± 0.15 mJ, respectively, while for the latter, the values were 5.15 ± 0.22 N and 0.99 ± 0.18 mJ, respectively.

In vivo bioadhesion

The results of *in vivo* bioadhesion test show that CH1 exhibited an appreciable adhesion for ~ 1 h CH2 ~ 2 h, and CH3, CH4 and CH5 ~ 3h. None of the patches became detached during the respective periods indicated above.

In vitro drug permeation through porcine buccal membrane

The results indicate that drug permeation from the patch evaluated (CH5) was slow but steady and that 54.8 % of metoprolol succinate permeated through the buccal membrane in 8 h.

In vivo drug release from metoprolol succinate patch

The pharmacokinetic parameters, namely, maximum concentration (C_{max}), time to reach maximum concentration (T_{max}) and AUC_{total} (relatve bioavailability) for patch CH5 are given in Table 2. Plasma concentration of metoprolol succinate gradually increased and attained maximum of 354.6 ± 12.1 ng/ml in approx 6 h; thereafter, drug level declined

Table 1: Composition and some physicochemical and mechanical properties of mucoadhesive buccal patches of metoprolol succinate

Patch code	Na CMC (%w/v)	Chitosan (%w/v)	Mean moisture absorbed (%)	Tensile strength (Kg/mm^2)	Elongation at break ($\%mm^2$)	Cumulative drug release in 6 h (%)
MC 1	1.0		72.26	6.7±1.3	131.2±1.7	85.2±0.2
MC 2	2.0		86.54	9.0±0.2	112.0±7.8	84.8±1.5
MC 3	3.0		100.91	12.7±1.1†	94.1±1.4	80.0±2.3
MC 4	4.0		124.77	14.3±2.3	85.7±4.8	82.5±3.9
MC 5	5.0		136.02	15.1±1.9†		81.9±0.5
MC 6	6.0		154.12	16.7±1.3	62.7±2.3	81.8±1.2
CH 1		1.0	61.88	3.3±1.9	40.5±1.3†	68.9±4.1
CH 2		2.0	67.50	7.2±0.2	36.9±4.3	68.9±0.7
CH 3		3.0	76.00	10.1±1.1	29.8±2.2	67.9±3.5
CH 4		4.0	81.26	11.7±1.7†	20.5±5.3	67.6±0.8
CH 5		5.0	90.44	12.9±2.3†	14.4±0.3†	67.1±2.5
CH 6		6.0	98.16	13.2±0.2	11.1±2.1	67.0±0.1

***Note**: Each formulation contained 2 %w/v metoprolol succinate and 5%w/v propylene glycol*

gradually. The pharmacokinetic parameters of metoprolol succinate after the application of buccal patch significantly differed from that of the oral solution. Unlike oral form, drug concentration after application of the buccal patch was largely steady over a period of 10 h. This contrasts with the oral solution that showed a C_{max} of 254.6 ± 24.4 ng/ml within 4 h and declined slowly after 8 h. The AUC_{total} for the buccal patch was significantly ($p < 0.005$) higher than that of the oral solution, indicating improved bioavailability for the buccal patch (Table 2).

Table 2: Pharmacokinetics of metoprolol succinate administered via oral and buccal routes

Route	C_{max}	T_{max} (h)	AUC_{total} (ng.hr/ml)
Oral	254.6±24.4	4.0±0.7	2007.2±4.7
Buccal	354.6±12.1	6.0±1.8	4616.5±8.0

DISCUSSION

The porcine buccal membrane tissue was isolated successfully as evidenced by the fact that there was no detectable level of phenol red (the marker used) in the receptor compartment whereas metoprolol succinate penetrated freely. The results in vivo absorption data for the buccal patch also revealed that metoprolol succinate penetrated through the oral cavity and that the animal did not swallow the solution of the drug.

For the patch containing chitosan (CH), drug release was governed by polymer content. No lag time was observed as the patch was directly exposed to the dissolution medium. Increase in polymer content correlated with decrease in drug release rate. However, there was no significant difference between the patches with regard to cumulative drug released. This may be due to the fact that for all the formulations, the drug dissolved completely in the dissolution medium. Patches made with chitosan exhibited lower swelling than those made with Na CMC and this might be responsible for the lower drug release from the lower.

Tensile strength increased with increase in polymer content but elongation at break decreased as polymer content rose. The pattern was similar for patches made with either chitosan or Na CMC.

Metoprolol succinate was adequately released from the patches and permeated through the porcine buccal membrane and could therefore permeate through the human buccal membrane. The *in vivo* data for the

buccal patches of metoprolol succinate indeed confirmed this as the bioavailability of the drug actually increased. A mean oral bioavailability of of 25 % has previously been reported for metoprolol succinate [21]. In contrast, the buccal patch used in the present study showed 60 % bioavailability. This increase in bioavailability may be due to the elimination of hepatic first-pass metabolism for drugs given by buccal route. This probably also accounts for the prolonged steady-state concentration of metoprolol succinate in blood.

CONCLUSION

Buccal patches containing 5 % chitosan (CH5) demonstrated optimal characteristics of the various chitosan concentrations evaluated. Buccal delivery of metoprolol succinate in patch form in rabbits showed superior bioavailability over the oral route. The results for these animals may not be substantially different from those for humans since the structure and permeability of the buccal membrane of rabbits is similar to those of humans. Thus, the development of a bioadhesive buccal patch of metoprolol succinate holds some promise since it will lead to decreased dosing frequency and hence reduced side effects.

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REFERENCES

1. *Cilurzo F, Cupone I, Selmin F. Fast dissolving films made of maltodextrins. Eur J Pharm Biopharm 2008; 70: 895-900.*
2. *Mashru RC, Sutariya MG. Development and evaluation of fast dissolving film of salbutamol sulphate. Drug Dev Ind Pharm 2005; 1: 25-34.*
3. *Asha S, Sathesh BP, Divakar G, Purohit KP. Development and evaluation of buccoadhesive drug delivery system for atorvastatin calcium. J Current Pharm Res 2010; 1: 31-38.*
4. *Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery: A promising option for orally less efficient drugs. J Control Rel 2006; 114: 15-40.*
5. *Nafee NA, Ismail FA, Boraje NA. Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride. Acta Pharm 2003; 53: 199-212.*
6. *Morales JO, McConville JT. Manufacture and characterization of mucoadhesive buccal films. Eur J Pharm Biopharm 2011; 77: 187-199.*
7. *Andrew GP, Laverty TP, Jones DS. Mucoadhesive polymeric platform for controlled drug delivery. Eur J Pharm Biopharm 2009; 71: 505-518.*
8. *Gandhi RB, Roninson JR. Bioadhesion in drug Delivery. Indian J Pharm Sci 1988; 50: 145-152.*
9. *Hao J, Heng PWS. Buccal Delivery System, Drug Dev Ind Pharm 2003; 29: 821-832.*
10. *Shojaei AH, Li X. Determination of transport route of acyclovir across buccal mucosa. Proc Int Symp Control Release Bioact Mater 1997; 24: 427-428.*
11. *Randhawa MA, Malik SA, Javed M. Buccal absorption of weak acidic drugs is not related to their degree of ionization as estimated from the Henderson-Hasselbalch equation. Pak J Med Research 2003; 42: 116-119.*
12. *Riikka L, Eera S, Kaisa T, Mikko B. Intraorally fast dissolving particles of a poorly soluble drug: Preparation and in vitro characterization. Eur J Pharm Biopharm 2009; 71: 271-281.*
13. *Ellen H, Marianne H, Arne S. Mucoadhesive and drug permeation of free mixed films of pectin and Chitosan : An in vivo study. Eur J Pharm Biopharm 2009; 71: 325-331.*
14. *Aleksandra M, Ewa K, Tomasz C. Electro-osmotic flow as a result of Buccal iontophoresis-Buccal mucosa properties, Eur J Pharm Biopharm 2009; 72: 595-599.*
15. *Ana F, Juliane H, Andreas BS. In-vitro evaluation of natural and methylated cyclodextrin as Buccal permeation enhancing system for omeprazole delivery. Eur J Pharm Biopharm 2009; 71: 339-345.*
16. *Khairnar A, Parridhi J Dheeraj B. Development of mucoadhesive buccal patch containing aceclofenac: In vitro evaluation. Int J Pharm Tech Research 2009; 1: 978-981.*
17. *Perioli L, Ambrogi V. Development of mucoadhesive patches for buccal administration of Ibuprofen. J Control Rel 2004; 99: 73-82.*
18. *Henrihsen I, Green LK Bioadhesion of hydrated chitosan: an in vitro and in vivo study. Int J Pharm 1996; 145: 231-240.*
19. *Lehr CM, Bouwstra JA. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymer. Int J Pharm 1992; 78: 43-48.*
20. *Nafee NA, Ismail FA. Mucoadhesive delivery system. II. Formulation and In-vitro/In-vivo evaluation of buccal mucoadhesive tablets*

containing water soluble drugs. Drug Dev Ind Pharm 2004; 30: 995-1004.

21. *Panigrahy RN, Mahale AM, Dhaked PS. Formulation and invitro evaluation of combined floating mucoadhesive tablet of Metoprolol succinate. Int J Pharm Sci 2011; 3: 221-226.*